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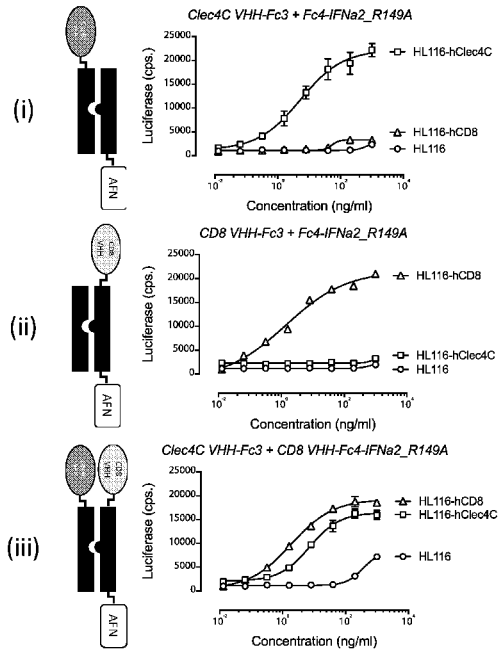
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(54) Title: BI-FUNCTIONAL PROTEINS AND CONSTRUCTION THEREOF

FIG. 49



(57) Abstract: The present invention relates, in part, to Fc-based chimeric protein complexes and their use as therapeutic agents. The present invention further relates to pharmaceutical compositions comprising the Fc-based chimeric protein complexes and their use in the treatment of various diseases.

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BI-FUNCTIONAL PROTEINS AND CONSTRUCTION THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application Nos. 62/649,238, filed March 28, 2018; 62/649,248, filed March 28, 2018; and 62/649,264, filed March 28, 2018; the entire contents of all of which are hereby incorporated by reference in their entirety.

FIELD

The present invention relates, in part, to fragment crystallizable region (Fc)-based chimeric protein complexes and their use as therapeutic agents.

DESCRIPTION OF THE TEXT FILE SUBMITTED ELECTRONICALLY

The contents of the text file submitted electronically herewith are incorporated herein by reference in their entirety: A computer readable format copy of the Sequence Listing (filename: ORN-042PC_Sequence_listing, date recorded: March 27, 2019; file size: 1,521,030 bytes).

BACKGROUND

Effector function-encoding biologics represent a class of biologics with many potential therapeutic applications. In order for such agents to be useful for the treatment of disease, maximizing their tolerability and therapeutic index is of critical importance, in particular when encoding potent effector functions (*e.g.*, cytokines, many of which are systemically toxic if administered to humans as such). Thus, there is a need for engineering such agents with high inherent safety profile, which requires targeted delivery of an effector function to select target site(s) (*e.g.* antigen on a cell type of interest) with high precision, and in a regulated fashion.

An example of such agents, is a chimeric protein having a signaling agent (*e.g.*, cytokine), connected to a targeting element, in which the signaling agent is wild type or modified (*e.g.* by mutation) to cause an attenuation of the signaling agent's activity (*e.g.*, substantially reducing its ability to interact with/engage its receptor) in a manner such that its effector function can be recovered upon binding of the targeting element to its target (*e.g.*, antigen on target cell).

However, such chimeric proteins are amenable to therapeutic use only if certain conditions are met, e.g., the ability to be produced in a large scale, an *in vivo* half-life that ensures adequate time of exposure to the drug to elicit a therapeutically beneficial effect, a proper size to avoid rapid clearance or limited tissue penetrance and bio-distribution, and other properties that ensure adequate solubility, stability and storage without significant loss of function. Importantly all, or substantially most, of the above properties should be achieved without a loss of the conditional targeting of the effector function and retention of conditional engagement of a modified signaling agent with its receptor. Often, it is difficult to achieve all these objectives with chimeric proteins encoded or represented by a single, contiguous polypeptide chain. There is a need in the art where such desirable properties of the biologic can be achieved while maintaining the tolerability and therapeutic index of the biologic.

There is a need in the art where such desirable properties of the biologic can be achieved while maintaining the tolerability and therapeutic index of the biologic. Further, there is a need for effector function-encoding biologics that are amenable to production use as a therapy to the treatment or prevention of disease.

SUMMARY

The present technology provides fragment crystallizable region (Fc)-based chimeric protein complexes in which most, if not all, of the above outlined requirements are met. These constructs encode biological therapeutic agents whose effector function can be delivered in a highly precise fashion to a target of choice and without, or with a mitigated amount of systemic adverse events, thereby limiting systemic cross-reactivities and associated adverse events, while also providing features that impart pharmaceutical properties enabling the production of therapeutic agents with, for example, desired *in vivo* exposure time (*e.g.* half-life), size (*e.g.* for biodistribution and clearance characteristics), as well as large scale production and/or purification for commercial production (*e.g.* having adequate solubility, purity, stability and storage properties).

In some aspects, the present technology relates to Fc-based chimeric protein complexes comprising a targeting moiety that comprises a recognition domain which recognizes and/or binds to a target, a wild type or modified signaling agent, wherein the modified signaling agent has one or more mutations that confer improved safety relative to a wild type signaling agent, and an Fc domain, having one or more Fc chains. In some embodiments, the Fc domain has one or more mutations that reduce or eliminate an effector function of the Fc domain, promote Fc chain pairing of the Fc domain, and/or stabilize a hinge region in the Fc domain. In some embodiments, the one or more Fc chains of the Fc domain have one or more mutations that reduce or eliminate an effector function of the Fc domain, promote Fc chain pairing of the Fc domain, and/or stabilize a hinge region in the Fc domain.

In some embodiments, such Fc-based chimeric protein complexes are heterodimeric. In some embodiments, the Fc-based chimeric protein complexes are heterodimeric and the targeting moiety and the signaling agent are oriented in trans. In some embodiments, the Fc-based chimeric protein complexes are heterodimeric and pairing is via Ridgway knob-in-hole construction (as described herein). In some embodiments, the Fc-based chimeric protein complexes are heterodimeric and pairing is via Merchant knob-in-hole construction (as described herein).

In some embodiments, such Fc-based chimeric protein complexes are homodimeric.

In some embodiments, the one or more mutations in the modified signaling agent reduces the affinity or activity at the signaling agent's receptor relative to a wild type signaling agent. In some embodiments, the targeting moiety restores the affinity or activity of the modified signaling agent.

In some embodiments, the Fc-based chimeric protein complexes comprise one or more additional targeting moieties and/or wild type or modified signaling agents. In some embodiments, the Fc-based chimeric protein complexes are multispecific. In some embodiments, the targeting moieties are a single domain antibody (VHH).

In another aspect, the present technology relates to the use of Fc-based chimeric protein complexes to treat or prevent various diseases and disorders. In some embodiments, the Fc-based chimeric protein complexes are used

to treat cancer, infections, metabolic diseases, (neuro)degenerative diseases, and cardiovascular diseases and immune disorders.

BRIEF DESCRIPTION OF DRAWINGS

FIGs. 1A-F, 2A-H, 3A-H, 4A-D, 5A-F, 6A-J, 7A-D, 8A-F, 9A-J, 10A-F, 11A-L, 12A-L, 13A-F, 14A-L, 15A-L, 16A-J, 17A-J, 18A-F, 19A-F, 20A-E, 38, 46A-D, 47, and **49** show various non-limiting illustrative schematics of the Fc-based chimeric protein complexes of the present invention. In embodiments, each schematic is a composition of the present invention. Where applicable in the figures,"TM" refers to a "targeting moiety" as described herein, "SA" refers to a "signaling agent" as described herein, "  " is an optional "linker" as described herein, the two long parallel rectangles are human Fc domains, having one or more Fc chains, *e.g.* from IgG1, from IgG2, or from IgG4, as described herein and optionally with effector knock-out and/or stabilization mutations as also described herein, and the two long parallel rectangles with one having a protrusion and the other having an indentation are human Fc domains, having one or more Fc chains, *e.g.* from IgG1, from IgG2, or from IgG4 as described herein, with knob-in-hole and/or ionic pair (a/k/a charged pairs, ionic bond, or charged residue pair) mutations as described herein and optionally with effector knock-out and/or stabilization mutations as also described herein.

FIGs. 1A-F show illustrative homodimeric 2-chain complexes. These figures show illustrative configurations for the homodimeric 2-chain complexes.

FIGs. 2A-H show illustrative homodimeric 2-chain complexes with two targeting moieties (TM) (as described herein, more targeting moieties may be present in some embodiments). In embodiments, the position of TM1 and TM2 are interchangeable. In embodiments, the constructs shown in the box (*i.e.*, **FIGS. 2B** and **2C**) have signaling agent (SA) between TM1 and TM2 or between TM1 and Fc.

FIGs. 3A-H show illustrative homodimeric 2-chain complexes with two signaling agents (as described herein, more signaling agents may be present in some embodiments). In embodiments, the position of SA1 and SA2 are interchangeable. In embodiments, the constructs shown in the box (*i.e.*, **FIGS. 3G** and **3H**) have TM between SA1 and SA2 or TM at N- or C-terminus.

FIGs. 4A-D show illustrative heterodimeric 2-chain complexes with split TM and SA chains, namely the TM on the knob chain of the Fc and the SA on hole chain of the Fc.

FIGs. 5A-F show illustrative heterodimeric 2-chain complexes with split TM and SA chains, namely with both TMs on the knob chain of the Fc and with SA on hole chain of the Fc, with two targeting moieties (as described herein, more targeting moieties may be present in some embodiments). In embodiments, the position of TM1 and TM2 are interchangeable. In some embodiments, TM1 and TM2 can be identical.

FIGs. 6A-J show illustrative heterodimeric 2-chain complexes with split TM and SA chains, namely with TM on the knob chain of the Fc and with a SA on the hole chain of the Fc, with two signaling agents (as described herein, more signaling agents may be present in some embodiments). In these orientations/configurations, one SA is on the knob chain and one SA is on the hole chain. In embodiments, the position of SA1 and SA2 are interchangeable.

FIGs. 7A-D show illustrative heterodimeric 2-chain complexes with split TM and SA chains, namely the SA on the knob chain of the Fc and the TM on hole chain of the Fc.

FIGs. 8A-F show illustrative heterodimeric 2-chain complexes with split TM and SA chains, namely with SA on the knob chain of the Fc and both TMs on hole chain of the Fc, with two targeting moieties (as described herein, more targeting moieties may be present in some embodiments). In embodiments, the position of TM1 and TM2 are interchangeable. In some embodiments, TM1 and TM2 can be identical.

FIGs. 9A-J show illustrative heterodimeric 2-chain complexes with split TM and SA chains, namely with SA on the knob chain of the Fc and TM on hole chain of the Fc, with two signaling agents (as described herein, more signaling agents may be present in some embodiments). In these orientations/configurations, one SA is on the knob chain and one SA is on the hole chain. In embodiments, the position of SA1 and SA2 are interchangeable.

FIGs. 10A-F show illustrative heterodimeric 2-chain complexes with TM and SA on the same chain, namely the SA and TM both on the knob chain of the Fc.

F**IGs. 11A-L** show illustrative heterodimeric 2-chain complexes with a TM and a SA on the same chain, namely with SA and with TM both on the knob chain of the Fc, with two targeting moieties (as described herein, more targeting moieties may be present in some embodiments). In embodiments, the position of TM1 and TM2 are interchangeable. In some embodiments, TM1 and TM2 can be identical.

FIGs. 12A-L show illustrative heterodimeric 2-chain complexes with a TM and a SA on the same chain, namely with SA and with TM both on the knob chain of the Fc, with two signaling agents (as described herein, more signaling agents may be present in some embodiments). In embodiments, the position of SA1 and SA2 are interchangeable.

FIGs. 13A-F show illustrative heterodimeric 2-chain complexes with TM and SA on the same chain, namely the SA and TM both on the hole chain of the Fc.

FIGs. 14A-L show illustrative heterodimeric 2-chain complexes with a TM and a SA on the same chain, namely with SA and with TM both on the hole chain of the Fc, with two targeting moieties (as described herein, more targeting moieties are present in some embodiments). In embodiments, the position of TM1 and TM2 are interchangeable. In embodiments, TM1 and TM2 can be identical.

FIGs. 15A-L show illustrative heterodimeric 2-chain complexes with a TM and a SA on the same chain, namely with SA and with TM both on the hole chain of the Fc, with two signaling agents (as described herein, more signaling agents may be present in some embodiments). In embodiments, the position of SA1 and SA2 are interchangeable.

FIGs. 16A-J show illustrative heterodimeric 2-chain complexes with two targeting moieties (as described herein, more targeting moieties may be present in some embodiments) and with SA on knob Fc and TM on each chain. In embodiments, TM1 and TM2 can be identical.

FIGs. 17A-J show illustrative heterodimeric 2-chain complexes with two targeting moieties (as described herein, more targeting moieties may be present in some embodiments) and with SA on hole Fc and TM on each chain. In embodiments, TM1 and TM2 can be identical.

FIGs. 18A-F show illustrative heterodimeric 2-chain complexes with two signaling agents (as described herein, more signaling agents may be present in some embodiments) and with split SA and TM chains: SA on knob and TM on hole Fc.

FIGs. 19A-F show illustrative heterodimeric 2-chain complexes with two signaling agents (as described herein, more signaling agents may be present in some embodiments) and with split SA and TM chains: TM on knob and SA on hole Fc.

FIGs. 20A-E show five variations of homodimeric or heterodimeric Fc-based chimeric protein complexes that were constructed as described in Example 1. In these illustrative constructs, anti-human C-type lectin domain containing 9A (Clec9A) VHHs were the targeting moiety and human interferon alpha 2 with a R149A mutation was the signaling agent.

FIG. 21 shows an SDS-PAGE gel resolving purified proteins of **FIGs. 20A-E**.

FIG. 22 shows a freezing-thawing stability experiment.

FIG. 23 shows biological activity of the heterodimeric Fc-based chimeric protein complexes.

FIG. 24 shows plasma concentrations of Fc-AcTaferons (Fc-AFNs) after intravenous administration in mouse. Average values of 3 individual samples per time point time (+SEM) are plotted.

FIG. 25 shows tumor growth curves in humanized mice after treatment with buffer or two different Fc-AFN constructs. Average values (in mm^3) of 6 animals per time point time (+SEM) are plotted.

FIG. 26 shows biological activity of linker-length variants on HL116-hClec9A cells. HL116-hClec9A cells were stimulated for 6 hours with a serial dilution of linker length variants. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 27 shows biological activity of effector-variants on HL116 and HL116-hClec9A cells. Parental HL116 or the derived HL116-hClec9A cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 28 shows binding of (complement component 1q) C1q to Fc domain (CH2 and CH3 domains) of the human IgG1 heavy chain and the hinge region (hIgG1) or Fc Actaferons (AFNs) with different effector-mutations in bio-layer interferometry (BLI).

FIG. 29 shows effect of Interferon (IFN) mutations on biological activity in HL116 and HL116-hClec9A cells. Parental HL116 or the derived HL116-hClec9A cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 30 shows biological activity of different Fc formats on HL116 and HL116-hClec9A cells. Parental HL116 or the derived HL116-hClec9A cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 31 shows biological activity of Fc AFNs with different knob in hole (KiH) on HL116 and HL116-hClec9A cells. Parental HL116 or the derived HL116-hClec9A cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 32 shows biological activity of mono- and bivalent Fc AFNs on HL116 and HL116-hClec9A cells. Parental HL116 or the derived HL116-hClec9A cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 33 shows relative binding of mono- and bivalent targeted Fc AFN to HL116-hClec9A cells.

FIG. 34 shows biological activity of Fc AFNs on HL116 and HL116-hClec9A cells. Parental HL116 or the derived HL116-hClec9A cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of duplicate measurements are plotted.

FIG. 35 shows plasma concentrations of Fc-AFNs after intravenous administration in mouse. Average values of 3 individual samples per time point time (+SEM) are plotted.

FIG. 36 shows tumor growth curves in humanized mice after treatment with buffer or four different Fc-AFN constructs. Average values (in mm^3) of 5 animals per time point time (+SEM) are plotted.

FIG. 37 shows tumor growth curves in humanized mice after treatment with buffer or increasing doses of a single Fc-AFN construct. Average values (in mm^3) of 5 animals per time point time (+SEM) are plotted.

FIG. 38 shows schematic representation and biological activity of PD-L1 VHH AFN variants. Parental HL116 cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 39 shows tumor growth curves in humanized mice after treatment with PBS, PD-L1 inhibitor (atezolizumab) or PD-L1 targeted Fc-AFN. Average values (in mm^3) of 6 animals per time point time (+SEM) are plotted.

FIG. 40 shows biological activity of IFNa2 and Clec4C VHH Fc AFN on HL116 and HL116-hClec4C cells. Parental HL116 or the derived HL116-hClec4C cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 41 shows biological activity of IFNa2 and CD20 VHH Fc AFN on HL116 and HL116-hCD20 cells. Parental HL116 or the derived HL116-hCD20 cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 42 shows biological activity of CD13 VHH Fc AFN on parental HL116 cells. Parental HL116 were stimulated for 6 hours with a serial dilution of CD13 Fc AFNs in the presence or absence of an excess CD13 VHH. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 43 shows biological activity of IFNa2 and FAP VHH Fc AFNs on HL116 and HL116-hFAP cells. Parental HL116 or the derived HL116-hFAP cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 44 shows biological activity of IFNa2 and CD8 VHH Fc AFN on HL116 and HL116-hCD8 cells. Parental HL116 or the derived HL116-hCD8 cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 45 shows relative binding of bispecific CLEC9A and PD-L1 targeting Fc AFN to parental PD-L1 positive HL116 cells (top) and HL116-hClec9A cells (expressing both targets; bottom), including competition with the free PD-L1 VHH 2LIG99

FIGs. 46A-D show illustrative heterodimeric 2-chain complexes with two targeting moieties (as described herein, more targeting moieties are present in some embodiments) and with SA on knob Fc and TM on each chain. Each targeting moiety is present in 2 copies and the positions of TM1 and TM2 are interchangeable.

FIG. 47 shows schematic representation and biological activity of bi-specific Clec9A-PD-L1 Fc AFN variants. Parental HL116 (left) and HL116-hClec9A (right) cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 48 shows tumor growth curves in humanized mice after treatment with PBS, mono- or bispecific Fc-AFNs. Average values (in mm^2) of 4-5 animals per time point time (+SEM) are plotted.

FIG. 49 shows schematic representation and biological activity of bi-specific Clec4C-CD8 Fc AFN variants. Parental HL116, HL116-hClec4C and HL116-hCD8 cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 50 shows biological activity of IFNa2 and scFv Xcr1 Fc AFN on HL116 and HL116-hXcr1 cells. Parental HL116 or the derived HL116-hXcr1 cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 51 shows biological activity of IFNa2 and scFv CD20 Fc AFN on HL116 and HL116-hCD20 cells. Parental HL116 or the derived HL116-hCD20 cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 52 shows biological activity of tumor necrosis factor (TNFα) and CD20 Fc AcTafactors (AFRs) on HEK-Dual and HEK-Dual-hCD20 cells. Parental HEK-Dual or the derived HEK-Dual-hCD20 cells were stimulated overnight with a serial dilution of Fc AFRs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 53 shows pSTAT1 upon FMS-like tyrosine kinase 3 ligand (FLT3L)-Fc-AFN in transient transfected Hek293T cells. FLT3 or MOCK (empty vector) transfected Hek293T cells were stimulated as indicated and stained for pSTAT1. Average % of pSTAT1 positive cells (± STDEV) of duplicate measurements are plotted.

FIG. 54 shows biological activity of IFNa2 and the extracellular (ec) portion of programmed cell death protein 1 (PD-1) (PD-1ec) Fc AFN on HL116 cells. Parental HL116 cells were stimulated for 6 hours with a serial dilution of Fc AFNs in the presence or absence of an excess neutralizing VHH. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 55 shows biological activity of IFNa2 and PD-L1ec Fc AFN on HL116 and HL116-hPD-1 cells. Parental HL116 or the derived HL116-hPD-1 cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 56 shows biological activity of NGR peptide based Fc AFN targeting CD13. Parental HL116 cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of duplicate measurements are plotted. Specificity is demonstrated by comparison with CLEC9A targeted Fc AFN (R1CHCL50)

FIG. 57 shows biological activity of targeted wild type and mutant IFNa2 on C-Type Lectin Domain Family 4 Member C (Clec4C) positive and negative cells. Peripheral blood mononuclear cells (PBMC's) from healthy donors were stained with Clec4C Ab and stimulated with Clec4C-targeted wild type or mutant IFNa2 for 15 minutes. After fixation and permeabilization, cells were stained with a pSTAT1 Ab. Data are plotted as percentage of pSTAT1 positive cells.

FIG. 58 shows biological activity of targeted wild type and mutant IFNa2 on CD8 positive and negative cells. Peripheral blood mononuclear cells (PBMC's) from healthy donors were stained with CD8 Ab and stimulated with CD8-targeted wild type or mutant IFNa2 for 15 minutes. After fixation and permeabilization, cells were stained with a pSTAT1 Ab. Data are plotted as percentage of pSTAT1 positive cells.

FIG. 59 shows biological activity of targeted wild type and mutant IFNa2 on CD19 positive (i.e. B-cells) and negative cells. PBMC's from healthy donors were stained with CD19 Ab and stimulated with CD20-targeted wild type or mutant IFNa2 for 15 minutes. After fixation and permeabilization, cells were stained with a pSTAT1 Ab. Data are plotted as percentage of pSTAT1 positive cells.

FIG. 60 shows an overview of point mutation in IFNa2. This Figure shows the sequence of mature human IFNa2 (SEQ ID NO: 2) from Amino Acid No. 30-39 and 142-165.

FIG. 61 shows biological activity of different Clec9A VHH Fc AFNs on HL116 and HL116-hClec9A cells. Parental HL116 or the derived HL116-hClec9A cells were stimulated for 6 hours with indicated concentrations of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted. For each mutant the bars are, left to right, 1000 ng/ml, 10 ng/ml, 0.1 ng/ml, and not stimulated

FIG. 62 shows biological activity of IFNa1 and Clec9A VHH Fc AFN on HL116 and HL116-hClec9A cells. Parental HL116 or the derived HL116-hClec9A cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 63 shows biological activity of IFNb and Clec9A VHH Fc AFN on HL116 and HL116-hClec9A cells. Parental HL116 or the derived HL116-hClec9A cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 64 shows biological activity of AcTaleukin (ALN) on transient transfected HEK-Blue IL-1β cells. MOCK (an empty vector) or human CD8 transfected cells were stimulated overnight with a serial dilution wild type IL-1β or ALN. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 65 shows biological activity of TNFα and CD20 VHH Fc AFR on HEK-Dual and HEK-Dual-hCD20 cells. Parental HEK-Dual or the derived HEK-Dual-hCD20 cells were stimulated overnight with a serial dilution of Fc AFR. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 66 shows biological activity of IFNa2 and bi-AcTakine on HL116 and HL116-hCD8 cells. Parental HL116 or the derived HL116-hCD8 cells were stimulated for 6 hours with a serial dilution of bi-AcTakine. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 67 shows biological activity of bi-AcTakine on transient transfected HEK-Blue IL-1β cells. MOCK or human CD8 transfected cells were stimulated overnight with a serial dilution wild type IL-1β or bi-AcTakine. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 68 shows biological activity of Clec9A Fc AFN variant based on human IgG1 and IgG4. Parental HL116 and HL116-hClec9A cells were stimulated for 6 hours with a serial dilution of Fc AFNs. Average luciferase values (± STDEV) of triplicate measurements are plotted.

FIG. 69 shows the plasma concentrations of a CLEC9A AFN (which is not an Fc-based chimeric protein complex) after intravenous administration in mouse. Average values of 3 individual samples per time point time (+SEM) are plotted.

DETAILED DESCRIPTION

The present technology is based, in part, on the discovery of signaling agents, that are optionally modified to have reduced affinity or activity for one or more of its receptors, and targeting moieties that recognize and bind to a specific target. In some embodiments, one or more signaling agents and one or more targeting moieties are linked and/or conjugated and/or fused to Fc-based chimeric proteins that can pair to form Fc-based chimeric protein complexes. Such Fc-based chimeric protein complexes, surprisingly, have dramatically improved half-lives in vivo, as compared to chimeras lacking an Fc and, especially in the heterodimer configuration as described herein, are particularly amendable to production, purification, and pharmaceutical formulation due to enhanced solubility, stability and other drug-like properties. Accordingly, the present Fc-based chimeric protein complex engineering approach yields agents that are particularly suited for use as therapies.

In some embodiments, these Fc-based chimeric protein complexes may bind and directly or indirectly recruit immune cells to sites in need of therapeutic action (*e.g.* a tumor or tumor microenvironment). In some embodiments, the Fc-based chimeric protein complexes enhance tumor antigen presentation for elicitation of effective antitumor immune response. In some embodiments these Fc-based chimeric protein complexes may bind tumor cells, tumor microenvironment-associated cells or stromal targets. In some embodiments. these Fc-based chimeric protein complexes may bind to tissue-specific and/or cell-specific specific markers (*e.g.* antigens, targets) associated with disease-affected or disease-associated organs, tissues and cells. In some embodiments these Fc-based chimeric protein complexes may bind to more than one target/protein marker/antigen present on the same or different cells. In some embodiments these Fc-based chimeric protein complexes may bind to two or more cell types. In some embodiments these Fc-based chimeric protein complexes may bind to more than one cell type and promote formation of a cell complex (*e.g.* an immune cell and a tumor cell).

In some embodiments, the Fc-based chimeric protein complexes modulate antigen presentation. In some embodiments, the Fc-based chimeric protein complexes temper the immune response to avoid or reduce autoimmunity. In some embodiments, the Fc-based chimeric protein complexes provide immunosuppression. In

some embodiments, the Fc-based chimeric protein complexes cause an increase a ratio of Tregs to CD8+ T cells and/or CD4+ T cells in a patient. In some embodiments, the present methods relate to reduction of auto-reactive T cells in a patient.

In some embodiments, the Fc-based chimeric protein complexes are a complex of proteins formed, for example, by disulfide bonding and/or ionic pairing. In embodiments, the complex of proteins includes one or more fusion proteins. In some embodiments, the Fc-based chimeric protein complex has a configuration and/or orientation/configuration as shown in any one of **Figs. 1A-F, 2A-H, 3A-H, 4A-D, 5A-F, 6A-J, 7A-D, 8A-F, 9A-J, 10A-F, 11A-L, 12A-L, 13A-F, 14A-L, 15A-L, 16A-J, 17A-J, 18A-F, 19A-F, 20A-E, 38, 46A-D, 47** and **49**. In some embodiments, the Fc-based chimeric protein complex has a configuration and/or orientation/configuration as shown in **Fig. 7B**.

The present technology provides pharmaceutical compositions comprising the Fc-based chimeric protein complexes and their use in the treatment of various diseases, including, *e.g.*, cancer, autoimmune, neurodegenerative diseases, metabolic diseases, cardiovascular diseases and degenerative diseases.

Fc Domains

The fragment crystallizable domain (Fc domain) is the tail region of an antibody that interacts with Fc receptors located on the cell surface of cells that are involved in the immune system, *e.g.*, B lymphocytes, dendritic cells, natural killer cells, macrophages, neutrophils, eosinophils, basophils, and mast cells. In IgG, IgA and IgD antibody isotypes, the Fc domain is composed of two identical protein chains, derived from the second and third constant domains of the antibody's two heavy chains. In IgM and IgE antibody isotypes, the Fc domain contains three heavy chain constant domains (C_H domains 2–4) in each polypeptide chain.

In some embodiments, the Fc-based chimeric protein complex of the present technology include(s) chimeric proteins with Fc domains that promotes formation of such protein complexes. In some embodiments, the Fc domains are from selected from IgG, IgA, IgD, IgM, or IgE. In some embodiments, the Fc domains are from selected from IgG1, IgG2, IgG3, or IgG4.

In some embodiments, the Fc domains are from selected from human IgG, IgA, IgD, IgM, or IgE. In some embodiments, the Fc domains are from selected from human IgG1, IgG2, IgG3, or IgG4.

In some embodiments, the Fc domains of the Fc-based chimeric protein complex comprise the CH2 and CH3 regions of IgG. In some embodiments, the IgG is human IgG. In some embodiments, the human IgG is selected from IgG1, IgG2, IgG3, or IgG4.

In some embodiments, the Fc domains comprise one or more mutations. In some embodiments, the mutation(s) to the Fc domains reduces or eliminates the effector function the Fc domains. In some embodiments, the mutated Fc domain has reduced affinity or binding to a target receptor. By way of example, in some embodiments, the mutation to the Fc domains reduces or eliminates the binding of the Fc domains to FcγR. In some embodiments, the FcγR is selected from FcγRI; FcγRIIa, 131 R/R; FcγRIIa, 131 H/H, FcγRIIb; and FcγRIII. In some embodiments, the mutation to the Fc domains reduces or eliminated binding to complement proteins, such as, *e.g.*, C1q. In some

embodiments, the mutation to the Fc domains reduces or eliminated binding to both FcγR and complement proteins, such as, *e.g.*, C1q.

In some embodiments, the Fc domains comprise the LALA mutation to reduce or eliminate the effector function of the Fc domains. By way of example, in some embodiments, the LALA mutation comprises L234A and L235A substitutions in human IgG (*e.g.*, IgG1) (wherein the numbering is based on the commonly used numbering of the CH2 residues for human IgG1 according to EU convention (PNAS, Edelman et al., 1969; 63 (1) 78-85)).

In some embodiments, the Fc domains of human IgG comprise a mutation at one or more of L234, L235, K322, D265, P329, and P331 to reduce or eliminate the effector function of the Fc domains. By way of example, in some embodiments, the mutations are selected from L234A, L234F, L235A, L235E, L235Q, K322A, K322Q, D265A, P329G, P329A, P331G, and P331S.

In some embodiments, the Fc domains comprise the FALA mutation to reduce or eliminate the effector function of the Fc domains. By way of example, in some embodiments, the FALA mutation comprises F234A and L235A substitutions in human IgG4.

In some embodiments, the Fc domains of human IgG4 comprise a mutation at one or more of F234, L235, K322, D265, and P329 to reduce or eliminate the effector function of the Fc domains. By way of example, in some embodiments, the mutations are selected from F234A, L235A, L235E, L235Q, K322A, K322Q, D265A, P329G, and P329A.

In some embodiments, the mutation(s) to the Fc domain stabilize a hinge region in the Fc domain. By way of example, in some embodiments, the Fc domain comprises a mutation at S228 of human IgG to stabilize a hinge region. In some embodiments, the mutation is S228P.

In some embodiments, the mutation(s) to the Fc domain promote chain pairing in the Fc domain. In some embodiments, chain pairing is promoted by ionic pairing (a/k/a charged pairs, ionic bond, or charged residue pair).

In some embodiments, the Fc domain comprises a mutation at one more of the following amino acid residues of IgG to promote of ionic pairing: D356, E357, L368, K370, K392, D399, and K409.

By way of example, in some embodiments, the human IgG Fc domain comprise one of the mutation combinations in Table 1 to promote of ionic pairing.

Table 1

Substitution(s) on one Fc Chain	Substitution(s) on other Fc Chain
D356K D399K	K392D K409D
E357R L368R	K370D K409D
E357R L368K	K370D K409D
E357R D399K	K370D K409D
E357R	K370D
L368R D399K	K392D K409D
L368K D399K	K392D K409D
L368R D399K	K409D
L368K D399K	K409D
L368R	K409D
L368K	K409D

Table 1	
Substitution(s) on one Fc Chain	**Substitution(s) on other Fc Chain**
K370D K409D	E357R D399K
K370D K409D	E357R L368R
K370D K409D	E357R L368K
K370D K409D	E357R D399K
K370D K409D	E357R L368R
K370D K409D	E357R L368K
K370D	E357R
K370D	E357R
K392D K409D	D356K D399K
K392D K409D	L368R D399K
K392D K409D	L368K D399K
K392D K409D	D399K
D399K	K392D K409D
D399K	K409D
K409D	L368R
K409D	L368K
K409D	L368R D399K
K409D	L368K D399K
K409D	L368R
K409D	L368K
K409D	L368R D399K
K409D	L368K D399K
K409D	D399K

In some embodiments, chain pairing of the individual Fc-domains in a chimeric protein complex is promoted by knob-in-hole mutations. In some embodiments, the Fc domain comprises one or more mutations to allow for a knob-in-hole interaction in the Fc domain. In some embodiments, a first Fc chain is engineered to express the "knob" and a second Fc chain is engineered to express the complementary "hole." By way of example, in some embodiments, human IgG Fc domain comprises the mutations of Table 2 to allow for a knob-in-hole interaction.

Table 2	
Substitution(s) on one Fc Chain	**Substitution(s) on other Fc Chain**
T366Y	Y407T
T366Y/F405A	T394W/Y407T
T366W	Y407A
T366W	Y407V
T366Y	Y407A
T366Y	Y407V
T366Y	Y407T

In some embodiments, the Fc domains in the Fc-based chimeric protein complexes of the present technology comprise any combination of the above-disclosed mutations. By way of example, in some embodiments, the Fc domain comprises mutations that promote ionic pairing and/or a knob-in-hole interaction. By way of example, in some embodiments, the Fc domain comprises mutations that have one or more of the following properties: promote

ionic pairing, induce a knob-in-hole interaction, reduce or eliminate the effector function of the Fc domain, and cause Fc stabilization (*e.g.* at hinge).

By way of example, in some embodiments, a human IgG Fc domain comprise mutations disclosed in Table 3, which promote ionic pairing and/or promote a knob-in-hole interaction in the Fc domain.

Table 3

Substitution(s) on one Fc Chain	Substitution(s) on other Fc Chain
T366W K370D	E357R Y407A
T366W K370D	E357R Y407V
T366W K409D	L368R Y407A
T366W K409D	L368R Y407V
T366W K409D	L368K Y407A
T366W K409D	L368K Y407V
T366W K409D	L368R D399K Y407A
T366W K409D	L368R D399K Y407V
T366W K409D	L368K D399K Y407A
T366W K409D	L368K D399K Y407V
T366W K409D	D399K Y407A
T366W K409D	D399K Y407V
T366W K392D K409D	D399K Y407A
T366W K392D K409D	D399K Y407V
T366W K392D K409D	D356K D399K Y407A
T366W K392D K409D	D356K D399K Y407V
T366W K370D K409D	E357R D399K Y407A
T366W K370D K409D	E357R D399K Y407V
T366W K370D K409D	E357R L368R Y407A
T366W K370D K409D	E357R L368R Y407V
T366W K370D K409D	E357R L368K Y407A
T366W K370D K409D	E357R L368K Y407V
T366W K392D K409D	L368R D399K Y407A
T366W K392D K409D	L368R D399K Y407V
T366W K392D K409D	L368K D399K Y407A
T366W K392D K409D	L368K D399K Y407V
E357R T366W	K370D Y407A
E357R T366W	K370D Y407V
T366W L368R	Y407A K409D
T366W L368R	Y407V K409D
T366W L368K	Y407A K409D
T366W L368K	Y407V K409D
T366W L368R D399K	Y407A K409D
T366W L368R D399K	Y407V K409D
T366W L368K D399K	Y407A K409D
T366W L368K D399K	Y407V K409D
T366W D399K	Y407A K409D
T366W D399K	Y407V K409D
1366W D399K	K392D Y407A K409D
T366W D399K	K392D Y407V K409D
T366W D356K D399K	K392D Y407A K409D
T366W D356K D399K	K392D Y407V K409D
E357R T366W D399K	K370D Y407A K409D
E357R T366W D399K	K370D Y407V K409D

Table 3	
Substitution(s) on one Fc Chain	**Substitution(s) on other Fc Chain**
E357R T366W L368R	K370D Y407A K409D
E357R T366W L368R	K370D Y407V K409D
E357R T366W L368K	K370D Y407A K409D
E357R T366W L368K	K370D Y407V K409D
T366W L368R D399K	K392D Y407A K409D
T366W L368R D399K	K392D Y407V K409D
T366W L368K D399K	K392D Y407A K409D

By way of example, in some embodiments, human IgG Fc domains comprise mutations disclosed in Table 4, which promote ionic pairing, promote a knob-in-hole interaction, or a combination thereof ofs the Fc domains. In embodiments, the "Chain 1" and "Chain 2" of Table 4 can be interchanged (*e.g.* Chain 1 can have Y407T and Chain 2 can have T366Y).

Table 4			
Chain 1 mutation	**Chain 2 mutation**	**Reference**	**IgG**
T366Y	Y407T	Ridgway *et al.*, 1996 Protein Engineering, Design and Selection, Volume 9, Issue 7, 1 July 1996, Pages 617–62	IgG1
T366Y/F405A	T394W/Y407T	Ridgway *et al.*, 1996 Protein Engineering, Design and Selection, Volume 9, Issue 7, 1 July 1996, Pages 617–62	IgG1
T366W	Y407A	Atwell *et al.*, 1997 JMB Volume 270, Issue 1, 4 July 1997, Pages 26-35	IgG1
T366W	T366S/L368V/Y407A	Atwell *et al.*, 1997 JMB Volume 270, Issue 1, 4 July 1997, Pages 26-35	IgG1
T366W	L368A/Y407A	Atwell *et al.*, 1997 JMB Volume 270, Issue 1, 4 July 1997, Pages 26-35	IgG1
T366W	T366S/L368A/Y407A	Atwell *et al.*, 1997 JMB Volume 270, Issue 1, 4 July 1997, Pages 26-35	IgG1
T366W	T366S/L368G/Y407V	Atwell *et al.*, 1997 JMB Volume 270, Issue 1, 4 July 1997, Pages 26-35	IgG1
T366W/D399C	T366S/L368A/K392C/Y407V	Merchant *et al.*, 1998 Nature Biotechnology volume 16, pages 677–681 (1998)	IgG1
T366W/K392C	T366S/L368A/D399C/Y407V	Merchant *et al.*, 1998 Nature Biotechnology volume 16, pages 677–681 (1998)	IgG1
S354C/T366W	Y349C/T366S/L368A/Y407V	Merchant *et al.*, 1998 Nature Biotechnology volume 16, pages 677–681 (1998)	IgG1

Y349C/T366W	S354C/T366S/L368A/Y407V	Merchant *et al.*, 1998 Nature Biotechnology volume 16, pages 677–681 (1998)	IgG1
E356C/T366W	Y349C/T366S/L368A/Y407V	Merchant *et al.*, 1998 Nature Biotechnology volume 16, pages 677–681 (1998)	IgG1
Y349C/T366W	E356C/T366S/L368A/Y407V	Merchant *et al.*, 1998 Nature Biotechnology volume 16, pages 677–681 (1998)	IgG1
E357C/T366W	Y349C/T366S/L368A/Y407V	Merchant *et al.*, 1998 Nature Biotechnology volume 16, pages 677–681 (1998)	IgG1
Y349C/T366W	E357C/T366S/L368A/Y407V	Merchant *et al.*, 1998 Nature Biotechnology volume 16, pages 677–681 (1998)	IgG1
D339R	K409E	Gunasekaran *et al.*, 2010 The Journal of Biological Chemistry 285, 19637-19646.	IgG1
D339K	K409E	Gunasekaran *et al.*, 2010 The Journal of Biological Chemistry 285, 19637-19646.	IgG1
D339R	K409D	Gunasekaran *et al.*, 2010 The Journal of Biological Chemistry 285, 19637-19646.	IgG1
D339K	K409D	Gunasekaran *et al.*, 2010 The Journal of Biological Chemistry 285, 19637-19646.	IgG1
D339K	K360D/K409E	Gunasekaran *et al.*, 2010 The Journal of Biological Chemistry 285, 19637-19646.	IgG1
D339K	K392D/K409E	Gunasekaran *et al.*, 2010 The Journal of Biological Chemistry 285, 19637-19646.	IgG1
D339K/E356K	K392D/K409E	Gunasekaran *et al.*, 2010 The Journal of Biological Chemistry 285, 19637-19646.	IgG1
D339K/E357K	K392D/K409E	Gunasekaran *et al.*, 2010 The Journal of Biological Chemistry 285, 19637-19646.	IgG1
D339K/E356K	K409E/K439D	Gunasekaran *et al.*, 2010 The Journal of Biological Chemistry 285, 19637-19646.	IgG1
D339K/E357K	K370D/K409E	Gunasekaran *et al.*, 2010 The Journal of Biological Chemistry 285, 19637-19646.	IgG1
D339K/E356K/E357K	K370D/K392D/K409E	Gunasekaran *et al.*, 2010 The Journal of Biological Chemistry 285, 19637-19646.	IgG1
S364H/F405A	Y349T/T394F	Moore *et al.*, 2011 mAbs, 3:6, 546-557	IgG1
S364H/T394F	Y349T/F405A	Moore *et al.*, 2011 mAbs, 3:6, 546-557	IgG1
D221R/P228R/K409R	D221E/P228E/L368E	Strop *et al.*, 2012 JMB Volume 420, Issue 3, 13 July 2012, Pages 204-219	IgG1
C223R/E225R/P228R/K409R	C223E/P228E/L368E	Strop *et al.*, 2012 JMB Volume 420, Issue 3, 13 July 2012, Pages 204-219	IgG2
F405L	K409R	Labrijn *et al.*, 2013 PNAS March 26, 2013. 110 (13) 5145-5150	IgG1
F405A/Y407V	T394W	Von Kreudenstein *et al.*, 2013 mAbs Volume 5, 2013 - Issue 5, pp.644-654	IgG1
F405A/Y407V	T366I/T394W	Von Kreudenstein *et al.*, 2013 mAbs Volume 5, 2013 - Issue 5, pp.644-654	IgG1
F405A/Y407V	T366L/T394W	Von Kreudenstein *et al.*, 2013 mAbs Volume 5, 2013 - Issue 5, pp.644-654	IgG1
F405A/Y407V	T366L/K392M/T394W	Von Kreudenstein *et al.*, 2013 mAbs Volume 5, 2013 - Issue 5, pp.644-654	IgG1
L351Y/F405A/Y407V	T366L/K392M/T394W	Von Kreudenstein *et al.*, 2013 mAbs	IgG1

		Volume 5, 2013 - Issue 5, pp.644-654	
T350V/L351Y/F405A/Y407V	T350V/T366L/K392M/T394W	Von Kreudenstein *et al.*, 2013 mAbs Volume 5, 2013 - Issue 5, pp.644-654	IgG1
T350V/L351Y/F405A/Y407V	T350V/T366L/K392L/T394W	Von Kreudenstein *et al.*, 2013 mAbs Volume 5, 2013 - Issue 5, pp.644-654	IgG1
K409W	D339V/F405T	Choi *et al.*, 2013 PNAS January 2, 2013. 110 (1) 270-275	IgG1
K360E	Q347R	Choi *et al.*, 2013 PNAS January 2, 2013. 110 (1) 270-275	IgG1
K360E/K409W	D339V/Q347R/F405T	Choi *et al.*, 2013 PNAS January 2, 2013. 110 (1) 270-275	IgG1
Y349C/K360E/K409W	D339V/Q347R/S354C/F405T	Choi *et al.*, 2013 PNAS January 2, 2013. 110 (1) 270-275	IgG1
K392A/K409D	E356K/D399K	Leaver-Fey *et al.*, 2016 Structure Volume 24, Issue 4, 5 April 2016, Pages 641-651	IgG1
T366W	T366S/L358A/Y407A	Leaver-Fey *et al.*, 2016 Structure Volume 24, Issue 4, 5 April 2016, Pages 641-651	IgG1
D339M/Y407A	T336V/K409V	Leaver-Fey *et al.*, 2016 Structure Volume 24, Issue 4, 5 April 2016, Pages 641-651	IgG1
D339M/K360D/Y407A	T336V/E345R/Q347R/K409V	Leaver-Fey *et al.*, 2016 Structure Volume 24, Issue 4, 5 April 2016, Pages 641-651	IgG1
Y349S/T366V/K370Y/K409V	E357D/S364Q/Y407A	Leaver-Fey *et al.*, 2016 Structure Volume 24, Issue 4, 5 April 2016, Pages 641-651	IgG1
Y349S/T366M/K370Y/K409V	E356G/E357D/S364Q/Y407A	Leaver-Fey *et al.*, 2016 Structure Volume 24, Issue 4, 5 April 2016, Pages 641-651	IgG1
Y349S/T366M/K370Y/K409V	E357D/S364R/Y407A	Leaver-Fey *et al.*, 2016 Structure Volume 24, Issue 4, 5 April 2016, Pages 641-651	IgG1
And any combination as described in Tables 1-3 of US20150284475A1			

By way of example, in some embodiments, a human IgG Fc domains comprise mutations disclosed in Table 5, which reduce or eliminate FcγR and/or complement binding in the Fc domain. In embodiments, the table 5 mutations are in both chains.

Table 5

Chain 1 mutation	Reference	IgG
L234A/L235A	Alegre *et al.*, 1994 Transplantation 57:1537–1543	IgG1
F234A/L235A	Alegre *et al.*, 1994 Transplantation 57:1537–1543	IgG4
L235E	Morgan *et al.*, 1995 Immunology. 1995 Oct; 86(2): 319–324.	IgG1

L235E	Morgan *et al.*, 1995 Immunology. 1995 Oct; 86(2): 319–324.	IgG4
L235A	Morgan *et al.*, 1995 Immunology. 1995 Oct; 86(2): 319–324.	IgG1
G237A	Morgan *et al.*, 1995 Immunology. 1995 Oct; 86(2): 319–324.	IgG1
N297H	Tao and Morrison, J. Immunol. 1989; 143:2595-2601	IgG1
N297Q	Tao and Morrison, J. Immunol. 1989; 143:2595-2601	IgG1
N297K	Tao and Morrison, J. Immunol. 1989; 143:2595-2601	IgG3
N297Q	Tao and Morrison, J. Immunol. 1989; 143:2595-2601	IgG3
D265A	Idusogie *et al.*, 2000 J Immunol April 15, 2000, 164 (8) 4178-4184	IgG1
D270A, V, K	Idusogie *et al.*, 2000 J Immunol April 15, 2000, 164 (8) 4178-4184	IgG1
K322A, L, M, D, E	Idusogie *et al.*, 2000 J Immunol April 15, 2000, 164 (8) 4178-4184	IgG1
P329A, X	Idusogie *et al.*, 2000 J Immunol April 15, 2000, 164 (8) 4178-4184	IgG1
P331A, S, G, X	Idusogie *et al.*, 2000 J Immunol April 15, 2000, 164 (8) 4178-4184	IgG1
D265A	Idusogie *et al.*, 2000 J Immunol April 15, 2000, 164 (8) 4178-4184	IgG1
L234A	Hezareh *et al.*, 2001 J. Virol. December 2001 vol. 75 no. 24 12161-12168	IgG1
L234A/L235A	Hezareh *et al.*, 2001 J. Virol. December 2001 vol. 75 no. 24 12161-12168	IgG1
L234F/L235E/P331S	Oganesyan *et al.*, 2008 Acta Cryst. (2008). D64, 700-704	IgG1
H268Q/V309L/A330S/P331S	An *et al.*, 2009 mAbs Volume 1, 2009 - Issue 6, pp. 572-579	IgG1
G236R/L328R	Moore *et al.*, 2011 mAbs Volume 3, 2011 - Issue 6, pp. 546-557	IgG1

N297G	Couch *et al.*, 2013 Sci. Transl. Med., 5 (2013) 183ra57, 1–12	IgG1
N297G/D265A	Couch *et al.*, 2013 Sci. Transl. Med., 5 (2013) 183ra57, 1–12	IgG1
V234A/G237A/P328S/H268A/V309L/A330S/P331S	Vafa *et al.*, 2014 Methods Volume 65, Issue 1, 1 January 2014, Pages 114-126	IgG2
L234A/L235A/P329G	Lo *et al.*, 2016 The Journal of Biological Chemistry 292, 3900-3908	IgG1
N297D	Schlothauer *et al.*, 2016 Protein Engineering, Design and Selection, Volume 29, Issue 10, 1 October 2016, Pages 457–466	IgG1
S228P/L235E	Schlothauer *et al.*, 2016 Protein Engineering, Design and Selection, Volume 29, Issue 10, 1 October 2016, Pages 457–466	IgG4
S228P/L235E/P329G	Schlothauer *et al.*, 2016 Protein Engineering, Design and Selection, Volume 29, Issue 10, 1 October 2016, Pages 457–466	IgG4
L234F/L235A/K322Q	Borrok *et al.*, 2017 J Pharm Sci April 2017 Volume 106, Issue 4, Pages 1008–1017	IgG1
L234F/L235Q/P331G	Borrok *et al.*, 2017 J Pharm Sci April 2017 Volume 106, Issue 4, Pages 1008–1017	IgG1
L234F/L235Q/K322Q	Borrok *et al.*, 2017 J Pharm Sci April 2017 Volume 106, Issue 4, Pages 1008–1017	IgG1
L234A/L235A/G237A/P328S/H268A/A330S/P331S	Tam *et al.*, 2017 Open Access Antibodies 2017, 6(3), 12; doi:10.3390/antib6030012	IgG1
S228P/F234A/L235A	Tam *et al.*, 2017 Open Access Antibodies 2017, 6(3), 12; doi:10.3390/antib6030012	IgG4
S228P/F234A/L235A/G237A/P238S	Tam *et al.*, 2017 Open Access Antibodies 2017, 6(3), 12; doi:10.3390/antib6030012	IgG4
S228P/F234A/L235A/G236−/G237A/P238S	Tam *et al.*, 2017 Open Access Antibodies 2017, 6(3), 12; doi:10.3390/antib6030012	IgG4

In some embodiments, the Fc domains in the Fc-based chimeric protein complexes of the present technology are homodimeric, *i.e.*, the Fc domain in the chimeric protein complex comprises two identical protein chains.

In some embodiments, the Fc domains in the Fc-based chimeric protein complexes of the present technology are heterodimeric, *i.e.*, the Fc domain in the chimeric protein complex comprises two non-identical protein chains.

In some embodiments, heterodimeric Fc domains are engineered using ionic pairing and/or knob-in-hole mutations described herein. In some embodiments, the heterodimeric Fc-based chimeric protein complexes have a trans orientation/configuration. In a trans orientation/configuration, the targeting moiety and signaling agent are, in embodiments, not found on the same polypeptide chain in the present Fc-based chimeric protein complexes. In some embodiments, the signaling agent and targeting moiety are on the same end (N-terminus or C-terminus) of the Fc domain. In some embodiments, the signaling agent and targeting moiety are on different ends (N-terminus or C-terminus) of the Fc domain.

In some embodiments, heterodimeric Fc domains are engineered using ionic pairing and/or knob-in-hole mutations described herein. In some embodiments, the heterodimeric Fc-based chimeric protein complexes have a trans orientation.

In a trans orientation, the targeting moiety and signaling agent are, in embodiments, not found on the same polypeptide chain in the present Fc-based chimeric protein complexes. In a trans orientation, the targeting moiety and signaling agent are, in embodiments, found on separate polypeptide chains in the Fc-based chimeric protein complexes. In a cis orientation, the targeting moiety and signaling agent are, in embodiments, found on the same polypeptide chain in the Fc-based chimeric protein complexes.

In some embodiments, where more than one targeting moiety is present in the heterodimeric protein complexes described herein, one targeting moiety may be in trans orientation (relative to the signaling agent), whereas another targeting moiety may be in cis orientation (relative to the signaling agent). In some embodiments, the signaling agent and target moiety are on the same ends/sides (N-terminal or C-terminal ends) of an Fc domain. In some embodiments, the signaling agent and targeting moiety are on different sides/ends of an Fc domain (N-terminal and C-terminal ends).

In some embodiments, where more than one targeting moiety is present in the heterodimeric protein complexes described herein, the targeting moieties may be found on the same Fc chain or on two different Fc chains in the heterodimeric protein complex (in the latter case the targeting moieties would be in trans relative to each other, as they are on different Fc chains). In some embodiments, where more than one targeting moiety is present on the same Fc chain, the targeting moieties may be on the same or different sides/ends of an Fc chain (N-terminal or/and C-terminal ends).

In some embodiments, where more than one signaling agent is present in the heterodimeric protein complexes described herein, the signaling agents may be found on the same Fc chain or on two different Fc chains in the heterodimeric protein complex (in the latter case the signaling agents would be in trans relative to each other, as they are on different Fc chains). In some embodiments, where more than one signaling agent is present on the

same Fc chain, the signaling agents may be on the same or different sides/ends of an Fc chain (N-terminal or/and C-terminal ends).

In some embodiments, where more than one signaling agent is present in the heterodimeric protein complexes described herein, one signaling agent may be in trans orientation (as relates to the targeting moiety), whereas another signaling agent may be in cis orientation (as relates to the targeting moiety).

In some embodiments, the Fc domains include or start with the core hinge region of wild-type human IgG1, which contains the sequence Cys-Pro-Pro-Cys (SEQ ID NO: 1341). In some embodiments, the Fc domains also include the upper hinge, or parts thereof (*e.g.*, DKTHTCPPC (SEQ ID NO: 1342; see WO2009053368), EPKSCDKTHTCPPC (SEQ ID NO: 1343), or EPKSSDKTHTCPPC (SEQ ID NO: 1344; see Lo et al., Protein Engineering vol.11 no. 6 pp.495–500, 1998)).

Signaling Agents (SA)

In some embodiments, the Fc-based chimeric protein complexes of the present technology include one or more signaling agents (SA). The signaling agents, as disclosed herein, can be a wild type signaling agent or a modified signaling agent.

In various embodiments, the Fc-based chimeric protein complex comprises a wild type signaling agent that has improved target selectivity and safety relative to a signaling agent which is not fused to an Fc, or a signaling agent which is not in the context of a complex, e.g., without limitation, a heterodimeric complex. In various embodiments, the Fc-based chimeric protein complex comprises a wild type signaling agent that has improved target selective activity relative to a signaling agent which is not fused to an Fc, or a signaling agent which is not in the context of a complex, e.g., without limitation, a heterodimeric complex. In various embodiments, the Fc-based chimeric protein complex allows for conditional activity.

In various embodiments, the Fc-based chimeric protein complex comprises a wild type signaling agent that has one or more of attenuated activity such as one or more of reduced binding affinity, reduced endogenous activity, and reduced specific bioactivity as compared to the signaling agent which is not fused to an Fc, or a signaling agent which is not in the context of a complex, *e.g.*, without limitation, a heterodimeric complex.

In various embodiments, the Fc-based chimeric protein complex comprises a wild type signaling agent that has improved safety, *e.g.* reduced systemic toxicity, reduced side effects, and reduced off-target effects relative to a signaling agent which is not fused to an Fc, or a signaling agent which is not in the context of a complex, *e.g.*, without limitation, a heterodimeric complex. In various embodiments, improved safety means that the present Fc-based chimeric protein provides lower toxicity (*e.g.* systemic toxicity and/or tissue/organ-associated toxicities); and/or lessened or substantially eliminated side effects; and/or increased tolerability, lessened or substantially eliminated adverse events; and/or reduced or substantially eliminated off-target effects; and/or an increased therapeutic window of the wild type signaling agent as compared to the signaling agent which is not fused to an Fc, or a signaling agent which is not in the context of a complex, *e.g.*, without limitation, a heterodimeric complex.

In some embodiments, the reduced affinity or activity at the receptor is restorable by inclusion in the present complex having one or more of the targeting moieties as described herein.

In various embodiments, the Fc-based chimeric protein complex comprises a wild type signaling agent that has reduced, substantially reduced, or ablated affinity, *e.g.* binding (*e.g.* K_D) and/or activation (for instance, when the modified signaling agent is an agonist of its receptor, measurable as, for example, K_A and/or EC_{50}) and/or inhibition (for instance, when the modified signaling agent is an antagonist of its receptor, measurable as, for example, K_I and/or IC_{50}), for one or more of its receptors. In various embodiments, the reduced affinity at the signaling agent's receptor allows for attenuation of activity. In such embodiments, the modified signaling agent has about 1%, or about 3%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 10%-20%, about 20%-40%, about 50%, about 40%-60%, about 60%-80%, about 80%-100% of the affinity for the receptor as compared to the signaling agent which is not fused to an Fc, or a signaling agent which is not in the context of a complex, *e.g.*, without limitation, a heterodimeric complex. In some embodiments, the binding affinity is at least about 2-fold lower, about 3-fold lower, about 4-fold lower, about 5-fold lower, about 6-fold lower, about 7-fold lower, about 8-fold lower, about 9-fold lower, at least about 10-fold lower, at least about 15-fold lower, at least about 20-fold lower, at least about 25-fold lower, at least about 30-fold lower, at least about 35-fold lower, at least about 40-fold lower, at least about 45-fold lower, at least about 50-fold lower, at least about 100-fold lower, at least about 150-fold lower, or about 10-50-fold lower, about 50-100-fold lower, about 100-150-fold lower, about 150-200-fold lower, or more than 200-fold lower as compared to the signaling agent which is not fused to an Fc, or a signaling agent which is not in the context of a complex, *e.g.*, without limitation, a heterodimeric complex.

In various embodiments, the Fc-based chimeric protein complex comprises a wild type signaling agent that has reduced endogenous activity of the signaling agent to about 75%, or about 70%, or about 60%, or about 50%, or about 40%, or about 30%, or about 25%, or about 20%, or about 10%, or about 5%, or about 3%, or about 1%, *e.g.*, as compared to the signaling agent which is not fused to an Fc, or a signaling agent which is not in the context of a complex, *e.g.*, without limitation, a heterodimeric complex.

In various embodiments, the signaling agent has one or more mutations that confer improved target selectivity and safety relative to a wild type signaling agent. In various embodiments, the signaling agent has one or more mutations that confer improved target selective activity relative to a wild type signaling agent. In various embodiments, the signaling agent has one or more mutations that allow for conditional activity.

In various embodiments, the signaling agent is modified to have reduced affinity or activity for one or more of its receptors, which allows for attenuation of activity (inclusive of agonism or antagonism) and/or prevents non-specific signaling or undesirable sequestration of the Fc-based chimeric protein complex.

In various embodiments, the signaling agent is agonistic in its wild type form and bears one or more mutations that attenuate its agonistic activity.

In various embodiments, the signaling agent is antagonistic in its wild type form and bears one or more mutations that attenuate its antagonistic activity. In various embodiments, the signaling agent is antagonistic due to one or

more mutations, *e.g.* an agonistic signaling agent is converted to an antagonistic signaling agent and, such a converted signaling agent, optionally, also bears one or more mutations that attenuate its antagonistic activity (*e.g.* as described in WO 2015/007520, the entire contents of which are hereby incorporated by reference).

Accordingly, in various embodiments, the signaling agent is a modified (*e.g.* mutant) form (*e.g.*, having one or more mutations) of a wild type signaling agent. In various embodiments, the modifications (*e.g.* mutations) allow for the modified signaling agent to have one or more of attenuated activity such as one or more of reduced binding affinity, reduced endogenous activity, and reduced specific bioactivity as compared to the unmodified or unmutated signaling agent, *i.e.* the wild type form of the signaling agent (*e.g.* comparing the same signaling agent in a wild type form versus a modified or mutant form). In some embodiments, the mutations which attenuate or reduce binding or affinity include those mutations which substantially reduce or ablate binding or activity. In some embodiments, the mutations which attenuate or reduce binding or affinity are different from those mutations which substantially reduce or ablate binding or activity. Consequentially, in various embodiments, the mutations allow for the signaling agent to have improved safety, *e.g.* reduced systemic toxicity, reduced side effects, and reduced off-target effects relative to unmutated, *i.e.* wild type, signaling agent (*e.g.* comparing the same signaling agent in a wild type form versus a modified (*e.g.* mutant) form).

As described herein, the signaling agent may have improved safety due to one of more modifications, *e.g.* mutations. In various embodiments, improved safety means that the present Fc-based chimeric protein provides lower toxicity (*e.g.* systemic toxicity and/or tissue/organ-associated toxicities); and/or lessened or substantially eliminated side effects; and/or increased tolerability, lessened or substantially eliminated adverse events; and/or reduced or substantially eliminated off-target effects; and/or an increased therapeutic window.

In various embodiments, the signaling agent is modified to have one or more mutations that reduce its binding affinity or activity for one or more of its receptors. In some embodiments, the signaling agent is modified to have one or more mutations that substantially reduce or ablate binding affinity or activity for the receptors. In some embodiments, the activity provided by the wild type signaling agent is agonism at the receptor (*e.g.* activation of a cellular effect at a site of therapy). For example, the wild type signaling agent may activate its receptor. In such embodiments, the mutations result in the modified signaling agent to have reduced or ablated activating activity at the receptor. For example, the mutations may result in the modified signaling agent to deliver a reduced activating signal to a target cell or the activating signal could be ablated. In some embodiments, the activity provided by the wild type signaling agent is antagonism at the receptor (*e.g.* blocking or dampening of a cellular effect at a site of therapy). For example, the wild type signaling agent may antagonize or inhibit the receptor. In these embodiments, the mutations result in the modified signaling agent to have a reduced or ablated antagonizing activity at the receptor. For example, the mutations may result in the modified signaling agent to deliver a reduced inhibitory signal to a target cell or the inhibitory signal could be ablated. In various embodiments, the signaling agent is antagonistic due to one or more mutations, *e.g.* an agonistic signaling agent is converted to an antagonistic signaling agent (*e.g.* as described in WO 2015/007520, the entire contents of which are hereby incorporated by reference) and, such a converted signaling agent, optionally, also bears one or more mutations that reduce its

binding affinity or activity for one or more of its receptors or that substantially reduce or ablate binding affinity or activity for one or more of its receptors.

In some embodiments, the reduced affinity or activity at the receptor is restorable by inclusion in the present complex having one or more of the targeting moieties as described herein. In other embodiments, the reduced affinity or activity at the receptor is not substantially restorable by the activity of one or more of the targeting moieties.

In various embodiments, the Fc-based chimeric protein complex of the present technology reduces off-target effects because their signaling agents have mutations that weaken or ablate binding affinity or activity at a receptor. In various embodiments, this reduction in side effects is observed relative with, for example, the wild type signaling agents. In various embodiments, the signaling agent is active on target cells because the targeting moiety(ies) compensates for the missing/insufficient binding (*e.g.*, without limitation and/or avidity) required for substantial activation. In various embodiments, the wild type or modified signaling agent is substantially inactive *en route* to the site of therapeutic activity and has its effect substantially on specifically targeted cell types which greatly reduces cross-reactivities and/or potentially associated side effects.

In some embodiments, the signaling agent may include one or more mutations that attenuate or reduce binding or affinity for one receptor (*i.e.*, a therapeutic receptor) and one or more mutations that substantially reduce or ablate binding or activity at a second receptor. In such embodiments, these mutations may be at the same or at different positions (*i.e.*, the same mutation or multiple mutations). In some embodiments, the mutation(s) that reduce binding and/or activity at one receptor is different from the mutation(s) that substantially reduce or ablate at another receptor. In some embodiments, the mutation(s) that reduce binding and/or activity at one receptor is the same as the mutation(s) that substantially reduce or ablate at another receptor. In some embodiments, the present Fc-based chimeric protein complexes have a modified signaling agent that has both mutations that attenuate binding and/or activity at a therapeutic receptor and therefore allow for a more controlled, on-target therapeutic effect (*e.g.* relative wild type signaling agent) and mutations that substantially reduce or ablate binding and/or activity at another receptor and therefore reduce side effects (*e.g.* relative to wild type signaling agent).

In some embodiments, the substantial reduction or ablation of binding or activity is not substantially restorable with a targeting moiety described herein. In some embodiments, the substantial reduction or ablation of binding or activity is restorable with a targeting moiety. In various embodiments, substantially reducing or ablating binding or activity at a second receptor also may prevent deleterious effects that are mediated by the other receptor. Alternatively, or in addition, substantially reducing or ablating binding or activity at the other receptor causes the therapeutic effect to improve as there is a reduced or eliminated sequestration of the therapeutic Fc-based chimeric protein complexes away from the site of therapeutic action. For instance, in some embodiments, this obviates the need of high doses of the present Fc-based chimeric protein complexes that compensate for loss at the other receptor. Such ability to reduce dose further provides a lower likelihood of side effects.

In various embodiments, the modified signaling agent comprises one or more mutations that cause the signaling agent to have reduced, substantially reduced, or ablated affinity, *e.g.* binding (*e.g.* K_D) and/or activation (for

instance, when the modified signaling agent is an agonist of its receptor, measurable as, for example, K_A and/or EC_{50}) and/or inhibition (for instance, when the modified signaling agent is an antagonist of its receptor, measurable as, for example, K_I and/or IC_{50}), for one or more of its receptors. In various embodiments, the reduced affinity at the signaling agent's receptor allows for attenuation of activity (inclusive of agonism or antagonism). In such embodiments, the modified signaling agent has about 1%, or about 3%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 10%-20%, about 20%-40%, about 50%, about 40%-60%, about 60%-80%, about 80%-100% of the affinity for the receptor relative to the wild type signaling agent. In some embodiments, the binding affinity is at least about 2-fold lower, about 3-fold lower, about 4-fold lower, about 5-fold lower, about 6-fold lower, about 7-fold lower, about 8-fold lower, about 9-fold lower, at least about 10-fold lower, at least about 15-fold lower, at least about 20-fold lower, at least about 25-fold lower, at least about 30-fold lower, at least about 35-fold lower, at least about 40-fold lower, at least about 45-fold lower, at least about 50-fold lower, at least about 100-fold lower, at least about 150-fold lower, or about 10-50-fold lower, about 50-100-fold lower, about 100-150-fold lower, about 150-200-fold lower, or more than 200-fold lower relative to the wild type signaling agent.

In embodiments wherein the Fc-based chimeric protein complex comprises a modified signaling agent having mutations that reduce binding at one receptor and substantially reduce or ablate binding at a second receptor, the attenuation or reduction in binding affinity of the modified signaling agent for one receptor is less than the substantial reduction or ablation in affinity for the other receptor. In some embodiments, the attenuation or reduction in binding affinity of the modified signaling agent for one receptor is less than the substantial reduction or ablation in affinity for the other receptor by about 1%, or about 3%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%. In various embodiments, substantial reduction or ablation refers to a greater reduction in binding affinity and/or activity than attenuation or reduction.

In various embodiments, the modified signaling agent comprises one or more mutations that reduce the endogenous activity of the signaling agent to about 75%, or about 70%, or about 60%, or about 50%, or about 40%, or about 30%, or about 25%, or about 20%, or about 10%, or about 5%, or about 3%, or about 1%, *e.g.*, relative to the wild type signaling agent.

In some embodiments, the modified signaling agent comprises one or more mutations that cause the signaling agent to have reduced affinity for its receptor that is lower than the binding affinity of the targeting moiety(ies) for its(their) receptor(s). In some embodiments, this binding affinity differential is between signaling agent/receptor and targeting moiety/receptor on the same cell. In some embodiments, this binding affinity differential allows for the signaling agent, *e.g.* mutated signaling agent, to have localized, on-target effects and to minimize off-target effects that underlie side effects that are observed with wild type signaling agent. In some embodiments, this binding affinity is at least about 2-fold, or at least about 5-fold, or at least about 10-fold, or at least about 15-fold

lower, or at least about 25-fold, or at least about 50-fold lower, or at least about 100-fold, or at least about 150-fold.

Receptor binding activity may be measured using methods known in the art. For example, affinity and/or binding activity may be assessed by Scatchard plot analysis and computer-fitting of binding data (*e.g.* Scatchard, The attractions of proteins for small molecules and ions. Ann NY Acad Sci 51: 660-672, 1949) or by reflectometric interference spectroscopy under flow through conditions, as described by Brecht *et al. Biosens Bioelectron* 1993;8:387-392, the entire contents of all of which are hereby incorporated by reference.

The amino acid sequences of the wild type signaling agents described herein are well known in the art. Accordingly, in various embodiments the modified signaling agent comprises an amino acid sequence that has at least about 60%, or at least about 61%, or at least about 62%, or at least about 63%, or at least about 64%, or at least about 65%, or at least about 66%, or at least about 67%, or at least about 68%, or at least about 69%, or at least about 70%, or at least about 71%, or at least about 72%, or at least about 73%, or at least about 74%, or at least about 75%, or at least about 76%, or at least about 77%, or at least about 78%, or at least about 79%, or at least about 80%, or at least about 81%, or at least about 82%, or at least about 83%, or at least about 84%, or at least about 85%, or at least about 86%, or at least about 87%, or at least about 88%, or at least about 89%, or at least about 90%, or at least about 91%, or at least about 92%, or at least about 93%, or at least about 94%, or at least about 95%, or at least about 96%, or at least about 97%, or at least about 98%, or at least about 99% sequence identity with the known wild type amino acid sequences of the signaling agents described herein (*e.g.* about 60%, or about 61%, or about 62%, or about 63%, or about 64%, or about 65%, or about 66%, or about 67%, or about 68%, or about 69%, or about 70%, or about 71%, or about 72%, or about 73%, or about 74%, or about 75%, or about 76%, or about 77%, or about 78%, or about 79%, or about 80%, or about 81%, or about 82%, or about 83%, or about 84%, or about 85%, or about 86%, or about 87%, or about 88%, or about 89%, or about 90%, or about 91%, or about 92%, or about 93%, or about 94%, or about 95%, or about 96%, or about 97%, or about 98%, or about 99% sequence identity).

In various embodiments the modified signaling agent comprises an amino acid sequence that has at least about 60%, or at least about 61%, or at least about 62%, or at least about 63%, or at least about 64%, or at least about 65%, or at least about 66%, or at least about 67%, or at least about 68%, or at least about 69%, or at least about 70%, or at least about 71%, or at least about 72%, or at least about 73%, or at least about 74%, or at least about 75%, or at least about 76%, or at least about 77%, or at least about 78%, or at least about 79%, or at least about 80%, or at least about 81%, or at least about 82%, or at least about 83%, or at least about 84%, or at least about 85%, or at least about 86%, or at least about 87%, or at least about 88%, or at least about 89%, or at least about 90%, or at least about 91%, or at least about 92%, or at least about 93%, or at least about 94%, or at least about 95%, or at least about 96%, or at least about 97%, or at least about 98%, or at least about 99% sequence identity with any amino acid sequences of the signaling agents described herein (*e.g.* about 60%, or about 61%, or about 62%, or about 63%, or about 64%, or about 65%, or about 66%, or about 67%, or about 68%, or about 69%, or about 70%, or about 71%, or about 72%, or about 73%, or about 74%, or about 75%, or about 76%, or about 77%,

or about 78%, or about 79%, or about 80%, or about 81%, or about 82%, or about 83%, or about 84%, or about 85%, or about 86%, or about 87%, or about 88%, or about 89%, or about 90%, or about 91%, or about 92%, or about 93%, or about 94%, or about 95%, or about 96%, or about 97%, or about 98%, or about 99% sequence identity).

In various embodiments, the modified signaling agent comprises an amino acid sequence having one or more amino acid mutations. In some embodiments, the one or more amino acid mutations may be independently selected from substitutions, insertions, deletions, and truncations. In some embodiments, the amino acid mutations are amino acid substitutions, and may include conservative and/or non-conservative substitutions, as described elsewhere herein.

In various embodiments, the modified signaling comprises a truncation of one or more amino acids, *e.g.* an N-terminal truncation and/or a C-terminal truncation.

In various embodiments, the substitutions may also include non-classical amino acids as described elsewhere herein.

As described herein, the modified signaling agents bear mutations that affect affinity and/or activity at one or more receptors. In various embodiments, there is reduced affinity and/or activity at a therapeutic receptor, *e.g.* a receptor through which a desired therapeutic effect is mediated (*e.g.* agonism or antagonism). In various embodiments, the modified signaling agents bear mutations that substantially reduce or ablate affinity and/or activity at a receptor, *e.g.* a receptor through which a desired therapeutic effect is not mediated (*e.g.* as the result of promiscuity of binding). The receptors of any signaling agents, as described herein, are known in the art.

Illustrative mutations which provide reduced affinity and/or activity (*e.g.* agonistic) at a receptor are found in WO 2013/107791 and PCT/EP2017/061544 (*e.g.* with regard to interferons), WO 2015/007542 (*e.g.* with regard to interleukins), and WO 2015/007903 (*e.g.* with regard to TNF), the entire contents of each of which are hereby incorporated by reference. Illustrative mutations which provide reduced affinity and/or activity (*e.g.* antagonistic) at a therapeutic receptor are found in WO 2015/007520, the entire contents of which are hereby incorporated by reference.

In various embodiments, the signaling agent is an immune-modulating agent, *e.g.* one or more of an interleukin, interferon, and tumor necrosis factor.

In some embodiments, the signaling agent is a wild type interleukin or a modified interleukin, including for example IL-1; 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-19; IL-20; IL-21; IL-22; IL-23; IL-24; IL-25; IL-26; IL-27; IL-28; IL-29; IL-30; IL-31; IL-32; IL-33; IL-35; IL-36 or a fragment, variant, analogue, or family-member thereof. Interleukins are a group of multi- functional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (*e.g.*, T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons. Interleukin activity can be determined using assays known in the art: Matthews *et al.*, in *Lymphokines and Interferons: A Practical Approach*, Clemens *et al.*, eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) Cytokine 1, 14-20.

In some embodiments, the signaling agent is a wild type interferon or a modified version of an interferon such as interferon types I, II, and III. Illustrative interferons, including for example, interferon-α-1, 2, 4, 5, 6, 7, 8, 10, 13, 14, 16, 17, and 21, interferon-β and interferon-γ, interferon κ, interferon ε, interferon τ, and interferon ϖ.

In some embodiments, the signaling agent is a wild type tumor necrosis factor (TNF) or a modified version of a tumor necrosis factor (TNF) or a protein in the TNF family, including but not limited to, TNF-α, TNF-β, LT-β, CD40L, CD27L, CD30L, FASL, 4-1BBL, OX40L, and TRAIL.

In some embodiments, the modified signaling agent comprises one or more mutations that cause the signaling agent to have reduced affinity and/or activity for a type I cytokine receptor, a type II cytokine receptor, a chemokine receptor, a receptor in the Tumor Necrosis Factor Receptor (TNFR) superfamily, TGF-beta Receptors, a receptor in the immunoglobulin (Ig) superfamily, and/or a receptor in the tyrosine kinase superfamily.

In various embodiments, the receptor for the signaling agent is a Type I cytokine receptor. Type I cytokine receptors are known in the art and include, but are not limited to receptors for IL2 (beta-subunit), IL3, IL4, IL5, IL6, IL7, IL9, IL11, IL12, GM-CSF, G-CSF, LIF, CNTF, and also the receptors for Thrombopoietin (TPO), Prolactin, and Growth hormone. Illustrative type I cytokine receptors include, but are not limited to, GM-CSF receptor, G-CSF receptor, LIF receptor, CNTF receptor, TPO receptor, and type I IL receptors.

In various embodiments, the receptor for the signaling agent is a Type II cytokine receptor. Type II cytokine receptors are multimeric receptors composed of heterologous subunits, and are receptors mainly for interferons. This family of receptors includes, but is not limited to, receptors for interferon-α, interferon-β and interferon-γ, IL10, IL22, and tissue factor. Illustrative type II cytokine receptors include, but are not limited to, IFN-α receptor (*e.g.* IFNAR1 and IFNAR2), IFN- β receptor, IFN- γ receptor (*e.g.* IFNGR1 and IFNGR2), and type II IL receptors.

In various embodiments, the receptor for the signaling agent is a G protein-coupled receptor. Chemokine receptors are G protein-coupled receptors with seven transmembrane structure and coupled to G-protein for signal transduction. Chemokine receptors include, but are not limited to, CC chemokine receptors, CXC chemokine receptors, CX3C chemokine receptors, and XC chemokine receptor (XCR1). Exemplary chemokine receptors include, but are not limited to, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR3B, CXCR4, CXCR5, CSCR6, CXCR7, XCR1, and CX3CR1.

In various embodiments, the receptor for the signaling agent is a TNFR family member. Tumor necrosis factor receptor (TNFR) family members share a cysteine-rich domain (CRD) formed of three disulfide bonds surrounding a core motif of CXXCXXC creating an elongated molecule. Exemplary tumor necrosis factor receptor family members include: CDI 20a (TNFRSFIA), CD 120b (TNFRSFIB), Lymphotoxin beta receptor (LTBR, TNFRSF3), CD 134 (TNFRSF4), CD40 (CD40, TNFRSF5), FAS (FAS, TNFRSF6), TNFRSF6B (TNFRSF6B), CD27 (CD27, TNFRSF7), CD30 (TNFRSF8), CD137 (TNFRSF9), TNFRSFIOA (TNFRSFIOA), TNFRSFIOB, (TNFRSFIOB), TNFRSFIOC (TNFRSFIOC), TNFRSFIOD (TNFRSFIOD), RANK (TNFRSFI IA), Osteoprotegerin (TNFRSFI IB), TNFRSF12A (TNFRSF12A), TNFRSF13B (TNFRSF13B), TNFRSF13C (TNFRSF13C), TNFRSF14 (TNFRSF14), Nerve growth factor receptor (NGFR, TNFRSF16), TNFRSF17 (TNFRSF17), TNFRSF18 (TNFRSF18), TNFRSF19 (TNFRSF19), TNFRSF21 (TNFRSF21), and TNFRSF25 (TNFRSF25). In an embodiment, the TNFR

family member is CD120a (TNFRSF1A) or TNF-R1. In another embodiment, the TNFR family member is CD 120b (TNFRSFIB) or TNF-R2.

In various embodiments, the receptor for the signaling agent is a TGF-beta receptor. TGF-beta receptors are single pass serine/threonine kinase receptors. TGF-beta receptors include, but are not limited to, TGFBR1, TGFBR2, and TGFBR3.

In various embodiments, the receptor for the signaling agent is an Ig superfamily receptor. Receptors in the immunoglobulin (Ig) superfamily share structural homology with immunoglobulins. Receptors in the Ig superfamily include, but are not limited to, interleukin-1 receptors, CSF-1R, PDGFR (*e.g.* PDGFRA and PDGFRB), and SCFR.

In various embodiments, the receptor for the signaling agent is a tyrosine kinase superfamily receptor. Receptors in the tyrosine kinase superfamily are well known in the art. There are about 58 known receptor tyrosine kinases (RTKs), grouped into 20 subfamilies. Receptors in the tyrosine kinase superfamily include, but are not limited to, FGF receptors and their various isoforms such as FGFR1, FGFR2, FGFR3, FGFR4, and FGFR5.

In embodiments, the interferon is a type I interferon. In embodiments, the type I interferon is selected from IFN-α2, IFN-α1, IFN-β, IFN-γ, Consensus IFN, IFN-ε, IFN-κ, IFN-τ, IFN-δ, and IFN-v.

In some embodiments, the signaling agent is a wild type interferon α or a modified interferon α. In embodiments, the modified IFN-α agent has reduced affinity and/or activity for the IFN-α/β receptor (IFNAR), *i.e.*, IFNAR1 and/or IFNAR2 chains. In some embodiments, the modified IFN-α agent has substantially reduced or ablated affinity and/or activity for the IFN-α/β receptor (IFNAR), *i.e.*, IFNAR1 and/or IFNAR2 chains.

Mutant forms of interferon α2 are known to the person skilled in the art. In an illustrative embodiment, the modified signaling agent is the allelic form IFN-α2a having the amino acid sequence of:

IFN-α2a:

CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTK
DSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCA
WEVVRAEIMRSFSLSTNLQESLRSKE (SEQ ID NO: 1).

In an illustrative embodiment, the modified signaling agent is the allelic form IFN-α2b having the amino acid sequence of (which differs from IFN-α2a at amino acid position 23):

IFN-α2b:

CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTK
DSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCA
WEVVRAEIMRSFSLSTNLQESLRSKE (SEQ ID NO: 2).

In some embodiments, said IFN-α2 mutant (IFN-α2a or IFN-α2b) is mutated at one or more amino acids at positions 144-154, such as amino acid positions 148, 149 and/or 153. In some embodiments, the IFN-α2 mutant comprises one or more mutations selected from L153A, R149A, and M148A. Such mutants are described, for example, in WO2013/107791 and Piehler *et al.*, (2000) J. Biol. Chem, 275:40425-33, the entire contents of all of which are hereby incorporated by reference.

In some embodiments, the IFN-α2 mutants have reduced affinity and/or activity for IFNAR1. In some embodiments, the IFN-α2 mutant comprises one or more mutations selected from F64A, N65A, T69A, L80A, Y85A, and Y89A, as described in WO2010/030671, the entire contents of which is hereby incorporated by reference.

In some embodiments, the IFN-α2 mutant comprises one or more mutations selected from K133A, R144A, R149A, and L153A as described in WO2008/124086, the entire contents of which is hereby incorporated by reference.

In some embodiments, the IFN-α2 mutant comprises one or more mutations selected from R120E and R120E/K121E, as described in WO2015/007520 and WO2010/030671, the entire contents of which are hereby incorporated by reference. In such embodiments, said IFN-α2 mutant antagonizes wildtype IFN-α2 activity. In such embodiments, said mutant IFN-α2 has reduced affinity and/or activity for IFNAR1 while affinity and/or activity of IFNR2 is retained.

In some embodiments, the human IFN-α2 mutant comprises (1) one or more mutations selected from R120E and R120E/K121E, which, without wishing to be bound by theory, create an antagonistic effect and (2) one or more mutations selected from K133A, R144A, R149A, and L153A, which, without wishing to be bound by theory, allow for an attenuated effect at, for example, IFNAR2. In an embodiment, the human IFN-α2 mutant comprises R120E and L153A.

In some embodiments, the human IFN-α2 mutant comprises one or more mutations selected from, L15A, A19W, R22A, R23A, S25A, L26A, F27A, L30A, L30V, K31A, D32A, R33K, R33A, R33Q, H34A, D35A, Q40A, D114R, L117A, R120A, R120E, R125A, R125E, K131A, E132A, K133A, K134A, R144A, A145G, A145M, M148A, R149A, S152A, L153A, and N156A as disclosed in WO 2013/059885 and WO 2016/065409, the entire disclosures of which are hereby incorporated by reference. In some embodiments, the human IFN-α2 mutant comprises the mutations H57Y, E58N, Q61S, and/or L30A as disclosed in WO 2013/059885. In some embodiments, the human IFN-α2 mutant comprises the mutations H57Y, E58N, Q61S, and/or R33A as disclosed in WO 2013/059885. In some embodiments, the human IFN-α2 mutant comprises the mutations H57Y, E58N, Q61S, and/or M148A as disclosed in WO 2013/059885. In some embodiments, the human IFN-α2 mutant comprises the mutations H57Y, E58N, Q61S, and/or L153A as disclosed in WO 2013/059885. In some embodiments, the human IFN-α2 mutant comprises the mutations N65A, L80A, Y85A, and/or Y89A as disclosed in WO 2013/059885. In some embodiments, the human IFN-α2 mutant comprises the mutations N65A, L80A, Y85A, Y89A, and/or D114A as disclosed in WO 2013/059885. In some embodiments, the human IFN-α2 mutant comprises one or more mutations selected from R144X_1, A145X_2, R33A and T106X_3, wherein X_1 is selected from A, S, T, Y, L, and I, and wherein X_2 is selected from G, H, Y, K, and D and wherein X_3 is selected from A and E.

In some embodiments, the human IFN-α2 mutant comprises one or more mutations at one of positions R33, R144, A145, M148, and L153. In some embodiments, the human IFN-α2 mutant comprises one or more mutations selected from R33A, R144A, R144I, R144L, R144S, R144T, R144Y, A145D, A145G, A145H, A145K, A145Y, M148A, and L153A.

In some embodiments, the human IFN-α2 mutant comprises one or more mutations selected from L15A, R22A, R23A, S25A, L26A, F27A, L30A, L30V, K31A, D32A, R33A, R33K, R33Q, H34A, Q40A, D113R, L116A, R119A,

R119E, R124A, R124E, K130A, E131A, K132A, K133A, M147A, R148A, S 149A, L152A, N155A, (L30A, H57Y, E58N and Q61S), (M147A, H57Y, E58N and Q61S), (L152A, H57Y, E58N and Q61S), (R143A, H57Y, E58N and Q61S), (N65A, L80A, Y85A and Y89A,) (N65A, L80A, Y85A, Y89A and D113A), (N65A, L80A, Y85A, Y89A and L116A), (N65A, L80A, Y85A, Y89A and RI 190A), (Y85A, Y89A and D113A), (D113A and RI119A), (L116A and R119A), (L116A, R119A and K120A), (R119A and K120A), (R119E and K120E), replacement of R at position 143 with A, D, E, G, H, I, K, L, N, Q, S, T, V or Y, replacement of A at position 144 with D, E, G, H, I, K, L, M, N, Q, S, T, V or Y, and deletion of residues L160 to E164.

In some embodiments, the human IFN-α2 mutant comprises a mutation which does not permit O-linked glycosylation at a position when, *e.g.*, produced in mammalian cell culture. In some embodiments, the human IFN-α2 mutant comprises a mutation at T106. In some embodiments, T106 is substituted with A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, V, W, or Y.

In some embodiments, the human IFN-α2 mutant is a mutant of the IFN-α2-1b variant. Mutations in the IFN-α2-1b variant are disclosed in WO 2015/168474, the entire disclosures of which are hereby incorporated by reference. By way of example, in some embodiments IFN-α2-1b comprises one or more of the following mutations: H58A, E59A, R145A, M149A, and R150A.

In some embodiments, the signaling agent is a wild type interferon α1 or a modified interferon α1. In some embodiments, the present invention provides a chimeric protein that includes a wild type IFNα1. In various embodiments, the wild-type IFNα1 comprises the following amino acid sequence:

CDLPETHSLDNRRTLMLLAQMSRISPSSCLMDRHDFGFPQEEFDGNQFQKAPAISVLHEL
IQQIFNLFTTKDSSAAWDEDLLDKFCTELYQQLNDLEACVMQEERVGETPLMNADSILAV
KKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLSLSTNLQERLRRKE (SEQ ID NO: 1562).

In various embodiments, the chimeric protein of the invention comprises a modified version of IFNα1, *i.e.*, an IFNα1 variant including a IFNα1 mutant, as a signaling agent. In various embodiments, the IFNα1 variant encompasses mutants, functional derivatives, analogs, precursors, isoforms, splice variants, or fragments of the interferon.

In some embodiments, the IFNα1 interferon is modified to have a mutation at one or more amino acids at positions L15, A19, R23, S25, L30, D32, R33, H34, Q40, C86, D115, L118, K121, R126, E133, K134, K135, R145, A146, M149, R150, S153, L154, and N157 with reference to SEQ ID NO: 1562. The mutations can optionally be a hydrophobic mutation and can be, *e.g.*, selected from alanine, valine, leucine, and isoleucine. In some embodiments, the IFNα1 interferon is modified to have a one or more mutations selected from L15A, A19W, R23A, S25A, L30A, L30V, D32A, R33K, R33A, R33Q, H34A, Q40A, C86S, C86A, D115R, L118A, K121A, K121E, R126A, R126E, E133A, K134A, K135A, R145A, R145D, R145E, R145G, R145H, R145I, R145K, R145L, R145N, R145Q, R145S, R145T, R145V, R145Y, A146D, A146E, A146G, A146H, A146I, A146K, A146L, A146M, A146N, A146Q, A146R, A146S, A146T, A146V, A146Y, M149A, R150A, S153A, L154A, and N157A with reference to SEQ ID NO: 1562. In some embodiments, the IFNα1 mutant comprises one or more multiple mutations selected from L30A/H58Y/E59N_Q62S, R33A/H58Y/E59N/Q62S, M149A/H58Y/E59N/Q62S, L154A/H58Y/E59N/Q62S,

R145A/H58Y/E59N/Q62S, D115A/R121A, L118A/R121A, L118A/R121A/K122A, R121A/K122A, and R121E/K122E with reference to SEQ ID NO: 1562).

In an embodiment, the IFNα1 interferon is modified to have a mutation at amino acid position C86 with reference to SEQ ID NO: 1562. The mutation at position C86 can be, *e.g.*, C86S or C86A. These C86 mutants of IFNα1 are called reduced cysteine based aggregation mutants.

In some embodiments, the signaling agent is a wild type interferon β or modified interferon β. In such embodiments, the modified interferon β agent has reduced affinity and/or activity for the IFN-α/β receptor (IFNAR), *i.e.*, IFNAR1 and/or IFNAR2 chains. In some embodiments, the modified interferon β agent has substantially reduced or ablated affinity and/or activity for the IFN-α/β receptor (IFNAR), *i.e.*, IFNAR1 and/or IFNAR2 chains.

In an illustrative embodiment, the modified signaling agent is IFN-β. In various embodiments, the IFN-β encompasses functional derivatives, analogs, precursors, isoforms, splice variants, or fragments of IFN-β. In various embodiments, the IFN-β encompasses IFN-β derived from any species. In an embodiment, the Fc-based chimeric protein complex comprises a modified version of mouse IFN-β. In another embodiment, the Fc-based chimeric protein complex comprises a modified version of human IFN-β. Human IFN-β is a polypeptide with a molecular weight of about 22 kDa comprising 166 amino acid residues. The amino acid sequence of human IFN-β is:

MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIY
EMLQNIFAIFRQDSSSTGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSL
HLKRYYGRILHYLKAKEYSHCAWTIVRVEILRNFYFINRLTGYLRN (SEQ ID NO: 3).

In some embodiments, the human IFN-β is IFN-β-1a that is a glycosylated form of human IFN-β. In some embodiments, the human IFN-β is IFN-β-1b that is a non-glycosylated form of human IFN-β that has a Met-1 deletion and a Cys-17 to Ser mutation.

In various embodiments, the modified IFN-β has one or more mutations that reduce its binding to or its affinity for the IFNAR1 subunit of IFNAR. In one embodiment, the modified IFN-β has reduced affinity and/or activity at IFNAR1. In various embodiments, the modified IFN-β is human IFN-β and has one or more mutations at positions F67, R71, L88, Y92, I95, N96, K123, and R124. In some embodiments, the one or more mutations are substitutions selected from F67G, F67S, R71A, L88G, L88S, Y92G, Y92S, I95A, N96G, K123G, and R124G. In an embodiment, the modified IFN-β comprises the F67G mutation. In an embodiment, the modified IFN-β comprises the K123G mutation. In an embodiment, the modified IFN-β comprises the F67G and R71A mutations. In an embodiment, the modified IFN-β comprises the L88G and Y92G mutations. In an embodiment, the modified IFN-β comprises the Y92G, I95A, and N96G mutations. In an embodiment, the modified IFN-β comprises the K123G and R124G mutations. In an embodiment, the modified IFN-β comprises the F67G, L88G, and Y92G mutations. In an embodiment, the modified IFN-β comprises the F67S, L88S, and Y92S mutations.

In some embodiments, the modified IFN-β has one or more mutations that reduce its binding to or its affinity for the IFNAR2 subunit of IFNAR. In one embodiment, the modified IFN-β has reduced affinity and/or activity at IFNAR2. In various embodiments, the modified IFN-β is human IFN-β and has one or more mutations at positions

W22, R27, L32, R35, V148, L151, R152, and Y155. In some embodiments, the one or more mutations are substitutions selected from W22G, R27G, L32A, L32G, R35A, R35G, V148G, L151G, R152A, R152G, and Y155G. In an embodiment, the modified IFN-β comprises the W22G mutation. In an embodiment, the modified IFN-β comprises the L32A mutation. In an embodiment, the modified IFN-β comprises the L32G mutation. In an embodiment, the modified IFN-β comprises the R35A mutation. In an embodiment, the modified IFN-β comprises the R35G mutation. In an embodiment, the modified IFN-β comprises the V148G mutation. In an embodiment, the modified IFN-β comprises the R152A mutation. In an embodiment, the modified IFN-β comprises the R152G mutation. In an embodiment, the modified IFN-β comprises the Y155G mutation. In an embodiment, the modified IFN-β comprises the W22G and R27G mutations. In an embodiment, the modified IFN-β comprises the L32A and R35A mutation. In an embodiment, the modified IFN-β comprises the L151G and R152A mutations. In an embodiment, the modified IFN-β comprises the V148G and R152A mutations.

In some embodiments, the modified IFN-β has one or more of the following mutations: R35A, R35T, E42K, M62I, G78S, A141Y, A142T, E149K, and R152H. In some embodiments, the modified IFN-β has one or more of the following mutations: R35A, R35T, E42K, M62I, G78S, A141Y, A142T, E149K, and R152H in combination with C17S or C17A.

In some embodiments, the modified IFN-β has one or more of the following mutations: R35A, R35T, E42K, M62I, G78S, A141Y, A142T, E149K, and R152H in combination with any of the other IFN-β mutations described herein.

The crystal structure of human IFN-β is known and is described in Karpusas *et al.*, (1998) PNAS, 94(22): 11813–11818. Specifically, the structure of human IFN-β has been shown to include five α-helices (*i.e.*, A, B, C, D, and E) and four loop regions that connect these helices (*i.e.*, AB, BC, CD, and DE loops). In various embodiments, the modified IFN-β has one or more mutations in the A, B, C, D, E helices and/or the AB, BC, CD, and DE loops which reduce its binding affinity or activity at a therapeutic receptor such as IFNAR. Exemplary mutations are described in WO2000/023114 and US20150011732, the entire contents of which are hereby incorporated by reference. In an exemplary embodiment, the modified IFN-β is human IFN-β comprising alanine substitutions at amino acid positions 15, 16, 18, 19, 22, and/or 23. In an exemplary embodiment, the modified IFN-β is human IFN-β comprising alanine substitutions at amino acid positions 28-30, 32, and 33. In an exemplary embodiment, the modified IFN-β is human IFN-β comprising alanine substitutions at amino acid positions 36, 37, 39, and 42. In an exemplary embodiment, the modified IFN-β is human IFN-β comprising alanine substitutions at amino acid positions 64 and 67 and a serine substitution at position 68. In an exemplary embodiment, the modified IFN-β is human IFN-β comprising alanine substitutions at amino acid positions 71-73. In an exemplary embodiment, the modified IFN-β is human IFN-β comprising alanine substitutions at amino acid positions 92, 96, 99, and 100. In an exemplary embodiment, the modified IFN-β is human IFN-β comprising alanine substitutions at amino acid positions 128, 130, 131, and 134. In an exemplary embodiment, the modified IFN-β is human IFN-β comprising alanine substitutions at amino acid positions 149, 153, 156, and 159. In some embodiments, the mutant IFNβ comprises SEQ ID NO:3 and a mutation at W22, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at R27, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at W22, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V) and a mutation at R27, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at L32, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at R35, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at L32, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), isoleucine (I), methionine (M), and valine (V) and a mutation at R35, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at F67, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at R71, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at F67, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V) and a mutation at R71, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at L88, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at Y92, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at F67, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V) and a mutation at L88, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), isoleucine (I), methionine (M), and valine (V) and a mutation at Y92, the mutation being an aliphatic

hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at L88, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), isoleucine (I), methionine (M), and valine (V) and a mutation at Y92, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at I95, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), methionine (M), and valine (V) and a mutation at Y92, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at N96, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V) and a mutation at Y92, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at Y92, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V) and a mutation at I95, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), methionine (M), and valine (V) and a mutation at N96, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at K123, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at R124, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at K123, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V) and a mutation at R124, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at L151, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at R152, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at L151, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), isoleucine (I), methionine (M), and valine (V) and a mutation at R152, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at V148, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), and methionine (M).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at V148, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V) and a mutation at R152, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the mutant IFNβ comprises SEQ ID NO: 3 and a mutation at Y155, the mutation being an aliphatic hydrophobic residue selected from glycine (G), alanine (A), leucine (L), isoleucine (I), methionine (M), and valine (V).

In some embodiments, the present invention relates to an Fc-based chimeric protein complex comprising: (a) a modified IFN-β, having the amino acid sequence of SEQ ID NO: 3 and a mutation at position W22, wherein the mutation is an aliphatic hydrophobic residue; and (b) one or more targeting moieties, said targeting moieties comprising recognition domains which specifically bind to antigens or receptors of interest, the modified IFN-β and the one or more targeting moieties are optionally connected with one or more linkers. In various embodiments the mutation at position W22 is aliphatic hydrophobic residue is selected from G, A, L, I, M, and V. In various embodiments, the mutation at position W22 is G.

Additional exemplary IFNβ mutants are provided in PCT/EP2017/061544, the entire disclosure of which is incorporated by reference herein.

In some embodiments, the signaling agent is a wild type or modified interferon γ. In such embodiments, the modified interferon γ agent has reduced affinity and/or activity for the interferon-gamma receptor (IFNGR), *i.e.*, IFNGR1 and IFNGR2 chains. In some embodiments, the modified interferon γ agent has substantially reduced or ablated affinity and/or activity for the interferon-gamma receptor (IFNGR), *i.e.*, IFNGR1 and/or IFNGR2 chains.

For example, the mutant IFN-γ can include a mutation, by way of non-limiting example, a truncation. In embodiments, the mutant IFN-γ has a truncation at the C-terminus, *e.g.* of about 5 to about 20 amino acid residues, or of about 16 amino acid residues, or of about 15 amino acid residues, or of about 14 amino acid residues, or of about 7 amino acid residues, or of about 5 amino acid residues. In embodiments, the mutant IFN-γ has one or more mutations at positions Q1, V5, E9, K12, H19, S20, V22, A23, D24, N25, G26, T27, L30, K108, H111, E112, I114, Q115, A118, E119, and K125. In embodiments, the mutant IFN-γ has one or more mutations are substitutions selected from V5E, S20E, V22A, A23G, A23F, D24G, G26Q, H111A, H111D, I114A, Q115A, and A118G. In embodiments, the mutant IFN-γ comprises the V22A mutation. In embodiments, the mutant IFN-γ comprises the A23G mutation. In embodiments, the mutant IFN-γ comprises the D24G mutation. In embodiments, the mutant IFN-γ comprises the H111A mutation or the H111D mutation. In embodiments, the mutant IFN-γ comprises the

I114A mutation. In embodiments, the mutant IFN-γ comprises the Q115A mutation. In embodiments, the mutant IFN-γ comprises the A118G mutation. In embodiments, the mutant IFN-γ comprises the A23G mutation and the D24G mutation. In embodiments, the mutant IFN-γ comprises the I114A mutation and the A118G mutation. IFN-γ is shown in SEQ ID NO: 1563 below and all mutations are relative to SEQ ID NO: 1563.

In some embodiments, the wild type or modified signaling agent is a consensus interferon. The consensus interferon is generated by scanning the sequences of several human non-allelic IFN-α subtypes and assigning the most frequently observed amino acid in each corresponding position. The consensus interferon differs from IFN-α2b at 20 out of 166 amino acids (88% homology), and comparison with IFN-β shows identity at over 30% of the amino acid positions. In various embodiments, the consensus interferon comprises the following amino acid sequence:

MCDLPQTHSLGNRRALILLAQMRRISPFSCLKDRHDFGFPQEEFDGNQFQKAQAISVLHEMIQQTFNLFSTKDSS AAWDESLLEKFYTELYQQLNDLEACVIQEVGVEETPLMNVDSILAVKKYFQRITLYLTEKKYSPCAWEVVRAEIMR SFSLSTNLQERLRRKE (SEQ ID NO: 4).

In some embodiments, the consensus interferon comprises the amino acid sequence of SEQ ID NO: 5, which differs from the amino acid sequence of SEQ ID NO: 4 by one amino acid, *i.e.*, SEQ ID NO: 5 lacks the initial methionine residue of SEQ ID NO: 4:

CDLPQTHSLGNRRALILLAQMRRISPFSCLKDRHDFGFPQEEFDGNQFQKAQAISVLHEMIQQTFNLFSTKDSSA AWDESLLEKFYTELYQQLNDLEACVIQEVGVEETPLMNVDSILAVKKYFQRITLYLTEKKYSPCAWEVVRAEIMRS FSLSTNLQERLRRKE (SEQ ID NO: 5).

In various embodiments, the consensus interferon comprises a wild type or modified version of the consensus interferon, *i.e.*, a consensus interferon variant, as a signaling agent. In various embodiments, the consensus interferon variant encompasses functional derivatives, analogs, precursors, isoforms, splice variants, or fragments of the consensus interferon.

In an embodiment, the consensus interferon variants are selected form the consensus interferon variants disclosed in U.S. Patent Nos. 4,695,623, 4,897,471, 5,541,293, and 8,496,921, the entire contents of all of which are hereby incorporated by reference. For example, the consensus interferon variant may comprise the amino acid sequence of IFN-CON_2 or IFN-CON_3 as disclosed in U.S. Patent Nos. 4,695,623, 4,897,471, and 5,541,293. In an embodiment, the consensus interferon variant comprises the amino acid sequence of IFN-CON_2:

CDLPQTHSLGNRRTLMLLAQMRRISPFSCLKDRHDFGFPQEEFDGNQFQKAQAISVLHEMIQQTFNLFSTKDSS AAWDESLLEKFYTELYQQLNDLEACVIQEVGVEETPLMNVDSILAVKKYFQRITLYLTEKKYSPCAWEVVRAEIMR SFSLSTNLQERLRRKE (SEQ ID NO: 6).

In an embodiment, the consensus interferon variant comprises the amino acid sequence of IFN-CON_3:

CDLPQTHSLGNRRALILLAQMRRISPFSCLKDRHDFGFPQEEFDGNQFQKAQAISVLHEMIQQTFNLFSTKDSSA AWDESLLEKFYTELYQQLNDLEACVIQEVGVEETPLMNEDSILAVRKYFQRITLYLTEKKYSPCAWEVVRAEIMRS FSLSTNLQERLRRKE (SEQ ID NO: 7).

In an embodiment, the consensus interferon variant comprises the amino acid sequence of any one of the variants disclosed in U.S. Patent No. 8,496,921. For example, the consensus variant may comprise the amino acid sequence of:

MCDLPQTHSLGNRRALILLAQMRRISPFSCLKDRHDFGFPQEEFDGNQFQKAQAISVLHEMIQQTFNLFSTKDSS AAWDESLLEKFYTELYQQLNDLEACVIQEVGVEETPLMNEDSILAVRKYFQRITLYLTEKKYSPCAWEVVRAEIMR SFSLSTNLQERLRRKE (SEQ ID NO: 8).

In another embodiment, the consensus interferon variant may comprise the amino acid sequence of:

MCDLPQTHSLGNRRALILLAQMRRISPFSCLKDRHDFGFPQEEFDGNQFQKAQAISVLHEMIQQTFNLFSTKDSS AAWDESLLEKFYTELYQQLNDLEACVIQEVGVEETPLMNEDSILAVRKYFQRITLYLTEKKYSPCAWEVVRAEIMR SFSLCTNLQERLRRKE (SEQ ID NO: 9).

In some embodiments, the consensus interferon variant may be PEGylated, *i.e.*, comprises a PEG moiety. In an embodiment, the consensus interferon variant may comprise a PEG moiety attached at the S156C position of SEQ ID NO: 9.

In some embodiments, the engineered interferon is a variant of human IFN-α2a, with an insertion of Asp at approximately position 41 in the sequence Glu-Glu-Phe-Gly-Asn-Gln (SEQ ID NO: 10) to yield Glu-Glu-Phe-Asp-Gly-Asn-Gln (SEQ ID NO: 11) (which resulted in a renumbering of the sequence relative to IFN-α2a sequence) and the following mutations of Arg23Lys, Leu26Pro, Glu53Gln, Thr54Ala, Pro56Ser, Asp86Glu, Ile104Thr, Gly106Glu, Thr110Glu, Lys117Asn, Arg125Lys, and Lys136Thr. All embodiments herein that describe consensus interferons apply equally to this engineered interferon

In various embodiments, the consensus interferon variant comprises an amino acid sequence having one or more amino acid mutations. In some embodiments, the one or more amino acid mutations may be independently selected from substitutions, insertions, deletions, and truncations.

In some embodiments, the amino acid mutations are amino acid substitutions, and may include conservative and/or non-conservative substitutions.

In various embodiments, the substitutions may also include non-classical amino acids (*e.g.* selenocysteine, pyrrolysine, *N*-formylmethionine β-alanine, GABA and δ-Aminolevulinic acid, 4-aminobenzoic acid (PABA), D-isomers of the common amino acids, 2,4-diaminobutyric acid, α-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ-Abu, ε-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosme, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β-alanine, fluoro-amino acids, designer amino acids such as β methyl amino acids, C α-methyl amino acids, N α-methyl amino acids, and amino acid analogs in general).

In various embodiments, the consensus interferon is modified to have one or more mutations. In some embodiments, the mutations allow for the consensus interferon variant to have one or more of attenuated activity such as one or more of reduced binding affinity, reduced endogenous activity, and reduced specific bioactivity relative to unmutated, *e.g.,* the wild type form of the consensus interferon (*e.g.*, the consensus interferon having

an amino acid sequence of SEQ ID NO: 4 or 5). For instance, the one or more of attenuated activity such as reduced binding affinity, reduced endogenous activity, and reduced specific bioactivity relative to unmutated, *e.g.* the wild type form of the consensus interferon, may be at a therapeutic receptor such as IFNAR. Consequentially, in various embodiments, the mutations allow for the consensus interferon variant to have reduced systemic toxicity, reduced side effects, and reduced off-target effects relative to unmutated, *e.g.* the wild type form of the consensus interferon.

In various embodiments, the consensus interferon is modified to have a mutation that reduces its binding affinity or activity at a therapeutic receptor such as IFNAR. In some embodiments, the activity provided by the consensus interferon is agonism at the therapeutic receptor (*e.g.* activation of a cellular effect at a site of therapy). For example, the consensus interferon may activate the therapeutic receptor. In such embodiments, the mutation results in the consensus interferon variant to have reduced activating activity at the therapeutic receptor.

In some embodiments, the reduced affinity or activity at the therapeutic receptor is restorable by inclusion in the present complex having one or more of the targeting moieties as described herein. In other embodiments, the reduced affinity or activity at the therapeutic receptor is not substantially restorable by inclusion in the present complex having one or more of the targeting moieties as described herein. In various embodiments, the therapeutic Fc-based chimeric protein complexes of the present invention reduce off-target effects because the consensus interferon variant has mutations that weaken binding affinity or activity at a therapeutic receptor. In various embodiments, this reduces side effects observed with, for example, the wild type consensus interferon. In various embodiments, the consensus interferon variant is substantially inactive *en route* to the site of therapeutic activity and has its effect substantially on specifically targeted cell types which greatly reduces undesired side effects.

In various embodiments, the consensus interferon variant has one or more mutations that cause the consensus interferon variant to have attenuated or reduced affinity, *e.g.* binding (*e.g.* K_D) and/or activation (measurable as, for example, K_A and/or EC_{50}) for one or more therapeutic receptors. In various embodiments, the reduced affinity at the therapeutic receptor allows for attenuation of activity and/or signaling from the therapeutic receptor.

In various embodiments, the consensus interferon variant has one or more mutations that reduce its binding to or its affinity for the IFNAR1 subunit of IFNAR. In one embodiment, the consensus interferon variant has reduced affinity and/or activity at IFNAR1. In some embodiments, the consensus interferon variant has one or more mutations that reduce its binding to or its affinity for the IFNAR2 subunit of IFNAR. In some embodiments, the consensus interferon variant has one or more mutations that reduce its binding to or its affinity for both IFNAR1 and IFNAR2 subunits.

In some embodiments, the consensus interferon variant has one or more mutations that reduce its binding to or its affinity for IFNAR1 and one or more mutations that substantially reduce or ablate binding to or its affinity for IFNAR2. In some embodiments, Fc-based chimeric protein complexes with such consensus interferon variant can provide target-selective IFNAR1 activity (*e.g.* IFNAR1 activity is restorable via targeting through the targeting moiety, *e.g.*, SIRPα).

In some embodiments, the consensus interferon variant has one or more mutations that reduce its binding to or its affinity for IFNAR2 and one or more mutations that substantially reduce or ablate binding to or its affinity for IFNAR1. In some embodiments, Fc-based chimeric protein complexes with such consensus interferon variant can provide target-selective IFNAR2 activity (*e.g.* IFNAR2 activity is restorable via targeting through the targeting moiety, *e.g.*, SIRPα).

In some embodiments, the consensus interferon variant has one or more mutations that reduce its binding to or its affinity for IFNAR1 and one or more mutations that reduce its binding to or its affinity for IFNAR2. In some embodiments, Fc-based chimeric protein complexes with such consensus interferon variant can provide target-selective IFNAR1 and/or IFNAR2 activity (*e.g.* IFNAR1 and/IFNAR2 activity is restorable via targeting through the targeting moiety, *e.g.*, SIRPα).

In some embodiments, the consensus interferon is modified to have a mutation at one or more amino acids at positions 145-155, such as amino acid positions 149, 150 and/or 154, with reference to SEQ ID NO:5. In some embodiments, the consensus interferon is modified to have a mutation at one or more amino acids at positions 145-155, such as amino acid positions 149, 150 and/or 154, with reference to SEQ ID NO: 5, the substitutions optionally being hydrophobic and selected from alanine, valine, leucine, and isoleucine. In some embodiments, the consensus interferon mutant comprises one or more mutations selected from M149A, R150A, and L154A, and, with reference to SEQ ID NO: 5.

In an embodiment, the consensus interferon is modified to have a mutation at amino acid position 121 (*i.e.,* K121), with reference to SEQ ID NO: 5. In an embodiment, the consensus interferon comprises a K121E mutation, with reference to SEQ ID NO: 5.

In various embodiments, the wild type or modified signaling agent is selected from a wild type or modified versions of cytokines, growth factors, and hormones. Illustrative examples of such cytokines, growth factors, and hormones include, but are not limited to, lymphokines, monokines, traditional polypeptide hormones, such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor-α and tumor necrosis factor-β; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF-α; platelet-growth factor; transforming growth factors (TGFs) such as TGF-α and TGF-β; insulin-like growth factor-I and –II ; osteo inductive factors; interferons such as, for example, interferon-α, interferon-β and interferon-γ (and interferon type I, II, and III), colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as, for example, IL-1β, IL-1α, 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-15, and IL-18; a tumor necrosis factor such as, for example, TNF-α or TNF-β; and other polypeptide factors including, for example, LIF and kit ligand (KL). As used herein, cytokines, growth factors, and hormones

include proteins obtained from natural sources or produced from recombinant bacterial, eukaryotic or mammalian cell culture systems and biologically active equivalents of the native sequence cytokines.

In some embodiments, the signaling agent is a wild type or modified version of a growth factor selected from, but not limited to, transforming growth factors (TGFs) such as TGF-α and TGF-β (and subtypes thereof including the various subtypes of TGF-β including TGFβ1, TGFβ2, and TGFβ3), epidermal growth factor (EGF), insulin-like growth factor such as insulin-like growth factor-I and -II, fibroblast growth factor (FGF), heregulin, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF).

In an embodiment, the growth factor is a modified version of a fibroblast growth factor (FGF). Illustrative FGFs include, but are not limited to, FGF1, FGF2, FGF3, FGF4, FGF5, FGF6, FGF7, FGF8, FGF9, FGF10, FGF11, FGF12, FGF13, FGF14, murine FGF15, FGF16, FGF17, FGF18, FGF19, FGF20, FGF21, FGF22, and FGF23.

In some embodiments, the wild type or modified signaling agent is vascular endothelial growth factor (VEGF). VEGF is a potent growth factor that plays major roles in physiological but also pathological angiogenesis, regulates vascular permeability and can act as a growth factor on cells expressing VEGF receptors. Additional functions include, among others, stimulation of cell migration in macrophage lineage and endothelial cells. Several members of the VEGF family of growth factors exist, as well as at least three receptors (VEGFR-1, VEGFR -2, and VEGFR -3). Members of the VEGF family can bind and activate more than one VEGFR type. For example, VEGF-A binds VEGFR-1 and -2, while VEGF-C can bind VEGFR-2 and -3. VEGFR-1 and -2 activation regulates angiogenesis while VEGFR-3 activation is associated with lymphangiogenesis. The major pro-angiogenic signal is generated from activation of VEGFR-2. VEGFR-1 activation has been reported to be possibly associated with negative role in angiogenesis. It has also been reported that VEGFR-1 signaling is important for progression of tumors *in vivo* via bone marrow-derived VEGFR-1 positive cells (contributing to formation of premetastatic niche in the bone). Several therapies based on VEGF-A directed/neutralizing therapeutic antibodies have been developed, primarily for use in treatment of various human tumors relying on angiogenesis. These are not without side effects though. This may not be surprising considering that these operate as general, non-cell/tissue specific VEGF/VEGFR interaction inhibitors. Hence, it would be desirable to restrict VEGF (*e.g.* VEGF-A)/VEGFR-2 inhibition to specific target cells (*e.g.* tumor vasculature endothelial cells).

In some embodiments, the VEGF is VEGF-A, VEGF-B, VEFG-C, VEGF-D, or VEGF-E and isoforms thereof including the various isoforms of VEGF-A such as $VEGF_{121}$, $VEGF_{121}$b, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{165}$b, $VEGF_{189}$, and $VEGF_{206}$. In some embodiments, the modified signaling agent has reduced affinity and/or activity for VEGFR-1 (Flt-1) and/or VEGFR-2 (KDR/Flk-1). In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for VEGFR-1 (Flt-1) and/or VEGFR-2 (KDR/Flk-1). In an embodiment, the modified signaling agent has reduced affinity and/or activity for VEGFR-2 (KDR/Flk-1) and/or substantially reduced or ablated affinity and/or activity for VEGFR-1 (Flt-1). Such an embodiment finds use, for example, in wound healing methods or treatment of ischemia-related diseases (without wishing to be bound by theory, mediated by VEGFR-2's effects on endothelial cell function and angiogenesis). In various embodiments, binding to VEGFR-1 (Flt-1), which is linked to cancers and pro-inflammatory activities, is avoided. In various embodiments,

VEGFR-1 (Flt-1) acts a decoy receptor and therefore substantially reduces or ablates affinity at this receptor avoids sequestration of the therapeutic agent. In an embodiment, the modified signaling agent has substantially reduced or ablated affinity and/or activity for VEGFR-1 (Flt-1) and/or substantially reduced or ablated affinity and/or activity for VEGFR-2 (KDR/Flk-1). In some embodiments, the VEGF is VEGF-C or VEGF-D. In such embodiments, the modified signaling agent has reduced affinity and/or activity for VEGFR-3. Alternatively, the modified signaling agent has substantially reduced or ablated affinity and/or activity for VEGFR-3.

Proangiogenic therapies are also important in various diseases (*e.g.* ischemic heart disease, bleeding *etc.*), and include VEGF-based therapeutics. Activation of VEGFR-2 is proangiogenic (acting on endothelial cells). Activation of VEFGR-1 can cause stimulation of migration of inflammatory cells (including, for example, macrophages) and lead to inflammation associated hypervascular permeability. Activation of VEFGR-1 can also promote bone marrow associated tumor niche formation. Thus, VEGF based therapeutic selective for VEGFR-2 activation would be desirable in this case. In addition, cell specific targeting, *e.g.* to endothelial cells, would be desirable.

In some embodiments, the modified signaling agent has reduced affinity and/or activity (*e.g.* antagonistic) for VEGFR-2 and/or has substantially reduced or ablated affinity and/or activity for VEGFR-1. When targeted to tumor vasculature endothelial cells via a targeting moiety that binds to a tumor endothelial cell marker (*e.g.* PSMA and others), such construct inhibits VEGFR-2 activation specifically on such marker-positive cells, while not activating VEGFR-1 *en route* and on target cells (if activity ablated), thus eliminating induction of inflammatory responses, for example. This would provide a more selective and safe anti-angiogenic therapy for many tumor types as compared to VEGF-A neutralizing therapies.

In some embodiments, the modified signaling agent has reduced affinity and/or activity (*e.g.* agonistic) for VEGFR-2 and/or has substantially reduced or ablated affinity and/or activity for VEGFR-1. Through targeting to vascular endothelial cells, such construct, in some embodiments, promotes angiogenesis without causing VEGFR-1 associated induction of inflammatory responses. Hence, such a construct would have targeted proangiogenic effects with substantially reduced risk of side effects caused by systemic activation of VEGFR-2 as well as VEGR-1.

In an illustrative embodiment, the modified signaling agent is a modified $VEGF_{165}$, the wild type amino acid sequence of $VEGF_{165}$ is:

APMAEGGGQNHHEVVKFMDVYQRSYCHPIETLVDIFQEYPDEIEYIFKPSCVPLMRCGGCCNDEGLECVPTEES
NITMQIMRIKPHQGQHIGEMSFLQHNKCECRPKKDRARQENPCGPCSERRKHLFVQDPQTCKCSCKNTDSRCK
ARQLELNERTCRCDKPRR (SEQ ID NO: 12).

In another illustrative embodiment, the modified signaling agent is a modified $VEGF_{165b}$, the wild type amino acid sequence of $VEGF_{165b}$ is:

APMAEGGGQNHHEVVKFMDVYQRSYCHPIETLVDIFQEYPDEIEYIFKPSCVPLMRCGGCCNDEGLECVPTEES
NITMQIMRIKPHQGQHIGEMSFLQHNKCECRPKKDRARQENPCGPCSERRKHLFVQDPQTCKCSCKNTDSRCK
ARQLELNERTCRSLTRKD (SEQ ID NO: 13).

In these embodiments, the modified signaling agent has a mutation at amino acid I83 (*e.g.*, a substitution mutation at I83, *e.g.*, I83K, I83R, or I83H). Without wishing to be bound by theory, it is believed that such mutations may result in reduced receptor binding affinity. See, for example, U.S. Patent No. 9,078,860, the entire contents of which are hereby incorporated by reference.

In some embodiments, the signaling agent is a wild type or modified version of a hormone selected from, but not limited to, human chorionic gonadotropin, gonadotropin releasing hormone, an androgen, an estrogen, thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, prolactin, growth hormone, adrenocorticotropic hormone, antidiuretic hormone, oxytocin, thyrotropin-releasing hormone, growth hormone releasing hormone, corticotropin-releasing hormone, somatostatin, dopamine, melatonin, thyroxine, calcitonin, parathyroid hormone, glucocorticoids, mineralocorticoids, adrenaline, noradrenaline, progesterone, insulin, glucagon, amylin, calcitriol, calciferol, atrial-natriuretic peptide, gastrin, secretin, cholecystokinin, neuropeptide Y, ghrelin, PYY3-36, insulin-like growth factor (IGF), leptin, thrombopoietin, erythropoietin (EPO), and angiotensinogen.

In some embodiments, the wild type or modified signaling agent is TNF-α. TNF is a pleiotropic cytokine with many diverse functions, including regulation of cell growth, differentiation, apoptosis, tumorigenesis, viral replication, autoimmunity, immune cell functions and trafficking, inflammation, and septic shock. It binds to two distinct membrane receptors on target cells: TNFR1 (p55) and TNFR2 (p75). TNFR1 exhibits a very broad expression pattern whereas TNFR2 is expressed preferentially on certain populations of lymphocytes, Tregs, endothelial cells, certain neurons, microglia, cardiac myocytes and mesenchymal stem cells. Very distinct biological pathways are activated in response to receptor activation, although there is also some overlap. As a general rule, without wishing to be bound by theory, TNFR1 signaling is associated with induction of apoptosis (cell death) and TNFR2 signaling is associated with activation of cell survival signals (*e.g.* activation of NFkB pathway). Administration of TNF is systemically toxic, and this is largely due to TNFR1 engagement. However, it should be noted that activation of TNFR2 is also associated with a broad range of activities and, as with TNFR1, in the context of developing TNF based therapeutics, control over TNF targeting and activity is important.

In some embodiments, the modified signaling agent has reduced affinity and/or activity for TNFR1 and/or TNFR2. In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for TNFR1 and/or TNFR2. TNFR1 is expressed in most tissues, and is involved in cell death signaling while, by contrast, TNFR2 is involved in cell survival signaling. Accordingly, in embodiments directed to methods of treating cancer, the modified signaling agent has reduced affinity and/or activity for TNFR1 and/or substantially reduced or ablated affinity and/or activity for TNFR2. In these embodiments, the Fc-based chimeric protein complexes may be targeted to a cell for which apoptosis is desired, *e.g.* a tumor cell or a tumor vasculature endothelial cell. In embodiments directed to methods of promoting cell survival, for example, in neurogenesis for the treatment of neurodegenerative disorders, the modified signaling agent has reduced affinity and/or activity for TNFR2 and/or substantially reduced or ablated affinity and/or activity for TNFR1. Stated another way, the present Fc-based

chimeric protein complexes, in some embodiments, comprise modified TNF-α agent that allows of favoring either death or survival signals.

In some embodiments, the Fc-based chimeric protein complex has a modified TNF having reduced affinity and/or activity for TNFR1 and/or substantially reduced or ablated affinity and/or activity for TNFR2. Such an Fc-based chimeric protein complex, in some embodiments, is a more potent inducer of apoptosis as compared to a wild type TNF and/or an Fc-based chimeric protein complex bearing only mutation(s) causing reduced affinity and/or activity for TNFR1. Such an Fc-based chimeric protein complex, in some embodiments, finds use in inducing tumor cell death or a tumor vasculature endothelial cell death (*e.g.* in the treatment of cancers). Also, in some embodiments, these Fc-based chimeric protein complexes avoid or reduce activation of T_{reg} cells via TNFR2, for example, thus further supporting TNFR1-mediated antitumor activity *in vivo*.

In some embodiments, the Fc-based chimeric protein complex has a modified TNF having reduced affinity and/or activity for TNFR2 and/or substantially reduced or ablated affinity and/or activity for TNFR1. Such an Fc-based chimeric protein complex, in some embodiments, is a more potent activator of cell survival in some cell types, which may be a specific therapeutic objective in various disease settings, including without limitation, stimulation of neurogenesis. In addition, such a TNFR2-favoring Fc-based chimeric protein complexes also are useful in the treatment of autoimmune diseases (*e.g.* Crohn's, diabetes, MS, colitis *etc.* and many others described herein). In some embodiments, the Fc-based chimeric protein complex is targeted to auto-reactive T cells. In some embodiments, the Fc-based chimeric protein complex promotes T_{reg} cell activation and indirect suppression of cytotoxic T cells.

In some embodiments, the Fc-based chimeric protein complex causes the death of auto-reactive T cells, *e.g.* by activation of TNFR2 and/or avoidance TNFR1 (*e.g.* a modified TNF having reduced affinity and/or activity for TNFR2 and/or substantially reduced or ablated affinity and/or activity for TNFR1). Without wishing to be bound by theory these auto-reactive T cells, have their apoptosis/survival signals altered *e.g.* by NFkB pathway activity/signaling alterations. In some embodiments, the Fc-based chimeric protein complex causes the death of autoreactive T cells having lesions or modifications in the NFκB pathway, which underlie an imbalance of their cell death (apoptosis)/survival signaling properties and, optionally, altered susceptibility to certain death-inducing signals (*e.g.*, TNFR2 activation).

In some embodiments, a TNFR-2 based Fc-based chimeric protein complex has additional therapeutic applications in diseases, including autoimmune disease, various heart disease, de-myelinating and neurodegenerative disorders, and infectious disease, among others.

In an embodiment, the wild type TNF-α has the amino acid sequence of:

VRSSSRTPSDKPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYSQVLFKGQGCPSTH VLLTHTISRIAVSYQTKVNLLSAIKSPCQRETPEGAEAKPWYEPIYLGGVFQLEKGDRLSAEINRPDYLDFAESGQ VYFGIIAL (SEQ ID NO: 14).

In such embodiments, the modified TNF-α agent has mutations at one or more amino acid positions 29, 31, 32, 84, 85, 86, 87, 88, 89, 145, 146 and 147 which produces a modified TNF-α with reduced receptor binding affinity. *See*, for example, U.S. Patent No. 7,993,636, the entire contents of which are hereby incorporated by reference.

In some embodiments, the modified human TNF-α moiety has mutations at one or more amino acid positions R32, N34, Q67, H73, L75, T77, S86, Y87, V91, I97, T105, P106, A109, P113, Y115, E127, N137, D143, A145, and E146 as described, for example, in WO/2015/007903, the entire contents of which is hereby incorporated by reference (numbering according to the human TNF sequence, Genbank accession number BAG70306, version BAG70306.1 GI: 197692685). In some embodiments, the modified human TNF-α moiety has substitution mutations selected from L29S, R32G, R32W, N34G, Q67G, H73G, L75G, L75A, L75S, T77A, S86G, S86T, Y87Q, Y87L, Y87A, Y87F, Y87H, V91G, V91A, I97A, I97Q, I97S, T105G, P106G, A109Y, P113G, Y115G, Y115A, E127G, N137G, D143N, A145G, A145R, A145T, E146D, E146K, and S147D. In some embodiments, the human TNF-α moiety has a mutation selected from Y87Q, Y87L, Y87A, Y87F, and Y87H. In another embodiment, the human TNF-α moiety has a mutation selected from I97A, I97Q, and I97S. In a further embodiment, the human TNF-α moiety has a mutation selected from Y115A and Y115G. In some embodiments, the human TNF-α moiety has an E146K mutation. In some embodiments, the human TNF-α moiety has an Y87H and an E146K mutation. In some embodiments, the human TNF-α moiety has an Y87H and an A145R mutation. In some embodiments, the human TNF-α moiety has a R32W and a S86T mutation. In some embodiments, the human TNF-α moiety has a R32W and an E146K mutation. In some embodiments, the human TNF-α moiety has a L29S and a R32W mutation. In some embodiments, the human TNF-α moiety has a D143N and an A145R mutation. In some embodiments, the human TNF-α moiety has a D143N and an A145R mutation. In some embodiments, the human TNF-α moiety has an A145T, an E146D, and a S147D mutation. In some embodiments, the human TNF-α moiety has an A145T and a S147D mutation.

In some embodiments, the modified TNF-α agent has one or more mutations selected from N39Y, S147Y, and Y87H, as described in WO2008/124086, the entire contents of which is hereby incorporated by reference.

In some embodiments, the modified human TNF-α moiety has mutations that provide receptor selectivity as described in PCT/IB2016/001668, the entire contents of which are hereby incorporated by reference. In some embodiments, the mutations to TNF are TNF-R1 selective. In some embodiments, the mutations to TNF which are TNF-R1 selective are at one or more of positions R32, S86, and E146. In some embodiments, the mutations to TNF which are TNF-R1 selective are one or more of R32W, S86T, and E146K. In some embodiments, the mutations to TNF which are TNF-R1 selective are one or more of R32W, R32W/S86T, R32W/E146K and E146K. In some embodiments, the mutations to TNF are TNF-R2 selective. In some embodiments, the mutations to TNF which are TNF-R2 selective are at one or more of positions A145, E146, and S147. In some embodiments, the mutations to TNF which are TNF-R2 selective are one or more of A145T, A145R, E146D, and S147D. In some embodiments, the mutations to TNF which are TNF-R2 selective are one or more of A145R, A145T/S147D, and A145T/E146D/S147D.

In an embodiment, the wild type or modified signaling agent is TNF-β. TNF-β can form a homotrimer or a heterotrimer with LT-β (LT-α1β2). In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for TNFR1 and/or TNFR2 and/or herpes virus entry mediator (HEVM) and/or LT-βR.

In an embodiment, the wild type TNF-β has the amino acid sequence of:

LPGVGLTPSAAQTARQHPKMHLAHSNLKPAAHLIGDPSKQNSLLWRANTDRAFLQDGFSLSNNSLLVPTSGIYFV YSQVVFSGKAYSPKATSSPLYLAHEVQLFSSQYPFHVPLLSSQKMVYPGLQEPWLHSMYHGAAFQLTQGDQLS THTDGIPHLVLSPSTVFFGAFAL (SEQ ID NO: 15).

In such embodiments, the modified TNF-β agent may comprise mutations at one or more amino acids at positions 106-113, which produce a modified TNF-β with reduced receptor binding affinity to TNFR2. In an embodiment, the modified signaling agent has one or more substitution mutations at amino acid positions 106-113. In illustrative embodiments, the substitution mutations are selected from Q107E, Q107D, S106E, S106D, Q107R, Q107N, Q107E/S106E, Q107E/S106D, Q107D/S106E, and Q107D/S106D. In another embodiment, the modified signaling agent has an insertion of about 1 to about 3 amino acids at positions 106-113.

In some embodiments, the wild type or modified agent is a TNF family member (*e.g.* TNF-alpha, TNF-beta) which can be a single chain trimeric version as described in WO 2015/007903 and PCT/IB2016/001668, the entire contents of which are incorporated by reference.

In some embodiments, the modified agent is a TNF family member (*e.g.* TNF-alpha, TNF-beta) which has reduced affinity and/or activity, *i.e.* antagonistic activity (*e.g.* natural antagonistic activity or antagonistic activity that is the result of one or more mutations, *see, e.g.,* WO 2015/007520, the entire contents of which are hereby incorporated by reference) at TNFR1. In these embodiments, the modified agent is a TNF family member (*e.g.* TNF-alpha, TNF-beta) which also, optionally, has substantially reduced or ablated affinity and/or activity for TNFR2. In some embodiments, the modified agent is a TNF family member (*e.g.* TNF-alpha, TNF-beta) which has reduced affinity and/or activity, *i.e.* antagonistic activity (*e.g.* natural antagonistic activity or antagonistic activity that is the result of one or more mutations, *see, e.g.,* WO 2015/007520, the entire contents of which are hereby incorporated by reference) at TNFR2. In these embodiments, the modified agent is a TNF family member (*e.g.* TNF-alpha, TNF-beta) which also, optionally, has substantially reduced or ablated affinity and/or activity for TNFR1. The constructs of such embodiments find use in, for example, methods of dampening TNF response in a cell specific manner. In some embodiments, the antagonistic TNF family member (*e.g.* TNF-alpha, TNF-beta) is a single chain trimeric version as described in WO 2015/007903.

In an embodiment, the wild type or modified signaling agent is TRAIL. In some embodiments, the modified TRAIL agent has reduced affinity and/or activity for DR4 (TRAIL-RI) and/or DR5 (TRAIL-RII) and/or DcR1 and/or DcR2. In some embodiments, the modified TRAIL agent has substantially reduced or ablated affinity and/or activity for DR4 (TRAIL-RI) and/or DR5 (TRAIL-RII) and/or DcR1 and/or DcR2.

In an embodiment, the wild type TRAIL has the amino acid sequence of:

MAMMEVQGGPSLGQTCVLIVIFTVLLQSLCVAVTYVYFTNELKQMQDKYSKSGIACFLKEDDSYWDPNDEESMN SPCWQVKWQLRQLVRKMILRTSEETISTVQEKQQNISPLVRERGPQRVAAHITGTRGRSNTLSSPNSKNEKALG RKINSWESSRSGHSFLSNLHLRNGELVIHEKGFYYIYSQTYFRFQEEIKENTKNDKQMVQYIYKYTSYPDPILLMK SARNSCWSKDAEYGLYSIYQGGIFELKENDRIFVSVTNEHLIDMDHEASFFGAFLVG (SEQ ID NO: 16).

In such embodiments, the modified TRAIL agent may comprise a mutation at amino acid positions T127-R132, E144-R149, E155-H161, Y189-Y209, T214-1220, K224-A226, W231, E236-L239, E249-K251, T261-H264 and H270-E271 (Numbering based on the human sequence, Genbank accession number NP _003801, version 10 NP _003801.1, GI: 4507593; see above).

such embodiments, the modified TRAIL agent may comprise a truncation, *e.g.,* without limitation, as described in, for example, Trebing *et al.*, (2014) Cell Death and Disease, 5:e1035, the entire disclosure of which is hereby incorporated by reference

In some embodiments, the modified TRAIL agent may comprise one or more mutations that sustantially reduce its affinity and/or activity for TRAIL-R1. In such embodiments, the modified TRAIL agent may specifically bind to TRIL-R2. Exemplary mutations include mutations at one or more amino acid positions Y189, R191, Q193, H264, I266, and D267. For example, the mutations may be one or more of Y189Q, R191K, Q193R, H264R, I266L and D267Q. In an embodiment, the modified TRAIL agent comprises the mutations Y189Q, R191K, Q193R, H264R, I266L and D267Q.

In some embodiments, the modified TRAIL agent may comprise one or more mutations that substantially reduce its affinity and/or activity for TRAIL-R2. In such embodiments, the modified TRAIL agent may specifically bind to TRIL-R1. Exemplary mutations include mutations at one or more amino acid positions G131, R149, S159, N199, K201, and S215. For example, the mutations may be one or more of G131R, R149I, S159R, N199R, K201H, and S215D. In an embodiment, the modified TRAIL agent comprises the mutations G131R, R149I, S159R, N199R, K201H, and S215D. Additional TRAIL mutations are described in, for example, Trebing *et al.*, (2014) Cell Death and Disease, 5:e1035, the entire disclosure of which is hereby incorporated by reference.

In an embodiment, the wild type or modified signaling agent is TGFα. In such embodiments, the modified TGFα agent has reduced affinity and/or activity for the epidermal growth factor receptor (EGFR). In some embodiments, the modified TGFα agent has substantially reduced or ablated affinity and/or activity for the epidermal growth factor receptor (EGFR).

In an embodiment, the wild type or modified signaling agent is TGFβ. In such embodiments, the modified signaling agent has reduced affinity and/or activity for TGFBR1 and/or TGFBR2. In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for TGFBR1 and/or TGFBR2. In some embodiments, the modified signaling agent optionally has reduced or substantially reduced or ablated affinity and/or activity for TGFBR3 which, without wishing to be bound by theory, may act as a reservoir of ligand for TGF-beta receptors. In some embodiments, the TGFβ may favor TGFBR1 over TGFBR2 or TGFBR2 over TGFBR1. Similarly, LAP, without wishing to be bound by theory, may act as a reservoir of ligand for TGF-beta receptors. In some embodiments, the modified signaling agent has reduced affinity and/or activity for TGFBR1 and/or TGFBR2

and/or substantially reduced or ablated affinity and/or activity for Latency Associated Peptide (LAP). In some embodiments, such Fc-based chimeric protein complexes find use in Camurati-Engelmann disease, or other diseases associated with inappropriate TGFβ signaling.

In some embodiments, the wild type or modified agent is a TGF family member (*e.g.* TGFα, TGFβ) which has reduced affinity and/or activity, *i.e.* antagonistic activity (*e.g.* natural antagonistic activity or antagonistic activity that is the result of one or more mutations, *see, e.g.,* WO 2015/007520, the entire contents of which are hereby incorporated by reference) at one or more of TGFBR1, TGFBR2, TGFBR3. In these embodiments, the modified agent is a TGF family member (*e.g.* TGFα, TGFβ) which also, optionally, has substantially reduced or ablated affinity and/or activity at one or more of TGFBR1, TGFBR2, and TGFBR3.

In some embodiments, the modified agent is a TGF family member (*e.g.* TGFα, TGFβ) which has reduced affinity and/or activity, *i.e.* antagonistic activity (*e.g.* natural antagonistic activity or antagonistic activity that is the result of one or more mutations, *see, e.g.,* WO 2015/007520, the entire contents of which are hereby incorporated by reference) at TGFBR1 and/or TGFBR2. In these embodiments, the modified agent is a TGF family member (*e.g.* TGFα, TGFβ) which also, optionally, has substantially reduced or ablated affinity and/or activity at TGFBR3.

In an embodiment, the wild type or modified signaling agent is an interleukin. In an embodiment, the modified signaling agent is IL-1. In an embodiment, the modified signaling agent is IL-1α or IL-1β. In some embodiments, the modified signaling agent has reduced affinity and/or activity for IL-1R1 and/or IL-1RAcP. In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for IL-1R1 and/or IL-1RAcP. In some embodiments, the modified signaling agent has reduced affinity and/or activity for IL-1R2. In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for IL-1R2. For instance, in some embodiments, the present modified IL-1 agents avoid interaction at IL-1R2 and therefore substantially reduce its function as a decoy and/or sink for therapeutic agents.

In an embodiment, the wild type IL-1β has the amino acid sequence of:

APVRSLNCTLRDSQQKSLVMSGPYELKALHLQGQDMEQQVVFSMSFVQGEESNDKIPVALGLKEKNLYLSCVLK DDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINNKLEFESAQFPNWYISTSQAENMPVFLGGTKGGQDITDFTMQ FVSS (SEQ ID NO: 17).

IL-1β is a proinflammatory cytokine and an important immune system regulator. It is a potent activator of CD4 T cell responses, increases proportion of Th17 cells and expansion of IFNγ and IL-4 producing cells. IL-1β is also a potent regulator of $CD8^+$ T cells, enhancing antigen-specific $CD8^+$ T cell expansion, differentiation, migration to periphery and memory. IL-1β receptors comprise IL-1R1 and IL-1R2. Binding to and signaling through the IL-1R1 constitutes the mechanism whereby IL-1β mediates many of its biological (and pathological) activities. IL1-R2 can function as a decoy receptor, thereby reducing IL-1β availability for interaction and signaling through the IL-1R1.

In some embodiments, the modified IL-1β has reduced affinity and/or activity (*e.g.* agonistic activity) for IL-1R1. In some embodiments, the modified IL-1β has substantially reduced or ablated affinity and/or activity for IL-1R2. In such embodiments, there is restorable IL-1β / IL-1R1 signaling and prevention of loss of therapeutic Fc-based chimeric protein complexes at IL-R2 and therefore a reduction in dose of IL-1β that is required (*e.g.* relative to wild

type or an Fc-based chimeric protein complex bearing only an attenuation mutation for IL-R1). Such constructs find use in, for example, methods of treating cancer, including, for example, stimulating the immune system to mount an anti-cancer response.

In some embodiments, the modified IL-1β has reduced affinity and/or activity (*e.g.* antagonistic activity, *e.g.* natural antagonistic activity or antagonistic activity that is the result of one or more mutations, *see, e.g.,* WO 2015/007520, the entire contents of which are hereby incorporated by reference) for IL-1R1. In some embodiments, the modified IL-1β has substantially reduced or ablated affinity and/or activity for IL-1R2. In such embodiments, there is the IL-1β / IL-1R1 signaling is not restorable and prevention of loss of therapeutic Fc-based chimeric protein complexes at IL-R2 and therefore a reduction in dose of IL-1β that is required (*e.g.* relative to wild type or an Fc-based chimeric protein complex bearing only an attenuation mutation for IL-R1). Such constructs find use in, for example, methods of treating autoimmune diseases, including, for example, suppressing the immune system.

In such embodiments, the modified signaling agent has a deletion of amino acids 52-54 which produces a modified human IL-1β with reduced binding affinity for type I IL-1R and reduced biological activity. See, for example, WO 1994/000491, the entire contents of which are hereby incorporated by reference. In some embodiments, the modified human IL-1β has one or more substitution mutations selected from A117G/P118G, R120X, L122A, T125G/L126G, R127G, Q130X, Q131G, K132A, S137G/Q138Y, L145G, H146X, L145A/L147A, Q148X, Q148G/Q150G, Q150G/D151A, M152G, F162A, F162A/Q164E, F166A, Q164E/E167K, N169G/D170G, I172A, V174A, K208E, K209X, K209A/K210A, K219X, E221X, E221 S/N224A, N224S/K225S, E244K, N245Q (where X can be any change in amino acid, *e.g.*, a non-conservative change), which exhibit reduced binding to IL-1R, as described, for example, in WO2015/007542 and WO/2015/007536, the entire contents of which is hereby incorporated by reference (numbering base on the human IL-1 β sequence, Genbank accession number NP_000567, version NP-000567.1 , GI: 10835145). In some embodiments, the modified human IL-1β may have one or more mutations selected from R120A, R120G, Q130A, Q130W, H146A, H146G, H146E, H146N, H146R, Q148E, Q148G, Q148L, K209A, K209D, K219S, K219Q, E221S and E221K. In an embodiment, the modified human IL-1β comprises the mutations Q131G and Q148G. In an embodiment, the modified human IL-1β comprises the mutations Q148G and K208E. In an embodiment, the modified human IL-1β comprises the mutations R120G and Q131G. In an embodiment, the modified human IL-1β comprises the mutations R120G and H146A. In an embodiment, the modified human IL-1β comprises the mutations R120G and H146N. In an embodiment, the modified human IL-1β comprises the mutations R120G and H146R. In an embodiment, the modified human IL-1β comprises the mutations R120G and H146E. In an embodiment, the modified human IL-1β comprises the mutations R120G and H146G. In an embodiment, the modified human IL-1β comprises the mutations R120G and K208E. In an embodiment, the modified human IL-1β comprises the mutations R120G, F162A, and Q164E.

In an embodiment, the wild type or modified signaling agent is IL-2. In such an embodiment, the modified signaling agent has reduced affinity and/or activity for IL-2Rα and/or IL-2Rβ and/or IL-2Rγ. In some embodiments, the modified signaling agent has reduced affinity and/or activity for IL-2Rβ and/or IL-2Rγ. In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for IL-2Rα. Such embodiments

may be relevant for treatment of cancer, for instance when the modified IL-2 is agonistic at IL-2Rβ and/or IL-2Rγ. For instance, the present constructs may favor attenuated activation of $CD8^+$ T cells (which can provide an anti-tumor effect), which have IL2 receptors β and γ and disfavor T_{regs} (which can provide an immune suppressive, pro-tumor effect), which have IL2 receptors α, β, and γ. Further, in some embodiments, the preferences for IL-2Rβ and/or IL-2Rγ over IL-2Rα avoid IL-2 side effects such as pulmonary edema. Also, IL-2-based Fc-based chimeric protein complexes are useful for the treatment of diseases (*e.g.*, autoimmune disease), for instance when the modified IL-2 is antagonistic (*e.g.* natural antagonistic activity or antagonistic activity that is the result of one or more mutations, *see, e.g.,* WO 2015/007520, the entire contents of which are hereby incorporated by reference) at IL-2Rβ and/or IL-2Rγ. For instance, the present constructs may favor attenuated suppression of $CD8^+$ T cells (and therefore dampen the immune response), which have IL2 receptors β and γ and disfavor T_{regs} which have IL2 receptors α, β, and γ. Alternatively, in some embodiments, the Fc-based chimeric protein complexes bearing IL-2 favor the activation of T_{regs}, and therefore immune suppression, and activation of disfavor of $CD8^+$ T cells. For instance, these constructs find use in the treatment of diseases or diseases that would benefit from immune suppression, *e.g.*, autoimmune disorders.

In some embodiments, the Fc-based chimeric protein complex has targeting moieties as described herein directed to $CD8^+$ T cells as well as a modified IL-2 agent having reduced affinity and/or activity for IL-2Rβ and/or IL-2Rγ and/or substantially reduced or ablated affinity and/or activity for IL-2Rα. In some embodiments, these constructs provide targeted $CD8^+$ T cell activity and are generally inactive (or have substantially reduced activity) towards T_{reg} cells. In some embodiments, such constructs have enhanced immune stimulatory effect compared to wild type IL-2 (*e.g.*, without wishing to be bound by theory, by not stimulating Tregs), whilst eliminating or reducing the systemic toxicity associated with IL-2.

In an embodiment, the wild type IL-2 has the amino acid sequence of:

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSK NFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT (SEQ ID NO: 18).

In such embodiments, the modified IL-2 agent has one or more mutations at amino acids L72 (L72G, L72A, L72S, L72T, L72Q, L72E, L72N, L72D, L72R, or L72K), F42 (F42A, F42G, F42S, F42T, F42Q, F42E, F42N, F42D, F42R, or F42K) and Y45 (Y45A, Y45G, Y45S, Y45T, Y45Q, Y45E, Y45N, Y45D, Y45R or Y45K). Without wishing to be bound by theory, it is believed that these modified IL-2 agents have reduced affinity for the high-affinity IL-2 receptor and preserves affinity to the intermediate-affinity IL-2 receptor, as compared to the wild-type IL-2. See, for example, US Patent Publication No. 2012/0244112, the entire contents of which are hereby incorporated by reference.

In some embodiments, the modified IL-2 agent has one or more mutations at amino acids R38, F42, Y45, and E62. For example, the modified IL-2 agent may comprise one or more of R38A, F42A, Y45A, and E62A. In some embodiments, the modified IL-2 agent may comprise a mutation at C125. For example, the mutation may be C125S. In such embodiments, the modified IL-2 agent may have substantially reduced affinity and/or activity for IL-2Rα, as described in, for example, Carmenate *et al.* (2013) The Journal of Immunology, 190:6230-6238, the entire disclosure of which is hereby incorporated by reference. In some embodiments, the modified IL-2 agent with

mutations at R38, F42, Y45, and/or E62 is able to induce an expansion of effector cells including CD8+ T cells and NK cells but not Treg cells. In some embodiments, the modified IL-2 agent with mutations at R38, F42, Y45, and/or E62 is less toxic than wildtype IL-2 agents. An Fc-based chimeric protein complex comprising the modified IL-2 agent with substantially reduced affnity and/or activity for IL-2Rα may find application in oncology for example.

In some embodiments, the modified IL-2 signaling agent comprises a deletion of the Ala at the N-terminus of SEQ ID NO: 18. In some embodiments, the modified IL-2 agent comprises the substitution of a Ser for the Cys at position 125 of SEQ ID NO: 18. In some embodiments, the modified IL-2 agent comprises a deletion of the Ala at the N-terminus and the substitution of a Ser for the Cys at position 125 of SEQ ID NO: 18.

In other embodiments, the modified IL-2 agent may have substantially reduced affnity and/or activity for IL-2Rβ, as described in, for example, WO2016/025385, the entire disclosure of which is hereby incorporated by reference. In such embodiments, the modified IL-2 agent may induce an expansion of Treg cells but not effector cells such as CD8+ T cells and NK cells. An Fc-based chimeric protein complex comprising the modified IL-2 agent with substantially reduced affnity and/or activity for IL-2Rβ may find application in the treatment of autoimmune disease for example. In some embodiments, the modified IL-2 agent may comprise one or more mutations at amino acids N88, D20, and/or A126. For example, the modified IL-2 agent may comprise one or more of N88R, N88I, N88G, D20H, Q126L, and Q126F.

In various embodiments, the modified IL-2 agent may comprise a mutation at D109 or C125. For example, the mutation may be D109C or C125S. In some embodiments, the modified IL-2 with a mutation at D109 or C125 may be utilized for attachment to a PEG moiety.

In an embodiment, the wild type or modified signaling agent is IL-3. In some embodiments, the modified signaling agent has reduced affinity and/or activity for the IL-3 receptor, which is a heterodimer with a unique alpha chain paired with the common beta (beta c or CD131) subunit. In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for the IL-3 receptor, which is a heterodimer with a unique alpha chain paired with the common beta (beta c or CD131) subunit.

In an embodiment, the wild type or modified signaling agent is IL-4. In such an embodiment, the modified signaling agent has reduced affinity and/or activity for type 1 and/or type 2 IL-4 receptors. In such an embodiment, the modified signaling agent has substantially reduced or ablated affinity and/or activity for type 1 and/or type 2 IL-4 receptors. Type 1 IL-4 receptors are composed of the IL-4Rα subunit with a common γ chain and specifically bind IL-4. Type 2 IL-4 receptors include an IL-4Rα subunit bound to a different subunit known as IL-13Rα1. In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity the type 2 IL-4 receptors.

In an embodiment, the wild type IL-4 has the amino acid sequence of:

HKCDITLQEIIKTLNSLTEQKTLCTELTVTDIFAASKNTTEKETFCRAATVLRQFYSHHEKDTRCLGATAQQFHRHK QLIRFLKRLDRNLWGLAGLNSCPVKEANQSTLENFLERLKTIMREKYSKCSS (SEQ ID NO: 19).

In such embodiments, the modified IL-4 agent has one or more mutations at amino acids R121 (R121A, R121D, R121E, R121F, R121H, R121I, R121K, R121N, R121P, R121T, R121W), E122 (E122F), Y124 (Y124A, Y124Q, Y124R, Y124S, Y124T) and S125 (S125A). Without wishing to be bound by theory, it is believed that these modified IL-4 agents maintain the activity mediated by the type I receptor, but significantly reduces the biological activity mediated by the other receptors. See, for example, US Patent No. 6,433,157, the entire contents of which are hereby incorporated by reference.

In an embodiment, the wild type or modified signaling agent is IL-6. IL-6 signals through a cell-surface type I cytokine receptor complex including the ligand-binding IL-6R chain (CD126), and the signal-transducing component gp130. IL-6 may also bind to a soluble form of IL-6R (sIL-6R), which is the extracellular portion of IL-6R. The sIL-6R/IL-6 complex may be involved in neurites outgrowth and survival of neurons and, hence, may be important in nerve regeneration through remyelination. Accordingly, in some embodiments, the modified signaling agent has reduced affinity and/or activity for IL-6R/gp130 and/or sIL-6R. In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for IL-6R/gp130 and/or sIL-6R.

In an embodiment, the wild type IL-6 has the amino acid sequence of:

APVPPGEDSKDVAAPHRQPLTSSERIDKQIRYILDGISALRKETCNKSNMCESSKEALAENNLNLPKMAEKDGCF QSGFNEETCLVKIITGLLEFEVYLEYLQNRFESSEEQARAVQMSTKVLIQFLQKKAKNLDAITTPDPTTNASLTTKL QAQNQWLQDMTTHLILRSFKEFLQSSLRALRQM (SEQ ID NO: 20).

In such embodiments, the modified signaling agent has one or more mutations at amino acids 58, 160, 163, 171 or 177. Without wishing to be bound by theory, it is believed that these modified IL-6 agents exhibit reduced binding affinity to IL-6Ralpha and reduced biological activity. See, for example, WO 97/10338, the entire contents of which are hereby incorporated by reference.

In an embodiment, the wild type or modified signaling agent is IL-10. In such an embodiment, the modified signaling agent has reduced affinity and/or activity for IL-10 receptor-1 and IL-10 receptor-2. In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for IL-10 receptor-1 and IL-10 receptor-2

In an embodiment, the wild type or modified signaling agent is IL-11. In such an embodiment, the modified signaling agent has reduced affinity and/or activity for IL-11Rα and/or IL-11Rβ and/or gp130. In such an embodiment, the modified signaling agent has substantially reduced or ablated affinity and/or activity for IL-11Rα and/or IL-11Rβ and/or gp130.

In an embodiment, the wild type or modified signaling agent is IL-12. In such an embodiment, the modified signaling agent has reduced affinity and/or activity for IL-12Rβ1 and/or IL-12Rβ2. In such an embodiment, the modified signaling agent has substantially reduced or ablated affinity and/or activity for IL-12Rβ1 and/or IL-12Rβ2.

In an embodiment, the wild type or modified signaling agent is IL-13. In such an embodiment, the modified signaling agent has reduced affinity and/or activity for the IL-4 receptor (IL-4Rα) and IL-13Rα1. In some embodiments, the

modified signaling agent has substantially reduced or ablated affinity and/or activity for IL-4 receptor (IL-4Rα) or IL-13Rα1.

In an embodiment, the wild type IL-13 has the amino acid sequence of:

SPGPVPPSTALRELIEELVNITQNQKAPLCNGSMVWSINLTAGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKV SAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLFREGRFN (SEQ ID NO: 21).

In such embodiments, the modified IL-13 agent has one or more mutations at amino acids 13, 16, 17, 66, 69, 99, 102, 104, 105, 106, 107, 108, 109, 112, 113 and 114. Without wishing to be bound by theory, it is believed that these modified IL-13 agents exhibit reduced biological activity. See, for example, WO 2002/018422, the entire contents of which are hereby incorporated by reference.

In an embodiment, the signaling agent is a wild type or modified IL-15. In embodiments, the modified IL-15 has reduced affinity and/or activity for interleukin 15 receptor.

In an embodiment, the wild type IL-15 has the amino acid sequence of: SEQ ID NO: 1564.

In such embodiments, the modified IL-15 agent has one or more mutations at amino acids S7, D8, K10, K11, E46, L47, V49, I50, D61, N65, L66, I67, I68, L69, N72, Q108.

In an embodiment, the wild type or modified signaling agent is IL-18. In some embodiments, the modified signaling agent has reduced affinity and/or activity for IL-18Rα and/or IL-18Rβ. In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for IL-18Rα and/or IL-18Rβ. In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for IL-18Rα type II, which is an isoform of IL-18Rα that lacks the TIR domain required for signaling.

In an embodiment, the wild type IL-18 has the amino acid sequence of:

MAAEPVEDNCINFVAMKFIDNTLYFIAEDDENLESDYFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDCRD NAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKIISFKEMNPPDNIKDTKSDIIFFQRSVPGHDNKMQFESS SYEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNEDL (SEQ ID NO: 22).

In such embodiments, the modified IL-18 agent may comprise one or more mutations in amino acids or amino acid regions selected from Y37-K44, R49-Q54, D59-R63, E67-C74, R80, M87-A97, N 127-K129, Q139-M149, K165-K171, R183 and Q190-N191, as described in WO/2015/007542, the entire contents of which are hereby incorporated by reference (numbering based on the human IL-18 sequence, Genbank accession number AAV38697, version AAV38697.1, GI: 54696650).

In an embodiment, the wild type or modified signaling agent is IL-33. In such an embodiment, the modified signaling agent has reduced affinity and/or activity for the ST-2 receptor and IL-1RAcP. In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for the ST-2 receptor and IL-1RAcP.

In an embodiment, the wild type IL-33 has the amino acid sequence of:

MKPKMKYSTNKISTAKWKNTASKALCFKLGKSQQKAKEVCPMYFMKLRSGLMIKKEACYFRRETTKRPSLKTGR KHKRHLVLAACQQQSTVECFAFGISGVQKYTRALHDSSITGISPITEYLASLSTYNDQSITFALEDESYEIYVEDLKK

DEKKDKVLLSYYESQHPSNESGDGVDGKMLMVTLSPTKDFWLHANNKEHSVELHKCEKPLPDQAFFVLHNMHS NCVSFECKTDPGVFIGVKDNHLALIKVDSSENLCTENILFKLSET (SEQ ID NO: 23).

In such embodiments, the modified IL-33 agent may comprise one or more mutations in amino acids or amino acid regions selected from I113-Y122, S127-E139, E144-D157, Y163-M183, E200, Q215, L220-C227 and T260-E269, as described in WO/2015/007542, the entire contents of which are hereby incorporated by reference (numbering based on the human sequence, Genbank accession number NP_254274, version NP_254274.1, GI:15559209).

In an embodiment, the modified signaling agent is epidermal growth factor (EGF). EGF is a member of a family of potent growth factors. Members include EGF, HB-EGF, and others such as TGFalpha, amphiregulin, neuregulins, epiregulin, betacellulin. EGF family receptors include EGFR (ErbB1), ErbB2, ErbB3 and ErbB4. These may function as homodimeric and /or heterodimeric receptor subtypes. The different EGF family members exhibit differential selectivity for the various receptor subtypes. For example, EGF associates with ErbB1/ErbB1, ErbB1/ErbB2, ErbB4/ErbB2 and some other heterodimeric subtypes. HB-EGF has a similar pattern, although it also associates with ErbB4/4. Modulation of EGF (EGF-like) growth factor signaling, positively or negatively, is of considerable therapeutic interest. For example, inhibition of EGFRs signaling is of interest in the treatment of various cancers where EGFR signaling constitutes a major growth-promoting signal. Alternatively, stimulation of EGFRs signaling is of therapeutic interest in, for example, promoting wound healing (acute and chronic), oral mucositis (a major side-effect of various cancer therapies, including, without limitation radiation therapy).

In some embodiments, the modified signaling agent has reduced affinity and/or activity for ErbB1, ErbB2, ErbB3, and/or ErbB4. Such embodiments find use, for example, in methods of treating wounds. In some embodiments, the modified signaling agent binds to one or more ErbB1, ErbB2, ErbB3, and ErbB4 and antagonizes the activity of the receptor. In such embodiments, the modified signaling agent has reduced affinity and/or activity for ErbB1, ErbB2, ErbB3, and/or ErbB4 which allows for the activity of the receptor to be antagonized in an attenuated fashion. Such embodiments find use in, for example, treatments of cancer. In an embodiment, the modified signaling agent has reduced affinity and/or activity for ErbB1. ErbB1 is the therapeutic target of kinase inhibitors - most have side effects because they are not very selective (*e.g.*, gefitinib, erlotinib, afatinib, brigatinib and icotinib). In some embodiments, attenuated antagonistic ErbB1 signaling is more on-target and has less side effects than other agents targeting receptors for EGF.

In some embodiments, the modified signaling agent has reduced affinity and/or activity (*e.g.* antagonistic *e.g.* natural antagonistic activity or antagonistic activity that is the result of one or more mutations, *see, e.g.,* WO 2015/007520, the entire contents of which are hereby incorporated by reference) for ErbB1 and/or substantially reduced or ablated affinity and/or activity for ErbB4 or other subtypes it may interact with. Through specific targeting via the targeting moiety, cell-selective suppression (antagonism *e.g.* natural antagonistic activity or antagonistic activity that is the result of one or more mutations, *see, e.g.,* WO 2015/007520, the entire contents of which are hereby incorporated by reference) of ErbB1/ErbB1 receptor activation would be achieved – while not engaging other receptor subtypes potentially associated with inhibition-associated side effects. Hence, in contrast to EGFR kinase inhibitors, which inhibit EGFR activity in all cell types in the body, such a construct would provide a cell-

selective (*e.g.*, tumor cell with activated EGFR signaling due to amplification of receptor, overexpression *etc.*) anti-EGFR (ErbB1) drug effect with reduced side effects.

In some embodiments, the modified signaling agent has reduced affinity and/or activity (*e.g.* agonistic) for ErbB4 and/or other subtypes it may interact with. Through targeting to specific target cells through the targeting moiety, a selective activation of ErbB1 signaling is achieved (*e.g.* epithelial cells). Such a construct finds use, in some embodiments, in the treatment of wounds (promoting would healing) with reduced side effects, especially for treatment of chronic conditions and application other than topical application of a therapeutic (*e.g.* systemic wound healing).

In an embodiment, the wild type or modified signaling agent is insulin or insulin analogs. In some embodiments, the modified insulin or insulin analog has reduced affinity and/or activity for the insulin receptor and/or IGF1 or IGF2 receptor. In some embodiments, the modified insulin or insulin analog has substantially reduced or ablated affinity and/or activity for the insulin receptor and/or IGF1 or IGF2 receptor. Attenuated response at the insulin receptor allows for the control of diabetes, obesity, metabolic disorders and the like while directing away from IGF1 or IGF2 receptor avoids pro-cancer effects.

In an embodiment, the wild type or modified signaling agent is insulin-like growth factor-I or insulin-like growth factor-II (IGF-1 or IGF-2). In an embodiment, the modified signaling agent is IGF-1. In such an embodiment, the modified signaling agent has reduced affinity and/or activity for the insulin receptor and/or IGF1 receptor. In an embodiment, the modified signaling agent may bind to the IGF1 receptor and antagonize the activity of the receptor. In such an embodiment, the modified signaling agent has reduced affinity and/or activity for IGF1 receptor that allows for the activity of the receptor to be antagonized in an attenuated fashion. In some embodiments, the modified signaling agent has substantially reduced or ablated affinity and/or activity for the insulin receptor and/or IGF1 receptor. In some embodiments, the modified signaling agent has reduced affinity and/or activity for IGF2 receptor that allows for the activity of the receptor to be antagonized in an attenuated fashion. In an embodiment, the modified signaling agent has substantially reduced or ablated affinity and/or activity for the insulin receptor and accordingly does not interfere with insulin signaling. In various embodiments, this applies to cancer treatment. In various embodiments, the present agents may prevent IR isoform A from causing resistance to cancer treatments.

In some embodiments, the wild type or modified signaling agent is EPO. In various embodiments, the modified EPO agent has reduced affinity and/or activity for the EPO receptor (EPOR) receptor and/or the ephrin receptor (EphR) relative to wild type EPO or other EPO based agents described herein. In some embodiments, the modified EPO agent has substantially reduced or ablated affinity and/or activity for the EPO receptor (EPOR) receptor and/or the Eph receptor (EphR). Illustrative EPO receptors include, but are not limited to, an EPOR homodimer or an EPOR/CD131 heterodimer. Also included as an EPO receptor is beta-common receptor (βcR). Illustrative Eph receptors include, but are not limited to, EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA8, EPHA9, EPHA10, EPHB1, EPHB2, EPHB3, EPHB4, EPHB5, and EPHB6. In some embodiments, the modified EPO protein comprises one or more mutations that cause the EPO protein to have reduced affinity for receptors that comprise one or more different EPO receptors or Eph receptors (*e.g.* heterodimer, heterotrimers, *etc.*,

including by way of non-limitation: EPOR-EPHB4, EPOR- βcR-EPOR). Also provided are the receptors of EP Patent Publication No. 2492355 the entire contents of which are hereby incorporated by reference, including by way of non-limitation, NEPORs.

In some embodiments, the human EPO has the amino acid sequence of (the first 27 amino acids are the signal peptide):

MGVHECPAWLWLLLSLLSLPLGLPVLGAPPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVPDTKVNFY AWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNSSQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPP DAASAAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR (SEQ ID NO: 24).

In some embodiments, the human EPO protein is the mature form of EPO (with the signal peptide being cleaved off) which is a glycoprotein of 166 amino acid residues having the sequence of:

APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVPDTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVL RGQALLVNSSQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAASAAPLRTITADTFRKLFRVYSNFLRG KLKLYTGEACRTGDR (SEQ ID NO: 25).

The structure of the human EPO protein is predicted to comprise four-helix bundles including helices A, B, C, and D. In various embodiments, the modified EPO protein comprises one or more mutations located in four regions of the EPO protein which are important for bioactivity, *i.e.*, amino acid residues 10-20, 44-51, 96-108, and 142-156. In some embodiments, the one or more mutations are located at residues 11-15, 44-51, 100-108, and 147-151. These residues are localized to helix A (Val11, Arg14, and Tyr15), helix C (Ser100, Arg103, Ser104, and Leu108), helix D (Asn147, Arg150, Gly151, and Leu155), and the A/B connecting loop (residues 42-51). In some embodiments, the modified EPO protein comprises mutations in residues between amino acids 41-52 and amino acids 147, 150, 151, and 155. Without wishing to be bound by theory, it is believed that mutations of these residues have substantial effects on both receptor binding and in vitro biological activity. In some embodiments, the modified EPO protein comprises mutations at residues 11, 14, 15, 100, 103, 104, and 108. Without wishing to be bound by theory, it is believed that mutations of these residues have modest effects on receptor binding activity and much greater effects on in vitro biological activity. Illustrative substitutions include, but are not limited to, one or more of Val11Ser, Arg14Ala, Arg14Gln, Tyr15Ile, Pro42Asn, Thr44Ile, Lys45Asp, Val46Ala, Tyr51Phe, Ser100Glu, Ser100Thr, Arg103Ala, Ser104Ile, Ser104Ala, Leu108Lys, Asn147Lys, Arg150Ala, Gly151Ala, and Leu155Ala.

In some embodiments, the modified EPO protein comprises mutations that effect bioactivity and not binding, *e.g.* those listed in Eliot, *et al.* Mapping of the Active Site of Recombinant Human Erythropoietin January 15, 1997; *Blood*: 89 (2), the entire contents of which are hereby incorporated by reference.

In some embodiments, the modified EPO protein comprises one or more mutations involving surface residues of the EPO protein that are involved in receptor contact. Without wishing to be bound by theory, it is believed that mutations of these surface residues are less likely to affect protein folding thereby retaining some biological activity. Illustrative surface residues that may be mutated include, but are not limited to, residues 147 and 150. In illustrative embodiments, the mutations are substitutions including, one or more of N147A, N147K, R150A and R150E.

In some embodiments, the modified EPO protein comprises one or more mutations at residues N59, E62, L67, and L70, and one or more mutations that affect disulfide bond formation. Without wishing to be bound by theory, it is believed that these mutations affect folding and/or are predicted be in buried positions and thus affects biological activity indirectly.

In an embodiment, the modified EPO protein comprises a K20E substitution which significantly reduces receptor binding. *See* Elliott, *et al.,* (1997) *Blood,* 89:493-502, the entire contents of which are hereby incorporated by reference.

Additional EPO mutations that may be incorporated into the chimeric EPO protein of the invention are disclosed in, for example, Elliott, *et al.,* (1997) *Blood,* 89:493-502, the entire contents of which are hereby incorporated by reference and Taylor *et al*., (2010) *PEDS*, 23(4): 251-260, the entire contents of which are hereby incorporated by reference.

In some embodiments, the signaling agent is a toxin or toxic enzyme. In some embodiments, the toxin or toxic enzyme is derived from plants and bacteria. Illustrative toxins or toxic enzymes include, but are not limited to, the diphtheria toxin, Pseudomonas toxin, anthrax toxin, ribosome-inactivating proteins (RIPs) such as ricin and saporin, modeccin, abrin, gelonin, and poke weed antiviral protein. Additional toxins include those disclosed in Mathew *et al.*, (2009) Cancer Sci 100(8): 1359-65, the entire disclosures are hereby incorporated by reference. In such embodiments, the Fc-based chimeric protein complex of the invention may be utilized to induce cell death in cell-type specific manner. In such embodiments, the toxin may be modified, *e.g.* mutated, to reduce affinity and/or activity of the toxin for an attenuated effect, as described with other signaling agents herein.

Targeting Moieties (TM)

In some embodiments, the targeting moiety is a protein-based agent capable of specific binding, such as an antibody or derivatives thereof.

In some embodiments, the targeting moiety comprises antibody derivatives or formats. In some embodiments, the targeting moiety of the present Fc-based chimeric protein complex is a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (cysteine knot protein, knottin), a DARPin; a Tetranectin; an Affibody; a Transbody; an Anticalin; an AdNectin; an Affilin; a Microbody; a peptide aptamer; an alterases; a plastic antibodies; a phylomer; a stradobodies; a maxibodies; an evibody; a fynomer, an armadillo repeat protein, a Kunitz domain, an avimer, an atrimer, a probody, an immunobody, a triomab, a troybody; a pepbody; a vaccibody, a UniBody; affimers, a DuoBody, a Fv, a Fab, a Fab', a $F(ab')_2$, a peptide mimetic molecule, or a small (e.g. synthetic or natural) molecule , e.g. without limitation, as described in US Patent Nos. or Patent Publication Nos. US 7,417,130, US 2004/132094, US 5,831,012, US 2004/023334, US 7,250,297, US 6,818,418, US 2004/209243, US 7,838,629, US 7,186,524, US 6,004,746, US 5,475,096, US 2004/146938, US 2004/157209, US 6,994,982, US 6,794,144, US 2010/239633, US 7,803,907, US 2010/119446, and/or US 7,166,697, the contents of which are hereby incorporated by reference in their entireties. *See* also, Storz MAbs. 2011 May-Jun; 3(3): 310–317.

In one embodiment, the targeting moiety comprises a single-domain antibody, such as VHH from, for example, an organism that produces VHH antibody such as a camelid, a shark, or a designed VHH. VHHs are antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally-occurring heavy-chain antibodies. VHH technology is based on fully functional antibodies from camelids that lack light chains. These heavy-chain antibodies contain a single variable domain (VHH) and two constant domains (CH2 and CH3).

In an embodiment, the targeting moiety comprises a VHH. In some embodiments, the VHH is a humanized VHH or camelized VHH.

In some embodiments, the VHH comprises a fully human VH domain, *e.g.* a HUMABODY (Crescendo Biologics, Cambridge, UK). In some embodiments, fully human VH domain, *e.g.* a HUMABODY is monovalent, bivalent, or trivalent. In some embodiments, the fully human VH domain, *e.g.* a HUMABODY is mono- or multi-specific such as monospecific, bispecific, or trispecific. Illustrative fully human VH domains, *e.g.* HUMABODIES are described in, for example, WO 2016/113555 and WO2016/113557, the entire disclosure of which is incorporated by reference.

In various embodiments, the target (*e.g.* antigen, receptor) of interest can be found on one or more immune cells, which can include, without limitation, T cells, cytotoxic T lymphocytes, T helper cells, natural killer (NK) cells, natural killer T (NKT) cells, anti-tumor macrophages (*e.g.* M1 macrophages), B cells, dendritic cells, or subsets thereof. In some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) of interest and effectively, directly or indirectly, recruit one of more immune cells. In some embodiments, the target (*e.g.* antigen, receptor) of interest can be found on one or more tumor cells. In some embodiments, the present Fc-based chimeric protein complexes may directly or indirectly recruit an immune cell, *e.g.*, in some embodiments, to a therapeutic site (*e.g.* a locus with one or more disease cell or cell to be modulated for a therapeutic effect). In some embodiments, the present Fc-based chimeric protein complexes may directly or indirectly recruit an immune cell, *e.g.* an immune cell that can kill and/or suppress a tumor cell, to a site of action (such as, by way of non-limiting example, the tumor microenvironment).

In various embodiments, the targeting moieties can directly or indirectly recruit cells, such as disease cells and/or effector cells. In some embodiments, the present Fc-based chimeric protein complexes are capable of, or find use in methods involving, shifting the balance of immune cells in favor of immune attack of a tumor. For instance, the present Fc-based chimeric protein complexes can shift the ratio of immune cells at a site of clinical importance in favor of cells that can kill and/or suppress a tumor (*e.g.* T cells, cytotoxic T lymphocytes, T helper cells, natural killer (NK) cells, natural killer T (NKT) cells, anti-tumor macrophages (*e.g.* M1 macrophages), B cells, dendritic cells, or subsets thereof) and in opposition to cells that protect tumors (*e.g.* myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs); tumor associated neutrophils (TANs), M2 macrophages, tumor associated macrophages (TAMs), or subsets thereof). In some embodiments, the present Fc-based chimeric protein complex is capable of increasing a ratio of effector T cells to regulatory T cells.

For example, in some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) associated with T cells. In some embodiments, the recognition domains directly or indirectly recruit T cells. In an

embodiment, the recognition domains specifically bind to effector T cells. In some embodiments, the recognition domain directly or indirectly recruits effector T cells, *e.g.*, in some embodiments, to a therapeutic site (*e.g.* a locus with one or more disease cell or cell to be modulated for a therapeutic effect). Illustrative effector T cells include cytotoxic T cells (*e.g.* αβ TCR, $CD3^+$, $CD8^+$, $CD45RO^+$); $CD4^+$ effector T cells (*e.g.* αβ TCR, $CD3^+$, $CD4^+$, $CCR7^+$, CD62Lhi, $IL\text{-}7R/CD127^+$); $CD8^+$ effector T cells (*e.g.* αβ TCR, $CD3^+$, $CD8^+$, $CCR7^+$, CD62Lhi, $IL\text{-}7R/CD127^+$); effector memory T cells (*e.g.* CD62Llow, $CD44^+$, TCR, $CD3^+$, $IL\text{-}7R/CD127^+$, $IL\text{-}15R^+$, CCR7low); central memory T cells (*e.g.* $CCR7^+$, $CD62L^+$, $CD27^+$; or CCR7hi, $CD44^+$, CD62Lhi, TCR, $CD3^+$, IL-7R/$CD127^+$, $IL\text{-}15R^+$); $CD62L^+$ effector T cells; $CD8^+$ effector memory T cells (TEM) including early effector memory T cells ($CD27^+$ $CD62L^-$) and late effector memory T cells ($CD27^-$ $CD62L^-$) (TemE and TemL, respectively); $CD127(^+)CD25(low/-)$ effector T cells; $CD127(^-)CD25(^-)$ effector T cells; $CD8^+$ stem cell memory effector cells (TSCM) (*e.g.* CD44(low)CD62L(high)CD122(high)$sca(^+)$); TH1 effector T-cells (*e.g.* $CXCR3^+$, $CXCR6^+$ and $CCR5^+$; or αβ TCR, $CD3^+$, $CD4^+$, $IL\text{-}12R^+$, $IFN\gamma R^+$, $CXCR3^+$), TH2 effector T cells (*e.g.* $CCR3^+$, $CCR4^+$ and $CCR8^+$; or αβ TCR, $CD3^+$, $CD4^+$, $IL\text{-}4R^+$, $IL\text{-}33R^+$, $CCR4^+$, $IL\text{-}17RB^+$, $CRTH2^+$); TH9 effector T cells (*e.g.* αβ TCR, $CD3^+$, $CD4^+$); TH17 effector T cells (*e.g.* αβ TCR, $CD3^+$, $CD4^+$, $IL\text{-}23R^+$, $CCR6^+$, $IL\text{-}1R^+$); $CD4^+CD45RO^+CCR7^+$ effector T cells, $ICOS^+$ effector T cells; $CD4^+CD45RO^+CCR7(^-)$ effector T cells; and effector T cells secreting IL-2, IL-4 and/or IFN-γ.

Illustrative T cell antigens of interest include, for example (and inclusive of the extracellular domains, where applicable): CD8, CD3, SLAMF4, IL-2Rα, 4-1BB/TNFRSF9, IL-2 R β, ALCAM, B7-1, IL-4 R, B7-H3, BLAME/SLAMFS, CEACAM1, IL-6 R, CCR3, IL-7 Rα, CCR4, CXCRI/IL-S RA, CCR5, CCR6, IL-10R α, CCR 7, IL-l 0 R β, CCRS, IL-12 R β 1, CCR9, IL-12 R β 2, CD2, IL-13 R α 1, IL-13, CD3, CD4, ILT2/CDS5j, ILT3/CDS5k, ILT4/CDS5d, ILT5/CDS5a, Iutegrin α 4/CD49d, CDS, Integrin α E/CD103, CD6, Integrin α M/CD 11 b, CDS, Integrin α X/CD11c, Integrin β 2/CDIS, KIR/CD15S, CD27/TNFRSF7, KIR2DL1, CD2S, KIR2DL3, CD30/TNFRSFS, KIR2DL4/CD15Sd, CD31/PECAM-1, KIR2DS4, CD40 Ligand/TNFSF5, LAG-3, CD43, LAIR1, CD45, LAIR2, CDS3, Leukotriene B4-R1, CDS4/SLAMF5, NCAM-L1, CD94, NKG2A, CD97, NKG2C, CD229/SLAMF3, NKG2D, CD2F-10/SLAMF9, NT-4, CD69, NTB-A/SLAMF6, Common γ Chain/IL-2 R γ, Osteopontin, CRACC/SLAMF7, PD-1, CRTAM, PSGL-1, CTLA-4, RANK/TNFRSF11A, CX3CR1, CX3CL1, L-Selectin, CXCR3, SIRP β 1, CXCR4, SLAM, CXCR6, TCCR/WSX-1, DNAM-1, Thymopoietin, EMMPRIN/CD147, TIM-1, EphB6, TIM-2, Fas/TNFRSF6, TIM-3, Fas Ligand/TNFSF6, TIM-4, Fcγ RIII/CD16, TIM-6, TNFR1/TNFRSF1A, Granulysin, TNF RIII/TNFRSF1B, TRAIL RI/TNFRSFIOA, ICAM-1/CD54, TRAIL R2/TNFRSF10B, ICAM-2/CD102, TRAILR3/TNFRSF10C,IFN-γR1, TRAILR4/TNFRSF10D, IFN-γ R2, TSLP, IL-1 R1 and TSLP R. In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of these illustrative T cell antigens.

In various embodiments, the targeting moiety of the present Fc-based chimeric protein complex is a protein-based agent capable of specific binding to a cell receptor, such as a natural ligand for the cell receptor. In various embodiments, the cell receptor is found on one or more immune cells, which can include, without limitation, T cells, cytotoxic T lymphocytes, T helper cells, natural killer (NK) cells, natural killer T (NKT) cells, anti-tumor macrophages (*e.g.* M1 macrophages), B cells, dendritic cells, or subsets thereof. In some embodiments, the cell receptor is found

on megakaryocytes, thrombocytes, erythrocytes, mast cells, basophils, neutrophils, eosinophils, or subsets thereof.

In some embodiments, the targeting moiety is a natural ligand such as a chemokine. Exemplary chemokines that may be included in the Fc-based chimeric protein complex of the invention include, but are not limited to, CCL1, CCL2, CCL4, CCL5, CCL6, CCL7, CCL8, CCL9, CCL10, CCL11, CCL12, CCL13, CCL14, CCL15, CCL16, CL17, CCL18, CCL19, CCL20, CCL21, CCL22, CCL23, CCL24, CLL25, CCL26, CCL27, CXCL1, CXCL2, CXCL3, CXCL4, CXCL5, CXCL6, CXCL7, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL14, CXCL15, CXCL16, CXCL17, XCL1, XCL2, CX3CL1, HCC-4, and LDGF-PBP. In an illustrative embodiment, the targeting moiety may be XCL1 which is a chemokine that recognizes and binds to the dendritic cell receptor XCR1. In another illustrative embodiment, the targeting moiety is CCL1, which is a chemokine that recognizes and binds to CCR8. In another illustrative embodiment, the targeting moiety is CCL2, which is a chemokine that recognizes and binds to CCR2 or CCR9. In another illustrative embodiment, the targeting moiety is CCL3, which is a chemokine that recognizes and binds to CCR1, CCR5, or CCR9. In another illustrative embodiment, the targeting moiety is CCL4, which is a chemokine that recognizes and binds to CCR1 or CCR5 or CCR9. In another illustrative embodiment, the targeting moiety is CCL5, which is a chemokine that recognizes and binds to CCR1 or CCR3 or CCR4 or CCR5. In another illustrative embodiment, the targeting moiety is CCL6, which is a chemokine that recognizes and binds to CCR1. In another illustrative embodiment, the targeting moiety is CCL7, which is a chemokine that recognizes and binds to CCR2 or CCR9. In another illustrative embodiment, the targeting moiety is CCL8, which is a chemokine that recognizes and binds to CCR1 or CCR2 or CCR2B or CCR5 or CCR9. In another illustrative embodiment, the targeting moiety is CCL9, which is a chemokine that recognizes and binds to CCR1. In another illustrative embodiment, the targeting moiety is CCL10, which is a chemokine that recognizes and binds to CCR1. In another illustrative embodiment, the targeting moiety is CCL11, which is a chemokine that recognizes and binds to CCR2 or CCR3 or CCR5 or CCR9. In another illustrative embodiment, the targeting moiety is CCL13, which is a chemokine that recognizes and binds to CCR2 or CCR3 or CCR5 or CCR9. In another illustrative embodiment, the targeting moiety is CCL14, which is a chemokine that recognizes and binds to CCR1 or CCR9. In another illustrative embodiment, the targeting moiety is CCL15, which is a chemokine that recognizes and binds to CCR1 or CCR3. In another illustrative embodiment, the targeting moiety is CCL16, which is a chemokine that recognizes and binds to CCR1, CCR2, CCR5, or CCR8. In another illustrative embodiment, the targeting moiety is CCL17, which is a chemokine that recognizes and binds to CCR4. In another illustrative embodiment, the targeting moiety is CCL19, which is a chemokine that recognizes and binds to CCR7. In another illustrative embodiment, the targeting moiety is CCL20, which is a chemokine that recognizes and binds to CCR6. In another illustrative embodiment, the targeting moiety is CCL21, which is a chemokine that recognizes and binds to CCR7. In another illustrative embodiment, the targeting moiety is CCL22, which is a chemokine that recognizes and binds to CCR4. In another illustrative embodiment, the targeting moiety is CCL23, which is a chemokine that recognizes and binds to CCR1. In another illustrative embodiment, the targeting moiety is CCL24, which is a chemokine that recognizes and binds to CCR3. In another illustrative embodiment, the targeting moiety is CCL25, which is a chemokine that recognizes and binds to CCR9. In another illustrative embodiment, the targeting moiety

is CCL26, which is a chemokine that recognizes and binds to CCR3. In another illustrative embodiment, the targeting moiety is CCL27, which is a chemokine that recognizes and binds to CCR10. In another illustrative embodiment, the targeting moiety is CCL28, which is a chemokine that recognizes and binds to CCR3 or CCR10. In another illustrative embodiment, the targeting moiety is CXCL1, which is a chemokine that recognizes and binds to CXCR1 or CXCR2. In another illustrative embodiment, the targeting moiety is CXCL2, which is a chemokine that recognizes and binds to CXCR2. In another illustrative embodiment, the targeting moiety is CXCL3, which is a chemokine that recognizes and binds to CXCR2. In another illustrative embodiment, the targeting moiety is CXCL4, which is a chemokine that recognizes and binds to CXCR3B. In another illustrative embodiment, the targeting moiety is CXCL5, which is a chemokine that recognizes and binds to CXCR2. In another illustrative embodiment, the targeting moiety is CXCL6, which is a chemokine that recognizes and binds to CXCR1 or CXCR2. In another illustrative embodiment, the targeting moiety is CXCL8, which is a chemokine that recognizes and binds to CXCR1 or CXCR2. In another illustrative embodiment, the targeting moiety is CXCL9, which is a chemokine that recognizes and binds to CXCR3. In another illustrative embodiment, the targeting moiety is CXCL10, which is a chemokine that recognizes and binds to CXCR3. In another illustrative embodiment, the targeting moiety is CXCL11, which is a chemokine that recognizes and binds to CXCR3 or CXCR7. In another illustrative embodiment, the targeting moiety is CXCL12, which is a chemokine that recognizes and binds to CXCR4 or CXCR7. In another illustrative embodiment, the targeting moiety is CXCL13, which is a chemokine that recognizes and binds to CXCR5. In another illustrative embodiment, the targeting moiety is CXCL16, which is a chemokine that recognizes and binds to CXCR6. In another illustrative embodiment, the targeting moiety is LDGF-PBP, which is a chemokine that recognizes and binds to CXCR2. In another illustrative embodiment, the targeting moiety is XCL2, which is a chemokine that recognizes and binds to XCR1. In another illustrative embodiment, the targeting moiety is CX3CL1, which is a chemokine that recognizes and binds to CX3CR1.

In some embodiments, the targeting moiety is a natural ligand such as Flt3 or a truncated region thereof. In some embodiments, the targeting moiety is an extracellular domain of Flt3, or a functional portion thereof (e.g. one that is still able to bind the cognate ligand or receptor).

Functional equivalent of extracellular domains of natural ligands encompass N-terminal and/or C-terminally shortened versions that retain the binding capacitiy of the full-length extracellular domains.

In some embodiments, the targeting moiety is a NGR peptide or a truncated region thereof.

By way of non-limiting example, in various embodiments, the present Fc-based chimeric protein complex has a targeting moiety directed against a checkpoint marker expressed on a T cell, *e.g.* one or more of PD-1, CD28, CTLA4, ICOS, BTLA, KIR, LAG3, CD137, OX40, CD27, CD40L, TIM3, and A2aR.

In some embodiments, the targeting moiety is an extracellular domain of PD-1, PD-L1, or PD-L2, or a functional portion thereof (e.g. one that is still able to bind the cognate ligand or receptor).

For example, in some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) associated with B cells. In some embodiments, the recognition domains directly or indirectly recruit B cells, *e.g.*, in some embodiments, to a therapeutic site (*e.g.* a locus with one or more disease cell or cell to be modulated for a

therapeutic effect). Illustrative B cell antigens of interest include, for example, CD10, CD19, CD20, CD21, CD22, CD23, CD24, CD37, CD38, CD39, CD40, CD70, CD72, CD73, CD74, CDw75, CDw76, CD77, CD78, CD79a/b, CD80, CD81, CD82, CD83, CD84, CD85, CD86, CD89, CD98, CD126, CD127, CDw130, CD138, CDw150, and B-cell maturation antigen (BCMA). In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of these illustrative B cell antigens.

By way of further example, in some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) associated with Natural Killer cells. In some embodiments, the recognition domains directly or indirectly recruit Natural Killer cells, *e.g.*, in some embodiments, to a therapeutic site (*e.g.* a locus with one or more disease cell or cell to be modulated for a therapeutic effect). Illustrative Natural Killer cell antigens of interest include, for example TIGIT, 2B4/SLAMF4, KIR2DS4, CD155/PVR, KIR3DL1, CD94, LMIR1/CD300A, CD69, LMIR2/CD300c, CRACC/SLAMF7, LMIR3/CD300LF, DNAM-1, LMIR5/CD300LB, Fc-epsilon RII, LMIR6/CD300LE, Fc-γ RI/CD64, MICA, Fc-γ RIIB/CD32b, MICB, Fc-γ RIIC/CD32c, MULT-1, Fc-γ RIIA/CD32a, Nectin-2/CD112, Fc-γ RIII/CD16, NKG2A, FcRH1/IRTA5, NKG2C, FcRH2/IRTA4, NKG2D, FcRH4/IRTA1, NKp30, FcRH5/IRTA2, NKp44, Fc-Receptor-like 3/CD16-2, NKp46/NCR1, NKp80/KLRF1, NTB-A/SLAMF6, Rae-1, Rae-1 α, Rae-1 β, Rae-1 delta, H60, Rae-1 epsilon, ILT2/CD85j, Rae-1 γ, ILT3/CD85k, TREM-1, ILT4/CD85d, TREM-2, ILT5/CD85a, TREM-3, KIR/CD158, TREML1/TLT-1, KIR2DL1, ULBP-1, KIR2DL3, ULBP-2, KIR2DL4/CD158d and ULBP-3. In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of these illustrative NK cell antigens.

Also, in some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) associated with macrophages/monocytes. In some embodiments, the recognition domains directly or indirectly recruit macrophages/monocytes, *e.g.*, in some embodiments, to a therapeutic site (*e.g.* a locus with one or more disease cell or cell to be modulated for a therapeutic effect). Illustrative macrophages/monocyte antigens of interest include, for example SIRP1a, B7-1/CD80, ILT4/CD85d, B7-H1, ILT5/CD85a, Common β Chain, Integrin α 4/CD49d, BLAME/SLAMF8, Integrin α X/CDIIc, CCL6/C10, Integrin β 2/CD18, CD155/PVR, Integrin β 3/CD61, CD31/PECAM-1, Latexin, CD36/SR-B3, Leukotriene B4 R1, CD40/TNFRSF5, LIMPIIISR-B2, CD43, LMIR1/CD300A, CD45, LMIR2/CD300c, CD68, LMIR3/CD300LF, CD84/SLAMF5, LMIR5/CD300LB, CD97, LMIR6/CD300LE, CD163, LRP-1, CD2F-10/SLAMF9, MARCO, CRACC/SLAMF7, MD-1, ECF-L, MD-2, EMMPRIN/CD147, MGL2, Endoglin/CD105, Osteoactivin/GPNMB, Fc-γ RI/CD64, Osteopontin, Fc-γ RIIB/CD32b, PD-L2, Fc-γ RIIC/CD32c, Siglec-3/CD33, Fc-γ RIIA/CD32a, SIGNR1/CD209, Fc-γ RIII/CD16, SLAM, GM-CSF R α, TCCR/WSX-1, ICAM-2/CD102, TLR3, IFN-γ RI, TLR4, IFN- γ R2, TREM-I, IL-I RII, TREM-2, ILT2/CD85j, TREM-3, ILT3/CD85k, TREML1/TLT-1, 2B4/SLAMF 4, IL-10 R α, ALCAM, IL-10 R β, AminopeptidaseN/ANPEP, ILT2/CD85j, Common β Chain, ILT3/CD85k, Clq R1/CD93, ILT4/CD85d, CCR1, ILT5/CD85a, CCR2, Integrin α 4/CD49d, CCR5, Integrin α M/CDII b, CCR8, Integrin α X/CDIIc, CD155/PVR, Integrin β 2/CD18, CD14, Integrin β 3/CD61, CD36/SR-B3, LAIR1, CD43, LAIR2, CD45, Leukotriene B4-R1, CD68, LIMPIIISR-B2, CD84/SLAMF5, LMIR1/CD300A, CD97, LMIR2/CD300c, LMIR3/CD300LF, Coagulation Factor III/Tissue Factor, LMIR5/CD300LB, CX3CR1, CX3CL1, LMIR6/CD300LE, CXCR4, LRP-1, CXCR6, M-CSF R, DEP-1/CD148, MD-1, DNAM-1, MD-2,

EMMPRIN/CD147, MMR, Endoglin/CD105, NCAM-L1, Fc-γ RI/CD64, PSGL-1, Fc-γ RIIIICD16, RP105, G-CSF R, L-Selectin, GM-CSF R α, Siglec-3/CD33, HVEM/TNFRSF14, SLAM, ICAM-1/CD54, TCCR/WSX-1, ICAM-2/CD102, TREM-I, IL-6 R, TREM-2, CXCRI/IL-8 RA, TREM-3 and TREMLI/TLT-1. In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of these illustrative macrophage/monocyte antigens.

Also, in some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) associated with dendritic cells. In some embodiments, the recognition domains directly or indirectly recruit dendritic cells, *e.g.*, in some embodiments, to a therapeutic site (*e.g.* a locus with one or more disease cell or cell to be modulated for a therapeutic effect). Illustrative dendritic cell antigens of interest include, for example, CLEC9A, XCR1, RANK, CD36/SRB3, LOX-1/SR-E1, CD68, MARCO, CD163, SR-A1/MSR, CD5L, SREC-1, CL-PI/COLEC12, SREC-II, LIMPIIISRB2, RP105, TLR4, TLR1, TLR5, TLR2, TLR6, TLR3, TLR9, 4-IBB Ligand/TNFSF9, IL-12/IL-23 p40, 4-Amino-1,8-naphthalimide, ILT2/CD85j, CCL21/6Ckine, ILT3/CD85k, 8-oxo-dG, ILT4/CD85d, 8D6A, ILT5/CD85a, A2B5, lutegrin α 4/CD49d, Aag, Integrin β 2/CD18, AMICA, Langerin, B7-2/CD86, Leukotriene B4 RI, B7-H3, LMIR1/CD300A, BLAME/SLAMF8, LMIR2/CD300c, Clq R1/CD93, LMIR3/CD300LF, CCR6, LMIR5/CD300LB CCR7, LMIR6/CD300LE, CD40/TNFRSF5, MAG/Siglec-4-a, CD43, MCAM, CD45, MD-1, CD68, MD-2, CD83, MDL-1/CLEC5A, CD84/SLAMF5, MMR, CD97, NCAMLI, CD2F-10/SLAMF9, Osteoactivin GPNMB, Chern 23, PD-L2, CLEC-1, RP105, CLEC-2, CLEC-8, Siglec-2/CD22, CRACC/SLAMF7, Siglec-3/CD33, DC-SIGN, Siglec-5, DC-SIGNR/CD299, Siglec-6, DCAR, Siglec-7, DCIR/CLEC4A, Siglec-9, DEC-205, Siglec-10, Dectin-1/CLEC7A, Siglec-F, Dectin-2/CLEC6A, SIGNR1/CD209, DEP-1/CD148, SIGNR4, DLEC, SLAM, EMMPRIN/CD147, TCCR/WSX-1, Fc-γ R1/CD64, TLR3, Fc-γ RIIB/CD32b, TREM-1, Fc-γ RIIC/CD32c, TREM-2, Fc-γ RIIA/CD32a, TREM-3, Fc-γ RIII/CD16, TREML1/TLT-1, ICAM-2/CD102 and Vanilloid R1. In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of these illustrative DC antigens.

In some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) on immune cells selected from, but not limited to, megakaryocytes, thrombocytes, erythrocytes, mast cells, basophils, neutrophils, eosinophils, or subsets thereof. In some embodiments, the recognition domains directly or indirectly recruit megakaryocytes, thrombocytes, erythrocytes, mast cells, basophils, neutrophils, eosinophils, or subsets thereof, *e.g.*, in some embodiments, to a therapeutic site (*e.g.* a locus with one or more disease cell or cell to be modulated for a therapeutic effect).

In some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) associated with megakaryocytes and/or thrombocytes. Illustrative megakaryocyte and/or thrombocyte antigens of interest include, for example, GP IIb/IIIa, GPIb, vWF, PF4, and TSP. In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of these illustrative megakaryocyte and/or thrombocyte antigens.

In some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) associated with erythrocytes. Illustrative erythrocyte antigens of interest include, for example, CD34, CD36, CD38, CD41a (platelet glycoprotein IIb/IIIa), CD41b (GPIIb), CD71 (transferrin receptor), CD105, glycophorin A, glycophorin C, c-kit, HLA-

DR, H2 (MHC-II), and Rhesus antigens. In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of these illustrative erythrocyte antigens.

In some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) associated with mast cells. Illustrative mast cells antigens of interest include, for example, SCFR/CD117, $Fc_{\varepsilon}RI$, CD2, CD25, CD35, CD88, CD203c, C5R1, CMAI, FCERIA, FCER2, TPSABI. In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of these mast cell antigens.

In some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) associated with basophils. Illustrative basophils antigens of interest include, for example, $Fc_{\varepsilon}RI$, CD203c, CD123, CD13, CD107a, CD107b, and CD164. In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of these basophil antigens.

In some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) associated with neutrophils. Illustrative neutrophils antigens of interest include, for example, 7D5, CD10/CALLA, CD13, CD16 (FcRIII), CD18 proteins (LFA-1, CR3, and p150, 95), CD45, CD67, and CD177. In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of these neutrophil antigens.

In some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) associated with eosinophils. Illustrative eosinophils antigens of interest include, for example, CD35, CD44 and CD69. In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of these eosinophil antigens.

In various embodiments, the recognition domain may bind to any appropriate target, antigen, receptor, or cell surface markers known by the skilled artisan. In some embodiments, the antigen or cell surface marker is a tissue-specific marker. Illustrative tissue-specific markers include, but are not limited to, endothelial cell surface markers such as ACE, CD14, CD34, CDH5, ENG, ICAM2, MCAM, NOS3, PECAMI, PROCR, SELE, SELP, TEK, THBD, VCAMI, VWF; smooth muscle cell surface markers such as ACTA2, MYHIO, MYHI 1, MYH9, MYOCD; fibroblast (stromal) cell surface markers such as ALCAM, CD34, COLIAI, COL1A2, COL3A1, FAP, PH-4; epithelial cell surface markers such as CDID, K6IRS2, KRTIO, KRT13, KRT17, KRT18, KRT19, KRT4, KRT5, KRT8, MUCI, TACSTDI; neovasculature markers such as CD13, TFNA, Alpha-v beta-3 ($\alpha_V\beta_3$), E-selectin; and adipocyte surface markers such as ADIPOQ, FABP4, and RETN. In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of these antigens. In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of cells having these antigens.

In some embodiments, the recognition domains specifically bind to a target (*e.g.* antigen, receptor) associated with tumor cells. In some embodiments, the recognition domains directly or indirectly recruit tumor cells. For instance, in some embodiments, the direct or indirect recruitment of the tumor cell is to one or more effector cell (*e.g.* an immune cell as described herein) that can kill and/or suppress the tumor cell.

Tumor cells or cancer cells refer to an uncontrolled growth of cells or tissues and/or an abnormal increase in cell survival and/or inhibition of apoptosis which interferes with the normal functioning of bodily organs and systems.

For example, tumor cells include benign and malignant cancers, polyps, hyperplasia, as well as dormant tumors or micrometastases. Illustrative tumor cells include, but are not limited to cells of: basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and central nervous system cancer; breast cancer; cancer of the peritoneum; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer (including gastrointestinal cancer); glioblastoma; hepatic carcinoma; hepatoma; intra-epithelial neoplasm; kidney or renal cancer; larynx cancer; leukemia; liver cancer; lung cancer (*e.g.*, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung); melanoma; myeloma; neuroblastoma; oral cavity cancer (lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; salivary gland carcinoma; sarcoma; skin cancer; squamous cell cancer; stomach cancer; testicular cancer; thyroid cancer; uterine or endometrial cancer; cancer of the urinary system; vulval cancer; lymphoma including Hodgkin's and non-Hodgkin's lymphoma, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia; chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; as well as other carcinomas and sarcomas; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (*e.g.* that associated with brain tumors), and Meigs' syndrome.

Tumor cells, or cancer cells also include, but are not limited to, carcinomas, *e.g.* various subtypes, including, for example, adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma), sarcomas (including, for example, bone and soft tissue), leukemias (including, for example, acute myeloid, acute lymphoblastic, chronic myeloid, chronic lymphocytic, and hairy cell), lymphomas and myelomas (including, for example, Hodgkin and non-Hodgkin lymphomas, light chain, non-secretory, MGUS, and plasmacytomas), and central nervous system cancers (including, for example, brain (*e.g.* gliomas (*e.g.* astrocytoma, oligodendroglioma, and ependymoma), meningioma, pituitary adenoma, and neuromas, and spinal cord tumors (*e.g.* meningiomas and neurofibroma).

Illustrative tumor antigens include, but are not limited to, MART-1/Melan-A, gp100, Dipeptidyl peptidase IV (DPPIV), adenosine deaminase-binding protein (ADAbp), cyclophilin b, Colorectal associated antigen (CRC)-0017-1A/GA733, Carcinoembryonic Antigen (CEA) and its immunogenic epitopes CAP-1 and CAP-2, etv6, aml1, Prostate Specific Antigen (PSA) and its immunogenic epitopes PSA-1, PSA-2, and PSA-3, prostate-specific membrane antigen (PSMA), T-cell receptor/CD3-zeta chain, MAGE-family of tumor antigens (*e.g.*, MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A4, MAGE-A5, MAGE-A6, MAGE-A7, MAGE-A8, MAGE-A9, MAGE-A10, MAGE-A11, MAGE-A12, MAGE-Xp2 (MAGE-B2), MAGE-Xp3 (MAGE-B3), MAGE-Xp4 (MAGE-B4), MAGE-C1, MAGE-C2, MAGE-C3, MAGE-C4, MAGE-C5), GAGE-family of tumor antigens (*e.g.*, GAGE-1, GAGE-2, GAGE-3, GAGE-

4, GAGE-5, GAGE-6, GAGE-7, GAGE-8, GAGE-9), BAGE, RAGE, LAGE-1, NAG, GnT-V, MUM-1, CDK4, tyrosinase, p53, MUC family, HER2/neu, p21ras, RCAS1, α-fetoprotein, E-cadherin, α-catenin, β-catenin and γ-catenin, p120ctn, gp100 Pmel117, PRAME, NY-ESO-1, cdc27, adenomatous polyposis coli protein (APC), fodrin, Connexin 37, Ig-idiotype, p15, gp75, GM2 and GD2 gangliosides, viral products such as human papilloma virus proteins, Smad family of tumor antigens, Imp-1, NA, EBV-encoded nuclear antigen (EBNA)-1, brain glycogen phosphorylase, SSX-1, SSX-2 (HOM-MEL-40), SSX-1, SSX-4, SSX-5, SCP-1 CT-7, c-erbB-2, CD19, CD20, CD22, CD30, CD33, CD37, CD56, CD70, CD74, CD138, AGS16, MUC1 , GPNMB, Ep-CAM, PD-L1, PD-L2, PMSA, and BCMA (TNFRSF17). In various embodiments, a targeting moiety of the Fc-based chimeric protein complex binds one or more of these tumor antigens. In an embodiment, the Fc-based chimeric protein complex binds to HER2. In another embodiment, the Fc-based chimeric protein complex binds to PD-L2.

In various embodiments, the recognition domain of the present Fc-based chimeric protein complex binds but does not functionally modulate the target (*e.g.* antigen, receptor) of interest, *e.g.* the recognition domain is, or is akin to, a binding antibody. For instance, in various embodiments, the recognition domain simply targets the antigen or receptor but does not substantially inhibit, reduce or functionally modulate a biological effect that the antigen or receptor has. For example, some of the smaller antibody formats described above (*e.g.* as compared to, for example, full antibodies) have the ability to target hard to access epitopes and provide a larger spectrum of specific binding locales. In various embodiments, the recognition domain binds an epitope that is physically separate from an antigen or receptor site that is important for its biological activity (*e.g.* the antigen's active site).

Such non-neutralizing binding finds use in various embodiments of the present invention, including methods in which the present Fc-based chimeric protein complex is used to directly or indirectly recruit active immune cells to a site of need via an effector antigen, such as any of those described herein. For example, in various embodiments, the present Fc-based chimeric protein complex may be used to directly or indirectly recruit cytotoxic T cells via CD8 to a tumor cell in a method of reducing or eliminating a tumor (*e.g.* the Fc-based chimeric protein complex may comprise an anti-CD8 recognition domain and a recognition domain directed against a tumor antigen). In such embodiments, it is desirable to directly or indirectly recruit CD8-expressing cytotoxic T cells but not to functionally modulate the CD8 activity. On the contrary, in these embodiments, CD8 signaling is an important piece of the tumor reducing or eliminating effect. By way of further example, in various methods of reducing or eliminating tumors, the present Fc-based chimeric protein complex is used to directly or indirectly recruit dendritic cells (DCs) via CLEC9A (*e.g.* the Fc-based chimeric protein complex may comprise an anti-CLEC9A recognition domain and a recognition domain directed against a tumor antigen). In such embodiments, it is desirable to directly or indirectly recruit CLEC9A-expressing DCs but not to functionally modulate the CLEC9A activity. On the contrary, in these embodiments, CLEC9A signaling is an important piece of the tumor reducing or eliminating effect.

In various embodiments, the recognition domain of the present Fc-based chimeric protein complex binds to an immune modulatory antigen (*e.g.* immune stimulatory or immune inhibitory). In various embodiments, the immune modulatory antigen is one or more of 4-1BB, OX-40, HVEM, GITR, CD27, CD28, CD30, CD40, ICOS ligand; OX-40 ligand, LIGHT (CD258), GITR ligand, CD70, B7-1, B7-2, CD30 ligand, CD40 ligand, ICOS, ICOS ligand, CD137

ligand and TL1A. In various embodiments, such immune stimulatory antigens are expressed on a tumor cell. In various embodiments, the recognition domain of the present Fc-based chimeric protein complex binds but does not functionally modulate such immune stimulatory antigens and therefore allows recruitment of cells expressing these antigens without the reduction or loss of their potential tumor reducing or eliminating capacity.

In various embodiments, the recognition domain of the present Fc-based chimeric protein complex may be in the context of Fc-based chimeric protein complex that comprises two recognition domains that have neutralizing activity, or comprises two recognition domains that have non-neutralizing (*e.g.* binding) activity, or comprises one recognition domain that has neutralizing activity and one recognition domain that has non-neutralizing (*e.g.* binding) activity.

Clec9A Targeting Moieties

In some embodiments, the targeting moiety is a Clec9A targeting moiety that is a protein-based agent capable of specific binding to Clec9A. In some embodiments, the Clec9A targeting moiety is a protein-based agent capable of specific binding to Clec9A without functional modulation (*e.g.*, partial or full neutralization) of Clec9A. Clec9A is a group V C-type lectin-like receptor (CTLR) expressed on the surface of a subset of dendritic cells (*i.e.*, $BDCA_3$+ dendritic cells) specialized for the uptake and processing of materials from dead cells. Clec9A recognizes a conserved component within nucleated and nonnucleated cells, exposed when cell membranes are damaged. Clec9A is expressed at the cell surface as a glycosylated dimer and can mediate endocytosis, but not phagocytosis. Clec9A possesses a cytoplasmic immunoreceptor tyrosine-based activation-like motif that can recruit Syk kinase and induce proinflammatory cytokine production (see Huysamen *et al.* (2008), JBC, 283:16693-701).

In various embodiments, the Clec9A targeting moiety comprises an antigen recognition domain that recognizes an epitope present on Clec9A. In an embodiment, the antigen-recognition domain recognizes one or more linear epitopes present on Clec9A. In some embodiments, a linear epitope refers to any continuous sequence of amino acids present on Clec9A. In another embodiment, the antigen-recognition domain recognizes one or more conformational epitopes present on Clec9A. As used herein, a conformation epitope refers to one or more sections of amino acids (which may be discontinuous) which form a three-dimensional surface with features and/or shapes and/or tertiary structures capable of being recognized by an antigen recognition domain.

In various embodiments, the Clec9A targeting moiety can bind to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants of human Clec9A. In various embodiments, the Clec9A targeting moiety can bind to any forms of the human Clec9A, including monomeric, dimeric, heterodimeric, multimeric and associated forms. In an embodiment, the Clec9A binding agent binds to the monomeric form of Clec9A. In another embodiment, the Clec9A targeting moiety binds to a dimeric form of Clec9A. In a further embodiment, the Clec9A targeting moiety binds to glycosylated form of Clec9A, which may be either monomeric or dimeric.

In an embodiment, the Clec9A targeting moiety an antigen recognition domain that recognizes one or more epitopes present on human Clec9A. In an embodiment, the human Clec9A comprises the amino acid sequence of:

MHEEEIYTSLQWDSPAPDTYQKCLSSNKCSGACCLVMVISCVFCMGLLTA
SIFLGVKLLQVSTIAMQQQEKLIQQERALLNFTEWKRSCALQMKYCQAFMQ
NSLSSAHNSSPCPNNWIQNRESCYYVSEIWSIWHTSQENCLKEGSTLLQIE
SKEEMDFITGSLRKIKGSYDYWVGLSQDGHSGRWLWQDGSSPSPGLLPA
ERSQSANQVCGYVKSNSLLSSNCSTWKYFICEKYALRSSV (SEQ ID NO: 26).

In various embodiments, the Clec9A targeting moiety is capable of specific binding. In various embodiments, the Clec9A targeting moiety comprises an antigen recognition domain such as an antibody or derivatives thereof.

In some embodiments, the Clec9A targeting moiety comprises an antibody derivative or format. In some embodiments, the Clec9A targeting moiety comprises a targeting moiety which is a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (cysteine knot protein, knottin), a DARPin; a Tetranectin; an Affibody; a Transbody; an alphabody; a bicyclic peptide; an Anticalin; an AdNectin; an Affilin; an Affimer, a Microbody; an aptamer; an alterase; a plastic antibody; a phylomer; a stradobody; a maxibody; an evibody; a fynomer, an armadillo repeat protein, a Kunitz domain, an avimer, an atrimer, a probody, an immunobody, a triomab, a troybody; a pepbody; a vaccibody, a UniBody; a DuoBody, a Fv, a Fab, a Fab', a $F(ab')_2$, a peptide mimetic molecule, or a small (e.g. synthetic or natural) molecule , e.g. without limitation, as described in US Patent Nos. or Patent Publication Nos. US 7,417,130, US 2004/132094, US 5,831,012, US 2004/023334, US 7,250,297, US 6,818,418, US 2004/209243, US 7,838,629, US 7,186,524, US 6,004,746, US 5,475,096, US 2004/146938, US 2004/157209, US 6,994,982, US 6,794,144, US 2010/239633, US 7,803,907, US 2010/119446, and/or US 7,166,697, the contents of which are hereby incorporated by reference in their entireties. *See* also, Storz MAbs. 2011 May-Jun; 3(3): 310–317.

In some embodiments, the Clec9A targeting moiety is a single-domain antibody, such as a VHH. The VHH may be derived from, for example, an organism that produces VHH antibody such as a camelid, a shark, or the VHH may be a designed VHH. VHHs are antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally-occurring heavy-chain antibodies. VHH technology is based on fully functional antibodies from camelids that lack light chains. These heavy-chain antibodies contain a single variable domain (V_HH) and two constant domains (CH2 and CH3).

In an embodiment, the Clec9A targeting moiety comprises a VHH. In some embodiments, the VHH is a humanized VHH or camelized VHH.

In some embodiments, the VHH comprises a fully human V_H domain, *e.g.* a HUMABODY (Crescendo Biologics, Cambridge, UK). In some embodiments, fully human V_H domain, *e.g.* a HUMABODY is monovalent, bivalent, or trivalent. In some embodiments, the fully human V_H domain, *e.g.* a HUMABODY is mono- or multi-specific such as monospecific, bispecific, or trispecific. Illustrative fully human V_H domains, *e.g.* HUMABODIES are described in, for example, WO2016/113555 and WO2016/113557, the entire disclosure of which is incorporated by reference.

In some embodiments, the Clec9A targeting moiety is a VHH comprising a single amino acid chain having four “framework regions” or FRs and three “complementary determining regions” or CDRs. As used herein, “framework

region" or "FR" refers to a region in the variable domain which is located between the CDRs. As used herein, "complementary determining region" or "CDR" refers to variable regions in VHHs that contains the amino acid sequences capable of specifically binding to antigenic targets.

In various embodiments, the Clec9A targeting moiety comprises a VHH having a variable domain comprising at least one CDR1, CDR2, and/or CDR3 sequences. In various embodiments, the Clec9A targeting moiety comprises a VHH having a variable region comprising at least one FR1, FR2, FR3, and FR4 sequences.

In some embodiments, the CDR1 sequence is selected from SEQ ID Nos.: 27-112.

In some embodiments, the CDR2 sequence is selected from SEQ ID Nos.: 113-200.

In some embodiments, the CDR3 sequence is selected from SEQ ID Nos: 201-287, LGR, and VIK.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 27, SEQ ID NO: 113, and SEQ ID NO: 201.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 28, SEQ ID NO: 114, and SEQ ID NO: 202.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 29, SEQ ID NO: 115, and SEQ ID NO: 202.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 27, SEQ ID NO: 116, and SEQ ID NO: 203.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 30, SEQ ID NO: 117, and SEQ ID NO: 205.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 31, SEQ ID NO: 118, and SEQ ID NO: 205.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 32, SEQ ID NO: 119, and SEQ ID NO: 206.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 33, SEQ ID NO: 120, and SEQ ID NO: 207.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 33, SEQ ID NO: 120, and SEQ ID NO: 208.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 33, SEQ ID NO: 120, and SEQ ID NO: 209.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 34, SEQ ID NO: 121, and SEQ ID NO: 210.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 35, SEQ ID NO: 122, and SEQ ID NO: 211.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO:35, SEQ ID NO: 122, and SEQ ID NO: 212.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 36, SEQ ID NO: 123, and SEQ ID NO: 213.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 37, SEQ ID NO: 124, and SEQ ID NO: 214.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 38, SEQ ID NO: 125, and SEQ ID NO: 214.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 39, SEQ ID NO: 126, and SEQ ID NO: 214.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 40, SEQ ID NO: 127, and SEQ ID NO: 214.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 41, SEQ ID NO: 128, and SEQ ID NO: 214.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 42, SEQ ID NO: 128, and SEQ ID NO: 214.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 43, SEQ ID NO: 129, and SEQ ID NO: 215.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 44, SEQ ID NO: 130, and LGR.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 44, SEQ ID NO: 131, and LGR.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 44, SEQ ID NO: 132, and LGR.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 45, SEQ ID NO: 133, and LGR.

In an exemplary embodiment, the Clec9A targeting moiety comprises SEQ ID NO: 46, SEQ ID NO: 134, and VIK.

By way of example, in some embodiments, the Clec9A targeting moiety comprises an amino acid sequence selected from the following sequences:

R2CHCL8 (SEQ ID NO: 288); R1CHCL50 (SEQ ID NO: 289); R1CHCL21 (SEQ ID NO: 290); R2CHCL87 (SEQ ID NO: 291); R2CHCL24 (SEQ ID NO: 292); R2CHCL38 (SEQ ID NO: 293); R1CHCL16 (SEQ ID NO: 294); R2CHCL10 (SEQ ID NO: 295); R1CHCL34 (SEQ ID NO: 296); R1CHCL82 (SEQ ID NO: 297); R2CHCL3 (SEQ ID NO: 298); R2CHCL69 (SEQ ID NO:299); R1CHCL56 (SEQ ID NO: 300); R2CHCL32 (SEQ ID NO: 301); R2CHCL49 (SEQ ID NO: 302); R2CHCL53 (SEQ ID NO: 303); R2CHCL22 (SEQ ID NO: 304); R2CHCL25 (SEQ ID NO: 305); R2CHCL18 (SEQ ID NO: 306); R1CHCL23 (SEQ ID NO: 307); R1CHCL27 (SEQ ID NO: 308); R2CHCL13 (SEQ ID NO: 309); R2CHCL14 (SEQ ID NO: 310); R2CHCL42 (SEQ ID NO: 311); R2CHCL41 (SEQ ID NO: 312); R2CHCL94 (SEQ ID NO: 313); or R2CHCL27 (SEQ ID NO: 314).

By way of example, in some embodiments, the Clec9A targeting moiety comprises an amino acid sequence selected from the following sequences:

1LEC 7 (SEQ ID NO: 315); 1LEC 9 (SEQ ID NO: 316); 1LEC 26 (SEQ ID NO: 317); 1LEC 27 (SEQ ID NO: 318); 1LEC 28 (SEQ ID NO: 319); 1LEC 30 (SEQ ID NO: 320); 1LEC 38 (SEQ ID NO: 333); 1LEC 42 (SEQ ID NO: 334); 1LEC 51 (SEQ ID NO: 335); 1LEC 61 (SEQ ID NO: 336); 1LEC 62 (SEQ ID NO: 337); 1LEC 63 (SEQ ID NO: 338); 1LEC 64 (SEQ ID NO: 339); 1LEC 70 (SEQ ID NO: 340); 1LEC 84 (SEQ ID NO: 341); 1LEC 88 (SEQ ID NO: 342); 1LEC 91 (SEQ ID NO: 343); 1LEC 92 (SEQ ID NO: 344); 1LEC 94 (SEQ ID NO: 345); 2LEC 6 (SEQ ID NO: 346); 2LEC 13 (SEQ ID NO: 347); 2LEC 16 (SEQ ID NO: 348); 2LEC 20 (SEQ ID NO: 349); 2LEC 23 (SEQ ID NO: 350); 2LEC 24 (SEQ ID NO: 351); 2LEC 26 (SEQ ID NO: 352); 2LEC 38 (SEQ ID NO: 353); 2LEC 48 (SEQ ID NO: 354); 2LEC 53 (SEQ ID NO: 355); 2LEC 54 (SEQ ID NO: 356); 2LEC 55 (SEQ ID NO: 357); 2LEC 59 (SEQ ID NO: 358); 2LEC 60 (SEQ ID NO: 359); 2LEC 61 (SEQ ID NO: 360); 2LEC 62 (SEQ ID NO: 361); 2LEC 63 (SEQ ID NO: 362); 2LEC 67 (SEQ ID NO: 363); 2LEC 68 (SEQ ID NO: 364); 2LEC 76 (SEQ ID NO: 365); 2LEC 83 (SEQ ID NO: 366); 2LEC 88 (SEQ ID NO: 367); 2LEC 89 (SEQ ID NO: 368); 2LEC 90 (SEQ ID NO: 369); 2LEC 93 (SEQ ID NO: 370); 2LEC 95 (SEQ ID NO: 371); 3LEC 4 (SEQ ID NO: 372); 3LEC 6 (SEQ ID NO: 373); 3LEC 9 (SEQ ID NO: 374); 3LEC 11 (SEQ ID NO: 375); 3LEC 13 (SEQ ID NO: 376); 3LEC 15 (SEQ ID NO: 377); 3LEC 22 (SEQ ID NO: 378); 3LEC 23 (SEQ ID NO: 379); 3LEC 27 (SEQ ID NO: 380); 3LEC 30 (SEQ ID NO: 381); 3LEC 36 (SEQ ID NO: 382); 3LEC 55 (SEQ ID NO: 383); 3LEC 57 (SEQ ID NO: 384); 3LEC 61 (SEQ ID NO: 385); 3LEC 62 (SEQ ID NO: 386); 3LEC 66 (SEQ ID NO: 387); 3LEC 69 (SEQ ID NO: 388); 3LEC 76 (SEQ ID NO: 389); 3LEC 82 (SEQ ID NO: 390); 3LEC 89 (SEQ ID NO: 391); or 3LEC 94 (SEQ ID NO: 392).

In some embodiments, the Clec9A targeting moiety comprises an amino acid sequence selected from SEQ ID Nos: 315-320 and 333-392 (provided above) without the terminal histidine tag sequence (*i.e.*, HHHHHH; SEQ ID NO: 393).

In some embodiments, the Clec9A targeting moiety comprises an amino acid sequence selected from SEQ ID Nos: 315-320 and 333-392 (provided above) without the HA tag (*i.e.*, YPYDVPDYGS; SEQ ID NO: 394).

In some embodiments, the Clec9A targeting moiety comprises an amino acid sequence selected from SEQ ID Nos: 315-320 and 333-392 (provided above) without the AAA linker (*i.e.*, AAA).

In some embodiments, the Clec9A targeting moiety comprises an amino acid sequence selected from SEQ ID Nos: 315-320 and 333-392 (provided above) without the AAA linker, HA tag, and terminal histidine tag sequence (*i.e.*, AAAYPYDVPDYGSHHHHHH; SEQ ID NO: 395).

In an embodiment, the Clec9A targeting moiety comprises the anti-Clec9A antibody as disclosed in Tullett *et al.*, JCI Insight. 2016;1(7):e87102, the entire disclosures of which are hereby incorporated by reference.

In some embodiments, the present technology contemplates the use of any natural or synthetic analogs, mutants, variants, alleles, homologs and orthologs (herein collectively referred to as "analogs") of the Clec9A targeting moieties described herein. In various embodiments, the amino acid sequence of the Clec9A targeting moiety further includes an amino acid analog, an amino acid derivative, or other non-classical amino acids.

In various embodiments, the Clec9A targeting moiety comprising a sequence that is at least 60% identical to any one of the sequences disclosed herein. For example, the Clec9A targeting moiety may comprise a sequence that is at least about 60%, at least about 61%, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to any of the Clec9A sequences disclosed herein (*e.g.* about 60%, or about 61%, or about 62%, or about 63%, or about 64%, or about 65%, or about 66%, or about 67%, or about 68%, or about 69%, or about 70%, or about 71%, or about 72%, or about 73%, or about 74%, or about 75%, or about 76%, or about 77%, or about 78%, or about 79%, or about 80%, or about 81%, or about 82%, or about 83%, or about 84%, or about 85%, or about 86%, or about 87%, or about 88%, or about 89%, or about 90%, or about 91%, or about 92%, or about 93%, or about 94%, or about 95%, or about 96%, or about 97%, or about 98%, about 99% or about 100% sequence identity to any one of the Clec9A sequences disclosed herein).

In various embodiments, the Clec9A targeting moiety comprising an amino acid sequence having one or more amino acid mutations with respect to any one of the sequences disclosed herein. In various embodiments, the Clec9A targeting moiety comprises an amino acid sequence having one, or two, or three, or four, or five, or six, or seen, or eight, or nine, or ten, or fifteen, or twenty amino acid mutations with respect to any one of the sequences disclosed herein. In some embodiments, the one or more amino acid mutations may be independently selected from substitutions, insertions, deletions, and truncations.

In some embodiments, the amino acid mutations are amino acid substitutions, and may include conservative and/or non-conservative substitutions.

"Conservative substitutions" may be made, for instance, on the basis of similarity in polarity, charge, size, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the amino acid residues involved. The 20 naturally occurring amino acids can be grouped into the following six standard amino acid groups: (1) hydrophobic: Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr; Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe.

As used herein, "conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed within the same group of the six standard amino acid groups shown above. For example, the exchange of Asp by Glu retains one negative charge in the so modified polypeptide. In addition, glycine and proline may be substituted for one another based on their ability to disrupt α-helices.

As used herein, "non-conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed in a different group of the six standard amino acid groups (1) to (6) shown above.

In various embodiments, the substitutions may also include non-classical amino acids. Exemplary non-classical amino acids include, but are not limited to, selenocysteine, pyrrolysine, *N*-formylmethionine β-alanine, GABA and δ-Aminolevulinic acid, 4-aminobenzoic acid (PABA), D-isomers of the common amino acids, 2,4-diaminobutyric acid, α-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ-Abu, ε-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosme, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β-alanine, fluoro-amino acids, designer amino acids such as β methyl amino acids, C α-methyl amino acids, N α-methyl amino acids, and amino acid analogs in general.

In various embodiments, the amino acid mutation may be in the CDRs of the targeting moiety (*e.g.*, the CDR1, CDR2 or CDR3 regions). In another embodiment, amino acid alteration may be in the framework regions (FRs) of the targeting moiety (*e.g.*, the FR1, FR2, FR3, or FR4 regions).

Modification of the amino acid sequences may be achieved using any known technique in the art *e.g.*, site-directed mutagenesis or PCR based mutagenesis. Such techniques are described, for example, in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., 1989 and Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons, New York, N.Y., 1989.

In various embodiments, the mutations do not substantially reduce the present Clec9A binding agent's capability to specifically bind to Clec9A. In various embodiments, the mutations do not substantially reduce the present Clec9A binding agent's capability to specifically bind to Clec9A and without functionally modulating (*e.g.*, partially or fully neutralizing) Clec9A.

In various embodiments, the binding affinity of the Clec9A targeting moiety for the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or monomeric and/or dimeric forms and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric and/or dimeric forms) of human Clec9A may be described by the equilibrium dissociation constant (K_D). In various embodiments, the Clec9A targeting moiety binds to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric and/or dimeric forms) of human Clec9A with a K_D of less than about 1 uM, about 900 nM, about 800 nM, about 700 nM, about 600 nM, about 500 nM, about 400 nM, about 300 nM, about 200 nM, about 100 nM, about 90 nM, about 80 nM, about 70 nM, about 60 nM, about 50 nM, about 40 nM, about 30 nM, about 20 nM, about 10 nM, or about 5 nM, or about 1 nM.

In various embodiments, the Clec9A targeting moiety binds but does not functionally modulate (*e.g.*, partially or fully neutralize) the antigen of interest, *i.e.*, Clec9A. For instance, in various embodiments, the Clec9A targeting moiety simply targets the antigen but does not substantially functionally modulate (*e.g.* partially or fully inhibit, reduce or neutralize) a biological effect that the antigen has. In various embodiments, the Clec9A targeting moiety binds an epitope that is physically separate from an antigen site that is important for its biological activity (*e.g.* an antigen's active site).

Such binding without significant function modulation finds use in various embodiments of the present invention, including methods in which the Clec9A targeting moiety is used to directly or indirectly recruit active immune cells to a site of need via an effector antigen. For example, in various embodiments, the Clec9A targeting moiety may be used to directly or indirectly recruit dendritic cells via Clec9A to a tumor cell in a method of reducing or eliminating a tumor (*e.g.* the Clec9A binding agent may comprise a targeting moiety having an anti-Clec9A antigen recognition domain and a targeting moiety having a recognition domain (*e.g.* antigen recognition domain) directed against a tumor antigen or receptor). In such embodiments, it is desirable to directly or indirectly recruit dendritic cells but not to functionally modulate or neutralize the Clec9A activity. In these embodiments, Clec9A signaling is an important piece of the tumor reducing or eliminating effect.

In some embodiments, the Clec9A targeting moiety enhances antigen-presentation by dendritic cells. For example, in various embodiments, the Clec9A targeting moiety can directly or indirectly recruit dendritic cells via Clec9A to a tumor cell, where tumor antigens are subsequently endocytosed and presented on the dendritic cell for induction of potent humoral and cytotoxic T cell responses.

In other embodiments (for example, related to treating autoimmune or neurodegenerative disease), the Clec9A targeting moiety binds and neutralizes the antigen of interest, *i.e.*, Clec9A. For instance, in various embodiments, the present methods may inhibit or reduce Clec9A signaling or expression, *e.g.* to cause a reduction in an immune response.

CD8 Targeting Moieties

In various embodiments, the targeting moiety is a CD8 targeting moiety that is a protein-based agent capable of specific binding to CD8. In various embodiments, the CD8 targeting moiety is a protein-based agent capable of specific binding to CD8 without functionally modulating (*e.g.* partial or complete neutralization) CD8.

CD8 is a heterodimeric type I transmembrane glycoprotein, whose α and β chains are both comprised of an immunoglobulin (Ig)-like extracellular domain connected by an extended O-glycosylated stalk to a single-pass transmembrane domain and a short cytoplasmic tail. The cytoplasmic region of the CD8 α-chain contains two cysteine motifs that serve as a docking site for src tyrosine kinase p56lck (Lck). In contrast, this Lck binding domain appears to be absent from the CD8 β chain, suggesting that the β chain is not involved in downstream signaling. CD8 functions as a co-receptor for the T-cell receptor with its principle role being the recruitment of Lck to the TCR-pMHC complex following co-receptor binding to MHC. The increase in the local concentration of this kinase activates a signaling cascade that recruits and activates ζ-chain-associated protein kinase 70 (ZAP-70), subsequently leading to the amplification of T-cell activation signals.

In some embodiments, the CD8 targeting moiety comprises an antigen recognition domain that recognizes an epitope present on the CD8 α and/or β chains. In an embodiment, the antigen-recognition domain recognizes one or more linear epitopes on the CD8 α and/or β chains. In some embodiment, a linear epitope refers to any continuous sequence of amino acids present on the CD8 α and/or β chains. In another embodiment, the antigen-recognition domain recognizes one or more conformational epitopes present on the CD8 α and/or β chains. As used herein, a conformation epitope refers to one or more sections of amino acids (which may be discontinuous)

which form a three-dimensional surface with features and/or shapes and/or tertiary structures capable of being recognized by an antigen recognition domain.

In various embodiments, the CD8 targeting moiety may bind to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants of human CD8 α and/or β chains. In various embodiments, the CD8 targeting moiety may bind to any forms of the human CD8 α and/or β chains, including monomeric, dimeric, heterodimeric, multimeric and associated forms. In an embodiment, the CD8 binding agent binds to the monomeric form of CD8 α chain or CD8 β chain. In another embodiment, the CD8 targeting moiety binds to a homodimeric form comprised of two CD8 α chains or two CD8 β chains. In a further embodiment, the CD8 binding agent binds to a heterodimeric form comprised of one CD8 α chain and one CD8 β chain.

In an embodiment, the CD8 targeting moiety comprises an antigen recognition domain that recognizes one or more epitopes present on the human CD8 α chain. In an embodiment, the human CD8 α chain comprises the amino acid sequence of Isoform 1 (SEQ ID NO: 396).

In an embodiment, the human CD8 α chain comprises the amino acid sequence of Isoform 2 (SEQ ID NO: 397).

In an embodiment, the human CD8 α chain comprises the amino acid sequence of Isoform 3 (SEQ ID NO: 398).

In an embodiment, the CD8 targeting moiety comprises an antigen recognition domain that recognizes one or more epitopes present on the human CD8 β chain. In an embodiment, the human CD8 β chain comprises the amino acid sequence of Isoform 1 (SEQ ID NO: 399).

In an embodiment, the human CD8 β chain comprises the amino acid sequence of Isoform 2 (SEQ ID NO: 400).

In an embodiment, the human CD8 β chain comprises the amino acid sequence of Isoform 3 (SEQ ID NO: 401).

In an embodiment, the human CD8 β chain comprises the amino acid sequence of Isoform 4 (SEQ ID NO: 402).

In an embodiment, the human CD8 β chain comprises the amino acid sequence of Isoform 5 (SEQ ID NO: 403).

In an embodiment, the human CD8 β chain comprises the amino acid sequence of Isoform 6 (SEQ ID NO: 404).

In an embodiment, the human CD8 β chain comprises the amino acid sequence of Isoform 7 (SEQ ID NO: 405).

In an embodiment, the human CD8 β chain comprises the amino acid sequence of Isoform 8 (SEQ ID NO: 406).

In some embodiments, the CD8 targeting moiety is capable of specific binding. In various embodiments, the CD8 targeting moiety comprises an antigen recognition domain such as an antibody or derivatives thereof.

In some embodiments, the CD8 targeting moiety comprise an antibody derivative or format. In some embodiments, the CD8 targeting moiety comprises a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (cysteine knot protein, knottin), a DARPin; a Tetranectin; an Affibody; a Transbody; an Anticalin; an AdNectin; an alphabody; a bicyclic peptide; an Affilin; an Affimer, a Microbody; an aptamer; an alterase; a plastic antibody; a phylomer; a stradobody; a maxibody; an evibody; a fynomer, an armadillo repeat protein, a Kunitz domain, an avimer, an atrimer, a probody, an immunobody, a triomab, a troybody; a pepbody; a vaccibody, a UniBody; a DuoBody, a Fv, a Fab, a Fab', a

$F(ab')_2$, a peptide mimetic molecule, or a small (e.g. synthetic or natural) molecule , e.g. without limitation, as described in US Patent Nos. or Patent Publication Nos. US 7,417,130, US 2004/132094, US 5,831,012, US 2004/023334, US 7,250,297, US 6,818,418, US 2004/209243, US 7,838,629, US 7,186,524, US 6,004,746, US 5,475,096, US 2004/146938, US 2004/157209, US 6,994,982, US 6,794,144, US 2010/239633, US 7,803,907, US 2010/119446, and/or US 7,166,697, the contents of which are hereby incorporated by reference in their entireties. *See* also, Storz MAbs. 2011 May-Jun; 3(3): 310–317.

In some embodiments, the CD8 targeting moiety comprises a single-domain antibody, such as a VHH. The VHH may be derived from, for example, an organism that produces VHH antibody such as a camelid, a shark, or the VHH may be a designed VHH. VHHs are antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally-occurring heavy-chain antibodies. VHH technology is based on fully functional antibodies from camelids that lack light chains. These heavy-chain antibodies contain a single variable domain (V_HH) and two constant domains (CH2 and CH3).

In an embodiment, the CD8 targeting moiety comprises a VHH. In some embodiments, the VHH is a humanized VHH or camelized VHH.

In some embodiments, the VHH comprises a fully human V_H domain, *e.g.* a HUMABODY (Crescendo Biologics, Cambridge, UK). In some embodiments, fully human V_H domain, *e.g.* a HUMABODY is monovalent, bivalent, or trivalent. In some embodiments, the fully human V_H domain, *e.g.* a HUMABODY is mono- or multi-specific such as monospecific, bispecific, or trispecific. Illustrative fully human V_H domains, *e.g.* a HUMABODIES are described in, for example, WO2016/113555 and WO2016/113557, the entire disclosure of which is incorporated by reference.

In some embodiments, the CD8 targeting moiety comprises a VHH comprising a single amino acid chain having four “framework regions” or FRs and three “complementary determining regions” or CDRs. As used herein, “framework region” or “FR” refers to a region in the variable domain that is located between the CDRs. As used herein, “complementary determining region” or “CDR” refers to variable regions in VHHs that contains the amino acid sequences capable of specifically binding to antigenic targets.

In various embodiments, the CD8 targeting moiety comprises a VHH having a variable domain comprising at least one CDR1, CDR2, and/or CDR3 sequences.

In some embodiments, the CDR1 sequence is selected from SEQ ID Nos: 407-477.

In some embodiments, the CDR2 sequence is selected from SEQ ID Nos: 478-548.

In some embodiments, the CDR3 sequence is selected from SEQ ID Nos: 549-620.

In various embodiments, the CD8 targeting moiety comprises SEQ ID NO: 407, SEQ ID NO: 478, and SEQ ID NO: 549.

In various embodiments, the CD8 targeting moiety comprises SEQ ID NO: 407, SEQ ID NO: 478, and SEQ ID NO: 550.

In various embodiments, the CD8 targeting moiety comprises SEQ ID NO: 407, SEQ ID NO: 478, and SEQ ID NO: 551.

In various embodiments, the CD8 targeting moiety comprises SEQ ID NO: 407, SEQ ID NO: 479, and SEQ ID NO: 549.

In various embodiments, the CD8 targeting moiety comprises SEQ ID NO: 407, SEQ ID NO: 479, and SEQ ID NO: 550.

In various embodiments, the CD8 targeting moiety comprises SEQ ID NO: 407, SEQ ID NO: 479, and SEQ ID NO: 551.

In various embodiments, the CD8 targeting moiety comprises SEQ ID NO: 408, SEQ ID NO: 478, and SEQ ID NO: 549.

In various embodiments, the CD8 targeting moiety comprises SEQ ID NO: 408, SEQ ID NO: 478, and SEQ ID NO: 550.

In various embodiments, the CD8 targeting moiety comprises SEQ ID NO: 408, SEQ ID NO: 478, and SEQ ID NO: 551.

In various embodiments, the CD8 targeting moiety comprises SEQ ID NO: 408, SEQ ID NO: 479, and SEQ ID NO: 549.

In various embodiments, the CD8 targeting moiety comprises SEQ ID NO: 408, SEQ ID NO: 479, and SEQ ID NO: 550.

In various embodiments, the CD8 targeting moiety comprises SEQ ID NO: 408, SEQ ID NO: 479, and SEQ ID NO: 551.

By way of example, in some embodiments, the CD8 targeting moiety comprises an amino acid sequence selected from the following sequences: R3HCD27 (SEQ ID NO: 621); R3HCD129 (SEQ ID NO: 622); or R2HCD26 (SEQ ID NO: 623).

In various embodiments, the CD8 targeting moiety comprises an amino acid sequence selected from the following sequences: 1CDA 7 (SEQ ID NO: 624); 1CDA 12 (SEQ ID NO: 625); 1CDA 14 (SEQ ID NO: 626); 1CDA 15 (SEQ ID NO: 627); 1CDA 17 (SEQ ID NO: 628); 1CDA 18 (SEQ ID NO: 629); 1CDA 19 (SEQ ID NO: 630); 1CDA 24 (SEQ ID NO: 631); 1CDA 26 (SEQ ID NO: 632); 1CDA 28 (SEQ ID NO: 633); 1CDA 37 (SEQ ID NO: 634); 1CDA 43 (SEQ ID NO: 635); 1CDA 45 (SEQ ID NO: 636); 1CDA 47 (SEQ ID NO: 637); 1CDA 48 (SEQ ID NO: 638); 1CDA 58 (SEQ ID NO: 639); 1CDA 65 (SEQ ID NO: 640); 1CDA 68 (SEQ ID NO: 641); 1CDA 73 (SEQ ID NO: 642); 1CDA 75 (SEQ ID NO: 643); 1CDA 86 (SEQ ID NO: 644); 1CDA 87 (SEQ ID NO: 645); 1CDA 88 (SEQ ID NO: 646); 1CDA 89 (SEQ ID NO: 647); 1CDA 92 (SEQ ID NO: 648); 1CDA 93 (SEQ ID NO: 649); 2CDA 1 (SEQ ID NO: 650); 2CDA 5 (SEQ ID NO: 651); 2CDA 22 (SEQ ID NO: 652); 2CDA 28 (SEQ ID NO: 653); 2CDA 62 (SEQ ID NO: 654); 2CDA 68 (SEQ ID NO: 655); 2CDA 73 (SEQ ID NO: 656); 2CDA 74 (SEQ ID NO: 657); 2CDA 75 (SEQ ID NO: 658); 2CDA 77 (SEQ ID NO: 659); 2CDA 81 (SEQ ID NO: 660); 2CDA 87 (SEQ ID NO: 661); 2CDA 88 (SEQ ID NO: 662); 2CDA 89 (SEQ ID NO: 663); 2CDA 91 (SEQ ID NO: 664); 2CDA 92 (SEQ ID NO: 665); 2CDA 93 (SEQ ID NO: 666); 2CDA 94 (SEQ ID NO: 667); 2CDA 95 (SEQ ID NO: 668); 3CDA 3 (SEQ ID NO: 669); 3CDA 8 (SEQ ID NO: 670); 3CDA 11 (SEQ ID NO: 671); 3CDA 18 (SEQ ID NO: 672); 3CDA 19 (SEQ ID

NO: 673); 3CDA 21 (SEQ ID NO: 674); 3CDA 24 (SEQ ID NO: 675); 3CDA 28 (SEQ ID NO: 676); 3CDA 29 (SEQ ID NO: 677); 3CDA 31 (SEQ ID NO: 678); 3CDA 32 (SEQ ID NO: 679); 3CDA 33 (SEQ ID NO: 680); 3CDA 37 (SEQ ID NO: 681); 3CDA 40 (SEQ ID NO: 682); 3CDA 41 (SEQ ID NO:683); 3CDA 48 (SEQ ID NO: 684); 3CDA 57 (SEQ ID NO: 685); 3CDA 65 (SEQ ID NO: 686); 3CDA 70 (SEQ ID NO: 687); 3CDA 73 (SEQ ID NO: 688); 3CDA 83 (SEQ ID NO: 689); 3CDA 86 (SEQ ID NO: 690); 3CDA 88 (SEQ ID NO: 691); or 3CDA 90 (SEQ ID NO: 692).

In some embodiments, the CD8 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 624-692 (provided above) without the terminal histidine tag sequence (*i.e.*, HHHHHH; SEQ ID NO: 393).

In some embodiments, the CD8 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 621-692 (provided above) without the HA tag (*i.e.*, YPYDVPDYGS; SEQ ID NO: 394).

In some embodiments, the CD8 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 621-692 (provided above) without the AAA linker (*i.e.*, AAA).

In some embodiments, the CD8 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 621-623 (provided above) without the AAA linker and HA tag.

In some embodiments, the CD8 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 624-692 (provided above) without the AAA linker, HA tag, and terminal histidine tag sequence (*i.e.*, AAAYPYDVPDYGSHHHHHH; SEQ ID NO: 395).

In some embodiments, the CD8 targeting moiety comprises an amino acid sequence described in US Patent Publication No. 2014/0271462, the entire contents of which are incorporated by reference. In various embodiments, the CD8 binding agent comprises an amino acid sequence described in Table 0.1, Table 0.2, Table 0.3, and/or Figures 1A-12I of US Patent Publication No. 2014/0271462, the entire contents of which are incorporated by reference. In various embodiments, the CD8 binding agent comprises a HCDR1 of SEQ ID NO: 693 or 694 and/or a HCDR2 of SEQ ID NO: 693 or 694 and/or a HCDR3 of SEQ ID NO: 693 or 694 and/or a LCDR1 of SEQ ID NO: 695 and/or a LCDR2 of SEQ ID NO: 695 and/or a LCDR3 of SEQ ID NO: 695.

In some embodiments, the present technology contemplates the use of any natural or synthetic analogs, mutants, variants, alleles, homologs and orthologs (herein collectively referred to as “analogs”) of the CD8 targeting moiety described herein. In some embodiments, the amino acid sequence of the CD8 targeting moiety further includes an amino acid analog, an amino acid derivative, or other non-classical amino acids.

In some embodiments, the CD8 targeting moiety comprises a targeting moiety comprising a sequence that is at least 60% identical to any one of the CD8 sequences disclosed herein. For example, the CD8 targeting moiety may comprise a targeting moiety comprising a sequence that is at least about 60%, at least about 61%, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at

least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to any one of the CD8 sequences disclosed herein (*e.g.* about 60%, or about 61%, or about 62%, or about 63%, or about 64%, or about 65%, or about 66%, or about 67%, or about 68%, or about 69%, or about 70%, or about 71%, or about 72%, or about 73%, or about 74%, or about 75%, or about 76%, or about 77%, or about 78%, or about 79%, or about 80%, or about 81%, or about 82%, or about 83%, or about 84%, or about 85%, or about 86%, or about 87%, or about 88%, or about 89%, or about 90%, or about 91%, or about 92%, or about 93%, or about 94%, or about 95%, or about 96%, or about 97%, or about 98%, about 99% or about 100% sequence identity to any one of the CD8 sequences disclosed herein).

In various embodiments, the CD8 targeting moiety comprises an amino acid sequence having one or more amino acid mutations with respect to any one of the CD8 sequences disclosed herein. In various embodiments, the CD8 binding agent comprises a targeting moiety comprising an amino acid sequence having one, or two, or three, or four, or five, or six, or seen, or eight, or nine, or ten, or fifteen, or twenty amino acid mutations with respect to any one of the CD8 sequences disclosed herein. In some embodiments, the one or more amino acid mutations may be independently selected from substitutions, insertions, deletions, and truncations.

In some embodiments, the amino acid mutations are amino acid substitutions, and may include conservative and/or non-conservative substitutions.

"Conservative substitutions" may be made, for instance, on the basis of similarity in polarity, charge, size, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the amino acid residues involved. The 20 naturally occurring amino acids can be grouped into the following six standard amino acid groups: (1) hydrophobic: Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr; Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe.

As used herein, "conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed within the same group of the six standard amino acid groups shown above. For example, the exchange of Asp by Glu retains one negative charge in the so modified polypeptide. In addition, glycine and proline may be substituted for one another based on their ability to disrupt α-helices.

As used herein, "non-conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed in a different group of the six standard amino acid groups (1) to (6) shown above.

In various embodiments, the substitutions may also include non-classical amino acids (*e.g.* selenocysteine, pyrrolysine, *N*-formylmethionine β-alanine, GABA and δ-Aminolevulinic acid, 4-aminobenzoic acid (PABA), D-isomers of the common amino acids, 2,4-diaminobutyric acid, α-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ-Abu, ε-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosme, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β-alanine, fluoro-amino acids, designer amino acids such as β methyl amino acids, C α-methyl amino acids, N α-methyl amino acids, and amino acid analogs in general).

In various embodiments, the amino acid mutation may be in the CDRs of the targeting moiety (*e.g.*, the CDR1, CDR2 or CDR3 regions). In another embodiment, amino acid alteration may be in the framework regions (FRs) of the targeting moiety (*e.g.*, the FR1, FR2, FR3, or FR4 regions).

Modification of the amino acid sequences may be achieved using any known technique in the art *e.g.*, site-directed mutagenesis or PCR based mutagenesis. Such techniques are described, for example, in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., 1989 and Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons, New York, N.Y., 1989.

In various embodiments, the mutations do not substantially reduce the CD8 targeting moiety's capability to specifically bind to CD8. In various embodiments, the mutations do not substantially reduce the CD8 targeting moiety's capability to specifically bind to CD8 without functionally modulating CD8.

In various embodiments, the binding affinity of the CD8 targeting moiety for the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric, dimeric, heterodimeric, multimeric and/or associated forms) of human CD8 α and/or β chains may be described by the equilibrium dissociation constant (K_D). In various embodiments, the CD8 targeting moiety binds to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric, dimeric, heterodimeric, multimeric and/or associated forms) of human CD8 α and/or β chains with a K_D of less than about 1 uM, about 900 nM, about 800 nM, about 700 nM, about 600 nM, about 500 nM, about 400 nM, about 300 nM, about 200 nM, about 100 nM, about 90 nM, about 80 nM, about 70 nM, about 60 nM, about 50 nM, about 40 nM, about 30 nM, about 20 nM, about 10 nM, or about 5 nM, or about 1 nM.

In various embodiments, the CD8 targeting moiety binds but does not functionally modulate the antigen of interest, *i.e.*, CD8. For instance, in various embodiments, the CD8 targeting moiety simply targets the antigen but does not substantially functionally modulate the antigen, *e.g.* it does not substantially inhibit, reduce or neutralize a biological effect that the antigen has. In various embodiments, the CD8 targeting moiety binds an epitope that is physically separate from an antigen site that is important for its biological activity (*e.g.* an antigen's active site).

Such non-functionally modulating (*e.g.* non-neutralizing) binding finds use in various embodiments of the present invention, including methods in which the CD8 targeting moiety is used to directly or indirectly recruit active immune cells to a site of need via an effector antigen. For example, in various embodiments, the CD8 targeting moiety may be used to directly or indirectly recruit cytotoxic T cells via CD8 to a tumor cell in a method of reducing or eliminating a tumor (*e.g.* the CD8 binding agent may comprise a targeting moiety having an anti-CD8 antigen recognition domain and a targeting moiety having a recognition domain (*e.g.* an antigen recognition domain) directed against a tumor antigen or receptor). In such embodiments, it is desirable to directly or indirectly recruit CD8-expressing cytotoxic T cells but not to neutralize the CD8 activity. In these embodiments, CD8 signaling is an important piece of the tumor reducing or eliminating effect.

PD-1, PD-L1, or PD-L2 Targeting Moieties

In some embodiments, the targeting moiety is a PD-1, PD-L1, or PD-L2 targeting moiety that is a protein-based agent capable of specific binding to PD-1, PD-L1, or PD-L2. In some embodiments, the PD-1, PD-L1, or PD-L2 targeting moiety binds but does not functionally modulate (*e.g.*, partially or fully neutralize) the antigen of interest, *i.e.*, PD-1, PD-L1, or PD-L2. For instance, in various embodiments, the PD-1, PD-L1, or PD-L2 targeting moiety simply targets the antigen but does not substantially functionally modulate (*e.g.* partially or fully inhibit, reduce or neutralize) a biological effect that the antigen has. In various embodiments, the PD-1, PD-L1, or PD-L2 targeting moiety binds an epitope that is physically separate from an antigen site that is important for its biological activity (*e.g.* an antigen's active site).

PD-1 Targeting Moieties

Programmed cell death protein 1, also known as PD-1 and cluster of differentiation 279 (CD279), is a cell surface receptor that is primarily expressed on activated T cells, B cells, and macrophages. PD-1 has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (*i.e.*, PD-L1 and/or PD-L2). PD-1 plays an important role in down-regulating the immune system and promoting self tolerance by suppressing T cell inflammatory activity. PD-1 is a type I transmembrane glycoprotein containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail that is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains two tyrosine-based signaling motifs, an ITIM (immunoreceptor tyrosine-based inhibition motif) and an ITSM (immunoreceptor tyrosine-based switch motif).

In some embodiments, the PD-1 targeting moiety comprises an antigen recognition domain that recognizes an epitope present on PD-1. In an embodiment, the antigen-recognition domain recognizes one or more linear epitopes present on PD-1. In some embodiments, a linear epitope refers to any continuous sequence of amino acids present on PD-1. In another embodiment, the antigen-recognition domain recognizes one or more conformational epitopes present on PD-1. As used herein, a conformation epitope refers to one or more sections of amino acids (which may be discontinuous) which form a three-dimensional surface with features and/or shapes and/or tertiary structures capable of being recognized by an antigen recognition domain.

In some embodiments, the PD-1 targeting moiety may bind to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants of human PD-1. In various embodiments, the PD-1 targeting moiety may bind to any forms of the human PD-1. In an embodiment, the PD-1 targeting moiety binds to a phosphorylated form of PD-1.

In an embodiment, the PD-1 targeting moiety comprises an antigen recognition domain that recognizes one or more epitopes present on human PD-1. In an embodiment, the human PD-1 comprises the amino acid sequence of (signal peptide underlined):

MQIPQAPWPVVWAVLQLGWRPGWFLDSPDRPWNPPTFSPALLVVTEGD
NATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRV
TQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERR
AEVPTAHPSPSPRPAGQFQTLVVGVVGGLLGSLVLLVWVLAVICSRAARGT
IGARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQTEYA

TIVFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL (SEQ ID NO: 696).

In another embodiment, the human PD-1 comprises the amino acid sequence of SEQ ID NO: 696 without the amino-terminal signal peptide.

In some embodiments, the PD-1 targeting moiety is capable of specific binding. In various embodiments, the PD-1 targeting moiety comprises an antigen recognition domain such as an antibody or derivatives thereof.

In some embodiments, the PD-1 targeting moiety comprises an antibody derivative or format. In some embodiments, the PD-1 targeting moiety comprises a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (cysteine knot protein, knottin), a DARPin; a Tetranectin; an Affibody; a Transbody; an Anticalin; an AdNectin; an Affilin; an alphabody; a bicyclic peptide; an Affimer, a Microbody; an aptamer; an alterase; a plastic antibody; a phylomer; a stradobody; a maxibody; an evibody; a fynomer, an armadillo repeat protein, a Kunitz domain, an avimer, an atrimer, a probody, an immunobody, a triomab, a troybody; a pepbody; a vaccibody, a UniBody; a DuoBody, a Fv, a Fab, a Fab', a $F(ab')_2$, a peptide mimetic molecule, or a small (e.g. synthetic or natural) molecule , e.g. without limitation, as described in US Patent Nos. or Patent Publication Nos. US 7,417,130, US 2004/132094, US 5,831,012, US 2004/023334, US 7,250,297, US 6,818,418, US 2004/209243, US 7,838,629, US 7,186,524, US 6,004,746, US 5,475,096, US 2004/146938, US 2004/157209, US 6,994,982, US 6,794,144, US 2010/239633, US 7,803,907, US 2010/119446, and/or US 7,166,697, the contents of which are hereby incorporated by reference in their entireties. *See* also, Storz MAbs. 2011 May-Jun; 3(3): 310–317.

In some embodiments, the PD-1 targeting moiety comprises a single-domain antibody, such as a VHH. The VHH may be derived from, for example, an organism that produces VHH antibody such as a camelid, a shark, or the VHH may be a designed VHH. VHHs are antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally-occurring heavy-chain antibodies. VHH technology is based on fully functional antibodies from camelids that lack light chains. These heavy-chain antibodies contain a single variable domain (V_HH) and two constant domains (CH2 and CH3).

In an embodiment, the PD-1 targeting moiety comprises a VHH. In some embodiments, the VHH is a humanized VHH or camelized VHH.

In some embodiments, the VHH comprises a fully human V_H domain, *e.g.* a HUMABODY (Crescendo Biologics, Cambridge, UK). In some embodiments, fully human V_H domain, *e.g.* a HUMABODY is monovalent, bivalent, or trivalent. In some embodiments, the fully human V_H domain, *e.g.* a HUMABODY is mono- or multi-specific such as monospecific, bispecific, or trispecific. Illustrative fully human V_H domains, *e.g.* HUMABODIES are described in, for example, WO2016/113555 and WO2016/113557, the entire disclosure of which is incorporated by reference.

In some embodiments, the PD-1 targeting moiety comprises a VHH comprising a single amino acid chain having four “framework regions” or FRs and three “complementary determining regions” or CDRs. As used herein, “framework region” or “FR” refers to a region in the variable domain which is located between the CDRs. As used

herein, “complementary determining region” or “CDR” refers to variable regions in VHHs that contains the amino acid sequences capable of specifically binding to antigenic targets.

In various embodiments, the PD-1 targeting moiety comprises a VHH having a variable domain comprising at least one CDR1, CDR2, and/or CDR3 sequences. In various embodiments, the PD-1 binding agent comprises a VHH having a variable region comprising at least one FR1, FR2, FR3, and FR4 sequences.

In some embodiments, the CDR1 sequence is selected from SEQ ID Nos.: 697-710.

In some embodiments, the CDR2 sequence is selected from SEQ ID Nos.: 711-724.

In some embodiments, the CDR3 sequence is selected from SEQ ID Nos.: 725-738.

In various exemplary embodiments, the PD-1 targeting moiety comprises an amino acid sequence selected from the following sequences:

2PD23 (SEQ ID NO: 739); 2PD26 (SEQ ID NO: 740); 2PD90 (SEQ ID NO: 741); 2PD-106 (SEQ ID NO: 742); 2PD-16 (SEQ ID NO: 743); 2PD71 (SEQ ID NO: 744); 2PD-152 (SEQ ID NO: 745); 2PD-12 (SEQ ID NO: 746); 3PD55 (SEQ ID NO: 747); 3PD82 (SEQ ID NO: 748); 2PD8 (SEQ ID NO: 749); 2PD27 (SEQ ID NO: 750); 2PD82 (SEQ ID NO: 751); or 3PD36 (SEQ ID NO: 752).

In some embodiments, the PD-1 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 739-752 (provided above) without the terminal histidine tag sequence (*i.e.*, HHHHHH; SEQ ID NO: 393).

In some embodiments, the PD-1 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 739-752 (provided above) without the HA tag (*i.e.*, YPYDVPDYGS; SEQ ID NO: 394).

In some embodiments, the PD-1 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 739-752 (provided above) without the AAA linker (*i.e.*, AAA).

In some embodiments, the PD-1 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 739-752 (provided above) without the AAA linker, HA tag, and terminal histidine tag sequence (*i.e.*, AAAYPYDVPDYGSHHHHHH; SEQ ID NO: 395).

In some embodiments, the present technology contemplates the use of any natural or synthetic analogs, mutants, variants, alleles, homologs and orthologs (herein collectively referred to as “analogs”) of the PD-1 targeting moiety described herein. In some embodiments, the amino acid sequence of the PD1 targeting moiety further includes an amino acid analog, an amino acid derivative, or other non-classical amino acids.

In some embodiments, the PD-1 targeting moiety comprises the anti-PD-1 antibody pembrolizumab (aka MK-3475, KEYTRUDA), or fragments thereof. Pembrolizumab and other humanized anti-PD-1 antibodies are disclosed in Hamid, *et al.* (2013) New England Journal of Medicine 369 (2): 134-44, US 8,354,509, and WO 2009/114335, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, pembrolizumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 753; and/or a light chain comprising the amino acid sequence of (SEQ ID NO: 754).

In an embodiment, the PD-1 targeting moiety comprises the anti-PD-1 antibody, nivolumab (aka BMS-936558, MDX-1106, ONO-4538, OPDIVO), or fragments thereof. Nivolumab (clone 5C4) and other human monoclonal antibodies that specifically bind to PD-1 are disclosed in US 8,008,449 and WO 2006/121168, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, nivolumab or an antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 755; and/or a light chain comprising the amino acid sequence of (SEQ ID NO: 756).

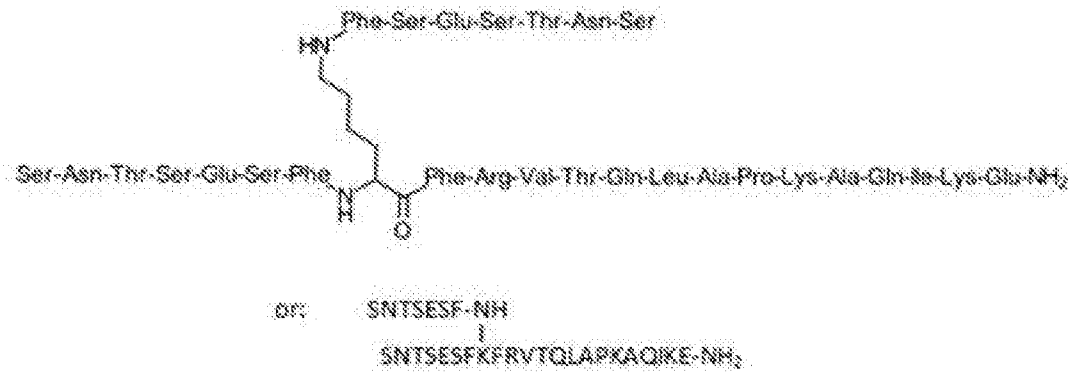
In an embodiment, the PD-1 targeting moiety comprises the anti-PD-1 antibody pidilizumab (aka CT-011, hBAT or hBAT-1), or fragments thereof. Pidilizumab and other humanized anti-PD-l monoclonal antibodies are disclosed in US 2008/0025980 and WO 2009/101611, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, the anti-PD-1 antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a light chain variable regions comprising an amino acid sequence selected from SEQ ID NOS: 15-18 of US 2008/0025980 (SEQ ID Nos: 757-760 of this application); and/or a heavy chain comprising an amino acid sequence selected from SEQ ID NOS: 20-24 of US 2008/0025980 (SEQ ID Nos: 761-765 of this application).

In an embodiment, the targeting moiety comprises a light chain comprising SEQ ID NO: 18 of US 2008/0025980 (SEQ ID NO: 760) and a heavy chain comprising SEQ ID NO: 22 of US 2008/0025980 (SEQ ID NO: 763).

In an embodiment, the PD-1 targeting moiety comprises AMP-514 (aka MEDI-0680).

In an embodiment, the PD-1 targeting moiety comprises the PD-L2-Fc fusion protein AMP-224, which is disclosed in WO2010/027827 and WO 2011/066342, the entire disclosures of which are hereby incorporated by reference. In such an embodiment, the targeting moiety may include a targeting domain which comprises SEQ ID NO: 4 of WO2010/027827 (SEQ ID NO: 766 of this application) and/or the B7-DC fusion protein which comprises SEQ ID NO:83 of WO2010/027827 (SEQ ID NO: 767 of this application).

In an embodiment, the PD-1 targeting moiety comprises the peptide AUNP 12 or any of the other peptides disclosed in US 2011/0318373 or 8,907,053. For example, the targeting moiety may comprise AUNP 12 (*i.e.*, Compound 8 or SEQ ID NO:49 of US 2011/0318373) which has the sequence of:



In an embodiment, the PD-1 targeting moiety comprises the anti-PD-1 antibody 1E3, or fragments thereof, as disclosed in US 2014/0044738, the entire disclosures of which are hereby incorporated by reference. In illustrative

embodiments, 1E3 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 768; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 769.

In an embodiment, the PD-1 targeting moiety comprises the anti-PD-1 antibody 1E8, or fragments thereof, as disclosed in US 2014/0044738, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 1E8 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 770; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 771.

In an embodiment, the PD-1 targeting moiety comprises the anti-PD-1 antibody 1H3, or fragments thereof, as disclosed in US 2014/0044738, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 1H3 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 772; and/or light chain variable region comprising the amino acid sequence of SEQ ID NO: 773.

In an embodiment, the PD-1 targeting moiety comprises a VHH directed against PD-1 as disclosed, for example, in US 8,907,065 and WO 2008/071447, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, the VHHs against PD-1 comprise SEQ ID NOS: 347-351 of US 8,907,065 (SEQ ID Nos: 774-778).

In an embodiment, the PD-1 targeting moiety comprises any one of the anti-PD-1 antibodies, or fragments thereof, as disclosed in US2011/0271358 and WO2010/036959, the entire contents of which are hereby incorporated by reference. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID NOS: 25-29 of US2011/0271358 (SEQ ID Nos: 779-783 of this application); and/or a light chain comprising an amino acid sequence selected from SEQ ID NOS: 30-33 of US2011/0271358 (SEQ ID Nos: 784-787 of this application).

In some embodiments, the PD-1 targeting moiety is an antibody directed against PD-1, or an antibody fragment thereof, selected from TSR-042 (Tesaro, Inc.), REGN2810 (Regeneron Pharmaceuticals, Inc.), PDR001 (Novartis Pharmaceuticals), and BGB-A317 (BeiGene Ltd.)

In one embodiment, the targeting moiety binds to PD-1 and the signaling moiety is a wild type IFNα or a modified IFNα. In some embodiments, the Fc chimeric protein is in one of the configurations shown in FIGs. 4A to 4D, where the targeting moiety binds to PD-1 and the signaling moiety is a wild type IFNα. In some embodiments, the targeting moiety binds to PD-1 (*e.g.*, scFv) and the signaling moiety is a wild type IFNα2.

PD-L1 Targeting Moieties

In some embodiments, the targeting moiety is a PD-L1 targeting moiety. Programmed death-ligand 1 (PD-L1) also known as cluster of differentiation 274 (CD274) or B7 homolog 1 (B7-H1) is a type 1 transmembrane protein that has been speculated to play a major role in suppressing the immune system. PD-L1 is upregulated on

macrophages and dendritic cells (DC) in response to LPS and GM-CSF treatment, and on T cells and B cells upon TCR and B cell receptor signaling.

In various embodiments, the PD-L1 targeting moiety comprises an antigen recognition domain that recognizes an epitope present on PD-L1. In an embodiment, the antigen-recognition domain recognizes one or more linear epitopes present on PD-L1. In some embodiment, a linear epitope refers to any continuous sequence of amino acids present on PD-L1. In another embodiment, the antigen-recognition domain recognizes one or more conformational epitopes present on PD-L1. As used herein, a conformation epitope refers to one or more sections of amino acids (which may be discontinuous) which form a three-dimensional surface with features and/or shapes and/or tertiary structures capable of being recognized by an antigen recognition domain.

In various embodiments, the PD-L1 targeting moiety may bind to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants of human PD-L1. In various embodiments, the PD-L1 targeting moiety may bind to any forms of the human PD-L1. In an embodiment, the PD-L1 targeting moiety binds to a phosphorylated form of PD-L1. In an embodiment, the PD-L1 targeting moiety binds to an acetylated form of PD-L1.

In an embodiment, the PD-L1 targeting moiety comprises an antigen recognition domain that recognizes one or more epitopes present on human PD-L1. In an embodiment, the human PD-L1 comprises the amino acid sequence of (signal peptide underlined):

Isoform 1:

MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAA
LIVYWEMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDV
KLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHELTC
QAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIF
YCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRL
RKGRMMDVKKCGIQDTNSKKQSDTHLEET (SEQ ID NO: 788);

Isoform 2:

MRIFAVFIFMTYWHLLNAPYNKINQRILVVDPVTSEHELTCQAEGYPKAEVIW
TSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPEENH
TAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGRMMDVKKCGI
QDTNSKKQSDTHLEET (SEQ ID NO: 789); or

Isoform 3:

MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAAL
IVYWEMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVK
LQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHELTCQA
EGYPKAEVIWTSSDHQVLSGD (SEQ ID NO: 790).

In various embodiments, the PD-L1 targeting moiety is capable of specific binding. In various embodiments, the PD-L1 targeting moiety comprises an antigen recognition domain such as an antibody or derivatives thereof. In an embodiment, the PD-L1 targeting moiety comprises an antibody.

In some embodiments, the PD-L1 targeting moiety comprises an antibody derivative or format. In some embodiments, the PD-L1 targeting moiety comprises a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (cysteine knot protein, knottin), a DARPin; a Tetranectin; an Affibody; a Transbody; an Anticalin; an AdNectin; an alphabody; a bicyclic peptide; an Affilin; an Affimer, a Microbody; an aptamer; an alterase; a plastic antibody; a phylomer; a stradobody; a maxibody; an evibody; a fynomer, an armadillo repeat protein, a Kunitz domain, an avimer, an atrimer, a probody, an immunobody, a triomab, a troybody; a pepbody; a vaccibody, a UniBody; a DuoBody, a Fv, a Fab, a Fab', a $F(ab')_2$, a peptide mimetic molecule, or a small (e.g. synthetic or natural) molecule , e.g. without limitation, as described in US Patent Nos. or Patent Publication Nos. US 7,417,130, US 2004/132094, US 5,831,012, US 2004/023334, US 7,250,297, US 6,818,418, US 2004/209243, US 7,838,629, US 7,186,524, US 6,004,746, US 5,475,096, US 2004/146938, US 2004/157209, US 6,994,982, US 6,794,144, US 2010/239633, US 7,803,907, US 2010/119446, and/or US 7,166,697, the contents of which are hereby incorporated by reference in their entireties. *See* also, Storz MAbs. 2011 May-Jun; 3(3): 310–317.

In some embodiments, the PD-L1 targeting moiety comprises a single-domain antibody, such as a VHH. The VHH may be derived from, for example, an organism that produces VHH antibody such as a camelid, a shark, or the VHH may be a designed VHH. VHHs are antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally-occurring heavy-chain antibodies. VHH technology is based on fully functional antibodies from camelids that lack light chains. These heavy-chain antibodies contain a single variable domain (V_HH) and two constant domains (CH2 and CH3).

In an embodiment, the PD-L1 targeting moiety comprises a VHH. In some embodiments, the VHH is a humanized VHH or camelized VHH.

In some embodiments, the VHH comprises a fully human V_H domain, *e.g.* a HUMABODY (Crescendo Biologics, Cambridge, UK). In some embodiments, fully human V_H domain, *e.g.* a HUMABODY is monovalent, bivalent, or trivalent. In some embodiments, the fully human V_H domain, *e.g.* a HUMABODY is mono- or multi-specific such as monospecific, bispecific, or trispecific. Illustrative fully human V_H domains, *e.g.* HUMABODIES are described in, for example, WO2016/113555 and WO2016/113557, the entire disclosure of which is incorporated by reference.

In some embodiments, the PD-L1 targeting moiety comprises a VHH comprising a single amino acid chain having four “framework regions” or FRs and three “complementary determining regions” or CDRs. As used herein, “framework region” or “FR” refers to a region in the variable domain which is located between the CDRs. As used herein, “complementary determining region” or “CDR” refers to variable regions in VHHs that contains the amino acid sequences capable of specifically binding to antigenic targets.

In various embodiments, the PD-L1 targeting moiety comprises a VHH having a variable domain comprising at least one CDR1, CDR2, and/or CDR3 sequences. In various embodiments, the PD-L1 targeting moiety comprises a VHH having a variable region comprising at least one FR1, FR2, FR3, and FR4 sequences.

In some embodiments, the CDR1 sequence is selected from SEQ ID Nos.: 791-821.

In some embodiments, the CDR2 sequence is selected from SEQ ID Nos.: 822-852.

In some embodiments, the CDR3 sequence is selected from SEQ ID Nos.: 853-883.

In various exemplary embodiments, the PD-L1 targeting moiety comprises an amino acid sequence selected from the following sequences: 2LIG2 (SEQ ID NO: 884); 2LIG3 (SEQ ID NO: 885); 2LIG16 (SEQ ID NO: 886); 2LIG22 (SEQ ID NO: 887); 2LIG27 (SEQ ID NO: 888); 2LIG29 (SEQ ID NO: 889); 2LIG30 (SEQ ID NO: 890); 2LIG34 (SEQ ID NO: 891); 2LIG35 (SEQ ID NO: 892); 2LIG48 (SEQ ID NO: 893); 2LIG65 (SEQ ID NO: 894); 2LIG85 (SEQ ID NO: 895); 2LIG86 (SEQ ID NO: 896); 2LIG89 (SEQ ID NO: 897); 2LIG97 (SEQ ID NO: 898); 2LIG99 (SEQ ID NO: 899); 2LIG109 (SEQ ID NO: 900); 2LIG127 (SEQ ID NO: 901); 2LIG139 (SEQ ID NO: 902); 2LIG176 (SEQ ID NO: 903); 2LIG189 (SEQ ID NO: 904); 3LIG3 (SEQ ID NO: 905); 3LIG7 (SEQ ID NO: 906); 3LIG8 (SEQ ID NO: 907); 3LIG9 (SEQ ID NO: 908); 3LIG18 (SEQ ID NO: 909); 3LIG20 (SEQ ID NO: 910); 3LIG28 (SEQ ID NO: 911); 3LIG29 (SEQ ID NO: 912); 3LIG30 (SEQ ID NO: 913); or 3LIG33 (SEQ ID NO: 914).

In some embodiments, the PD-L1 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 884-914 (provided above) without the terminal histidine tag sequence (*i.e.*, HHHHHH; SEQ ID NO: 393).

In some embodiments, the PD-L1 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 884-914 (provided above) without the HA tag (*i.e.*, YPYDVPDYGS; SEQ ID NO: 394).

In some embodiments, the PD-L1 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 884-914 (provided above) without the AAA linker (*i.e.*, AAA).

In some embodiments, the PD-L1 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 884-914 (provided above) without the AAA linker, HA tag, and terminal histidine tag sequence (*i.e.*, AAAYPYDVPDYGSHHHHHH; SEQ ID NO: 395).

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody MEDI4736 (aka durvalumab), or fragments thereof. MEDI4736 is selective for PD-L1 and blocks the binding of PD-L1 to the PD-1 and CD80 receptors. MEDI4736 and antigen-binding fragments thereof for use in the methods provided herein comprises a heavy chain and a light chain or a heavy chain variable region and a light chain variable region. The sequence of MEDI4736 is disclosed in WO/2016/06272, the entire contents of which are hereby incorporated by reference. In illustrative embodiments, MEDI4736 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 915; and/or a light chain comprising the amino acid sequence of SEQ ID NO: 916.

In illustrative embodiments, the MEDI4736 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 4 of

WO/2016/06272 (SEQ ID NO: 917); and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 3 of WO/2016/06272 (SEQ ID NO: 918).

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody atezolizumab (aka MPDL3280A, RG7446), or fragments thereof. In illustrative embodiments, atezolizumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 919; and/or a light chain comprising the amino acid sequence of SEQ ID NO: 920.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody avelumab (aka MSB0010718C), or fragments thereof. In illustrative embodiments, avelumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 921; and/or a light chain comprising the amino acid sequence of SEQ ID NO: 922.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody BMS-936559 (aka 12A4, MDX-1105), or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, BMS-936559 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 923; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 924.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 3G10, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 3G10 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 925; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 926.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 10A5, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 10A5 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 927; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 928.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 5F8, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 5F8 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 929; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 930.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 10H10, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 10H10 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 931; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 932.

In an embodiment, PD-L1 the targeting moiety comprises the anti-PD-L1 antibody 1B12, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 1B12 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 933; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 934.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 7H1, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 7H1 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 935; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 936.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 11E6, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 11E6 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 937; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 938.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 12B7, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 12B7 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 939; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 940.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 13G4, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 13G4 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 941; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 942.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 1E12, or fragments thereof, as disclosed in US 2014/0044738, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 1E12 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 943; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 944.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 1F4, or fragments thereof, as disclosed in US 2014/0044738, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 1F4 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 945; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 946.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 2G11, or fragments thereof, as disclosed in US 2014/0044738, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 2G11 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 947; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 948.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 3B6, or fragments thereof, as disclosed in US 2014/0044738, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 3B6 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 949; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 950.

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 3D10, or fragments thereof, as disclosed in US 2014/0044738 and WO2012/145493, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 3D10 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 951; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 952.

In an embodiment, the PD-L1 targeting moiety comprises any one of the anti-PD-L1 antibodies disclosed in US2011/0271358 and WO2010/036959, the entire contents of which are hereby incorporated by reference. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID Nos: 34-38 of US2011/0271358 (SEQ ID Nos.: 953-957) and/or a light chain comprising an amino acid sequence selected from SEQ ID Nos: 39-42 of US2011/0271358 (SEQ ID Nos.: 958-961).

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 2.7A4, or fragments thereof, as disclosed in WO 2011/066389, US8,779,108, and US2014/0356353, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 2.7A4 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID No: 2 of WO 2011/066389 (SEQ ID NO: 962); and/or a light chain variable region comprising the amino acid sequence of SEQ ID No: 7 of WO 2011/066389 (SEQ ID NO: 963).

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 2.9D10, or fragments thereof, as disclosed in WO 2011/066389, US8,779,108, and US2014/0356353, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 2.9D10 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID No: 12 of WO 2011/066389 (SEQ ID NO: 964); and/or a light chain variable region comprising the amino acid sequence of SEQ ID No: 17 of WO 2011/066389 (SEQ ID NO: 965).

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 2.14H9, or fragments thereof, as disclosed in WO 2011/066389, US8,779,108, and US2014/0356353, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 2.14H9 or an antigen-binding fragment thereof for use in

the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID No: 22 of WO 2011/066389 (SEQ ID NO: 966); and/or a light chain variable region comprising the amino acid sequence of SEQ ID No: 27 of WO 2011/066389 (SEQ ID NO: 967).

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 2.20A8, or fragments thereof, as disclosed in WO 2011/066389, US8,779,108, and US2014/0356353, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 2.20A8 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID No: 32 of WO 2011/066389 (SEQ ID NO: 968); and/or a light chain variable region comprising the amino acid sequence of SEQ ID No: 37 of WO 2011/066389 (SEQ ID NO: 969).

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 3.15G8, or fragments thereof, as disclosed in WO 2011/066389, US8,779,108, and US2014/0356353, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 3.15G8 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID No: 42 of WO 2011/066389 (SEQ ID NO: 970); and/or a light chain variable region comprising the amino acid sequence of SEQ ID No: 47 of WO 2011/066389 (SEQ ID NO: 971).

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 3.18G1, or fragments thereof, as disclosed in WO 2011/066389, US8,779,108, and US2014/0356353, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 3.18G1 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID No: 52 of WO 2011/066389 (SEQ ID NO: 972); and/or a light chain variable region comprising the amino acid sequence of SEQ ID No: 57 of WO 2011/066389 (SEQ ID NO: 973).

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 2.7A4OPT, or fragments thereof, as disclosed in WO 2011/066389, US8,779,108, and US2014/0356353, and US2014/0356353, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 2.7A4OPT or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID No: 62 of WO 2011/066389 (SEQ ID NO: 974); and/or a light chain variable region comprising the amino acid sequence of SEQ ID No: 67 of WO 2011/066389 (SEQ ID NO: 975).

In an embodiment, the PD-L1 targeting moiety comprises the anti-PD-L1 antibody 2.14H9OPT, or fragments thereof, as disclosed in WO 2011/066389, US8,779,108, and US2014/0356353, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, 2.14H9OPT or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID No: 72 of WO 2011/066389 (SEQ ID NO: 976); and/or a light chain variable region comprising the amino acid sequence of SEQ ID No: 77 of WO 2011/066389 (SEQ ID NO: 977).

In an embodiment, the PD-L1 targeting moiety comprises any one of the anti-PD-L1 antibodies disclosed in WO2016/061142, the entire contents of which are hereby incorporated by reference. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy

chain comprising an amino acid sequence selected from SEQ ID Nos: 18, 30, 38, 46, 50, 54, 62, 70, and 78 of WO2016/061142 (SEQ ID Nos.: 978, 979, 980, 981, 982, 983, 984, 985, and 986, respectively); and/or a light chain comprising an amino acid sequence selected from SEQ ID Nos: 22, 26, 34, 42, 58, 66, 74, 82, and 86 of WO2016/061142 (SEQ ID Nos.: 987, 988, 989, 990, 991, 992, 993, 994, and 995, respectively).

In an embodiment, the PD-L1 targeting moiety comprises any one of the anti-PD-L1 antibodies disclosed in WO2016/022630, the entire contents of which are hereby incorporated by reference. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID Nos: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, and 46 of WO2016/022630 (SEQ ID Nos.: 996, 997, 998, 999, 1000, 1001, 1002, 1003, 1004, 1005, 1006, and 1007, respectively); and/or a light chain comprising an amino acid sequence selected from SEQ ID Nos: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 of WO2016/022630 (SEQ ID Nos.: 1008, 1009, 1010, 1011, 1012, 1013, 1014, 1015, 1016, 1017, 1018, and 1019, respectively).

In an embodiment, the PD-L1 targeting moiety comprises any one of the anti-PD-L1 antibodies disclosed in WO2015/112900, the entire contents of which are hereby incorporated by reference. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID Nos: 38, 50, 82, and 86 of WO 2015/112900 (SEQ ID Nos.: 1020, 1021, 1022, and 1023, respectively); and/or a light chain comprising an amino acid sequence selected from SEQ ID Nos: 42, 46, 54, 58, 62, 66, 70, 74, and 78 of WO 2015/112900 (SEQ ID Nos.: 1024, 1025, 1026, 1027, 1028, 1029, 1030, 1031, and 1032, respectively).

In an embodiment, the PD-L1 targeting moiety comprises any one of the anti-PD-L1 antibodies disclosed in WO 2010/077634 and US 8,217,149, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, the anti-PD-L1 antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain region comprising the amino acid sequence of SEQ ID No: 20 of WO 2010/077634 (SEQ ID NO: 1033); and/or a light chain variable region comprising the amino acid sequence of SEQ ID No: 21 of WO 2010/077634 (SEQ ID NO: 1034). In an embodiment, the PD-L1 targeting moiety comprises any one of the anti-PD-L1 antibodies obtainable from the hybridoma accessible under CNCM deposit numbers CNCM I-4122, CNCM I-4080 and CNCM I-4081 as disclosed in US 20120039906, the entire disclosures of which are hereby incorporated by reference.

In an embodiment, the PD-L1 targeting moiety comprises a VHH directed against PD-L1 as disclosed, for example, in US 8,907,065 and WO 2008/071447, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, the VHHs against PD-L1 comprise SEQ ID NOS: 394-399 of US 8,907,065 (SEQ ID NOS: 1035-1040, respectively).

In some embodiments, the targeting moiety binds to PD-L1 and the signaling moiety is a wild type IFNα or a modified IFNα. In some embodiments, the Fc chimeric protein is in one of the forms shown in FIGs. 4A to 4D, where the targeting moiety binds to PD-L1 and the signaling moiety is a wild type IFNα. In some embodiments, the targeting moiety binds to PD-L1 (*e.g.*, scFv) and the signaling moiety is a wild type IFNα2.

PD-L2 Targeting Moieties

In some embodiments, the targeting moiety is directed against PD-L2. In some embodiments, the targeting moiety selectively binds a PD-L2 polypeptide. In some embodiments, the PD-L2 targeting moiety comprises an antibody, an antibody derivative or format, a peptide or polypeptide, or a fusion protein that selectively binds a PD-L2 polypeptide.

In an embodiment, the PD-L2 targeting moiety comprises a VHH directed against PD-L2 as disclosed, for example, in US 8,907,065 and WO 2008/071447, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, the VHHs against PD-L2 comprise SEQ ID Nos: 449-455 of US 8,907,065 (SEQ ID Nos: 1041-1047, respectively).

In an embodiment, the PD-L2 targeting moiety comprises any one of the anti-PD-L2 antibodies disclosed in US2011/0271358 and WO2010/036959, the entire contents of which are hereby incorporated by reference. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID Nos: 43-47 of US2011/0271358 (SEQ ID Nos.: 1048-1052, respectively); and/or a light chain comprising an amino acid sequence selected from SEQ ID Nos: 48-51 of US2011/0271358 (SEQ ID Nos.: 1053-1056, respectively).

In some embodiments, the present technology contemplates the use of any natural or synthetic analogs, mutants, variants, alleles, homologs and orthologs (herein collectively referred to as "analogs") of the PD-1, PD-L1, or PD-L2 targeting moieties described herein. In some embodiments, the amino acid sequence of the PD-1, PD-L1, or PD-L2 targeting moiety further includes an amino acid analog, an amino acid derivative, or other non-classical amino acids.

In various embodiments, the PD-1, PD-L1, or PD-L2 targeting moieties disclosed herein comprise a sequence that targets PD-1, PD-L1, or PD-L2 which is at least about 60%, at least about 61%, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to any of the PD-1, PD-L1, and/or PD-L2 sequences disclosed herein (*e.g.* about 60%, or about 61%, or about 62%, or about 63%, or about 64%, or about 65%, or about 66%, or about 67%, or about 68%, or about 69%, or about 70%, or about 71%, or about 72%, or about 73%, or about 74%, or about 75%, or about 76%, or about 77%, or about 78%, or about 79%, or about 80%, or about 81%, or about 82%, or about 83%, or about 84%, or about 85%, or about 86%, or about 87%, or about 88%, or about 89%, or about 90%, or about 91%, or about 92%, or about 93%, or about 94%, or about 95%, or about 96%, or about 97%, or about 98%, about 99% or about 100% sequence identity with any of the PD-1, PD-L1, and/or PD-L2 sequences disclosed herein).

In various embodiments, the PD-1, PD-L1, or PD-L2 targeting moiety comprises a binding agent comprising an amino acid sequence having one or more amino acid mutations with respect to any one of the PD-1, PD-L1, or PD-L2 sequences disclosed herein. In various embodiments, the PD-1, PD-L1, or PD-L2 targeting moiety comprises a binding agent comprising an amino acid sequence having one, or two, or three, or four, or five, or six, or seen, or eight, or nine, or ten, or fifteen, or twenty amino acid mutations with respect to any one of the sequences disclosed herein. In some embodiments, the one or more amino acid mutations may be independently selected from substitutions, insertions, deletions, and truncations.

In some embodiments, the amino acid mutations are amino acid substitutions, and may include conservative and/or non-conservative substitutions.

"Conservative substitutions" may be made, for instance, on the basis of similarity in polarity, charge, size, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the amino acid residues involved. The 20 naturally occurring amino acids can be grouped into the following six standard amino acid groups: (1) hydrophobic: Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr; Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe.

As used herein, "conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed within the same group of the six standard amino acid groups shown above. For example, the exchange of Asp by Glu retains one negative charge in the so modified polypeptide. In addition, glycine and proline may be substituted for one another based on their ability to disrupt α-helices.

As used herein, "non-conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed in a different group of the six standard amino acid groups (1) to (6) shown above.

In various embodiments, the substitutions may also include non-classical amino acids. Exemplary non-classical amino acids include, but are not limited to, selenocysteine, pyrrolysine, *N*-formylmethionine β-alanine, GABA and δ-Aminolevulinic acid, 4-aminobenzoic acid (PABA), D-isomers of the common amino acids, 2,4-diaminobutyric acid, α-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ-Abu, ε-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosme, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β-alanine, fluoro-amino acids, designer amino acids such as β methyl amino acids, C α-methyl amino acids, N α-methyl amino acids, and amino acid analogs in general.

In various embodiments, the amino acid mutation may be in the CDRs of the targeting moiety (*e.g.*, the CDR1, CDR2 or CDR3 regions). In another embodiment, amino acid alteration may be in the framework regions (FRs) of the targeting moiety (*e.g.*, the FR1, FR2, FR3, or FR4 regions).

Modification of the amino acid sequences may be achieved using any known technique in the art *e.g.*, site-directed mutagenesis or PCR based mutagenesis. Such techniques are described, for example, in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., 1989 and Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons, New York, N.Y., 1989.

In various embodiments, the mutations do not substantially reduce the present PD-1, PD-L1, or PD-L2 targeting moiety's capability to specifically bind to PD-1, PD-L1, or PD-L2. In various embodiments, the mutations do not substantially reduce the PD-1, PD-L1, or PD-L2 targeting moiety's capability to specifically bind to PD-1, PD-L1, or PD-L2 and without functionally modulating (*e.g.*, partially or fully neutralizing) PD-1, PD-L1, or PD-L2.

In various embodiments, the binding affinity of the PD-1, PD-L1, or PD-L2 targeting moiety for the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or monomeric and/or dimeric forms and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric and/or dimeric forms) of human PD-1, PD-L1, or PD-L2 may be described by the equilibrium dissociation constant (K_D). In various embodiments, the PD-1, PD-L1, or PD-L2 targeting moiety binds to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric and/or dimeric forms) of human PD-1, PD-L1, or PD-L2 with a K_D of less than about 1 uM, about 900 nM, about 800 nM, about 700 nM, about 600 nM, about 500 nM, about 400 nM, about 300 nM, about 200 nM, about 100 nM, about 90 nM, about 80 nM, about 70 nM, about 60 nM, about 50 nM, about 40 nM, about 30 nM, about 20 nM, about 10 nM, or about 5 nM, or about 1 nM.

In some embodiments, the PD-1, PD-L1, and/or PD-L2 targeting moieties disclosed herein may comprise any combination of heavy chain, light chain, heavy chain variable region, light chain variable region, complementarity determining region (CDR), and framework region sequences that target PD-1, PD-L1, and/or PD-L2 as disclosed herein.

Additional antibodies, antibody derivatives or formats, peptides or polypeptides, or fusion proteins that selectively bind or target PD-1, PD-L1 and/or PD-L2 are disclosed in WO 2011/066389, US 2008/0025980, US 2013/0034559, US 8,779,108, US 2014/0356353, US 8,609,089, US 2010/028330, US 2012/0114649, WO 2010/027827, WO 2011,/066342, US 8,907,065, WO 2016/062722, WO 2009/101611, WO2010/027827, WO 2011/066342, WO 2007/005874 , WO 2001/014556, US2011/0271358, WO 2010/036959, WO 2010/077634, US 8,217,149, US 2012/0039906, WO 2012/145493, US 2011/0318373, U.S. Patent No. 8,779,108, US 20140044738, WO 2009/089149, WO 2007/00587, WO 2016061142, WO 2016,02263, WO 2010/077634, and WO 2015/112900, the entire disclosures of which are hereby incorporated by reference.

SIRP1α Targeting Moieties

In some embodiments, the targeting moiety binds a signal regulatory protein α-1 (SIRP1α). SIRP1α (also known as SIRPα) belongs to a family of cell immune receptors encompassing inhibitory (SIRPα), activating (SIRPβ), nonsignaling (SIRPγ) and soluble (SIRPδ) members. SIRP1α is expressed primarily on myeloid cells, including macrophages, granulocytes, myeloid dendritic cells (DCs), mast cells, and their precursors, including hematopoietic stem cells. SIRP1α acts as an inhibitory receptor that interacts with a broadly expressed transmembrane glycoprotein CD47 to regulate phagocytosis. In particular, the binding of SIRP1α on macrophages by CD47 expressed on target cells, generates an inhibitory signal that negatively regulates phagocytosis of the target cell.

In some embodiments, the SIRP1α targeting moiety specifically recognizes and binds SIRP1α on macrophages.

In some embodiments, the SIRP1α targeting moiety specifically recognizes and binds SIRP1α on monocytes.

In some embodiments, the SIRP1α targeting moiety specifically recognizes and binds SIRP1α on TAMs (Tumor Associated Macrophages).

In some embodiments, the SIRP1α targeting moiety specifically recognizes and binds SIRP1α on dendritic cells, including without limitation cDC2 and pDC

In some embodiments, the SIRP1α targeting moiety recognizes one or more linear epitopes present on SIRP1α. In some embodiments, a linear epitope refers to any continuous sequence of amino acids present on SIRP1α. In another embodiment, the recognition domain recognizes one or more conformational epitopes present on SIRP1α. As used herein, a conformation epitope refers to one or more sections of amino acids (which may be discontinuous) which form a three-dimensional surface with features and/or shapes and/or tertiary structures capable of being recognized by an antigen recognition domain.

In some embodiments, the SIRP1α targeting moiety binds to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants of SIRP1α. In an embodiment, the SIRP1α is human SIRP1α. In various embodiments, the SIRP1α targeting moiety may bind to any forms of the human SIRP1α, including monomeric, dimeric, heterodimeric, multimeric and associated forms. In an embodiment, the SIRP1α targeting moiety binds to the monomeric form of SIRP1α. In another embodiment, the SIRP1α targeting moiety binds to a dimeric form of SIRP1α.

In some embodiments, the SIRP1α targeting moiety comprises a recognition domain that recognizes one or more epitopes present on human SIRP1α. In an embodiment, the SIRP1α targeting moiety comprises a recognition domain that recognizes human SIRP1α with a signal peptide sequence. An exemplary human SIRP1α polypeptide with a signal peptide sequence is SEQ ID NO:1057.

In some embodiments, the SIRP1α targeting moiety comprises a recognition domain that recognizes human SIRP1α without a signal peptide sequence. An exemplary human SIRP1α polypeptide without a signal peptide sequence is SEQ ID NO: 1058.

In some embodiments, the SIRP1α targeting moiety comprises a recognition domain that recognizes a polypeptide encoding human SIRP1α isoform 2 (SEQ ID NO: 1059).

In some embodiment, the SIRP1α targeting moiety comprises a recognition domain that recognizes a polypeptide encoding human SIRP1α isoform 4 (SEQ ID NO:1060).

In some embodiments, the SIRP1α targeting moiety may be any protein-based agent capable of specific binding, such as an antibody or derivatives thereof.

In some embodiments, the SIRP1α targeting moiety comprises antibody derivatives or formats. In some embodiments, the SIRP1α targeting moiety comprises a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (cysteine knot protein, knottin), a DARPin; a Tetranectin; an Affibody; a Transbody; an Anticalin; an AdNectin; an alphabody; a bicyclic peptide; an Affilin; a Microbody; a peptide aptamer; an alterase; a plastic antibodies; a

phylomer; a stradobody; a maxibody; an evibody; a fynomer, an armadillo repeat protein, a Kunitz domain, an avimer, an atrimer, a probody, an immunobody, a triomab, a troybody; a pepbody; a vaccibody, a UniBody; Affimers, a DuoBody, a Fv, a Fab, a Fab', a $F(ab')_2$, a peptide mimetic molecule, or a small (e.g. synthetic or natural) molecule , e.g. without limitation, as described in US Patent Nos. or Patent Publication Nos. US 7,417,130, US 2004/132094, US 5,831,012, US 2004/023334, US 7,250,297, US 6,818,418, US 2004/209243, US 7,838,629, US 7,186,524, US 6,004,746, US 5,475,096, US 2004/146938, US 2004/157209, US 6,994,982, US 6,794,144, US 2010/239633, US 7,803,907, US 2010/119446, and/or US 7,166,697, the contents of which are hereby incorporated by reference in their entireties. *See* also, Storz MAbs. 2011 May-Jun; 3(3): 310–317.

In some embodiments, the SIRP1α targeting moiety comprises a single-domain antibody, such as VHH from, for example, an organism that produces VHH antibody such as a camelid, a shark, or a designed VHH. VHHs are antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally-occurring heavy-chain antibodies. VHH technology is based on fully functional antibodies from camelids that lack light chains. These heavy-chain antibodies contain a single variable domain (VHH) and two constant domains (CH2 and CH3).

In some embodiments, the SIRP1α targeting moiety comprises a VHH. In some embodiments, the VHH is a humanized VHH or camelized VHH.

In some embodiments, the VHH comprises a fully human V_H domain, *e.g.* a HUMABODY (Crescendo Biologics, Cambridge, UK). In some embodiments, fully human V_H domain, *e.g.* a HUMABODY is monovalent, bivalent, or trivalent. In some embodiments, the fully human V_H domain, *e.g.* a HUMABODY is mono- or multi-specific such as monospecific, bispecific, or trispecific. Illustrative fully human V_H domains, *e.g.* HUMABODIES are described in, for example, WO 2016/113555 and WO2016/113557, the entire disclosure of which is incorporated by reference.

For example, in some embodiments, the SIRP1α targeting moiety comprises one or more antibodies, antibody derivatives or formats, peptides or polypeptides, VHHs, or fusion proteins that selectively bind SIRP1α. In some embodiments, the SIRP1α targeting moiety comprises an antibody or derivative thereof that specifically binds to SIRP1α. In some embodiments, the SIRP1α targeting moiety comprises a camelid heavy chain antibody (VHH) that specifically binds to SIRP1α.

In some embodiments, the SIRP1α targeting moiety is a VHH comprising a single amino acid chain having four "framework regions" or FRs and three "complementary determining regions" or CDRs. As used herein, "framework region" or "FR" refers to a region in the variable domain which is located between the CDRs. As used herein, "complementary determining region" or "CDR" refers to variable regions in VHHs that contains the amino acid sequences capable of specifically binding to antigenic targets. In various embodiments, the present Fc-based chimeric protein complex comprises a VHH having a variable domain comprising at least one CDR1, CDR2, and/or CDR3 sequences.

In some embodiments, the SIRP1α targeting moiety may comprise any combination of heavy chain, light chain, heavy chain variable region, light chain variable region, complementarity determining region (CDR), and framework region sequences that is known to recognize and bind to SIRP1α.

In some embodiments, the present technology contemplates the use of any natural or synthetic analogs, mutants, variants, alleles, homologs and orthologs (herein collectively referred to as "analogs") of the SIRP1α targeting moieties described herein. In various embodiments, the amino acid sequence of the SIRP1α targeting moiety further includes an amino acid analog, an amino acid derivative, or other non-classical amino acids.

In some embodiments, the SIRP1α targeting moiety comprises a sequence that is at least 60% identical to any one of the SIRP1α sequences disclosed herein. For example, in some embodiments, the SIRP1α targeting moiety comprises a sequence that is at least about 60%, at least about 61%, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to any of the SIRP1α sequences disclosed herein (*e.g.* about 60%, or about 61%, or about 62%, or about 63%, or about 64%, or about 65%, or about 66%, or about 67%, or about 68%, or about 69%, or about 70%, or about 71%, or about 72%, or about 73%, or about 74%, or about 75%, or about 76%, or about 77%, or about 78%, or about 79%, or about 80%, or about 81%, or about 82%, or about 83%, or about 84%, or about 85%, or about 86%, or about 87%, or about 88%, or about 89%, or about 90%, or about 91%, or about 92%, or about 93%, or about 94%, or about 95%, or about 96%, or about 97%, or about 98%, about 99% or about 100% sequence identity to any one of the SIRP1α sequences disclosed herein).

In some embodiments, the SIRP1α targeting moiety comprises an amino acid sequence having one or more amino acid mutations with respect to any targeting moiety sequence that is known to recognize and bind to SIRP1α. In various embodiments, the SIRP1α targeting moiety comprises an amino acid sequence having one, or two, or three, or four, or five, or six, or seen, or eight, or nine, or ten, or fifteen, twenty, thirty, forty, or fifty amino acid mutations with respect to any targeting moiety sequence that is known to recognize and bind to SIRP1α. In some embodiments, the one or more amino acid mutations may be independently selected from substitutions, insertions, deletions, and truncations.

In some embodiments, the amino acid mutations are amino acid substitutions, and may include conservative and/or non-conservative substitutions.

"Conservative substitutions" may be made, for instance, on the basis of similarity in polarity, charge, size, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the amino acid residues involved. The 20 naturally occurring amino acids can be grouped into the following six standard amino acid groups: (1) hydrophobic: Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr; Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe.

As used herein, "conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed within the same group of the six standard amino acid groups shown above. For example, the exchange of

Asp by Glu retains one negative charge in the so modified polypeptide. In addition, glycine and proline may be substituted for one another based on their ability to disrupt α-helices.

As used herein, "non-conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed in a different group of the six standard amino acid groups (1) to (6) shown above.

In various embodiments, the substitutions may also include non-classical amino acids. Exemplary non-classical amino acids include, but are not limited to, selenocysteine, pyrrolysine, *N*-formylmethionine β-alanine, GABA and δ-Aminolevulinic acid, 4-aminobenzoic acid (PABA), D-isomers of the common amino acids, 2,4-diaminobutyric acid, α-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ-Abu, ε-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosme, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β-alanine, fluoro-amino acids, designer amino acids such as β methyl amino acids, C α-methyl amino acids, N α-methyl amino acids, and amino acid analogs in general.

In various embodiments, the amino acid mutation may be in the CDRs of the targeting moiety (*e.g.*, the CDR1, CDR2 or CDR3 regions). In another embodiment, amino acid alteration may be in the framework regions (FRs) of the targeting moiety (*e.g.*, the FR1, FR2, FR3, or FR4 regions).

Modification of the amino acid sequences may be achieved using any known technique in the art *e.g.*, site-directed mutagenesis or PCR based mutagenesis. Such techniques are described, for example, in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., 1989 and Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons, New York, N.Y., 1989.

In various embodiments, the mutations do not substantially reduce the SIRP1α targeting moiety's capability to specifically recognize and bind to SIRP1α. In various embodiments, the mutations do not substantially reduce the SIRP1α targeting moiety's ability to bind specifically to SIRP1α and without functionally modulating (*e.g.*, partially or fully neutralizing) SIRP1α.

In various embodiments, the binding affinity of the SIRP1α targeting moiety for the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or monomeric and/or dimeric forms and/or any other naturally occurring or synthetic analogs, variants, or mutants of SIRP1α may be described by the equilibrium dissociation constant (K_D). In various embodiments, the SIRP1α targeting moiety that binds to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric and/or dimeric forms) of SIRP1α with a K_D of less than about 1 uM, about 900 nM, about 800 nM, about 700 nM, about 600 nM, about 500 nM, about 400 nM, about 300 nM, about 200 nM, about 100 nM, about 90 nM, about 80 nM, about 70 nM, about 60 nM, about 50 nM, about 40 nM, about 30 nM, about 20 nM, about 10 nM, or about 5 nM, or about 1 nM.

In various embodiments, the SIRP1α targeting moiety binds but does not functionally modulate the antigen of interest, *i.e.*, SIRP1α. For example, in some embodiments, the SIRP1α targeting moiety simply targets the antigen but does not substantially functionally modulate (*e.g.* substantially inhibit, reduce or neutralize) a biological effect that the antigen has. In various embodiments, the targeting moiety of the present Fc-based chimeric protein

complex binds an epitope that is physically separate from an antigen site that is important for its biological activity (*e.g.* an antigen's active site).

In some embodiments, the SIRP1α targeting moiety binds but functionally modulates the antigen of interest, *i.e.*, SIRP1α. For example, in some embodiments, the SIRP1α targeting moiety targets the antigen, *i.e.*, SIRP1α, and functionally modulates (*e.g.* inhibit, reduce or neutralize) a biological effect that the antigen has. Such binding along with functional modulation may find use in various embodiments of the present invention including methods in which the present Fc-based chimeric protein complex is used to directly or indirectly recruit active immune cells to a site of need via an effector antigen.

In some embodiments, the SIRP1α targeting moiety may be used to directly or indirectly recruit macrophages via SIRP1α to a tumor cell in a method of reducing or eliminating a tumor (*e.g.* the present Fc-based chimeric protein complex may comprise a targeting moiety having an anti-SIRP1α antigen recognition domain and a targeting moiety having a recognition domain (*e.g.* antigen recognition domain) directed against a tumor antigen or receptor). Evidence indicates that tumor cells frequently upregulate CD47 which engages SIRP1α so as to evade phagocytosis. Accordingly, in various embodiments, it may be desirable to directly or indirectly recruit macrophages to tumor cells and functionally inhibit, reduce, or neutralize the inhibitory activity of SIRP1α thereby resulting in phagocytosis of the tumor cells by the macrophages. In various embodiments, the present Fc-based chimeric protein complex enhances phagocytosis of tumor cells or any other undesirable cells by macrophages.

SIRP alpha targeting moieties may comprise CDRs of antibodies as described in WO200140307A1, WO2013056352A1, WO2015138600A2, WO2017178653A2, WO2018057669A1, WO2018107058A1, WO2018190719A2, WO2019023347A1, the contents of which are hereby incorporated by reference in their entireties.

FAP Targeting Moieties

Fibroblast activation protein (FAP) is a 170 kDa melanoma membrane-bound gelatinase that belongs to the serine protease family. FAP is selectively expressed in reactive stromal fibroblasts of epithelial cancers, granulation tissue of healing wounds, and malignant cells of bone and soft tissue sarcomas. FAP is believed to be involved in the control of fibroblast growth or epithelial-mesenchymal interactions during development, tissue repair, and epithelial carcinogenesis.

In some embodiments, the targeting moiety is a FAP targeting moiety that is a protein-based agent capable of specific binding to FAP. In some embodiments, the FAP targeting moiety is a protein-based agent capable of specific binding to FAP without functional modulation (*e.g.*, partial or full neutralization) of FAP.

In some embodiments, the fibroblast targeting moiety targets F2 fibroblasts. In some embodiments, the fibroblast targeting moiety directly or indirectly alters the microenvironment of the F2 fibroblasts. In some embodiments, the fibroblast binding agent directly or indirectly polarizes the F2 fibroblast into F1 fibroblast.

F2 fibroblast(s) refers to pro-tumorigenic (or tumor promoting) cancer-associated fibroblasts (CAFs) (a/k/a Type II-CAF). F1 fibroblast(s) refers to tumor suppressive CAFs (a/k/a Type I-CAF). Polarization refers to changing the phenotype of cell, *e.g.* changing a tumorigenic F2 fibroblast to a tumor suppressive F1 fibroblast.

In some embodiments, the FAP targeting moiety targets a FAP marker.

In some embodiments, the FAP targeting moiety comprises a binding agent having an antigen recognition domain that recognizes an epitope present on FAP. In some embodiments, the antigen-recognition domain recognizes one or more linear epitopes present on FAP. In some embodiments, a linear epitope refers to any continuous sequence of amino acids present on FAP. In another embodiment, the antigen-recognition domain recognizes one or more conformational epitopes present on FAP. As used herein, a conformation epitope refers to one or more sections of amino acids (which may be discontinuous), which form a three-dimensional surface with features and/or shapes and/or tertiary structures capable of being recognized by an antigen recognition domain.

In some embodiments, the FAP targeting moiety can bind to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants of human FAP. In some embodiments, the FAP targeting moiety can bind to any forms of the human FAP, including monomeric, dimeric, heterodimeric, multimeric and associated forms. In an embodiment, the FAP targeting moiety binds to the monomeric form of FAP. In another embodiment, the FAP targeting moiety binds to a dimeric form of FAP. In a further embodiment, the FAP targeting moiety binds to glycosylated form of FAP, which may be either monomeric or dimeric.

In an embodiment, the FAP targeting moiety comprises an antigen recognition domain that recognizes one or more epitopes present on human FAP. In some embodiments, the human FAP comprises the amino acid sequence of SEQ ID NO: 1061.

In some embodiments, the FAP targeting moiety is capable of specific binding. In some embodiments, the FAP targeting moiety comprises an antigen recognition domain such as an antibody or derivatives thereof.

In some embodiments, the FAP targeting moiety comprises an antibody derivative or format. In some embodiments, the FAP targeting moiety comprises a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (cysteine knot protein, knottin), a DARPin; a Tetranectin; an Affibody; a Transbody; an Anticalin; an AdNectin; an alphabody; a bicyclic peptide; an Affilin; an Affimer, a Microbody; an aptamer; an alterase; a plastic antibody; a phylomer; a stradobody; a maxibody; an evibody; a fynomer, an armadillo repeat protein, a Kunitz domain, an avimer, an atrimer, a probody, an immunobody, a triomab, a troybody; a pepbody; a vaccibody, a UniBody; a DuoBody, a Fv, a Fab, a Fab', a F(ab')2, a peptide mimetic molecule, or a small (e.g. synthetic or natural) molecule , e.g. without limitation, as described in US Patent Nos. or Patent Publication Nos. US 7,417,130, US 2004/132094, US 5,831,012, US 2004/023334, US 7,250,297, US 6,818,418, US 2004/209243, US 7,838,629, US 7,186,524, US 6,004,746, US 5,475,096, US 2004/146938, US 2004/157209, US 6,994,982, US 6,794,144, US 2010/239633, US 7,803,907, US 2010/119446, and/or US 7,166,697, the contents of which are hereby incorporated by reference in their entireties. See also, Storz MAbs. 2011 May-Jun; 3(3): 310-317.

In some embodiments, the FAP targeting moiety comprises a single-domain antibody, such as a VHH. The VHH may be derived from, for example, an organism that produces VHH antibody such as a camelid, a shark, or the VHH may be a designed VHH. VHHs are antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally-occurring heavy-chain antibodies. VHH technology is based on fully functional antibodies from camelids that lack light chains. These heavy-chain antibodies contain a single variable domain (VHH) and two constant domains (CH2 and CH3).

In an embodiment, the FAP targeting moiety comprises a VHH. In some embodiments, the VHH is a humanized VHH or camelized VHH.

In some embodiments, the VHH comprises a fully human VH domain, *e.g.* a HUMABODY (Crescendo Biologics, Cambridge, UK). In some embodiments, fully human VH domain, *e.g.* a HUMABODY is monovalent, bivalent, or trivalent. In some embodiments, the fully human VH domain, *e.g.* a HUMABODY is mono- or multi-specific such as monospecific, bispecific, or trispecific. Illustrative fully human VH domains, *e.g.* HUMABODIES are described in, for example, WO 2016/113555 and WO 2016/113557, the entire disclosures of which are incorporated by reference.

By way of example, but not by way of limitation, in some embodiments, a human VHH FAP targeting moiety comprises an amino acid sequence selected from the following sequences: 2HFA44 (SEQ ID NO: 1062); 2HFA52 (SEQ ID NO: 1063); 2HFA11 (SEQ ID NO: 1064); 2HFA4 (SEQ ID NO: 1065); 2HFA46 (SEQ ID NO: 1066); 2HFA10 (SEQ ID NO: 1067); 2HFA38 (SEQ ID NO: 1068); 2HFA20 (SEQ ID NO: 1069); 2HFA5 (SEQ ID NO: 1070); 2HFA19 (SEQ ID NO: 1071); 2HFA2 (SEQ ID NO: 1072); 2HFA41 (SEQ ID NO: 1073); 2HFA42 (SEQ ID NO: 1074); 2HFA12 (SEQ ID NO: 1075); 2HFA24 (SEQ ID NO: 1076); 2HFA67 (SEQ ID NO: 1077); 2HFA29 (SEQ ID NO: 1078); 2HFA51 (SEQ ID NO: 1079); 2HFA63 (SEQ ID NO: 1080); 2HFA62 (SEQ ID NO: 1081); 2HFA26 (SEQ ID NO: 1082); 2HFA25 (SEQ ID NO: 1083); 2HFA1 (SEQ ID NO: 1084); 2HFA3 (SEQ ID NO: 1085); 2HFA7 (SEQ ID NO: 1086); 2HFA31 (SEQ ID NO: 1087); 2HFA6 (SEQ ID NO: 1088); 2HFA53 (SEQ ID NO: 1089); 2HFA9 (SEQ ID NO: 1090); 2HFA73 (SEQ ID NO: 1091); 2HFA55 (SEQ ID NO: 1092); 2HFA71 (SEQ ID NO: 1093); 2HFA60 (SEQ ID NO: 1094); 2HFA65 (SEQ ID NO: 1095); 2HFA49 (SEQ ID NO: 1096); 2HFA57 (SEQ ID NO: 1097); 2HFA23 (SEQ ID NO: 1098); 2HFA36 (SEQ ID NO: 1099); 2HFA14 (SEQ ID NO: 1100); 2HFA43 (SEQ ID NO: 1101); and 2HFA50 (SEQ ID NO: 1102).

In some embodiments, the FAP targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 1062-1102 (provided above) without the terminal histidine tag sequence (*i.e.*, HHHHHH; SEQ ID NO: 393).

In some embodiments, the FAP targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 1062-1102 (provided above) without the HA tag (*i.e.*, YPYDVPDYGS; SEQ ID NO: 394).

In some embodiments, the FAP targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 1062-1102 (provided above) without the AAA linker (*i.e.*, AAA).

In some embodiments, the FAP targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 1062-1102 (provided above) without the AAA linker, HA tag, and terminal histidine tag sequence (*i.e.*, AAAYPYDVPDYGSHHHHHH; SEQ ID NO: 395).

By way of example, but not by way of limitation, in some embodiments, a human VHH FAP targeting moiety comprises an amino acid sequence selected from the following sequences: 2HFA44 (SEQ ID NO: 1103); 2HFA52 (SEQ ID NO: 1104); 2HFA11 (SEQ ID NO: 1105); 2HFA4 (SEQ ID NO: 1106); 2HFA46 (SEQ ID NO: 1107); 2HFA10 (SEQ ID NO: 1108); 2HFA38 (SEQ ID NO: 1109); 2HFA20 (SEQ ID NO: 1110); 2HFA5 (SEQ ID NO: 1111); 2HFA19 (SEQ ID NO: 1112); 2HFA2 (SEQ ID NO: 1113); 2HFA41 (SEQ ID NO: 1114); 2HFA42 (SEQ ID NO: 1115); 2HFA12 (SEQ ID NO: 1116); 2HFA24 (SEQ ID NO: 1117); 2HFA67 (SEQ ID NO: 1118); 2HFA29 (SEQ ID NO: 1119); 2HFA51 (SEQ ID NO: 1120); 2HFA63 (SEQ ID NO: 1121); 2HFA62 (SEQ ID NO: 1122); 2HFA26 (SEQ ID NO: 1123); 2HFA25 (SEQ ID NO: 1124); 2HFA1 (SEQ ID NO: 1125); 2HFA3 (SEQ ID NO: 1126); 2HFA7 (SEQ ID NO: 1127); 2HFA31 (SEQ ID NO: 1128); 2HFA6 (SEQ ID NO: 1129); 2HFA53 (SEQ ID NO: 1130); 2HFA9 (SEQ ID NO: 1131); 2HFA73 (SEQ ID NO: 1132); 2HFA55 (SEQ ID NO: 1133); 2HFA71 (SEQ ID NO: 1134); 2HFA60 (SEQ ID NO: 1135); 2HFA65 (SEQ ID NO: 1136); 2HFA49 (SEQ ID NO: 1137); 2HFA57 (SEQ ID NO: 1138); 2HFA23 (SEQ ID NO: 1139); 2HFA36 (SEQ ID NO: 1140); 2HFA14 (SEQ ID NO: 1141); 2HFA43 (SEQ ID NO: 1142); and 2HFA50 (SEQ ID NO: 1143).

In some embodiments, the FAP targeting moiety comprises a binding agent that is a VHH comprising a single amino acid chain having four "framework regions" or FRs and three "complementary determining regions" or CDRs. As used herein, "framework region" or "FR" refers to a region in the variable domain which is located between the CDRs. As used herein, "complementary determining region" or "CDR" refers to variable regions in VHHs that contains the amino acid sequences capable of specifically binding to antigenic targets.

In some embodiments, the FAP targeting moiety comprises a VHH having a variable domain comprising at least one CDR1, CDR2, and/or CDR3 sequences. In some embodiments, the FAP targeting moiety comprises a VHH having a variable region comprising at least one FR1, FR2, FR3, and FR4 sequences.

In some embodiments, a human FAP targeting moiety comprises a CDR1 sequence selected from SEQ ID Nos.: 1144-1172. In some embodiments, a human FAP targeting moiety comprises a CDR2 sequence selected from SEQ ID Nos.: 1173-1201. In some embodiments, a human FAP targeting moiety comprises a CDR3 sequence selected from SEQ ID Nos.: 1202-1232.

In some embodiments, the FAP targeting moiety has at least 90% identity with any FAP amino acid sequence selected disclosed herein. In some embodiments, the FAP targeting moiety has about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% identity with any FAP amino acid sequence selected disclosed herein.

In various illustrative embodiments, the murine FAP targeting moiety has at least 90% identity with the amino acid sequence of sibrotuzumab.

In some embodiments, the present technology contemplates the use of any natural or synthetic analogs, mutants, variants, alleles, homologs and orthologs (herein collectively referred to as "analogs") of the FAP targeting moieties as described herein. In some embodiments, the amino acid sequence of the FAP targeting moiety further includes an amino acid analog, an amino acid derivative, or other non-classical amino acids.

In some embodiments, the FAP targeting moiety comprises a sequence that is at least 60% identical to any one of the FAP sequences disclosed herein. For example, the FAP targeting moiety may comprise a sequence that is at least about 60%, at least about 61%, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to any of the FAP sequences disclosed herein (*e.g.* about 60%, or about 61%, or about 62%, or about 63%, or about 64%, or about 65%, or about 66%, or about 67%, or about 68%, or about 69%, or about 70%, or about 71%, or about 72%, or about 73%, or about 74%, or about 75%, or about 76%, or about 77%, or about 78%, or about 79%, or about 80%, or about 81%, or about 82%, or about 83%, or about 84%, or about 85%, or about 86%, or about 87%, or about 88%, or about 89%, or about 90%, or about 91%, or about 92%, or about 93%, or about 94%, or about 95%, or about 96%, or about 97%, or about 98%, about 99% or about 100% sequence identity to any one of the FAP sequences disclosed herein).

In some embodiments, the FAP targeting moiety comprises an amino acid sequence having one or more amino acid mutations with respect to any one of the sequences disclosed herein. In some embodiments, the FAP targeting moiety comprises an amino acid sequence having one, or two, or three, or four, or five, or six, or seen, or eight, or nine, or ten, or fifteen, or twenty amino acid mutations with respect to any one of the sequences disclosed herein. In some embodiments, the one or more amino acid mutations may be independently selected from substitutions, insertions, deletions, and truncations.

In some embodiments, the amino acid mutations are amino acid substitutions, and may include conservative and/or non-conservative substitutions.

"Conservative substitutions" may be made, for instance, on the basis of similarity in polarity, charge, size, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the amino acid residues involved. The 20 naturally occurring amino acids can be grouped into the following six standard amino acid groups: (1) hydrophobic: Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr; Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe.

As used herein, "conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed within the same group of the six standard amino acid groups shown above. For example, the exchange of Asp by Glu retains one negative charge in the so modified polypeptide. In addition, glycine and proline may be substituted for one another based on their ability to disrupt a-helices.

As used herein, "non-conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed in a different group of the six standard amino acid groups (1) to (6) shown above.

In some embodiments, the substitutions include non-classical amino acids. Illustrative non-classical amino acids include, but are not limited to, selenocysteine, pyrrolysine, *N*-formylmethionine β-alanine, GABA and δ-Aminolevulinic acid, 4-aminobenzoic acid (PABA), D-isomers of the common amino acids, 2,4-diaminobutyric acid, α-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ-Abu, ε-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosme, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β-alanine, fluoro-amino acids, designer amino acids such as β methyl amino acids, C α-methyl amino acids, N α-methyl amino acids, and amino acid analogs in general.

In some embodiments, one or more amino acid mutations are in the CDRs of the FAP targeting moiety (*e.g.*, the CDR1, CDR2 or CDR3 regions). In another embodiment, one or more amino acid mutations are in the framework regions (FRs) of the targeting moiety (*e.g.*, the FR1, FR2, FR3, or FR4 regions).

Modification of the amino acid sequences may be achieved using any known technique in the art *e.g.*, site-directed mutagenesis or PCR based mutagenesis. Such techniques are described, for example, in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., 1989 and Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons, New York, N.Y., 1989.

In some embodiments, the mutations do not substantially reduce the FAP targeting moiety's capability to specifically bind to FAP. In some embodiments, the mutations do not substantially reduce the present FAP targeting moiety's capability to specifically bind to FAP and without functionally modulating (*e.g.*, partially or fully neutralizing) FAP.

In some embodiments, the binding affinity of the FAP targeting moiety for the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or monomeric and/or dimeric forms and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric and/or dimeric forms) of human FAP may be described by the equilibrium dissociation constant (K_D). In some embodiments, the FAP targeting moiety binds to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric and/or dimeric forms) of human FAP with a K_D of less than about 1 μM, about 900 nM, about 800 nM, about 700 nM, about 600 nM, about 500 nM, about 400 nM, about 300 nM, about 200 nM, about 100 nM, about 90 nM, about 80 nM, about 70 nM, about 60 nM, about 50 nM, about 40 nM, about 30 nM, about 20 nM, about 10 nM, or about 5 nM, or about 1 nM.

In some embodiments, the FAP targeting moiety binds but does not functionally modulate (*e.g.*, partially or fully neutralize) the antigen of interest, *i.e.*, FAP. For instance, in some embodiments, the FAP targeting moiety simply targets the antigen but does not substantially functionally modulate (*e.g.* partially or fully inhibit, reduce or neutralize) a biological effect that the antigen has. In some embodiments, the FAP targeting moiety binds an epitope that is physically separate from an antigen site that is important for its biological activity (*e.g.* an antigen's active site).

Such binding without significant function modulation finds use in some embodiments of the present technology, including methods in which the FAP targeting moiety is used to directly or indirectly recruit active immune cells to

a site of need via an effector antigen. For example, in some embodiments, the FAP targeting moiety can be used to directly or indirectly recruit dendritic cells via FAP to a tumor cell in a method of reducing or eliminating a tumor (*e.g.* the FAP targeting moiety may comprise a binding agent having an anti-FAP antigen recognition domain and a targeting moiety having a recognition domain (*e.g.* antigen recognition domain) directed against a tumor antigen or receptor). In such embodiments, it is desirable to directly or indirectly recruit dendritic cells but not to functionally modulate or neutralize the FAP activity. In these embodiments, FAP signaling is an important piece of the tumor reducing or eliminating effect.

In some embodiments, the FAP targeting moiety enhances antigen-presentation by dendritic cells. For example, in some embodiments, the FAP targeting moiety directly or indirectly recruits dendritic cells via FAP to a tumor cell, where tumor antigens are subsequently endocytosed and presented on the dendritic cell for induction of potent humoral and cytotoxic T cell responses.

In other embodiments (for example, related to treating cancer, autoimmune, or neurodegenerative disease), the FAP targeting moiety comprises a binding agent that binds and neutralizes the antigen of interest, *i.e.*, FAP. For instance, in some embodiments, the present methods may inhibit or reduce FAP signaling or expression, *e.g.* to cause a reduction in an immune response.

XCR1 Targeting Moieties

In some embodiments, the targeting moiety is an XCR1 targeting moiety that is capable of specific binding to XCR1. In various embodiments, the XCR1 targeting moiety is a protein-based agent capable of specific binding to XCR1 without functional modulation (*e.g.*, partial or full neutralization) of XCR1. XCR1 is a chemokine receptor belonging to the G protein-coupled receptor superfamily. The family members are characterized by the presence of 7 transmembrane domains and numerous conserved amino acids. XCR1 is most closely related to RBS11 and the MIP1-alpha/RANTES receptor. XCR1 transduces a signal by increasing the intracellular calcium ions level. XCR1 is the receptor for XCL1 and XCL2 (or lymphotactin-1 and -2).

In some embodiments, the XCR1 targeting moiety comprises an antigen recognition domain that recognizes an epitope present on XCR1. In some embodiments, the antigen-recognition domain recognizes one or more linear epitopes present on XCR1. In some embodiment, a linear epitope refers to any continuous sequence of amino acids present on XCR1. In another embodiment, the antigen-recognition domain recognizes one or more conformational epitopes present on XCR1. As used herein, a conformation epitope refers to one or more sections of amino acids (which may be discontinuous) which form a three-dimensional surface with features and/or shapes and/or tertiary structures capable of being recognized by an antigen recognition domain.

In some embodiments, the XCR1 targeting moiety can bind to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants of human XCR1. In various embodiments, the XCR1 targeting moiety can bind to any forms of the human XCR1, including monomeric, dimeric, heterodimeric, multimeric and associated forms. In an embodiment, the Fc-based chimeric protein complex binds to the monomeric form of XCR1. In another embodiment, the XCR1 targeting

moiety binds to a dimeric form of XCR1. In a further embodiment, the XCR1 targeting moiety binds to glycosylated form of XCR1, which may be either monomeric or dimeric.

In an embodiment, the XCR1 targeting moiety comprises an antigen recognition domain that recognizes one or more epitopes present on human XCR1. In an embodiment, the human XCR1 comprises the amino acid sequence of SEQ ID NO: 1233.

In various embodiments, the XCR1 targeting moiety is capable of specific binding. In various embodiments, the XCR1 targeting moiety comprises an antigen recognition domain such as an antibody or derivatives thereof.

In some embodiments, the XCR1 targeting moiety comprises an antibody derivative or format. In some embodiments, the XCR1 targeting moiety comprises a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (cysteine knot protein, knottin), a DARPin; a Tetranectin; an Affibody; an Affimer, a Transbody; an Anticalin; an AdNectin; an alphabody; a bicyclic peptide; an Affilin; a Microbody; a peptide aptamer; an alterase; a plastic antibody; a phylomer; a stradobody; a maxibody; an evibody; a fynomer, an armadillo repeat protein, a Kunitz domain, an avimer, an atrimer, a probody, an immunobody, a triomab, a troybody; a pepbody; a vaccibody, a UniBody; a DuoBody, a Fv, a Fab, a Fab', a $F(ab')_2$, a peptide mimetic molecule, or a small (e.g. synthetic or natural) molecule , e.g. without limitation, as described in US Patent Nos. or Patent Publication Nos. US 7,417,130, US 2004/132094, US 5,831,012, US 2004/023334, US 7,250,297, US 6,818,418, US 2004/209243, US 7,838,629, US 7,186,524, US 6,004,746, US 5,475,096, US 2004/146938, US 2004/157209, US 6,994,982, US 6,794,144, US 2010/239633, US 7,803,907, US 2010/119446, and/or US 7,166,697, the contents of which are hereby incorporated by reference in their entireties. *See* also, Storz MAbs. 2011 May-Jun; 3(3): 310–317.

In some embodiments, the XCR1 targeting moiety comprises a single-domain antibody, such as a VHH. The VHH may be derived from, for example, an organism that produces VHH antibody such as a camelid, a shark, or the VHH may be a designed VHH. VHHs are antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally-occurring heavy-chain antibodies. VHH technology is based on fully functional antibodies from camelids that lack light chains. These heavy-chain antibodies contain a single variable domain (V_HH) and two constant domains (CH2 and CH3). In an embodiment, the Fc-based chimeric protein complex comprises a VHH.

In some embodiments, the XCR1 targeting moiety comprises a VHH comprising a single amino acid chain having four “framework regions” or FRs and three “complementary determining regions” or CDRs. As used herein, “framework region” or “FR” refers to a region in the variable domain which is located between the CDRs. As used herein, “complementary determining region” or “CDR” refers to variable regions in VHHs that contains the amino acid sequences capable of specifically binding to antigenic targets.

In some embodiments, the XCR1 targeting moiety comprises a VHH having a variable domain comprising at least one CDR1, CDR2, and/or CDR3 sequences. In various embodiments, the XCR1 targeting moiety comprises a VHH having a variable region comprising at least one FR1, FR2, FR3, and FR4 sequences.

In some embodiments, the present invention contemplates the use of any natural or synthetic analogs, mutants, variants, alleles, homologs and orthologs (herein collectively referred to as "analogs") of the XCR1 targeting moieties described herein. In various embodiments, the amino acid sequence of the XCR1 targeting moiety further includes an amino acid analog, an amino acid derivative, or other non-classical amino acids.

In some embodiments, the XCR1 targeting moiety comprises a sequence that is at least 60% identical to any one of the XCR1sequences disclosed herein. For example, the XCR1 targeting moiety may comprise a sequence that is at least about 60%, at least about 61%, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to any of the XCR1 sequences disclosed herein (*e.g.* about 60%, or about 61%, or about 62%, or about 63%, or about 64%, or about 65%, or about 66%, or about 67%, or about 68%, or about 69%, or about 70%, or about 71%, or about 72%, or about 73%, or about 74%, or about 75%, or about 76%, or about 77%, or about 78%, or about 79%, or about 80%, or about 81%, or about 82%, or about 83%, or about 84%, or about 85%, or about 86%, or about 87%, or about 88%, or about 89%, or about 90%, or about 91%, or about 92%, or about 93%, or about 94%, or about 95%, or about 96%, or about 97%, or about 98%, about 99% or about 100% sequence identity to any one of the XCR1 sequences disclosed herein).

In some embodiments, the XCR1 targeting moiety comprises an amino acid sequence having one or more amino acid mutations with respect to any one of the sequences disclosed herein. In various embodiments, the XCR1 targeting moiety comprises an amino acid sequence having one, or two, or three, or four, or five, or six, or seen, or eight, or nine, or ten, or fifteen, or twenty amino acid mutations with respect to any one of the sequences disclosed herein. In some embodiments, the one or more amino acid mutations may be independently selected from substitutions, insertions, deletions, and truncations.

In some embodiments, the amino acid mutations are amino acid substitutions, and may include conservative and/or non-conservative substitutions.

"Conservative substitutions" may be made, for instance, on the basis of similarity in polarity, charge, size, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the amino acid residues involved. The 20 naturally occurring amino acids can be grouped into the following six standard amino acid groups: (1) hydrophobic: Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr; Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe.

As used herein, "conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed within the same group of the six standard amino acid groups shown above. For example, the exchange of

Asp by Glu retains one negative charge in the so modified polypeptide. In addition, glycine and proline may be substituted for one another based on their ability to disrupt α-helices.

As used herein, "non-conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed in a different group of the six standard amino acid groups (1) to (6) shown above.

In various embodiments, the substitutions may also include non-classical amino acids. Exemplary non-classical amino acids include, but are not limited to, selenocysteine, pyrrolysine, *N*-formylmethionine β-alanine, GABA and δ-Aminolevulinic acid, 4-aminobenzoic acid (PABA), D-isomers of the common amino acids, 2,4-diaminobutyric acid, α-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ-Abu, ε-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosme, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β-alanine, fluoro-amino acids, designer amino acids such as β methyl amino acids, C α-methyl amino acids, N α-methyl amino acids, and amino acid analogs in general.

In various embodiments, the amino acid mutation may be in the CDRs of the targeting moiety (*e.g.*, the CDR1, CDR2 or CDR3 regions). In another embodiment, amino acid alteration may be in the framework regions (FRs) of the targeting moiety (*e.g.*, the FR1, FR2, FR3, or FR4 regions).

Modification of the amino acid sequences may be achieved using any known technique in the art *e.g.*, site-directed mutagenesis or PCR based mutagenesis. Such techniques are described, for example, in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., 1989 and Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons, New York, N.Y., 1989.

In various embodiments, the mutations do not substantially reduce the XCR1 targeting moiety's capability to specifically bind to XCR1. In various embodiments, the mutations do not substantially reduce the XCR1 targeting moiety's capability to specifically bind to XCR1 and without functionally modulating (*e.g.*, partially or fully neutralizing) XCR1.

In various embodiments, the binding affinity of the XCR1 targeting moiety for the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or monomeric and/or dimeric forms and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric and/or dimeric forms) of human XCR1 may be described by the equilibrium dissociation constant (K_D). In various embodiments, the Fc-based chimeric protein complex comprises a targeting moiety that binds to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric and/or dimeric forms) of human XCR1 with a K_D of less than about 1 uM, about 900 nM, about 800 nM, about 700 nM, about 600 nM, about 500 nM, about 400 nM, about 300 nM, about 200 nM, about 100 nM, about 90 nM, about 80 nM, about 70 nM, about 60 nM, about 50 nM, about 40 nM, about 30 nM, about 20 nM, about 10 nM, or about 5 nM, or about 1 nM.

In various embodiments, the XCR1 targeting moiety binds but does not functionally modulate (*e.g.*, partially or fully neutralize) the antigen of interest, *i.e.*, XCR1. For instance, in various embodiments, the XCR1 targeting moiety simply targets the antigen but does not substantially functionally modulate (*e.g.* partially or fully inhibit, reduce or

neutralize) a biological effect that the antigen has. In various embodiments, the XCR1 targeting moiety binds an epitope that is physically separate from an antigen site that is important for its biological activity (*e.g.* an antigen's active site).

Such binding without significant function modulation finds use in various embodiments of the present invention, including methods in which the XCR1 targeting moiety is used to directly or indirectly recruit active immune cells to a site of need via an effector antigen. For example, in various embodiments, the XCR1 targeting moiety can be used to directly or indirectly recruit dendritic cells via XCR1 to a tumor cell in a method of reducing or eliminating a tumor (*e.g.* the XCR1 targeting moiety can comprise a binding agent having an anti-XCR1 antigen recognition domain and a targeting moiety having a recognition domain (*e.g.* antigen recognition domain) directed against a tumor antigen or receptor). In such embodiments, it is desirable to directly or indirectly recruit dendritic cells but not to functionally modulate or neutralize the XCR1 activity. In these embodiments, XCR1 signaling is an important piece of the tumor reducing or eliminating effect.

In some embodiments, the XCR1 targeting moiety enhances antigen-presentation by dendritic cells. For example, in various embodiments, the XCR1 targeting moiety directly or indirectly recruits dendritic cells via XCR1 to a tumor cell, where tumor antigens are subsequently endocytosed and presented on the dendritic cell for induction of potent humoral and cytotoxic T cell responses.

In other embodiments (for example, related to treating autoimmune or neurodegenerative disease), the XCR1 targeting moiety comprises a binding agent that binds and neutralizes the antigen of interest, *i.e.*, XCR1. For instance, in various embodiments, the present methods may inhibit or reduce XCR1 signaling or expression, *e.g.* to cause a reduction in an immune response.

Non-cellular Structure Targeting Moieties

In some embodiments, the targeting moiety's target (*e.g.* antigen or receptor) is part of a non-cellular structure. In some embodiments, the antigen or receptor is not an integral component of an intact cell or cellular structure. In some embodiments, the antigen or receptor is an extracellular antigen or receptor. In some embodiments, the target is a non-proteinaceous, non-cellular marker, including, without limitation, nucleic acids, inclusive of DNA or RNA, such as, for example, DNA released from necrotic tumor cells or extracellular deposits such as cholesterol.

In some embodiments, the target of interest (*e.g.* antigen, receptor) is part of the non-cellular component of the stroma or the extracellular matrix (ECM) or the markers associated therewith. As used herein, stroma refers to the connective and supportive framework of a tissue or organ. Stroma may include a compilation of cells such as fibroblasts/myofibroblasts, glial, epithelia, fat, immune, vascular, smooth muscle, and immune cells along with the extracellular matrix (ECM) and extracellular molecules. In various embodiments, the target (*e.g.* antigen, receptor) of interest is part of the non-cellular component of the stroma such as the extracellular matrix and extracellular molecules. As used herein, the ECM refers to the non-cellular components present within all tissues and organs. The ECM is composed of a large collection of biochemically distinct components including, without limitation, proteins, glycoproteins, proteoglycans, and polysaccharides. These components of the ECM are usually produced by adjacent cells and secreted into the ECM via exocytosis. Once secreted, the ECM components often aggregate

to form a complex network of macromolecules. In various embodiments, the Fc-based chimeric protein complex of the invention comprises a targeting moiety that recognizes a target (*e.g.*, an antigen or receptor or non-proteinaceous molecule) located on any component of the ECM. Illustrative components of the ECM include, without limitation, the proteoglycans, the non-proteoglycan polysaccharides, fibers, and other ECM proteins or ECM non-proteins, *e.g.* polysaccharides and/or lipids, or ECM associated molecules (*e.g.* proteins or non-proteins, *e.g.* polysaccharides, nucleic acids and/or lipids).

In some embodiments, the targeting moiety recognizes a target (*e.g.* antigen, receptor) on ECM proteoglycans. Proteoglycans are glycosylated proteins. The basic proteoglycan unit includes a core protein with one or more covalently attached glycosaminoglycan (GAG) chains. Proteoglycans have a net negative charge that attracts positively charged sodium ions (Na+), which attracts water molecules via osmosis, keeping the ECM and resident cells hydrated. Proteoglycans may also help to trap and store growth factors within the ECM. Illustrative proteoglycans that may be targeted by the Fc-based chimeric protein complexes of the invention include, but are not limited to, heparan sulfate, chondroitin sulfate, and keratan sulfate. In an embodiment, the targeting moiety recognizes a target (*e.g.* antigen, receptor) on non-proteoglycan polysaccharides such as hyaluronic acid.

In some embodiments, the targeting moiety recognizes a target (*e.g.* antigen, receptor) on ECM fibers. ECM fibers include collagen fibers and elastin fibers. In some embodiments, the targeting moiety recognizes one or more epitopes on collagens or collagen fibers. Collagens are the most abundant proteins in the ECM. Collagens are present in the ECM as fibrillar proteins and provide structural support to resident cells. In one or more embodiments, the targeting moiety recognizes and binds to various types of collagens present within the ECM including, without limitation, fibrillar collagens (types I, II, III, V, XI), facit collagens (types IX, XII, XIV), short chain collagens (types VIII, X), basement membrane collagens (type IV), and/or collagen types VI, VII, or XIII. Elastin fibers provide elasticity to tissues, allowing them to stretch when needed and then return to their original state. In some embodiments, the target moiety recognizes one or more epitopes on elastins or elastin fibers.

In some embodiments, the targeting moiety recognizes one or more ECM proteins including, but not limited to, a tenascin, a fibronectin, a fibrin, a laminin, or a nidogen/entactin.

In an embodiment, the targeting moiety recognizes and binds to tenascin. The tenascin (TN) family of glycoproteins includes at least four members, tenascin-C, tenascin-R, tenascin-X, and tenascin W. The primary structures of tenascin proteins include several common motifs ordered in the same consecutive sequence: amino-terminal heptad repeats, epidermal growth factor (EGF)-like repeats, fibronectin type III domain repeats, and a carboxyl-terminal fibrinogen-like globular domain. Each protein member is associated with typical variations in the number and nature of EGF-like and fibronectin type III repeats. Isoform variants also exist particularly with respect to tenascin-C. Over 27 splice variants and/or isoforms of tenascin-C are known. In a particular embodiment, the targeting moiety recognizes and binds to tenascin-CA1. Similarly, tenascin-R also has various splice variants and isoforms. Tenascin-R usually exists as dimers or trimers. Tenascin-X is the largest member of the tenascin family and is known to exist as trimers. Tenascin-W exists as trimers. In some embodiments, the targeting moiety

recognizes one or more epitopes on a tenascin protein. In some embodiments, the targeting moiety recognizes the monomeric and/or the dimeric and/or the trimeric and/or the hexameric forms of a tenascin protein.

In some embodiments, the targeting moiety recognizes tenascin-CA1.

In some embodiments, the targeting moieties recognize and bind to fibronectin. Fibronectins are glycoproteins that connect cells with collagen fibers in the ECM, allowing cells to move through the ECM. Upon binding to integrins, fibronectins unfolds to form functional dimers. In some embodiments, the targeting moiety recognizes the monomeric and/or the dimeric forms of fibronectin. In some embodiments, the targeting moiety recognizes one or more epitopes on fibronectin. In illustrative embodiments, the targeting moiety recognizes fibronectin extracellular domain A (EDA) or fibronectin extracellular domain B (EDB). Elevated levels of EDA are associated with various diseases and disorders including psoriasis, rheumatoid arthritis, diabetes, and cancer. In some embodiments, the targeting moiety recognizes fibronectin that contains the EDA isoform and may be utilized to target the Fc-based chimeric protein complex to diseased cells including cancer cells. In some embodiments, the targeting moiety recognizes fibronectin that contains the EDB isoform. In various embodiments, such targeting moieties may be utilized to target the Fc-based chimeric protein complex to tumor cells including the tumor neovasculature.

In an embodiment, the targeting moiety recognizes and binds to fibrin. Fibrin is another protein substance often found in the matrix network of the ECM. Fibrin is formed by the action of the protease thrombin on fibrinogen which causes the fibrin to polymerize. In some embodiments, the targeting moiety recognizes one or more epitopes on fibrin. In some embodiments, the targeting moiety recognizes the monomeric as well as the polymerized forms of fibrin.

In an embodiment, the targeting moiety recognizes and binds to laminin. Laminin is a major component of the basal lamina, which is a protein network foundation for cells and organs. Laminins are heterotrimeric proteins that contain an α-chain, a β-chain, and a γ-chain. In some embodiments, the targeting moiety recognizes one or more epitopes on laminin. In some embodiments, the targeting moiety recognizes the monomeric, the dimeric as well as the trimeric forms of laminin.

In an embodiment, the targeting moiety recognizes and binds to a nidogen or entactin. Nidogens/entactins are a family of highly conserved, sulfated glycoproteins. They make up the major structural component of the basement membranes and function to link laminin and collagen IV networks in basement membranes. Members of this family include nidogen-1 and nidogen-2. In various embodiments, the targeting moiety recognizes an epitope on nidogen-1 and/or nidogen-2.

In various embodiments, the targeting moiety comprises an antigen recognition domain that recognizes an epitope present on any of the targets described herein. In an embodiment, the antigen-recognition domain recognizes one or more linear epitopes present on the protein. As used herein, a linear epitope refers to any continuous sequence of amino acids present on the protein. In another embodiment, the antigen-recognition domain recognizes one or more conformational epitopes present on the protein. As used herein, a conformation epitope refers to one or more sections of amino acids (which may be discontinuous) which form a three-dimensional surface with features and/or shapes and/or tertiary structures capable of being recognized by an antigen recognition domain.

In various embodiments, the targeting moiety may bind to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants of any of the targets described herein. In various embodiments, the targeting moiety may bind to any forms of the proteins described herein, including monomeric, dimeric, trimeric, tetrameric, heterodimeric, multimeric and associated forms. In various embodiments, the targeting moiety may bind to any post-translationally modified forms of the proteins described herein, such as glycosylated and/or phosphorylated forms.

In various embodiments, the targeting moiety comprises an antigen recognition domain that recognizes extracellular molecules such as DNA. In some embodiments, the targeting moiety comprises an antigen recognition domain that recognizes DNA. In an embodiment, the DNA is shed into the extracellular space from necrotic or apoptotic tumor cells or other diseased cells.

In some embodiments, the targeting moiety comprises an antigen recognition domain that recognizes one or more non-cellular structures associated with atherosclerotic plaques. Two types of atherosclerotic plaques are known. The fibro-lipid (fibro-fatty) plaque is characterized by an accumulation of lipid-laden cells underneath the intima of the arteries. Beneath the endothelium there is a fibrous cap covering the atheromatous core of the plaque. The core includes lipid-laden cells (macrophages and smooth muscle cells) with elevated tissue cholesterol and cholesterol ester content, fibrin, proteoglycans, collagen, elastin, and cellular debris. In advanced plaques, the central core of the plaque usually contains extracellular cholesterol deposits (released from dead cells), which form areas of cholesterol crystals with empty, needle-like clefts. At the periphery of the plaque are younger foamy cells and capillaries. A fibrous plaque is also localized under the intima, within the wall of the artery resulting in thickening and expansion of the wall and, sometimes, spotty localized narrowing of the lumen with some atrophy of the muscular layer. The fibrous plaque contains collagen fibers (eosinophilic), precipitates of calcium (hematoxylinophilic) and lipid-laden cells. In some embodiments, the targeting moiety recognizes and binds to one or more of the non-cellular components of these plaques such as the fibrin, proteoglycans, collagen, elastin, cellular debris, and calcium or other mineral deposits or precipitates. In some embodiments, the cellular debris is a nucleic acid, *e.g.* DNA or RNA, released from dead cells.

In various embodiments, the targeting moiety comprises an antigen recognition domain that recognizes one or more non-cellular structures found in the brain plaques associated with neurodegenerative diseases. In some embodiments, the targeting moiety recognizes and binds to one or more non-cellular structures located in the amyloid plaques found in the brains of patients with Alzheimer's disease. For example, the targeting moiety may recognize and bind to the peptide amyloid beta, which is a major component of the amyloid plaques. In some embodiments, the targeting moiety recognizes and binds to one or more non-cellular structures located in the brains plaques found in patients with Huntington's disease. In various embodiments, the targeting moiety recognizes and binds to one or more non-cellular structures found in plaques associated with other neurodegenerative or musculoskeletal diseases such as Lewy body dementia and inclusion body myositis

In some embodiments, the targeting moiety is a protein-based agent capable of specific binding, such as an antibody or derivatives thereof.

CD3 Targeting Moieties

In some embodiments, the present Fc-based chimeric protein complex has one or more targeting moieties directed against CD3 expressed on T cells. In some embodiments, the Fc-based chimeric protein complex has one or more targeting moieties which selectively bind a CD3 polypeptide. In some embodiments, the Fc-based chimeric protein complex comprises one or more antibodies, antibody derivatives or formats, peptides or polypeptides, or fusion proteins that selectively bind a CD3 polypeptide.

In some embodiments, the targeting moiety comprises the anti-CD3 antibody muromonab-CD3 (aka Orthoclone OKT3), or fragments thereof. Muromonab-CD3 is disclosed in U.S. Patent No. 4,361,549 and Wilde *et al.* (1996) 51:865-894, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, muromonab-CD3 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 1234; and/or a light chain comprising the amino acid sequence of SEQ ID NO: 1235.

In some embodiments, the targeting moiety comprises the anti-CD3 antibody otelixizumab, or fragments thereof. Otelixizumab is disclosed in U.S. Patent Publication No. 20160000916 and Chatenoud *et al.* (2012) 9:372-381, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, otelixizumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 1236; and/or a light chain comprising the amino acid sequence of SEQ ID NO: 1237.

In some embodiments, the targeting moiety comprises the anti-CD3 antibody teplizumab (AKA MGA031 and hOKT3γ1(Ala-Ala)), or fragments thereof. Teplizumab is disclosed in Chatenoud *et al.* (2012) 9:372-381, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, teplizumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 1238; and/or a light chain comprising the amino acid sequence of SEQ ID NO: 1239.

In some embodiments, the targeting moiety comprises the anti-CD3 antibody visilizumab (AKA Nuvion®; HuM291), or fragments thereof. Visilizumab is disclosed in U.S. 5,834,597 and WO2004052397, and Cole *et al.*, Transplantation (1999) 68:563-571, the entire disclosures of which are hereby incorporated by reference. In illustrative embodiments, visilizumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1240; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO: 1241.

In some embodiments, the targeting moiety comprises the anti-CD3 antibody foralumab (aka NI-0401), or fragments thereof. In various embodiments, the targeting moiety comprises any one of the anti-CD3 antibodies disclosed in US20140193399, US 7,728,114, US20100183554, and US 8,551,478, the entire disclosures of which are hereby incorporated by reference.

In illustrative embodiments, the anti-CD3 antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID Nos: 2

and 6 of US 7,728,114 (SEQ ID NO: 1242 and 1243, respectively) and/or a light chain variable region comprising the amino acid sequence of SEQ ID NOs 4 and 8 of US 7,728,114 (SEQ ID NO: 1244 and 1245).

In an embodiment, the targeting moiety comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:2 of US 7,728,114 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:4 of US 7,728,114. In an embodiment, the targeting moiety comprises any one of the anti-CD3 antibodies disclosed in US2016/0168247, the entire contents of which are hereby incorporated by reference. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID Nos: 6-9 of US2016/0168247 (SEQ ID Nos.: 1246-1249, respectively) and/or a light chain comprising an amino acid sequence selected from SEQ ID Nos: 10-12 of US2016/0168247 (SEQ ID Nos.: 1250-1252, respectively).

In an embodiment, the targeting moiety comprises any one of the anti-CD3 antibodies disclosed in US2015/0175699, the entire contents of which are hereby incorporated by reference. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID No: 9 of US2015/0175699 (SEQ ID NO: 1253); and/or a light chain comprising an amino acid sequence selected from SEQ ID No: 10 of US2015/0175699 (SEQ ID NO: 1254).

In an embodiment, the targeting moiety comprises any one of the anti-CD3 antibodies disclosed in US 8,784,821, the entire contents of which are hereby incorporated by reference. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID Nos: 2, 18, 34, 50, 66, 82, 98 and 114 of US 8,784,821 (SEQ ID Nos.: 1255, 1256, 1257, 1258, 1259, 1260, 1261, and 1262, respectively); and/or a light chain comprising an amino acid sequence selected from SEQ ID Nos: 10, 26, 42, 58, 74, 90, 106 and 122 of US 8,784,821 (SEQ ID No.: 1263, 1264, 1265, 1266, 1267, 1268, 1269, and 1270, respectively).

In an embodiment, the targeting moiety comprises any one of the anti-CD3 binding constructs disclosed in US20150118252, the entire contents of which are hereby incorporated by reference. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID Nos: 6 and 86 of US20150118252 (SEQ ID NO: 1271 and 1272, respectively); and/or a light chain comprising an amino acid sequence selected from SEQ ID No: 3 of US2015/0175699 (SEQ ID NO: 1273).

In an embodiment, the targeting moiety comprises any one of the anti-CD3 binding proteins disclosed in US2016/0039934, the entire contents of which are hereby incorporated by reference. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID Nos: 6-9 of US2016/0039934 (SEQ ID Nos.: 1274-1277); and/or a light chain comprising an amino acid sequence selected from SEQ ID Nos: 1-4 of US2016/0039934 (SEQ ID Nos.: 1278-1281).

In various embodiments, the targeting moieties of the invention may comprise a sequence that targets CD3 which is at least about 60%, at least about 61%, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to any of the sequences disclosed herein (*e.g.* about 60%, or about 61%, or about 62%, or about 63%, or about 64%, or about 65%, or about 66%, or about 67%, or about 68%, or about 69%, or about 70%, or about 71%, or about 72%, or about 73%, or about 74%, or about 75%, or about 76%, or about 77%, or about 78%, or about 79%, or about 80%, or about 81%, or about 82%, or about 83%, or about 84%, or about 85%, or about 86%, or about 87%, or about 88%, or about 89%, or about 90%, or about 91%, or about 92%, or about 93%, or about 94%, or about 95%, or about 96%, or about 97%, or about 98%, about 99% or about 100% sequence identity with any of the sequences disclosed herein).

In various embodiments, the targeting moieties of the invention may comprise any combination of heavy chain, light chain, heavy chain variable region, light chain variable region, complementarity determining region (CDR), and framework region sequences that target CD3 as disclosed herein. In various embodiments, the targeting moieties of the invention may comprise any heavy chain, light chain, heavy chain variable region, light chain variable region, complementarity determining region (CDR), and framework region sequences of the CD3-specific antibodies including, but not limited to, X35-3, VIT3, BMA030 (BW264/56), CLB-T3/3, CRIS7, YTH12.5, FI 11-409, CLB-T3.4.2, TR-66, WT32, SPv-T3b, 11D8, XIII-141, XIII-46, XIII-87, 12F6, T3/RW2-8C8, T3/RW2-4B6, OKT3D, M-T301, SMC2, WT31 and F101.01. These CD3-specific antibodies are well known in the art and, *inter alia*, described in Tunnacliffe (1989), Int. Immunol. 1, 546-550, the entire disclosures of which are hereby incorporated by reference.

Additional antibodies, antibody derivatives or formats, peptides or polypeptides, or fusion proteins that selectively bind or target CD3 are disclosed in US Patent Publication No. 2016/0000916, US Patent Nos. 4,361,549, 5,834,597, 6,491,916, 6,406,696, 6,143,297, 6,750,325 and International Publication No. WO 2004/052397, the entire disclosures of which are hereby incorporated by reference.

CD20 Targeting Moieties

In various embodiments, the CD20 targeting moiety is a protein-based agent capable of specific binding to CD20. In various embodiments, the CD20 targeting moiety is a protein-based agent capable of specific binding to CD20 without neutralization of CD20. CD20 is a non-glycosylated member of the membrane-spanning 4-A (MS4A) family. It functions as a B cell specific differentiation antigen in both mouse and human. In particular, human CD20 cDNA encodes a transmembrane protein consisting of four hydrophobic membrane-spanning domains, two extracellular loops and intracellular N- and C-terminal regions.

In various embodiments, the CD20 targeting moiety comprises a targeting moiety having an antigen recognition domain that recognizes an epitope present on CD20. In an embodiment, the antigen-recognition domain recognizes one or more linear epitopes present on CD20. In some embodiments, a linear epitope refers to any continuous sequence of amino acids present on CD20. In another embodiment, the antigen-recognition domain recognizes one or more conformational epitopes present on CD20. As used herein, a conformation epitope refers to one or more sections of amino acids (which may be discontinuous) which form a three-dimensional surface with features and/or shapes and/or tertiary structures capable of being recognized by an antigen recognition domain.

In various embodiments, the CD20 targeting moiety may bind to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants of CD20 (*e.g.*, human CD20). In various embodiments, the CD20 targeting moiety may bind to any forms of CD20 (*e.g.*, human CD20), including monomeric, dimeric, trimeric, tetrameric, heterodimeric, multimeric and associated forms. In an embodiment, the CD20 targeting moiety binds to the monomeric form of CD20. In another embodiment, the CD20 targeting moiety binds to a dimeric form of CD20. In another embodiment, the CD20 targeting moiety binds to a tetrameric form of CD20. In a further embodiment, the CD20 targeting moiety to phosphorylated form of CD20, which may be either monomeric, dimeric, or tetrameric.

In an embodiment, the CD20 targeting moiety comprises a targeting moiety with an antigen recognition domain that recognizes one or more epitopes present on human CD20. In an embodiment, the human CD20 comprises the amino acid sequence of SEQ ID NO: 1346.

In various embodiments, the CD20 targeting moiety comprises a targeting moiety capable of specific binding. In various embodiments, the CD20 targeting moiety comprises a targeting moiety having an antigen recognition domain such as an antibody or derivatives thereof.

In some embodiments, the CD20 targeting moiety comprises a targeting moiety which is an antibody derivative or format. In some embodiments, the CD20 targeting moiety comprises a targeting moiety that is a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (cysteine knot protein, knottin), a DARPin; a Tetranectin; an Affibody; an Affimer, a Transbody; an Anticalin; an AdNectin; an Affilin; a Microbody; a peptide aptamer; an alterases; a plastic antibodies; a phylomer; a stradobodies; a maxibodies; an evibody; a fynomer, an armadillo repeat protein, a Kunitz domain, an avimer, an atrimer, a probody, an immunobody, a triomab, a troybody; a pepbody; a vaccibody, a UniBody; a DuoBody, a Fv, a Fab, a Fab', a $F(ab')_2$, a peptide mimetic molecule, or a small (e.g. synthetic or natural) molecule , e.g. without limitation, as described in US Patent Nos. or Patent Publication Nos. US 7,417,130, US 2004/132094, US 5,831,012, US 2004/023334, US 7,250,297, US 6,818,418, US 2004/209243, US 7,838,629, US 7,186,524, US 6,004,746, US 5,475,096, US 2004/146938, US 2004/157209, US 6,994,982, US 6,794,144, US 2010/239633, US 7,803,907, US 2010/119446, and/or US 7,166,697, the contents of which are hereby incorporated by reference in their entireties. *See* also, Storz MAbs. 2011 May-Jun; 3(3): 310–317.

In some embodiments, the CD20 targeting moiety comprises a targeting moiety that is a single-domain antibody, such as a VHH. The VHH may be derived from, for example, an organism that produces VHH antibody such as a

camelid, a shark, or the VHH may be a designed VHH. VHHs are antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally-occurring heavy-chain antibodies. VHH technology is based on fully functional antibodies from camelids that lack light chains. These heavy-chain antibodies contain a single variable domain (V_HH) and two constant domains (CH2 and CH3). VHHs are commercially available under the trademark of NANOBODIES. In an embodiment, the CD20 targeting moiety comprises a Nanobody. In some embodiments, the single domain antibody as described herein is an immunoglobulin single variable domain or ISVD.

In some embodiments, the CD20 targeting moiety comprises a targeting moiety which is a VHH comprising a single amino acid chain having four "framework regions" or FRs and three "complementary determining regions" or CDRs. As used herein, "framework region" or "FR" refers to a region in the variable domain which is located between the CDRs. As used herein, "complementary determining region" or "CDR" refers to variable regions in VHHs that contains the amino acid sequences capable of specifically binding to antigenic targets.

In various embodiments, the CD20 targeting moiety comprises a VHH having a variable domain comprising at least one CDR1, CDR2, and/or CDR3 sequences.

In some embodiments, the CDR1 sequence is selected from SEQ ID Nos.: 1347-1366. In some embodiments, the CDR2 sequence is selected from SEQ ID Nos.: 1367-1383. In some embodiments, the CDR3 sequence is selected from SEQ ID Nos.: 1384-1396.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1347, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1367, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1384.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1347, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1368, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1384.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1348, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1367, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1384.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1349, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1367, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1384.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1350, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1369, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1385.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1351, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1370, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1386.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1352, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1371, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1387.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1353, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1371, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1388.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1354, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1372, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1389.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1355, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1373, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1390.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1355, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1374, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1390.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1355, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1375, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1390.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1356, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1374, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1390.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1357, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1376, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1391.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1358, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1377, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1392.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1359, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1377, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1392.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1360, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1377, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1392.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1361, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1378, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1392.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1362, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1379, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1392.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1363, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1377, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1392.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1364, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1380, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1393.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1365, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1381, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1394.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1366, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1382, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1395.

In various embodiments, the CD20 targeting moiety comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 1366, a CDR2 comprising the amino acid sequence of SEQ ID NO: 1383, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 1396.

In various embodiments, the CD20 targeting moiety comprises an amino acid sequence selected from the following sequences: 2HCD16 (SEQ ID NO: 1397); 2HCD22 (SEQ ID NO: 1398);

2HCD35 (SEQ ID NO: 1399); 2HCD42 (SEQ ID NO: 1400); 2HCD73 (SEQ ID NO: 1401); 2HCD81 (SEQ ID NO: 1402); R3CD105 (SEQ ID NO: 1403); R3CD18 (SEQ ID NO: 1404); R3CD7 (SEQ ID NO: 1405); 2HCD25 (SEQ ID NO: 1406); 2HCD78 (SEQ ID NO: 1407); 2HCD17 (SEQ ID NO: 1408); 2HCD40 (SEQ ID NO: 1409); 2HCD88 (SEQ ID NO: 1410); 2HCD59 (SEQ ID NO: 1411); 2HCD68 (SEQ ID NO: 1412); 2HCD43 (SEQ ID NO: 1413); 2MC57 (SEQ ID NO: 1414); R2MUC70 (SEQ ID NO: 1415); R3MUC17 (SEQ ID NO: 1416); R3MUC56 (SEQ ID NO: 1417); R3MUC57 (SEQ ID NO: 1418); R3MUC58 (SEQ ID NO: 1419); R2MUC85 (SEQ ID NO: 1420); R3MUC66 (SEQ ID NO: 1421); R2MUC21 (SEQ ID NO: 1422); 2MC52 (SEQ ID NO: 1423); R3MUC22 (SEQ ID NO: 1424); R3MUC75 (SEQ ID NO: 1425); 2MC39 (SEQ ID NO: 1426); 2MC51 (SEQ ID NO: 1427); 2MC38 (SEQ ID NO: 1428); 2MC82 (SEQ ID NO: 1429); 2MC20 (SEQ ID NO: 1430); 2MC42 (SEQ ID NO:1431); R2MUC36 (SEQ ID NO: 1432); R3MCD137 (SEQ ID NO: 1433); or R3MCD22 (SEQ ID NO: 1434).

In some embodiments, the CD20 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 1397-1434 (provided above) without the terminal histidine tag sequence (*i.e.*, HHHHHH; SEQ ID NO: 393).

In some embodiments, the CD20 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 1397-1434 (provided above) without the HA tag (*i.e.*, YPYDVPDYGS; SEQ ID NO: 394).

In some embodiments, the CD20 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 1397-1434 (provided above) without the AAA linker (*i.e.*, AAA).

In some embodiments, the CD20 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 1397-1434 (provided above) without the AAA linker and HA tag.

In some embodiments, the CD20 targeting moiety comprises an amino acid sequence selected from SEQ ID NOs: 1397-1434 (provided above) without the AAA linker, HA tag, and terminal histidine tag sequence (*i.e.*, AAAYPYDVPDYGSHHHHHH; SEQ ID NO: 395).

In various embodiments, the present technology contemplates the use of any natural or synthetic analogs, mutants, variants, alleles, homologs and orthologs (herein collectively referred to as "analogs") of the CD20 targeting moiety as described herein. In various embodiments, the amino acid sequence of the CD20 targeting moiety further includes an amino acid analog, an amino acid derivative, or other non-classical amino acids.

In various embodiments, the CD20 targeting moiety comprises a targeting moiety comprising a sequence that is at least 60% identical to any one of the CD20 sequences disclosed above. In various embodiments, the CD20 targeting moiety comprises a sequence that is at least 60% identical to any one of the CD20 sequences disclosed above minus the linker sequence, the HA tag and/or the HIS_6 tag. For example, the CD20 targeting moiety may comprise a sequence that is at least about 60%, at least about 61%, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to any one of the CD20 sequences disclosed herein (*e.g.* about 60%, or about 61%, or about 62%, or about 63%, or about 64%, or about 65%, or about 66%, or about 67%, or about 68%, or about 69%, or about 70%, or about 71%, or about 72%, or about 73%, or about 74%, or about 75%, or about 76%, or about 77%, or about 78%, or about 79%, or about 80%, or about 81%, or about 82%, or about 83%, or about 84%, or about 85%, or about 86%, or about 87%, or about 88%, or about 89%, or about 90%, or about 91%, or about 92%, or about 93%, or about 94%, or about 95%, or about 96%, or about 97%, or about 98%, about 99% or about 100% sequence identity to any one of the CD20 sequences disclosed herein).

In various embodiments, the CD20 targeting moiety comprises an amino acid sequence having one or more amino acid mutations. In various embodiments, the CD20 targeting moiety comprises an amino acid sequence having one, or two, or three, or four, or five, or six, or seen, or eight, or nine, or ten, or fifteen, or twenty amino acid mutations with respect to any one of the CD20 sequences disclosed above. In some embodiments, the one or

more amino acid mutations may be independently selected from substitutions, insertions, deletions, and truncations.

In some embodiments, the amino acid mutations are amino acid substitutions, and may include conservative and/or non-conservative substitutions.

"Conservative substitutions" may be made, for instance, on the basis of similarity in polarity, charge, size, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the amino acid residues involved. The 20 naturally occurring amino acids can be grouped into the following six standard amino acid groups: (1) hydrophobic: Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr; Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe.

As used herein, "conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed within the same group of the six standard amino acid groups shown above. For example, the exchange of Asp by Glu retains one negative charge in the so modified polypeptide. In addition, glycine and proline may be substituted for one another based on their ability to disrupt α-helices.

As used herein, "non-conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed in a different group of the six standard amino acid groups (1) to (6) shown above.

In various embodiments, the substitutions may also include non-classical amino acids (*e.g.* selenocysteine, pyrrolysine, *N*-formylmethionine β-alanine, GABA and δ-Aminolevulinic acid, 4-aminobenzoic acid (PABA), D-isomers of the common amino acids, 2,4-diaminobutyric acid, α-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ-Abu, ε-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosme, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β-alanine, fluoro-amino acids, designer amino acids such as β methyl amino acids, C α-methyl amino acids, N α-methyl amino acids, and amino acid analogs in general).

In various embodiments, the amino acid mutation may be in the CDRs of the targeting moiety (*e.g.*, the CDR1, CDR2 or CDR3 regions). In another embodiment, amino acid alteration may be in the framework regions (FRs) of the targeting moiety (*e.g.*, the FR1, FR2, FR3, or FR4 regions).

Modification of the amino acid sequences may be achieved using any known technique in the art *e.g.*, site-directed mutagenesis or PCR based mutagenesis. Such techniques are described, for example, in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., 1989 and Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons, New York, N.Y., 1989.

In various embodiments, the mutations do not substantially reduce the CD20 targeting moiety's capability to specifically bind to CD20. In various embodiments, the mutations do not substantially reduce the CD20 targeting moiety's capability to specifically bind to CD20 without neutralizing CD20.

In various embodiments, the binding affinity of the CD20 targeting moiety for the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or monomeric and/or dimeric and/or tetrameric forms and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric and/or dimeric

and/or tetrameric forms) of human CD20 may be described by the equilibrium dissociation constant (K_D). In various embodiments, the CD20 targeting moiety comprises a targeting moiety that binds to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric and/or dimeric and/or tetrameric forms) of human CD20 with a K_D of less than about 1 μM, about 900 nM, about 800 nM, about 700 nM, about 600 nM, about 500 nM, about 400 nM, about 300 nM, about 200 nM, about 100 nM, about 90 nM, about 80 nM, about 70 nM, about 60 nM, about 50 nM, about 40 nM, about 30 nM, about 20 nM, about 10 nM, or about 5 nM, or about 4.5 nM, or about 1 nM.

In various embodiments, the CD20 targeting moiety comprises a targeting moiety that binds but does not functionally modulate the antigen of interest, *i.e.*, CD20. For instance, in various embodiments, the targeting moiety of the CD20 targeting moiety simply targets the antigen but does not substantially functionally modulate (*e.g.* substantially inhibit, reduce or neutralize) a biological effect that the antigen has. In various embodiments, the CD20 targeting moiety binds an epitope that is physically separate from an antigen site that is important for its biological activity (*e.g.* an antigen's active site).

Such binding without significant function modulation finds use in various embodiments of the present application. In various embodiments, the CD20 targeting moiety binds to CD20 positive cells and induces the death of such cells. In some embodiments, the CD20 targeting moiety induces cell death as mediated by one or more of apoptosis or direct cell death, complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and/or or antibody-dependent cellular phagocytosis (ADCP). In some embodiments, the present CD20 targeting moiety induces translocation of CD20 into large lipid microdomains or 'lipid rafts' within the plasma membrane upon binding. This clustering process enhances the activation of complement and exerts strong complement-dependent cytotoxicity (CDC). In other embodiments, the CD20 targeting moiety induces direct cell death. In alternative embodiments, the therapeutic efficacy of the CD20 targeting moiety is not dependent on B cell depletion.

In various embodiments, the CD20 targeting moiety may be used to directly or indirectly recruit active immune cells to a site of need via an effector antigen. For example, in various embodiments, the CD20 targeting moiety may be used to directly or indirectly recruit an immune cell to a cancer or tumor cell in a method of reducing or eliminating a cancer or tumor (*e.g.* the CD20 targeting moiety may comprise an anti-CD20 antigen recognition domain and a targeting moiety having a recognition domain (*e.g.* antigen recognition domain) directed against Clec9A, which is an antigen expressed on dendritic cells). In these embodiments, CD20 signaling is an important piece of the cancer reducing or eliminating effect. In various embodiments, the CD20 targeting moiety may recruit a T cell, a B cell, a dendritic cell, a macrophage, and a natural killer (NK) cell.

Bispecific and Multispecific Targeting Moiety Formats

In some embodiments, the Fc-based chimeric protein complexes of the present technology comprise one or more targeting moieties disclosed herein. In various embodiments, the Fc-based chimeric protein complexes have targeting moieties that target two different cells (*e.g.* to make a synapse) or the same cell (*e.g.* to get a more concentrated signaling agent effect). In various embodiments, the Fc-based chimeric protein complexes have two or more copies of the same targeting moiety (multivalency), *e.g.* to increase the affinity of target binding.

In various embodiments, the Fc-based chimeric protein complexes of the present technology are multi-specific, *i.e.*, the Fc-based chimeric protein complex comprises two or more targeting moieties having recognition domains (*e.g.* antigen recognition domains) that recognize and bind two or more targets (*e.g.* antigens, or receptors, or epitopes). In such embodiments, the Fc-based chimeric protein complexes may comprise two more targeting moieties having recognition domains that recognize and bind two or more epitopes on the same antigen or on different antigens or on different receptors. In various embodiments, such multi-specific Fc-based chimeric protein complexes exhibit advantageous properties such as increased avidity and/or improved selectivity. In some embodiments, the Fc-based chimeric protein complex comprises two targeting moieties and is bispecific, *i.e.*, binds and recognizes two epitopes on the same antigen or on different antigens or different receptors. Accordingly, in various embodiments, the Fc-based chimeric protein complex encompasses such multi-specific Fc-based chimeric protein complexes comprising two or more targeting moieties.

In various embodiments, the multi-specific Fc-based chimeric protein complexes comprises two or more targeting moieties with each targeting moiety being an antibody or an antibody derivative as described herein. In an embodiment, the multi-specific Fc-based chimeric protein complex comprises at least one VHH comprising an antigen recognition domain against one target and one antibody or antibody derivative comprising a recognition domain against a tumor antigen and/or an immune cell marker.

In various embodiments, the present multi-specific Fc-based chimeric protein complexes have two or more targeting moieties that target different antigens or receptors, and one targeting moiety may be attenuated for its antigen or receptor, *e.g.* the targeting moiety binds its antigen or receptor with a low affinity or avidity (including, for example, at an affinity or avidity that is less than the affinity or avidity the other targeting moiety has for its for its antigen or receptor, for instance the difference between the binding affinities may be about 10-fold, or 25-fold, or 50-fold, or 100-fold, or 300-fold, or 500-fold, or 1000-fold, or 5000-fold; for instance the lower affinity or avidity targeting moiety may bind its antigen or receptor at a K_D in the mid- to high-nM or low- to mid-μM range while the higher affinity or avidity targeting moiety may bind its antigen or receptor at a K_D in the mid- to high-pM or low- to mid-nM range). For instance, in some embodiments, the present multi-specific Fc-based chimeric protein complex comprises an attenuated targeting moiety that is directed against a promiscuous antigen or receptor, which may improve targeting to a cell of interest (*e.g.* via the other targeting moiety) and prevent effects across multiple types of cells, including those not being targeted for therapy (*e.g.* by binding promiscuous antigen or receptor at a higher affinity than what is provided in these embodiments).

The multi-specific Fc-based chimeric protein complexes may be constructed using methods known in the art, see for example, U.S. Patent No. 9,067,991, U.S. Patent Publication No. 20110262348 and WO 2004/041862, the entire contents of which are hereby incorporated by reference. In an illustrative embodiment, the multi-specific Fc-based chimeric protein complex comprising two or more targeting moieties may be constructed by chemical crosslinking, for example, by reacting amino acid residues with an organic derivatizing agent as described by Blattler *et al.*, Biochemistry 24,1517-1524 and EP294703, the entire contents of which are hereby incorporated by reference. In another illustrative embodiment, the multi-specific Fc-based chimeric protein complex comprising two

or more targeting moieties is constructed by genetic fusion, *i.e.*, constructing a single polypeptide which includes the polypeptides of the individual targeting moieties. For example, a single polypeptide construct may be formed which encodes a first VHH with an antigen recognition domain against a first target and a second antibody or antibody derivative with an antigen recognition domain against *e.g.*, a tumor antigen or a checkpoint inhibitor. A method for producing bivalent or multivalent VHH polypeptide constructs is disclosed in PCT patent application WO 96/34103, the entire contents of which is hereby incorporated by reference. In a further illustrative embodiment, the multi-specific Fc-based chimeric protein complex may be constructed by using linkers. For example, the carboxy-terminus of a first VHH with an antigen recognition domain against a first target may be linked to the amino-terminus of a second antibody or antibody derivative with an antigen recognition domain against *e.g.*, a tumor antigen or a checkpoint inhibitor (or vice versa). Illustrative linkers that may be used are described herein. In some embodiments, the components of the multi-specific Fc-based chimeric protein complex are directly linked to each other without the use of linkers.

In various embodiments, the multi-specific Fc-based chimeric protein complex recognizes and binds to a target (*e.g.*, XCR1, Clec9A, FAP, PD-1, PD-L1, PD-L2, SIRP1α, or CD8) and one or more antigens found on one or more immune cells, which can include, without limitation, megakaryocytes, thrombocytes, erythrocytes, mast cells, basophils, neutrophils, eosinophils, monocytes, macrophages, natural killer cells, T lymphocytes (*e.g.*, cytotoxic T lymphocytes, T helper cells, natural killer T cells), B lymphocytes, plasma cells, dendritic cells, or subsets thereof. In some embodiments, the Fc-based chimeric protein complex specifically binds to an antigen of interest and effectively directly or indirectly recruits one of more immune cells.

In various embodiments, the multi-specific Fc-based chimeric protein complex recognizes and binds to target (*e.g.*, XCR1, Clec9A, FAP, PD-1, PD-L1, PD-L2, SIRP1α, or CD8) and one or more antigens found on tumor cells. In these embodiments, the present Fc-based chimeric protein complex may directly or indirectly recruit an immune cell to a tumor cell or the tumor microenvironment. In some embodiments, the present Fc-based chimeric protein complex may directly or indirectly recruit an immune cell, *e.g.* an immune cell that can kill and/or suppress a tumor cell (*e.g.*, a CTL), to a site of action (such as, by way of non-limiting example, the tumor microenvironment). In some embodiments, the present Fc-based chimeric protein complex enhances antigen presentation (*e.g.* tumor antigen presentation) by dendritic cells for the induction of a potent humoral and cytotoxic T cell response.

In some embodiments, the Fc-based chimeric protein complex may have two or more targeting moieties that bind to non-cellular structures. In some embodiments, there are two targeting moieties and one targets a cell while the other targets a non-cellular structure.

In some embodiments, the present Fc-based chimeric protein complex has (i) one or more of the targeting moieties which is directed against an immune cell selected from a T cell, a B cell, a dendritic cell, a macrophage, a NK cell, or subsets thereof and (ii) one or more of the targeting moieties which is directed against a tumor cell, along with any of the signaling agents described herein. In one embodiment, the Fc-based chimeric protein complex has (i) a targeting moiety directed against a T cell (including, without limitation an effector T cell) and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In one embodiment, the

present Fc-based chimeric protein complex has (i) a targeting moiety directed against a B cell and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a dendritic cell and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a macrophage and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a NK cell and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein.

By way of non-limiting example, in various embodiments, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a T cell, for example, mediated by targeting to CD8, SLAMF4, IL-2 R α, 4-1BB/TNFRSF9, IL-2 R β, ALCAM, B7-1, IL-4 R, B7-H3, BLAME/SLAMFS, CEACAM1, IL-6 R, CCR3, IL-7 Rα, CCR4, CXCRl/IL-S RA, CCR5, CCR6, IL-10R α, CCR 7, IL-l 0 R β, CCRS, IL-12 R β 1, CCR9, IL-12 R β 2, CD2, IL-13 R α 1, IL-13, CD3, CD4, ILT2/CDS5j, ILT3/CDS5k, ILT4/CDS5d, ILT5/CDS5a, lutegrin α 4/CD49d, CDS, Integrin α E/CD103, CD6, Integrin α M/CD 11 b, CDS, Integrin α X/CD11c, Integrin β 2/CDIS, KIR/CD15S, CD27/TNFRSF7, KIR2DL1, CD2S, KIR2DL3, CD30/TNFRSFS, KIR2DL4/CD15Sd, CD31/PECAM-1, KIR2DS4, CD40 Ligand/TNFSF5, LAG-3, CD43, LAIR1, CD45, LAIR2, CDS3, Leukotriene B4-R1, CDS4/SLAMF5, NCAM-L1, CD94, NKG2A, CD97, NKG2C, CD229/SLAMF3, NKG2D, CD2F-10/SLAMF9, NT-4, CD69, NTB-A/SLAMF6, Common γ Chain/IL-2 R γ, Osteopontin, CRACC/SLAMF7, PD-1, CRTAM, PSGL-1, CTLA-4, RANK/TNFRSF11A, CX3CR1, CX3CL1, L-Selectin, CXCR3, SIRP β 1, CXCR4, SLAM, CXCR6, TCCR/WSX-1, DNAM-1, Thymopoietin, EMMPRIN/CD147, TIM-1, EphB6, TIM-2, Fas/TNFRSF6, TIM-3, Fas Ligand/TNFSF6, TIM-4, Fcγ RIII/CD16, TIM-6, TNFR1/TNFRSF1A, Granulysin, TNF RIII/TNFRSF1B, TRAIL Rl/TNFRSFIOA, ICAM-1/CD54, TRAIL R2/TNFRSF10B, ICAM-2/CD102, TRAILR3/TNFRSF10C,IFN-γR1, TRAILR4/TNFRSF10D, IFN-γ R2, TSLP, IL-1 R1, or TSLP R; and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein.

By way of non-limiting example, in various embodiments, the present Fc-based chimeric protein complex has a targeting moiety directed against (i) a checkpoint marker expressed on a T cell, *e.g.* one or more of PD-1, CD28, CTLA4, ICOS, BTLA, KIR, LAG3, CD137, OX40, CD27, CD40L, TIM3, and A2aR and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a T cell, for example, mediated by targeting to CD8 and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In an embodiment, the present Fc-based chimeric protein complex has a targeting moiety directed against CD8 on T cells and a second targeting moiety directed against PD-L1 or PD-L2 on tumor cells.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a T cell, for example, mediated by targeting to CD4 and (ii) a targeting moiety is directed against a tumor cell, along

with any of the signaling agents described herein. In an embodiment, the present Fc-based chimeric protein complex has a targeting moiety directed against CD4 on T cells and a second targeting moiety directed against PD-L1 or PD-L2 on tumor cells.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a T cell, for example, mediated by targeting to CD3, CXCR3, CCR4, CCR9, CD70, CD103, or one or more immune checkpoint markers and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In an embodiment, the present Fc-based chimeric protein complex has a targeting moiety directed against CD3 on T cells and a second targeting moiety directed against PD-L1 or PD-L2 on tumor cells.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a T cell, for example, mediated by targeting to PD-1 and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein.

By way of non-limiting example, in various embodiments, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a B cell, for example, mediated by targeting to CD10, CD19, CD20, CD21, CD22, CD23, CD24, CD37, CD38, CD39, CD40, CD70, CD72, CD73, CD74, CDw75, CDw76, CD77, CD78, CD79a/b, CD80, CD81, CD82, CD83, CD84, CD85, CD86, CD89, CD98, CD126, CD127, CDw130, CD138, or CDw150; and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In an embodiment, the present Fc-based chimeric protein complex has a targeting moiety directed against CD20.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a B cell, for example, mediated by targeting to CD19, CD20 or CD70 and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a B cell, for example, mediated by targeting to CD20 and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In an embodiment, the present has a targeting moiety directed against CD20 on B cells and a second targeting moiety directed against PD-L1 or PD-L2 on tumor cells.

By way of non-limiting example, in various embodiments, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a NK cell, for example, mediated by targeting to 2B4/SLAMF4, KIR2DS4, CD155/PVR, KIR3DL1, CD94, LMIR1/CD300A, CD69, LMIR2/CD300c, CRACC/SLAMF7, LMIR3/CD300LF, DNAM-1, LMIR5/CD300LB, Fc-epsilon RII, LMIR6/CD300LE, Fc-γ RI/CD64, MICA, Fc-γ RIIB/CD32b, MICB, Fc-γ RIIC/CD32c, MULT-1, Fc-γ RIIA/CD32a, Nectin-2/CD112, Fc-γ RIII/CD16, NKG2A, FcRH1/IRTA5, NKG2C, FcRH2/IRTA4, NKG2D, FcRH4/IRTA1, NKp30, FcRH5/IRTA2, NKp44, Fc-Receptor-like 3/CD16-2, NKp46/NCR1, NKp80/KLRF1, NTB-A/SLAMF6, Rae-1, Rae-1 α, Rae-1 β, Rae-1 delta, H60, Rae-1 epsilon, ILT2/CD85j, Rae-1 γ, ILT3/CD85k, TREM-1, ILT4/CD85d, TREM-2, ILT5/CD85a, TREM-3, KIR/CD158, TREML1/TLT-1, KIR2DL1, ULBP-1, KIR2DL3, ULBP-2, KIR2DL4/CD158d, or ULBP-3; and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a NK cell, for example, mediated by targeting to Kir1alpha, DNAM-1 or CD64 and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a NK cell, for example, mediated by targeting to KIR1 and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In an embodiment, the present Fc-based chimeric protein complex has a targeting moiety directed against KIR1 on NK cells and a second targeting moiety directed against PD-L1 or PD-L2 on tumor cells.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a NK cell, for example, mediated by targeting to TIGIT or KIR1 and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In an embodiment, the present Fc-based chimeric protein complex has a targeting moiety directed against TIGIT on NK cells and a second targeting moiety directed against PD-L1 or PD-L2 on tumor cells.

By way of non-limiting example, in various embodiments, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a dendritic cell, for example, mediated by targeting to CLEC-9A, XCR1, RANK, CD36/SRB3, LOX-1/SR-E1, CD68, MARCO, CD163, SR-A1/MSR, CD5L, SREC-1, CL-PI/COLEC12, SREC-II, LIMPIIISRB2, RP105, TLR4, TLR1, TLR5, TLR2, TLR6, TLR3, TLR9, 4-IBB Ligand/TNFSF9, IL-12/IL-23 p40, 4-Amino-1,8-naphthalimide, ILT2/CD85j, CCL21/6Ckine, ILT3/CD85k, 8-oxo-dG, ILT4/CD85d, 8D6A, ILT5/CD85a, A2B5, lutegrin α 4/CD49d, Aag, Integrin β 2/CD18, AMICA, Langerin, B7-2/CD86, Leukotriene B4 RI, B7-H3, LMIR1/CD300A, BLAME/SLAMF8, LMIR2/CD300c, Clq R1/CD93, LMIR3/CD300LF, CCR6, LMIR5/CD300LB CCR7, LMIR6/CD300LE, CD40/TNFRSF5, MAG/Siglec-4-a, CD43, MCAM, CD45, MD-1, CD68, MD-2, CD83, MDL-1/CLEC5A, CD84/SLAMF5, MMR, CD97, NCAMLI, CD2F-10/SLAMF9, Osteoactivin GPNMB, Chern 23, PD-L2, CLEC-1, RP105, CLEC-2, Siglec-2/CD22, CRACC/SLAMF7, Siglec-3/CD33, DC-SIGN, Siglec-5, DC-SIGNR/CD299, Siglec-6, DCAR, Siglec-7, DCIR/CLEC4A, Siglec-9, DEC-205, Siglec-10, Dectin-1/CLEC7A, Siglec-F, Dectin-2/CLEC6A, SIGNR1/CD209, DEP-1/CD148, SIGNR4, DLEC, SLAM, EMMPRIN/CD147, TCCR/WSX-1, Fc-γ R1/CD64, TLR3, Fc-γ RIIB/CD32b, TREM-1, Fc-γ RIIC/CD32c, TREM-2, Fc-γ RIIA/CD32a, TREM-3, Fc-γ RIII/CD16, TREML1/TLT-1, ICAM-2/CD102, or Vanilloid R1; and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a dendritic cell, for example, mediated by targeting to CLEC-9A, DC-SIGN, CD64, CLEC4A, or DEC205 and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In an embodiment, the present Fc-based chimeric protein complex has a targeting moiety directed against CLEC9A on dendritic cells and a second targeting moiety directed against PD-L1 or PD-L2 on tumor cells.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a dendritic cell, for example, mediated by targeting to CLEC9A and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In an embodiment, the present Fc-based chimeric

protein complex has a targeting moiety directed against CLEC9A on dendritic cells and a second targeting moiety directed against PD-L1 or PD-L2 on tumor cells.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a dendritic cell, for example, mediated by targeting to XCR1 and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In an embodiment, the present Fc-based chimeric protein complex has a targeting moiety directed against XCR1 on dendritic cells and a second targeting moiety directed against PD-L1 or PD-L2 on tumor cells.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a dendritic cell, for example, mediated by targeting to RANK and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In an embodiment, the present Fc-based chimeric protein complex has a targeting moiety directed against RANK on dendritic cells and a second targeting moiety directed against PD-L1 or PD-L2 on tumor cells.

By way of non-limiting example, in various embodiments, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a monocyte/macrophage, for example, mediated by targeting to SIRP1a, B7-1/CD80, ILT4/CD85d, B7-H1, ILT5/CD85a, Common β Chain, Integrin α 4/CD49d, BLAME/SLAMF8, Integrin α X/CDIIc, CCL6/C10, Integrin β 2/CD18, CD155/PVR, Integrin β 3/CD61, CD31/PECAM-1, Latexin, CD36/SR-B3, Leukotriene B4 R1, CD40/TNFRSF5, LIMPIIISR-B2, CD43, LMIR1/CD300A, CD45, LMIR2/CD300c, CD68, LMIR3/CD300LF, CD84/SLAMF5, LMIR5/CD300LB, CD97, LMIR6/CD300LE, CD163, LRP-1, CD2F-10/SLAMF9, MARCO, CRACC/SLAMF7, MD-1, ECF-L, MD-2, EMMPRIN/CD147, MGL2, Endoglin/CD105, Osteoactivin/GPNMB, Fc-γ RI/CD64, Osteopontin, Fc-γ RIIB/CD32b, PD-L2, Fc-γ RIIC/CD32c, Siglec-3/CD33, Fc-γ RIIA/CD32a, SIGNR1/CD209, Fc-γ RIII/CD16, SLAM, GM-CSF R α, TCCR/WSX-1, ICAM-2/CD102, TLR3, IFN-γ RI, TLR4, IFN- γ R2, TREM-I, IL-I RII, TREM-2, ILT2/CD85j, TREM-3, ILT3/CD85k, TREML1/TLT-1, 2B4/SLAMF 4, IL-10 R α, ALCAM, IL-10 R β, AminopeptidaseN/ANPEP, ILT2/CD85j, Common β Chain, ILT3/CD85k, Clq R1/CD93, ILT4/CD85d, CCR1, ILT5/CD85a, CCR2, CD206, Integrin α 4/CD49d, CCR5, Integrin α M/CDII b, CCR8, Integrin α X/CDIIc, CD155/PVR, Integrin β 2/CD18, CD14, Integrin β 3/CD61, CD36/SR-B3, LAIR1, CD43, LAIR2, CD45, Leukotriene B4-R1, CD68, LIMPIIISR-B2, CD84/SLAMF5, LMIR1/CD300A, CD97, LMIR2/CD300c, CD163, LMIR3/CD300LF, Coagulation Factor III/Tissue Factor, LMIR5/CD300LB, CX3CR1, CX3CL1, LMIR6/CD300LE, CXCR4, LRP-1, CXCR6, M-CSF R, DEP-1/CD148, MD-1, DNAM-1, MD-2, EMMPRIN/CD147, MMR, Endoglin/CD105, NCAM-L1, Fc-γ RI/CD64, PSGL-1, Fc-γ RIIIICD16, RP105, G-CSF R, L-Selectin, GM-CSF R α, Siglec-3/CD33, HVEM/TNFRSF14, SLAM, ICAM-1/CD54, TCCR/WSX-1, ICAM-2/CD102, TREM-I, IL-6 R, TREM-2, CXCRI/IL-8 RA, TREM-3, or TREMLI/TLT-1; and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a monocyte/macrophage, for example, mediated by targeting to B7-H1, CD31/PECAM-1, CD163, CCR2, or Macrophage Mannose Receptor CD206 and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein.

In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a monocyte/macrophage, for example, mediated by targeting to SIRP1a and (ii) a targeting moiety is directed against a tumor cell, along with any of the signaling agents described herein. In an embodiment, the present Fc-based chimeric protein complex has a targeting moiety directed against SIRP1a on macrophage cells and a second targeting moiety directed against PD-L1 or PD-L2 on tumor cells.

In various embodiments, the present Fc-based chimeric protein complex has one or more targeting moieties directed against a checkpoint marker, *e.g.* one or more of PD-1/PD-L1 or PD-L2, CD28/CD80 or CD86, CTLA4/CD80 or CD86, ICOS/ICOSL or B7RP1, BTLA/HVEM, KIR, LAG3, CD137/CD137L, OX40/OX40L, CD27, CD40L, TIM3/Gal9, and A2aR. In one embodiment, the present Fc-based chimeric protein complex has (i) a targeting moiety directed against a checkpoint marker on a T cell, for example, PD-1 and (ii) a targeting moiety directed against a tumor cell, for example, PD-L1 or PD-L2, along with any of the signaling agents described herein. In an embodiment, the present Fc-based chimeric protein complex has a targeting moiety directed against PD-1 on T cells and a second targeting moiety directed against PD-L1 on tumor cells. In another embodiment, the present Fc-based chimeric protein complex has a targeting moiety directed against PD-1 on T cells and a second targeting moiety directed against PD-L2 on tumor cells.

In some embodiments, the present Fc-based chimeric protein complex comprises two or more targeting moieties directed to the same or different immune cells. In some embodiments, the present Fc-based chimeric protein complex has (i) one or more targeting moieties directed against an immune cell selected from a T cell, a B cell, a dendritic cell, a macrophage, a NK cell, or subsets thereof and (ii) one or more targeting moieties directed against either the same or another immune cell selected from a T cell, a B cell, a dendritic cell, a macrophage, a NK cell, or subsets thereof, along with any of the signaling agents described herein.

In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against a T cell and one or more targeting moieties directed against the same or another T cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against a T cell and one or more targeting moieties directed against a B cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against a T cell and one or more targeting moieties directed against a dendritic cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties against a T cell and one or more targeting moieties directed against a macrophage. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties against a T cell and one or more targeting moieties directed against a NK cell. For example, in an illustrative embodiment, the Fc-based chimeric protein complex may include a targeting moiety against CD8 and a targeting moiety against Clec9A. In another illustrative embodiment, the Fc-based chimeric protein complex may include a targeting moiety against CD8 and a targeting moiety against CD3. In another illustrative embodiment, the Fc-based chimeric protein complex may include a targeting moiety against CD8 and a targeting moiety against PD-1.

In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against a B cell and one or more targeting moieties directed against the same or another B cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against a B cell and one or more targeting moieties directed against a T cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against a B cell and one or more targeting moieties directed against a dendritic cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties against a B cell and one or more targeting moieties directed against a macrophage. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties against a B cell and one or more targeting moieties directed against a NK cell.

In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against a dendritic cell and one or more targeting moieties directed against the same or another dendritic cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against a dendritic cell and one or more targeting moieties directed against a T cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against a dendritic cell and one or more targeting moieties directed against a B cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties against a dendritic cell and one or more targeting moieties directed against a macrophage. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties against a dendritic cell and one or more targeting moieties directed against a NK cell.

In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against a macrophage and one or more targeting moieties directed against the same or another macrophage. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against a macrophage and one or more targeting moieties directed against a T cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against a macrophage and one or more targeting moieties directed against a B cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties against a macrophage and one or more targeting moieties directed against a dendritic cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties against a macrophage and one or more targeting moieties directed against a NK cell.

In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against an NK cell and one or more targeting moieties directed against the same or another NK cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against an NK cell and one or more targeting moieties directed against a T cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties directed against an NK cell and one or more targeting moieties directed against a B cell. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties against an NK cell and one or more targeting moieties

directed against a macrophage. In one embodiment, the present Fc-based chimeric protein complex comprises one or more targeting moieties against an NK cell and one or more targeting moieties directed against a dendritic cell.

In one embodiment, the present Fc-based chimeric protein complex comprises a targeting moiety directed against a tumor cell and a second targeting moiety directed against the same or a different tumor cell. In such embodiments, the targeting moieties may bind to any of the tumor antigens described herein.

In some embodiments, the Fc-based chimeric protein complex of the invention comprises one or more targeting moieties having recognition domains that bind to a target (*e.g.* antigen, receptor) of interest including those found on one or more cells selected from adipocytes (*e.g.*, white fat cell, brown fat cell), liver lipocytes, hepatic cells, kidney cells (*e.g.*, kidney parietal cell, kidney salivary gland, mammary gland, *etc.*), duct cells (of seminal vesicle, prostate gland, *etc.*), intestinal brush border cells (with microvilli), exocrine gland striated duct cells, gall bladder epithelial cells, ductulus efferens nonciliated cells, epididymal principal cells, epididymal basal cells, endothelial cells, ameloblast epithelial cells (tooth enamel secretion), planum semilunatum epithelial cells of vestibular system of ear (proteoglycan secretion), organ of Corti interdental epithelial cells (secreting tectorial membrane covering hair cells), loose connective tissue fibroblasts, corneal fibroblasts (corneal keratocytes), tendon fibroblasts, bone marrow reticular tissue fibroblasts, nonepithelial fibroblasts, pericytes, nucleus pulposus cells of intervertebral disc, cementoblasts/cementocytes (tooth root bonelike ewan cell secretion), odontoblasts/odontocytes (tooth dentin secretion), hyaline cartilage chondrocytes, fibrocartilage chondrocytes, elastic cartilage chondrocytes, osteoblasts/osteocytes, osteoprogenitor cells (stem cell of osteoblasts), hyalocytes of vitreous body of eye, stellate cells of perilymphatic space of ear, hepatic stellate cells (Ito cell), pancreatic stelle cells, skeletal muscle cells, satellite cells, heart muscle cells, smooth muscle cells, myoepithelial cells of iris, myoepithelial cells of exocrine glands, exocrine secretory epithelial cells (*e.g.*, salivary gland cells, mammary gland cells, lacrimal gland cells, sweat gland cells, sebaceious gland cells, prostate gland cells, gastric glad cells, pancreatic acinar cells, pneumocytes), a hormone secreting cells (*e.g.*, pituitary cells, neurosecretory cells, gut and respiratory tract cells, thyroid gland cells, parathyroid glad cells, adrenal gland cells, Leydig cells of testes, pancreatic islet cells), keratinizing epithelial cells, wet stratified barrier epithelial cells, neuronal cells (*e.g.*, sensory transducer cells, autonomic neuron cells, sense organ and peripheral neuron supporting cells, and central nervous system neurons and glial cells such as interneurons, principal cells, astrocytes, oligodendrocytes, and ependymal cells).

Fc-based Chimeric Protein Complexes

In embodiments. the Fc-based chimeric protein complexes of the present technology comprise at least one Fc domain disclosed herein, at least one signaling agent (SA) disclosed herein, and at least one targeting moiety (TM) disclosed herein.

It is understood that, the present Fc-based chimeric protein complexes may encompass a complex of two fusion proteins.

In some embodiments, the Fc-based chimeric protein complex is heterodimeric. In some embodiments, the heterodimeric Fc-based chimeric protein complex has a trans orientation/configuration. In some embodiments, the

heterodimeric Fc-based chimeric protein complex has a cis orientation/configuration. In some embodiments, the heterodimeric Fc-based chimeric protein complex does not comprise the signaling agent and targeting moiety on a single polypeptide. In some embodiments, the signaling agent and targeting moiety are on the same end (N-terminus or C-terminus) of the Fc domain or the Fc chains thereof. In some embodiments, the signaling agent and targeting moiety are on different ends (N-terminus or C-terminus) of the Fc domain or the Fc chains thereof.

In some embodiments, the Fc-based chimeric protein has an improved in vivo half-life relative to a chimeric protein lacking an Fc or a chimeric protein which is not a heterodimeric complex. In some embodiments, the Fc-based chimeric protein has an improved solubility, stability and other pharmacological properties relative to a chimeric protein lacking an Fc or a chimeric protein which is not a heterodimeric complex.

Heterodimeric Fc-based chimeric protein complexes are composed of two different polypeptides. In embodiments described herein, the targeting domain is on a different polypeptide than the signaling agent and accordingly, proteins that contain only one targeting domain copy, and also only one signaling agent copy can be made (this provides a configuration in which potential interference with desired properties can be controlled). Further, in embodiments, one targeting domain (*e.g.* VHH) only can avoid cross-linking of the antigen on the cell surface (which could elicit undesired effects in some cases) Further, in embodiments, one signaling agent may alleviate molecular "crowding" and potential interference with avidity mediated restoration of effector function in dependence of the targeting domain. Further, in embodiments, heterodimeric Fc-based chimeric protein complexes can have two targeting moieties and these can be placed on the two different polypeptides. For instance, in embodiments, the C-terminus of both targeting moieties (*e.g.* VHHs) can be masked to avoid potential autoantibodies or pre-existing antibodies (*e.g.* VHH autoantibodies or pre-existing antibodies). Further, in embodiments, heterodimeric Fc-based chimeric protein complexes, *e.g.* with the targeting domain on a different polypeptide than the signaling agent (*e.g.* wild type signaling agent), may favor "cross-linking" of two cell types (*e.g.* a tumor cell and an immune cell). Further, in embodiments, heterodimeric Fc-based chimeric protein complexes can have two signaling agents, each on different polypeptides to allow more complex effector responses (*e.g.* with any two of the signaling agents described herein, by way of illustration IFN alpha2 and TNF).

Further, in embodiments, heterodimeric Fc-based chimeric protein complexes, *e.g.* with the targeting domain on a different polypeptide than the signaling agent, combinatorial diversity of targeting moiety and signaling agent is provided in a practical manner. For instance, in embodiments, polypeptides with any of the targeting moieties described herein can be combined "off the shelf" with polypeptides with any of the signaling agents described herein to allow rapid generation of various combinations of targeting moieties and signaling agents in single Fc-based chimeric protein complexes.

In some embodiments, the Fc-based chimeric protein complex comprises one or more linkers. In some embodiments, the Fc-based chimeric protein complex includes a linker that connects the Fc domain, signaling agent(s) and targeting moiety(ies). In some embodiments, the Fc-based chimeric protein complex includes a linker that connects each signaling agent and targeting moiety (or, if more than one targeting moiety, a signaling agent to one of the targeting moieties). In some embodiments, the Fc-based chimeric protein complex includes a linker

that connects each signaling agent to the Fc domain. In some embodiments, the Fc-based chimeric protein complex includes a linker that connects each targeting moiety to the Fc domain. In some embodiments, the Fc-based chimeric protein complex includes a linker that connects a targeting moiety to another targeting moiety. In some embodiments, the Fc-based chimeric protein complex includes a linker that connects a signaling agent to another signaling agent.

In some embodiments, an Fc-based chimeric protein complex comprises two or more targeting moieties. In such embodiments, the targeting moieties can be the same targeting moiety or they can be different targeting moieties.

In some embodiments, an Fc-based chimeric protein complex comprises two or more signaling agents. In such embodiments, the signaling agents can be the same targeting moiety or they can be different targeting moieties.

By way of example, in some embodiments, the Fc-based chimeric protein complex comprise an Fc domain, at least two signaling agents (SA), and at least two targeting moieties (TM), wherein the Fc domain, signaling agents, and targeting moieties are selected from any of the Fc domains, signaling agents, and targeting moieties disclosed herein. In some embodiments, the Fc domain is homodimeric.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 1A-F**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 2A-H**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 3A-H**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 4A-D**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 5A-F**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 6A-J**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 7A-D**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIG. 7B**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 8A-F**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 9A-J**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 10A-F**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 11A-L.**

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 12A-L**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 13A-F**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 14A-L**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 15A-L**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 16A-J**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 17A-J**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 18A-F**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 19A-F**.

In various embodiments, the Fc-based chimeric protein complex takes the form of any of the schematics of **FIGS. 20A-E**.

In some embodiments, the signaling agents are linked to the targeting moieties and the targeting moieties are linked to the Fc domain on the same terminus (see **FIGs. 1A-F**). In some embodiments, the Fc domain is homodimeric.

In some embodiments, the signaling agents and targeting moieties are linked to the Fc domain, wherein the targeting moieties and signaling agents are linked on the same terminus (see **FIGs. 1A-F**). In some embodiments, the Fc domain is homodimeric.

In some embodiments, the targeting moieties are linked to signaling agents and the signaling agents are linked to the Fc domain on the same terminus (see **FIGs. 1A-F**). In some embodiments, the Fc domain is homodimeric.

In some embodiments, the homodimeric Fc-based chimeric protein complex has two or more targeting moieties. In some embodiments, there are four targeting moieties and two signaling agents, the targeting moieties are linked to the Fc domain and the signaling agents are linked to targeting moieties on the same terminus (see **FIGS. 2A-H**). In some embodiments, the Fc domain is homodimeric. In some embodiments, where there are four targeting

moieties and two signaling agents, two targeting moieties are linked to the Fc domain and two targeting moieties are linked to the signaling agents, which are linked to the Fc domain on the same terminus (see **FIGS. 2A-H**). In some embodiments, the Fc domain is homodimeric. In some embodiments, where there are four targeting moieties and two signaling agents, two targeting moieties are linked to each other and one of the targeting moieties of from each pair is linked to the Fc domain on the same terminus and the signaling agents are linked to the Fc domain on the same terminus (see **FIGS. 2A-H**). In some embodiments, the Fc domain is homodimeric. In some embodiments, where there are four targeting moieties and two signaling agents, two targeting moieties are linked to each other, wherein one of the targeting moieties of from each pair is linked to a signaling agent and the other targeting moiety of the pair is linked the Fc domain, wherein the targeting moieties linked to the Fc domain are linked on the same terminus (see **FIGS. 2A-H**). In some embodiments, the Fc domain is homodimeric.

In some embodiments, the homodimeric Fc-based chimeric protein complex has two or more signaling agents. In some embodiments, where there are four signaling agents and two targeting moieties, two signaling agents are linked to each other and one of the signaling agents of from pair is linked to the Fc domain on the same terminus and the targeting moieties are linked to the Fc domain on the same terminus (see **FIGs. 3A-H**). In some embodiments, the Fc domain is homodimeric. In some embodiments, where there are four signaling agents and two targeting moieties, two signaling agents are linked to the Fc domain one the same terminus and two of the signaling agents are each linked to a targeting moiety, wherein the targeting moieties are linked to the Fc domain at the same terminus (see **FIGs. 3A-H**). In some embodiments, the Fc domain is homodimeric. In some embodiments, where there are four signaling agents and two targeting moieties, two signaling agents are linked to each other and one of the signaling agents of from pair is linked to a targeting moiety and the targeting moieties are linked to the Fc domain on the same terminus (see **FIGs. 3A-H**). In some embodiments, the Fc domain is homodimeric.

By way of example, in some embodiments, the Fc-based chimeric protein complex comprise an Fc domain, wherein the Fc domain comprises ionic pairing mutation(s) and/or knob-in-hole mutation(s), at least one signaling agent, and at least one targeting moiety, wherein the ionic pairing motif and/or a knob-in-hole motif, signaling agent, and targeting moiety are selected from any of the ionic pairing motif and/or a knob-in-hole motif, signaling agents, and targeting moieties disclosed herein. In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, the signaling agent is linked to the targeting moiety, which is linked to the Fc domain (see **FIGs. 10A-F** and **13A-F**). In some embodiments, the targeting moiety is linked to the signaling agent, which is linked to the Fc domain (see **FIGs. 10A-F** and **13A-F**). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, the signaling agent and targeting moiety are linked to the Fc domain (**see FIGs. 4A-D, 7A-D, 10A-F**, and **13A-F**). In some embodiments, the targeting moiety and the signaling agent are linked to different Fc chains on the same terminus (see **FIGs. 4A-D** and **7A-D**). In some embodiments, the targeting moiety and the signaling agent are linked to different Fc chains on different termini (see **FIGs. 4A-D** and **7A-D**). In some

embodiments, the targeting moiety and the signaling agent are linked to the same Fc chain (see **FIGs. 10A-F** and **13A-F**). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, where there are one signaling agent and two targeting moieties, the signaling agent is linked to the Fc domain and two targeting moieties can be: 1) linked to each other with one of the targeting moieties linked to the Fc domain; or 2) each linked to the Fc domain (see **FIGs. 5A-F, 8A-F, 11A-L, 14A-L, 16A-J**, and **17A-J**). In some embodiments, the targeting moieties are linked on one Fc chain and the signaling agent is on the other Fc chain (see **FIGs. 5A-F** and **8A-F**). In some embodiments, the paired targeting moieties and the signaling agent are linked to the same Fc chain (see **FIGs. 11A-L** and **14A-L**). In some embodiments, a targeting moiety is linked to the Fc domain and the other targeting moiety is linked to the signaling agent, and the paired targeting moiety is linked to the Fc domain (see **FIGs. 11A-L, 14A-L, 16A-J**, and **17A-J).** In some embodiments, the unpaired targeting moiety and paired targeting moiety are linked to the same Fc chain (see **FIGs. 11A-L** and **14A-L**). In some embodiments, the unpaired targeting moiety and paired targeting moiety are linked to different Fc chains (see **FIGs. 16A-J** and **17A-J**). In some embodiments, the unpaired targeting moiety and paired targeting moiety are linked on the same terminus (see **FIGs. 16A-J** and **17A-J**). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, where there are one signaling agent and two targeting moieties, a targeting moiety is linked to the signaling agent, which is linked to the Fc domain, and the unpaired targeting moiety is linked the Fc domain (see **FIGs. 11A-L, 14A-L, 16A-J**, and **17A-J**). In some embodiments, the paired signaling agent and unpaired targeting moiety are linked to the same Fc chain (see **FIGs. 11A-L** and **14A-L**). In some embodiments, the paired signaling agent and unpaired targeting moiety are linked to different Fc chains (see **FIGs. 16A-J** and **17A-J**). In some embodiments, the paired signaling agent and unpaired targeting moiety are linked on the same terminus (see **FIGs. 16A-J** and **17A-J**). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, where there are one signaling agent and two targeting moieties, the targeting moieties are linked together and the signaling agent is linked to one of the paired targeting moieties, wherein the targeting moiety not linked to the signaling agent is linked to the Fc domain (see **FIGs. 11A-L** and 14A-**L**). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, where there are one signaling agent and two targeting moieties, the targeting moieties are linked together and the signaling agent is linked to one of the paired targeting moieties, wherein the signaling agent is linked to the Fc domain (see **FIGs. 11A-L** and **14A-L**). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, where there are one signaling agent and two targeting moieties, the targeting moieties are both linked to the signaling agent, wherein one of the targeting moieties is linked to the Fc domain (see **FIGs. 11A-**

L and **14A-L**). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, where there are one signaling agent and two targeting moieties, the targeting moieties and the signaling agent are linked to the Fc domain (see **FIGs. 16A-J** and **17A-J**). In some embodiments, the targeting moieties are linked on the terminus (see **FIGs. 16A-J** and **17A-J**). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, where there are two signaling agents and one targeting moiety, the signaling agents are linked to the Fc domain on the same terminus and the targeting moiety is linked to the Fc domain (see **FIGs. 6A-J** and **9A-J**). In some embodiments, the signaling agents are linked to the Fc domain on the same Fc chain and the targeting moiety is linked on the other Fc chain (see FIGs. 18A-F and 19A-F). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, where there are two signaling agents and one targeting moiety, a signaling agent is linked to the targeting moiety, which is linked to the Fc domain and the other signaling agent is linked to the Fc domain (see **FIGs. 6A-J, 9A-J, 12A-L**, and **15A-L**). In some embodiments, the targeting moiety and the unpaired signaling agent are linked to different Fc chains (see **FIGs. 6A-J** and **9A-J**). In some embodiments, the targeting moiety and the unpaired signaling agent are linked to different Fc chains on the same terminus (see **FIGs. 6A-J** and **9A-J**). In some embodiments, the targeting moiety and the unpaired signaling agent are linked to different Fc chains on different termini (see **FIGs. 6A-J** and **9A-J**). In some embodiments, the targeting moiety and the unpaired signaling agent are linked to the same Fc chains (see **FIGs. 12A-L** and **15A-L**). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, where there are two signaling agents and one targeting moiety, the targeting moiety is linked to a signaling agent, which is linked to the Fc domain and the other signaling agent is linked to the Fc domain (see **FIGs. 6A-J** and **9A-J**). In some embodiments, the paired signaling agent and the unpaired signaling agent are linked to different Fc chains (see **FIGs. 6A-J** and **9A-J**). In some embodiments, the paired signaling agent and the unpaired signaling agent are linked to different Fc chains on the same terminus (see **FIGs. 6A-J** and **9A-J**). In some embodiments, the paired signaling agent and the unpaired signaling agent are linked to different Fc chains on different termini (see **FIGs. 6A-J** and **9A-J**). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, where there are two signaling agents and one targeting moiety, the signaling agents are linked together and the targeting moiety is linked to one of the paired signaling agents, wherein the targeting moiety is linked to the Fc domain (see **FIGs. 12A-L** and **15A-L**). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, where there are two signaling agents and one targeting moiety, the signaling agents are linked together and one of the signaling agents is linked to the Fc domain and the targeting moiety is linked to the Fc domain (see **FIGs. 12A-L, 15A-L, 18A-F**, and **19A-F**). In some embodiments, the paired signaling agents and targeting moiety are linked to the same Fc chain (see **FIGs**. **12A-L** and **15A-L**). In some embodiments, the paired signaling agents and targeting moiety are linked to different Fc chains (see **FIGs. 18A-F** and **19A-F**). In some embodiments, the paired signaling agents and targeting moiety are linked to different Fc chains on the same terminus (see **FIGs. 18A-F** and **19A-F**). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, where there are two signaling agents and one targeting moiety, the signaling agents are both linked to the targeting moiety, wherein one of the signaling agents is linked to the Fc domain (see **FIGs. 12A-L** and **15A-L**). In some embodiments, the Fc domain is heterodimeric. In some embodiments, the Fc domain comprises a mutation that reduces or eliminates its effector function.

In some embodiments, where there are two signaling agents and one targeting moiety, the signaling agents are linked together and one of the signaling agents is linked to the targeting moiety and the other signaling agent is linked to the Fc domain (see **FIGs. 12A-L** and **15A-L**).

In some embodiments, where there are two signaling agents and one targeting moiety, each signaling agent is linked to the Fc domain and the targeting moiety is linked to one of the signaling agents (see **FIGs. 12A-L** and **15A-L**). In some embodiments, the signaling agents are linked to the same Fc chain (see **FIGs. 12A-L** and **15A-L**).

In some embodiments, a targeting moiety or signaling agent is linked to the Fc domain, comprising one or both of C_H2 and C_H3 domains, and optionally a hinge region. For example, vectors encoding the targeting moiety, signaling agent, or combination thereof, linked as a single nucleotide sequence to an Fc domain can be used to prepare such polypeptides.

In some embodiments, the linker may be utilized to link various functional groups, residues, or moieties as described herein to the Fc-based chimeric protein complex. In some embodiments, the linker is a single amino acid or a plurality of amino acids that does not affect or reduce the stability, orientation, binding, neutralization, and/or clearance characteristics of the binding regions and the binding protein. In various embodiments, the linker is selected from a peptide, a protein, a sugar, or a nucleic acid.

In some embodiments, the Fc-based chimeric protein complex comprises a linker connecting a targeting moiety and the signaling agent. In some embodiments, the Fc-based chimeric protein complex comprises a linker within the signaling agent (*e.g.* in the case of single chain TNF, which can comprise two linkers to yield a trimer or in the case of IFN gamma, which can comprise a linkers to yield a dimer).

The present technology contemplates the use of a variety of linker sequences. In various embodiments, the linker may be derived from naturally-occurring multi-domain proteins or are empirical linkers as described, for example, in Chichili *et al.*, (2013), Protein Sci. 22(2):153-167, Chen *et al.*, (2013), Adv Drug Deliv Rev. 65(10):1357-1369, the entire contents of which are hereby incorporated by reference. In some embodiments, the linker may be

designed using linker designing databases and computer programs such as those described in Chen *et al.*, (2013), Adv Drug Deliv Rev. 65(10):1357-1369 and Crasto *et al.*, (2000), Protein Eng. 13(5):309-312, the entire contents of which are hereby incorporated by reference. In various embodiments, the linker may be functional. For example, without limitation, the linker may function to improve the folding and/or stability, improve the expression, improve the pharmacokinetics, and/or improve the bioactivity of the Fc-based chimeric protein complex

In some embodiments, the linker is a polypeptide. In some embodiments, the linker is less than about 100 amino acids long. For example, the linker may be less than about 100, about 95, about 90, about 85, about 80, about 75, about 70, about 65, about 60, about 55, about 50, about 45, about 40, about 35, about 30, about 25, about 20, about 19, about 18, about 17, about 16, about 15, about 14, about 13, about 12, about 11, about 10, about 9, about 8, about 7, about 6, about 5, about 4, about 3, or about 2 amino acids long. In some embodiments, the linker is a polypeptide. In some embodiments, the linker is greater than about 100 amino acids long. For example, the linker may be greater than about 100, about 95, about 90, about 85, about 80, about 75, about 70, about 65, about 60, about 55, about 50, about 45, about 40, about 35, about 30, about 25, about 20, about 19, about 18, about 17, about 16, about 15, about 14, about 13, about 12, about 11, about 10, about 9, about 8, about 7, about 6, about 5, about 4, about 3, or about 2 amino acids long. In some embodiments, the linker is flexible. In another embodiment, the linker is rigid.

In some embodiments, the linker length allows for efficient binding of a targeting moiety, a signaling agent, and/or an Fc domain to their targets (*e.g.*, receptors). For instance, in some embodiments, the linker length allows for efficient binding of one of the targeting moieties and the signaling agent to receptors on the same cell as well as the efficient binding of the other targeting moiety to another cell. Illustrative pairs of cells are provided elsewhere herein.

In some embodiments the linker length is at least equal to the minimum distance between the binding sites of a targeting moiety, a signaling agent, and/or an Fc domain targets (*e.g.*, receptors) on the same cell. In some embodiments the linker length is at least twice, or three times, or four times, or five times, or ten times, or twenty times, or 25 times, or 50 times, or one hundred times, or more the minimum distance between the binding sites of a targeting moiety, a signaling agent, and/or an Fc domain targets on the same cell.

In some embodiments, a linker connects the two targeting moieties to each other and this linker has a short length and a linker connects a targeting moiety and a signaling agent this linker is longer than the linker connecting the two targeting moieties. For example, the difference in amino acid length between the linker connecting the two targeting moieties and the linker connecting a targeting moiety and a signaling agent may be about 100, about 95, about 90, about 85, about 80, about 75, about 70, about 65, about 60, about 55, about 50, about 45, about 40, about 35, about 30, about 25, about 20, about 19, about 18, about 17, about 16, about 15, about 14, about 13, about 12, about 11, about 10, about 9, about 8, about 7, about 6, about 5, about 4, about 3, or about 2 amino acids. In some embodiments, the linker is flexible. In another embodiment, the linker is rigid.

In various embodiments, the linker is substantially comprised of glycine and serine residues (*e.g.* about 30%, or about 40%, or about 50%, or about 60%, or about 70%, or about 80%, or about 90%, or about 95%, or about 97%

glycines and serines). For example, in some embodiments, the linker is $(Gly_4Ser)_n$, where n is from about 1 to about 8, *e.g.* 1, 2, 3, 4, 5, 6, 7, or 8 (SEQ ID NO: 1283 -SEQ ID NO: 1290, respectively). In an embodiment, the linker sequence is GGSGGSGGGGSGGGGS (SEQ ID NO: 1291). Additional illustrative linkers include, but are not limited to, linkers having the sequence LE, GGGGS (SEQ ID NO: 1283), $(GGGGS)_n$ (n=1-7) (SEQ ID NO: 1283 -SEQ ID NO: 1289), $(Gly)_8$ (SEQ ID NO: 1292), $(Gly)_6$ (SEQ ID NO: 1293), $(EAAAK)_n$ (n=1-3) (SEQ ID NO: 1294-SEQ ID NO: 1296), $A(EAAAK)_nA$ (n = 2-5) (SEQ ID NO: 1297-SEQ ID NO: 1300), AEAAAKEAAAKA (SEQ ID NO: 1297), $A(EAAAK)_4ALEA(EAAAK)_4A$ (SEQ ID NO: 1301), PAPAP (SEQ ID NO: 1302), KESGSVSSEQLAQFRSLD (SEQ ID NO: 1303), EGKSSGSGSESKST (SEQ ID NO: 1304), GSAGSAAGSGEF (SEQ ID NO: 1305), and $(XP)_n$, with X designating any amino acid, *e.g.*, Ala, Lys, or Glu. In various embodiments, the linker is GGS or $(GGS)_n$ (n=2-20) (SEQ ID NO: 1306- SEQ ID NO: 1324). In some embodiments, the linker is G. In some embodiments, the linker is AAA. In some embodiments, the linker is $(GGGGS)_n$ (n=9-20) (SEQ ID NO: 1325- SEQ ID NO: 1336). In some embodiments, the linker is one or more of GGGSE (SEQ ID NO: 1337), GSESG (SEQ ID NO: 1338), GSEGS (SEQ ID NO: 1339), GEGGSGEGSSGEGSSSEGGGSEGGGSEGGGSEGGS (SEQ ID NO: 1340), and a linker of randomly placed G, S, and E every 4 amino acid intervals.

In some embodiments, the linker is a hinge region of an antibody (*e.g.*, of IgG, IgA, IgD, and IgE, inclusive of subclasses (*e.g.* IgG1, IgG2, IgG3, and IgG4, and IgA1 and IgA2)). In various embodiments, the linker is a hinge region of an antibody (*e.g.*, of IgG, IgA, IgD, and IgE, inclusive of subclasses (*e.g.* IgG1, IgG2, IgG3, and IgG4, and IgA1 and IgA2)). The hinge region, found in IgG, IgA, IgD, and IgE class antibodies, acts as a flexible spacer, allowing the Fab portion to move freely in space. In contrast to the constant regions, the hinge domains are structurally diverse, varying in both sequence and length among immunoglobulin classes and subclasses. For example, the length and flexibility of the hinge region varies among the IgG subclasses. The hinge region of IgG1 encompasses amino acids 216-231 and, because it is freely flexible, the Fab fragments can rotate about their axes of symmetry and move within a sphere centered at the first of two inter-heavy chain disulfide bridges. IgG2 has a shorter hinge than IgG1, with 12 amino acid residues and four disulfide bridges. The hinge region of IgG2 lacks a glycine residue, is relatively short, and contains a rigid poly-proline double helix, stabilized by extra inter-heavy chain disulfide bridges. These properties restrict the flexibility of the IgG2 molecule. IgG3 differs from the other subclasses by its unique extended hinge region (about four times as long as the IgG1 hinge), containing 62 amino acids (including 21 prolines and 11 cysteines), forming an inflexible poly-proline double helix. In IgG3, the Fab fragments are relatively far away from the Fc fragment, giving the molecule a greater flexibility. The elongated hinge in IgG3 is also responsible for its higher molecular weight compared to the other subclasses. The hinge region of IgG4 is shorter than that of IgG1 and its flexibility is intermediate between that of IgG1 and IgG2. The flexibility of the hinge regions reportedly decreases in the order IgG3>IgG1>IgG4>IgG2.

According to crystallographic studies, the immunoglobulin hinge region can be further subdivided functionally into three regions: the upper hinge region, the core region, and the lower hinge region. *See* Shin *et al.*, 1992 *Immunological Reviews* 130:87. The upper hinge region includes amino acids from the carboxyl end of C_{H1} to the first residue in the hinge that restricts motion, generally the first cysteine residue that forms an interchain disulfide

bond between the two heavy chains. The length of the upper hinge region correlates with the segmental flexibility of the antibody. The core hinge region contains the inter-heavy chain disulfide bridges, and the lower hinge region joins the amino terminal end of the C_{H2} domain and includes residues in C_{H2}. *Id.* The core hinge region of wild-type human IgG1 contains the sequence Cys-Pro-Pro-Cys (SEQ ID NO: 1341), which when dimerized by disulfide bond formation, results in a cyclic octapeptide believed to act as a pivot, thus conferring flexibility. In various embodiments, the linker comprises, one, or two, or three of the upper hinge region, the core region, and the lower hinge region of any antibody (*e.g.*, of IgG, IgA, IgD, and IgE, inclusive of subclasses (*e.g.* IgG1, IgG2, IgG3, and IgG4, and IgA1 and IgA2)). The hinge region may also contain one or more glycosylation sites, which include a number of structurally distinct types of sites for carbohydrate attachment. For example, IgA1 contains five glycosylation sites within a 17-amino-acid segment of the hinge region, conferring resistance of the hinge region polypeptide to intestinal proteases, considered an advantageous property for a secretory immunoglobulin. In various embodiments, the linker of the present invention comprises one or more glycosylation sites. In various embodiments, the linker is a hinge-CH2-CH3 domain of a human IgG4 antibody.

In some embodiments, the linker is a synthetic linker such as PEG.

In various embodiments, the linker may be functional. For example, without limitation, the linker may function to improve the folding and/or stability, improve the expression, improve the pharmacokinetics, and/or improve the bioactivity of the Fc-based chimeric protein complex. In another example, the linker may function to target the Fc-based chimeric protein complex to a particular cell type or location.

Functional Groups

In some embodiments, the Fc-based chimeric protein complex of the present technology includes one or more functional groups, residues, or moieties. In various embodiments, the one or more functional groups, residues, or moieties are attached or genetically fused to any of the Fc-proteins, the signaling agents, and the targeting moieties described herein. In some embodiments, such functional groups, residues or moieties confer one or more desired properties or functionalities to the Fc-based chimeric protein complex of the present technology. Examples of such functional groups and of techniques for introducing them into the Fc-based chimeric protein complex are known in the art, for example, see *Remington's Pharmaceutical Sciences,* 16th ed., Mack Publishing Co., Easton, Pa. (1980).

In various embodiments, the Fc-based chimeric protein complex may by conjugated and/or fused with another agent to extend half-life or otherwise improve pharmacodynamic and pharmacokinetic properties. For example, in some embodiments, the Fc-based chimeric protein complex may be fused or conjugated with one or more of PEG, XTEN (*e.g.*, as rPEG), polysialic acid (POLYXEN), albumin (*e.g.*, human serum albumin or HSA), elastin-like protein (ELP), PAS, HAP, GLK, CTP, transferrin, and the like.

In some embodiments, the functional groups, residues, or moieties comprise a suitable pharmacologically acceptable polymer, such as poly(ethyleneglycol) (PEG) or derivatives thereof (such as methoxypoly(ethyleneglycol) or mPEG). In some embodiments, attachment of the PEG moiety increases the half-life and/or reduces the immunogenecity of the Fc-based chimeric protein complex. Generally, any suitable form of

pegylation can be used, such as the pegylation used in the art for antibodies and antibody fragments (including but not limited to single domain antibodies such as VHHs); see, for example, Chapman, *Nat. Biotechnol.,* 54, 531-545 (2002); by Veronese and Harris, *Adv. Drug Deliv. Rev.* 54, 453-456 (2003), by Harris and Chess, *Nat. Rev. Drug. Discov.,* 2, (2003) and in WO04060965, the entire contents of which are hereby incorporated by reference. Various reagents for pegylation of proteins are also commercially available, for example, from Nektar Therapeutics, USA. In some embodiments, site-directed pegylation is used, in particular via a cysteine-residue (see, for example, Yang *et al.*, Protein Engineering, 16, 10, 761-770 (2003), the entire contents of which is hereby incorporated by reference). For example, for this purpose, PEG may be attached to a cysteine residue that naturally occurs in the Fc-based chimeric protein complex. In some embodiments, the Fc-based chimeric protein complex is modified so as to suitably introduce one or more cysteine residues for attachment of PEG, or an amino acid sequence comprising one or more cysteine residues for attachment of PEG may be fused to the amino- and/or carboxy-terminus of the Fc-based chimeric protein complex, using techniques known in the art.

In some embodiments, the functional groups, residues, or moieties comprise N-linked or O-linked glycosylation. In some embodiments, the N-linked or O-linked glycosylation is introduced as part of a co-translational and/or post-translational modification.

In some embodiments, the functional groups, residues, or moieties comprise one or more detectable labels or other signal-generating groups or moieties. Suitable labels and techniques for attaching, using and detecting them are known in the art and, include, but are not limited to, fluorescent labels (such as fluorescein, isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde, and fluorescamine and fluorescent metals such as Eu or others metals from the lanthanide series), phosphorescent labels, chemiluminescent labels or bioluminescent labels (such as luminal, isoluminol, theromatic acridinium ester, imidazole, acridinium salts, oxalate ester, dioxetane or GFP and its analogs), radio-isotopes, metals, metals chelates or metallic cations or other metals or metallic cations that are particularly suited for use in in vivo, in vitro or in situ diagnosis and imaging, as well as chromophores and enzymes (such as malate dehydrogenase, staphylococcal nuclease, delta- V-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate dehydrogenase, triose phosphate isomerase, biotinavidin peroxidase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-Vl-phosphate dehydrogenase, glucoamylase and acetylcholine esterase). Other suitable labels include moieties that can be detected using NMR or ESR spectroscopy. Such labeled VHHs and polypeptides of the invention may, for example, be used for in vitro, in vivo or in situ assays (including immunoassays known per se such as ELISA, RIA, EIA and other "sandwich assays," *etc.*) as well as in vivo diagnostic and imaging purposes, depending on the choice of the specific label.

In some embodiments, the functional groups, residues, or moieties comprise a tag that is attached or genetically fused to the Fc-based chimeric protein complex. In some embodiments, the Fc-based chimeric protein complex may include a single tag or multiple tags. The tag for example is a peptide, sugar, or DNA molecule that does not inhibit or prevent binding of the Fc-based chimeric protein complex to at target of interest or any other antigen of interest, such as, *e.g.*, tumor antigens. In various embodiments, the tag is at least about: three to five amino acids

long, five to eight amino acids long, eight to twelve amino acids long, twelve to fifteen amino acids long, or fifteen to twenty amino acids long. Illustrative tags are described for example, in U.S. Patent Publication No. US2013/0058962. In some embodiment, the tag is an affinity tag such as glutathione-S-transferase (GST) and histidine (His) tag. In an embodiment, the Fc-based chimeric protein complex comprises a His tag.

In some embodiments, the functional groups, residues, or moieties comprise a chelating group, for example, to chelate one of the metals or metallic cations. Suitable chelating groups, for example, include, without limitation, diethyl-enetriaminepentaacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

In some embodiments, the functional groups, residues, or moieties comprise a functional group that is one part of a specific binding pair, such as the biotin-(strept)avidin binding pair. Such a functional group may be used to link the Fc-based chimeric protein complex to another protein, polypeptide or chemical compound that is bound to the other half of the binding pair, *i.e.*, through formation of the binding pair. For example, an Fc-based chimeric protein complex may be conjugated to biotin, and linked to another protein, polypeptide, compound or carrier conjugated to avidin or streptavidin. For example, such a conjugated Fc-based chimeric protein complex may be used as a reporter, for example, in a diagnostic system where a detectable signal-producing agent is conjugated to avidin or streptavidin. Such binding pairs may, for example, also be used to bind the Fc-based chimeric protein complex to a carrier, including carriers suitable for pharmaceutical purposes. One non-limiting example are the liposomal formulations described by Cao and Suresh, *Journal of Drug Targeting,* 8, 4, 257 (2000). Such binding pairs may also be used to link a therapeutically active agent to the Fc-based chimeric protein complex.

Modifications and Production of Fc-based Chimeric Protein Complex

In various embodiments, the Fc-based chimeric protein complex comprises a targeting moiety that is a VHH. In various embodiments, the VHH is not limited to a specific biological source or to a specific method of preparation. For example, the VHH can generally be obtained: (1) by isolating the V_HH domain of a naturally occurring heavy chain antibody; (2) by expression of a nucleotide sequence encoding a naturally occurring V_HH domain; (3) by "humanization" of a naturally occurring V_HH domain or by expression of a nucleic acid encoding a such humanized V_HH domain; (4) by "camelization" of a naturally occurring VH domain from any animal species, such as from a mammalian species, such as from a human being, or by expression of a nucleic acid encoding such a camelized VH domain; (5) by "camelization" of a "domain antibody" or "Dab" as described in the art, or by expression of a nucleic acid encoding such a camelized VH domain; (6) by using synthetic or semi-synthetic techniques for preparing proteins, polypeptides or other amino acid sequences known in the art; (7) by preparing a nucleic acid encoding a VHH using techniques for nucleic acid synthesis known in the art, followed by expression of the nucleic acid thus obtained; and/or (8) by any combination of one or more of the foregoing.

In an embodiment, the Fc-based chimeric protein complex comprises a VHH that corresponds to the V_HH domains of naturally occurring heavy chain antibodies directed against a target of interest. In some embodiments, such V_HH sequences can generally be generated or obtained by suitably immunizing a species of Camelid with a molecule of based on the target of interest (*e.g.*, XCR1, Clec9A, CD8, SIRP1α, FAP, *etc.*) (*i.e.*, so as to raise an immune response and/or heavy chain antibodies directed against the target of interest), by obtaining a suitable biological

sample from the Camelid (such as a blood sample, or any sample of B-cells), and by generating V_HH sequences directed against the target of interest, starting from the sample, using any suitable known techniques. In some embodiments, naturally occurring V_HH domains against the target of interest can be obtained from naive libraries of Camelid V_HH sequences, for example, by screening such a library using the target of interest or at least one part, fragment, antigenic determinant or epitope thereof using one or more screening techniques known in the art. Such libraries and techniques are, for example, described in WO9937681, WO0190190, WO03025020 and WO03035694, the entire contents of which are hereby incorporated by reference. In some embodiments, improved synthetic or semi-synthetic libraries derived from naive V_HH libraries may be used, such as V_HH libraries obtained from naive V_HH libraries by techniques such as random mutagenesis and/or CDR shuffling, as for example, described in WO0043507, the entire contents of which are hereby incorporated by reference. In some embodiments, another technique for obtaining V_HH sequences directed against a target of interest involves suitably immunizing a transgenic mammal that is capable of expressing heavy chain antibodies (*i.e.*, so as to raise an immune response and/or heavy chain antibodies directed against the target of interest), obtaining a suitable biological sample from the transgenic mammal (such as a blood sample, or any sample of B-cells), and then generating V_HH sequences directed against XCR1 starting from the sample, using any suitable known techniques. For example, for this purpose, the heavy chain antibody-expressing mice and the further methods and techniques described in WO02085945 and in WO04049794 (the entire contents of which are hereby incorporated by reference) can be used.

In an embodiment, the Fc-based chimeric protein complex comprises a VHH that has been "humanized" *i.e.*, by replacing one or more amino acid residues in the amino acid sequence of the naturally occurring V_HH sequence (and in particular in the framework sequences) by one or more of the amino acid residues that occur at the corresponding position(s) in a VH domain from a conventional 4-chain antibody from a human being. This can be performed using humanization techniques known in the art. In some embodiments, possible humanizing substitutions or combinations of humanizing substitutions may be determined by methods known in the art, for example, by a comparison between the sequence of a VHH and the sequence of a naturally occurring human VH domain. In some embodiments, the humanizing substitutions are chosen such that the resulting humanized VHHs still retain advantageous functional properties. Generally, as a result of humanization, the VHHs of the invention may become more "human-like," while still retaining favorable properties such as a reduced immunogenicity, compared to the corresponding naturally occurring V_HH domains. In various embodiments, the humanized VHHs of the invention can be obtained in any suitable manner known in the art and thus are not strictly limited to polypeptides that have been obtained using a polypeptide that comprises a naturally occurring V_HH domain as a starting material.

In an embodiment, the Fc-based chimeric protein complex comprises a VHH that has been "camelized," *i.e.*, by replacing one or more amino acid residues in the amino acid sequence of a naturally occurring VH domain from a conventional 4-chain antibody by one or more of the amino acid residues that occur at the corresponding position(s) in a V_HH domain of a heavy chain antibody of a camelid. In some embodiments, such "camelizing" substitutions

are inserted at amino acid positions that form and/or are present at the VH-VL interface, and/or at the so-called Camelidae hallmark residues (see, for example, WO9404678, the entire contents of which are hereby incorporated by reference). In some embodiments, the VH sequence that is used as a starting material or starting point for generating or designing the camelized VHH is a VH sequence from a mammal, for example, the VH sequence of a human being, such as a VH3 sequence. In various embodiments, the camelized VHHs can be obtained in any suitable manner known in the art (*i.e.*, as indicated under points (1)-(8) above) and thus are not strictly limited to polypeptides that have been obtained using a polypeptide that comprises a naturally occurring VH domain as a starting material.

In various embodiments, both "humanization" and "camelization" can be performed by providing a nucleotide sequence that encodes a naturally occurring V_HH domain or VH domain, respectively, and then changing, in a manner known in the art, one or more codons in the nucleotide sequence in such a way that the new nucleotide sequence encodes a "humanized" or "camelized" VHH, respectively. This nucleic acid can then be expressed in a manner known in the art, so as to provide the desired VHH of the invention. Alternatively, based on the amino acid sequence of a naturally occurring V_HH domain or VH domain, respectively, the amino acid sequence of the desired humanized or camelized VHH of the invention, respectively, can be designed and then synthesized de novo using techniques for peptide synthesis known in the art. Also, based on the amino acid sequence or nucleotide sequence of a naturally occurring V_HH domain or VH domain, respectively, a nucleotide sequence encoding the desired humanized or camelized VHH, respectively, can be designed and then synthesized de novo using techniques for nucleic acid synthesis known in the art, after which the nucleic acid thus obtained can be expressed in a manner known in the art, so as to provide the desired VHH of the invention. Other suitable methods and techniques for obtaining the VHHs of the invention and/or nucleic acids encoding the same, starting from naturally occurring VH sequences or V_HH sequences, are known in the art, and may, for example, comprise combining one or more parts of one or more naturally occurring VH sequences (such as one or more FR sequences and/or CDR sequences), one or more parts of one or more naturally occurring V_HH sequences (such as one or more FR sequences or CDR sequences), and/or one or more synthetic or semi-synthetic sequences, in a suitable manner, so as to provide a VHH of the invention or a nucleotide sequence or nucleic acid encoding the same.

Methods for producing the Fc-based chimeric protein complex of the present technology are described herein. For example, DNA sequences encoding the Fc-based chimeric protein complex of the present technology can be chemically synthesized using methods known in the art. Synthetic DNA sequences can be ligated to other appropriate nucleotide sequences, including, *e.g.*, expression control sequences, to produce gene expression constructs encoding the desired Fc-based chimeric protein complex of the present technology. Accordingly, in various embodiments, the present invention provides for isolated nucleic acids comprising a nucleotide sequence encoding the Fc-based chimeric protein complex of the present technology.

Nucleic acids encoding the Fc-based chimeric protein complex of the present technology can be incorporated (ligated) into expression vectors, which can be introduced into host cells through transfection, transformation, or transduction techniques. For example, nucleic acids encoding the Fc-based chimeric protein complex of the

present technology invention can be introduced into host cells by retroviral transduction. Illustrative host cells are *E. coli* cells, Chinese hamster ovary (CHO) cells, human embryonic kidney 293 (HEK 293) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), and myeloma cells. Transformed host cells can be grown under conditions that permit the host cells to express the genes that encode the Fc-based chimeric protein complex of the present technology. Accordingly, in various embodiments, the present invention provides expression vectors comprising nucleic acids that encode the Fc-based chimeric protein complex of the present technology. In various embodiments, the present invention additional provides host cells comprising such expression vectors.

Specific expression and purification conditions will vary depending upon the expression system employed. For example, if a gene is to be expressed in *E. coli*, it is first cloned into an expression vector by positioning the engineered gene downstream from a suitable bacterial promoter, *e.g.*, Trp or Tac, and a prokaryotic signal sequence. In another example, if the engineered gene is to be expressed in eukaryotic host cells, *e.g.*, CHO cells, it is first inserted into an expression vector containing for example, a suitable eukaryotic promoter, a secretion signal, enhancers, and various introns. The gene construct can be introduced into the host cells using transfection, transformation, or transduction techniques.

The Fc-based chimeric protein complex of the present technology can be produced by growing a host cell transfected with an expression vector encoding the Fc-based chimeric protein complex under conditions that permit expression of the protein. Following expression, the protein can be harvested and purified using techniques well known in the art, *e.g.*, affinity tags such as glutathione-S-transferase (GST) and histidine (His) tags or by chromatography. In an embodiment, the Fc-based chimeric protein complex comprises a His tag. In an embodiment, the Fc-based chimeric protein complex comprises a His tag and a proteolytic site to allow cleavage of the His tag.

Accordingly, in various embodiments, the present invention provides for a nucleic acid encoding an Fc-based chimeric protein complex of the present invention. In various embodiments, the present invention provides for a host cell comprising a nucleic acid encoding an Fc-based chimeric protein complex of the present invention.

In various embodiments, the methods of modifying and producing the Fc-based chimeric protein complex as described herein can be easily adapted for the modification and production of any multi-specific Fc-based chimeric protein complex comprising two or more targeting moieties and/or signaling agents.

In various embodiments, the present Fc-based chimeric protein complex may be expressed *in vivo*, for instance, in a patient. For example, in various embodiments, the present Fc-based chimeric protein complex may be administered in the form of nucleic acid which encodes the present Fc-based chimeric protein complex. In various embodiments, the nucleic acid is DNA or RNA. In some embodiments, the present Fc-based chimeric protein complex is encoded by a modified mRNA, *i.e.* an mRNA comprising one or more modified nucleotides. In some embodiments, the modified mRNA comprises one or modifications found in U.S. Patent No. 8,278,036, the entire contents of which are hereby incorporated by reference. In some embodiments, the modified mRNA comprises one or more of m5C, m5U, m6A, s2U, Ψ, and 2'-O-methyl-U. In some embodiments, the present invention relates

to administering a modified mRNA encoding one or more of the present Fc-based chimeric protein complexes. In some embodiments, the present invention relates to gene therapy vectors comprising the same. In some embodiments, the present invention relates to gene therapy methods comprising the same. In various embodiments, the nucleic acid is in the form of an oncolytic virus, *e.g.* an adenovirus, reovirus, measles, herpes simplex, Newcastle disease virus or vaccinia.

Pharmaceutically Acceptable Salts and Excipients

The Fc-based chimeric protein complex described herein can possess a sufficiently basic functional group, which can react with an inorganic or organic acid, or a carboxyl group, which can react with an inorganic or organic base, to form a pharmaceutically acceptable salt. A pharmaceutically acceptable acid addition salt is formed from a pharmaceutically acceptable acid, as is well known in the art. Such salts include the pharmaceutically acceptable salts listed in, for example, *Journal of Pharmaceutical Science*, 66, 2-19 (1977) and *The Handbook of Pharmaceutical Salts; Properties, Selection, and Use*. P. H. Stahl and C. G. Wermuth (eds.), Verlag, Zurich (Switzerland) 2002, which are hereby incorporated by reference in their entirety.

Pharmaceutically acceptable salts include, by way of non-limiting example, sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, camphorsulfonate, pamoate, phenylacetate, trifluoroacetate, acrylate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, isobutyrate, phenylbutyrate, α-hydroxybutyrate, butyne-1,4-dicarboxylate, hexyne-1,4-dicarboxylate, caprate, caprylate, cinnamate, glycollate, heptanoate, hippurate, malate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, phthalate, teraphthalate, propiolate, propionate, phenylpropionate, sebacate, suberate, p-bromobenzenesulfonate, chlorobenzenesulfonate, ethylsulfonate, 2-hydroxyethylsulfonate, methylsulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, naphthalene-1,5-sulfonate, xylenesulfonate, and tartarate salts.

The term “pharmaceutically acceptable salt” also refers to a salt of the compositions of the present invention having an acidic functional group, such as a carboxylic acid functional group, and a base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or tri-alkylamines, dicyclohexylamine; tributyl amine; pyridine; N-methyl, N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-OH-lower alkylamines), such as mono-; bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N,N-di-lower alkyl-N-(hydroxyl-lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like.

In some embodiments, the compositions described herein are in the form of a pharmaceutically acceptable salt.

Pharmaceutical Compositions and Formulations

In various embodiments, the present invention pertains to pharmaceutical compositions comprising the Fc-based chimeric protein complex described herein and a pharmaceutically acceptable carrier or excipient. In some embodiments, the present invention pertains to pharmaceutical compositions comprising the present Fc-based chimeric protein complex. In a further embodiment, the present invention pertains to pharmaceutical compositions comprising a combination of the present Fc-based chimeric protein complex and any other therapeutic agents described herein. Any pharmaceutical compositions described herein can be administered to a subject as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. Such compositions can optionally comprise a suitable amount of a pharmaceutically acceptable excipient so as to provide the form for proper administration.

In various embodiments, pharmaceutical excipients can be liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical excipients can be, for example, saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment, the pharmaceutically acceptable excipients are sterile when administered to a subject. Water is a useful excipient when any agent described herein is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, specifically for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. Any agent described herein, if desired, can also comprise minor amounts of wetting or emulsifying agents, or pH buffering agents. Other examples of suitable pharmaceutical excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro eds., 19th ed. 1995), incorporated herein by reference.

The present invention includes the described pharmaceutical compositions (and/or additional therapeutic agents) in various formulations. Any inventive pharmaceutical composition (and/or additional therapeutic agents) described herein can take the form of solutions, suspensions, emulsion, drops, tablets, pills, pellets, capsules, capsules containing liquids, gelatin capsules, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, lyophilized powder, frozen suspension, desiccated powder, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule. In another embodiment, the composition is in the form of a tablet. In yet another embodiment, the pharmaceutical composition is formulated in the form of a soft-gel capsule. In a further embodiment, the pharmaceutical composition is formulated in the form of a gelatin capsule. In yet another embodiment, the pharmaceutical composition is formulated as a liquid.

Where necessary, the inventive pharmaceutical compositions (and/or additional agents) can also include a solubilizing agent. Also, the agents can be delivered with a suitable vehicle or delivery device as known in the art. Combination therapies outlined herein can be co-delivered in a single delivery vehicle or delivery device.

The formulations comprising the inventive pharmaceutical compositions (and/or additional agents) of the present invention may conveniently be presented in unit dosage forms and may be prepared by any of the methods well known in the art of pharmacy. Such methods generally include the step of bringing the therapeutic agents into association with a carrier, which constitutes one or more accessory ingredients. Typically, the formulations are prepared by uniformly and intimately bringing the therapeutic agent into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into dosage forms of the desired formulation (*e.g.*, wet or dry granulation, powder blends, *etc.*, followed by tableting using conventional methods known in the art).

In various embodiments, any pharmaceutical compositions (and/or additional agents) described herein is formulated in accordance with routine procedures as a composition adapted for a mode of administration described herein.

Routes of administration include, for example: oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, sublingual, intranasal, intracerebral, intravaginal, transdermal, rectally, by inhalation, or topically. Administration can be local or systemic. In some embodiments, the administering is effected orally. In another embodiment, the administration is by parenteral injection. The mode of administration can be left to the discretion of the practitioner, and depends in-part upon the site of the medical condition. In most instances, administration results in the release of any agent described herein into the bloodstream.

In one embodiment, the Fc-based chimeric protein complex described herein is formulated in accordance with routine procedures as a composition adapted for oral administration. Compositions for oral delivery can be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered compositions can comprise one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving any Fc-based chimeric protein complex described herein are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be useful. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade. Suspensions, in addition to the active compounds, may contain suspending agents such as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth, *etc.*, and mixtures thereof.

Dosage forms suitable for parenteral administration (*e.g.* intravenous, intramuscular, intraperitoneal, subcutaneous and intra-articular injection and infusion) include, for example, solutions, suspensions, dispersions, emulsions, and the like. They may also be manufactured in the form of sterile solid compositions (*e.g.* lyophilized composition), which can be dissolved or suspended in sterile injectable medium immediately before use. They may contain, for example, suspending or dispersing agents known in the art. Formulation components suitable for parenteral administration include a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as EDTA; buffers such as acetates, citrates or phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose.

For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). The carrier should be stable under the conditions of manufacture and storage, and should be preserved against microorganisms. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol), and suitable mixtures thereof.

The compositions provided herein, alone or in combination with other suitable components, can be made into aerosol formulations (*i.e.*, "nebulized") to be administered via inhalation. Aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like.

Any inventive pharmaceutical compositions (and/or additional agents) described herein can be administered by controlled-release or sustained-release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,556, each of which is incorporated herein by reference in its entirety. Such dosage forms can be useful for providing controlled- or sustained-release of one or more active ingredients using, for example, hydropropyl cellulose, hydropropylmethyl cellulose, polyvinylpyrrolidone, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known to those skilled in the art, including those described herein, can be readily selected for use with the active ingredients of the agents described herein. The invention thus provides single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, stimulation by an appropriate wavelength of light, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

In another embodiment, a controlled-release system can be placed in proximity of the target area to be treated, thus requiring only a fraction of the systemic dose (see, *e.g.,* Goodson, in *Medical Applications of Controlled*

Release, *supra*, vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in the review by Langer, 1990, *Science* 249:1527-1533) may be used.

Pharmaceutical formulations preferably are sterile. Sterilization can be accomplished, for example, by filtration through sterile filtration membranes. Where the composition is lyophilized, filter sterilization can be conducted prior to or following lyophilization and reconstitution.

Administration and Dosage

It will be appreciated that the actual dose of the Fc-based chimeric protein complex described herein to be administered according to the present invention will vary according to the particular dosage form, and the mode of administration. Many factors that may modify the action of the Fc-based chimeric protein complex (*e.g.*, body weight, gender, diet, time of administration, route of administration, rate of excretion, condition of the subject, drug combinations, genetic disposition and reaction sensitivities) can be taken into account by those skilled in the art. Administration can be carried out continuously or in one or more discrete doses within the maximum tolerated dose. Optimal administration rates for a given set of conditions can be ascertained by those skilled in the art using conventional dosage administration tests.

In some embodiments, a suitable dosage of the Fc-based chimeric protein complex described herein is in a range of about 0.01 mg/kg to about 10 g/kg of body weight of the subject, about 0.01 mg/kg to about 1 g/kg of body weight of the subject, about 0.01 mg/kg to about 100 mg/kg of body weight of the subject, about 0.01 mg/kg to about 10 mg/kg of body weight of the subject, for example, about 0.01 mg/kg, about 0.02 mg/kg, about 0.03 mg/kg, about 0.04 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg, about 1.8 mg/kg, 1.9 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg body weight, about 100 mg/kg body weight, about 1 g/kg of body weight, about 10 g/kg of body weight, inclusive of all values and ranges there between.

Individual doses of the Fc-based chimeric protein complex described herein can be administered in unit dosage forms containing, for example, from about 0.01 mg to about 100 g, from about 0.01 mg to about 75 g, from about 0.01 mg to about 50 g, from about 0.01 mg to about 25 g, about 0.01 mg to about 10 g, about 0.01 mg to about 7.5 g, about 0.01 mg to about 5 g, about 0.01 mg to about 2.5 g, about 0.01 mg to about 1 g, about 0.01 mg to about 100 mg, from about 0.1 mg to about 100 mg, from about 0.1 mg to about 90 mg, from about 0.1 mg to about 80 mg, from about 0.1 mg to about 70 mg, from about 0.1 mg to about 60 mg, from about 0.1 mg to about 50 mg, from about 0.1 mg to about 40 mg active ingredient, from about 0.1 mg to about 30 mg, from about 0.1 mg to about 20 mg, from about 0.1 mg to about 10 mg, from about 0.1 mg to about 5 mg, from about 0.1 mg to about 3 mg, from about 0.1 mg to about 1 mg per unit dosage form, or from about 5 mg to about 80 mg per unit dosage form. For example, a unit dosage form can be about 0.01 mg, about 0.02 mg, about 0.03 mg, about 0.04 mg, about 0.05 mg, about 0.06 mg, about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.2 mg, about 0.3 mg,

about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 200 mg, about 500 mg, about 1 g, about 2.5 g, about 5 g, about 10 g, about 25 g, about 50 g, about 75 g, about 100 g, inclusive of all values and ranges there between.

In one embodiment, the Fc-based chimeric protein complex described herein are administered at an amount of from about 0.01 mg to about 100 g daily, from about 0.01 mg to about 75 g daily, from about 0.01 mg to about 50 g daily, from about 0.01 mg to about 25 g daily, from about 0.01 mg to about 10 g daily, from about 0.01 mg to about 7.5 g daily, from about 0.01 mg to about 5 g daily, from about 0.01 mg to about 2.5 g daily, from about 0.01 mg to about 1 g daily, from about 0.01 mg to about 100 mg daily, from about 0.1 mg to about 100 mg daily, from about 0.1 mg to about 95 mg daily, from about 0.1 mg to about 90 mg daily, from about 0.1 mg to about 85 mg daily, from about 0.1 mg to about 80 mg daily, from about 0.1 mg to about 75 mg daily, from about 0.1 mg to about 70 mg daily, from about 0.1 mg to about 65 mg daily, from about 0.1 mg to about 60 mg daily, from about 0.1 mg to about 55 mg daily, from about 0.1 mg to about 50 mg daily, from about 0.1 mg to about 45 mg daily, from about 0.1 mg to about 40 mg daily, from about 0.1 mg to about 35 mg daily, from about 0.1 mg to about 30 mg daily, from about 0.1 mg to about 25 mg daily, from about 0.1 mg to about 20 mg daily, from about 0.1 mg to about 15 mg daily, from about 0.1 mg to about 10 mg daily, from about 0.1 mg to about 5 mg daily, from about 0.1 mg to about 3 mg daily, from about 0.1 mg to about 1 mg daily, or from about 5 mg to about 80 mg daily. In various embodiments, the Fc-based chimeric protein complex is administered at a daily dose of about 0.01 mg, about 0.02 mg, about 0.03 mg, about 0.04 mg, about 0.05 mg, about 0.06 mg, about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 200 mg, about 500 mg, about 1 g, about 2.5 g, about 5 g, about 7.5 g, about 10 g, about 25 g, about 50 g, about 75 g, about 100 g, inclusive of all values and ranges there between.

In accordance with certain embodiments of the invention, the pharmaceutical composition comprising the Fc-based chimeric protein complex described herein may be administered, for example, more than once daily (*e.g.*, about two times, about three times, about four times, about five times, about six times, about seven times, about eight times, about nine times, or about ten times daily), about once per day, about every other day, about every third day, about once a week, about once every two weeks, about once every month, about once every two months, about once every three months, about once every six months, or about once every year.

Combination Therapy and Additional Therapeutic Agents

In various embodiments, the pharmaceutical composition of the present invention is co-administered in conjunction with additional therapeutic agent(s). Co-administration can be simultaneous or sequential.

In one embodiment, the additional therapeutic agent and the Fc-based chimeric protein complex are administered to a subject simultaneously. The term "simultaneously" as used herein, means that the additional therapeutic agent and the Fc-based chimeric protein complex are administered with a time separation of no more than about 60 minutes, such as no more than about 30 minutes, no more than about 20 minutes, no more than about 10 minutes, no more than about 5 minutes, or no more than about 1 minute. Administration of the additional therapeutic agent and the Fc-based chimeric protein complex be by simultaneous administration of a single formulation (*e.g.*, a formulation comprising the additional therapeutic agent and the Fc-based chimeric protein complex) or of separate formulations (*e.g.*, a first formulation including the additional therapeutic agent and a second formulation including the Fc-based chimeric protein complex).

Co-administration does not require the therapeutic agents to be administered simultaneously, if the timing of their administration is such that the pharmacological activities of the additional therapeutic agent and the Fc-based chimeric protein complex overlap in time, thereby exerting a combined therapeutic effect. For example, the additional therapeutic agent and the Fc-based chimeric protein complex can be administered sequentially. The term "sequentially" as used herein means that the additional therapeutic agent and the Fc-based chimeric protein complex are administered with a time separation of more than about 60 minutes. For example, the time between the sequential administration of the additional therapeutic agent and the Fc-based chimeric protein complex can be more than about 60 minutes, more than about 2 hours, more than about 5 hours, more than about 10 hours, more than about 1 day, more than about 2 days, more than about 3 days, more than about 1 week, or more than about 2 weeks, or more than about one month apart. The optimal administration times will depend on the rates of metabolism, excretion, and/or the pharmacodynamic activity of the additional therapeutic agent and the Fc-based chimeric protein complex being administered. Either the additional therapeutic agent or the Fc-based chimeric protein complex may be administered first.

Co-administration also does not require the therapeutic agents to be administered to the subject by the same route of administration. Rather, each therapeutic agent can be administered by any appropriate route, for example, parenterally or non-parenterally.

In some embodiments, the Fc-based chimeric protein complex described herein acts synergistically when co-administered with another therapeutic agent. In such embodiments, the Fc-based chimeric protein complex and the additional therapeutic agent may be administered at doses that are lower than the doses employed when the agents are used in the context of monotherapy.

In some embodiments, the present invention pertains to chemotherapeutic agents as additional therapeutic agents. For example, without limitation, such combination of the present Fc-based chimeric protein complex and chemotherapeutic agent find use in the treatment of cancers, as described elsewhere herein. Examples of chemotherapeutic agents include, but are not limited to, alkylating agents such as thiotepa and CYTOXAN cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine;

acetogenins (*e.g.*, bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; cally statin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (*e.g.*, cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB 1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (*e.g.*, calicheamicin, especially calicheamicin gammall and calicheamicin omegall (*see, e.g.*, Agnew, Chem. Intl. Ed. Engl., 33: 183-186 (1994)); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN doxorubicin (including morpholino- doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxy doxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as minoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (*e.g.*, T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, *e.g.*, TAXOL paclitaxel (Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE Cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, 111.), and TAXOTERE doxetaxel (Rhone-Poulenc Rorer, Antony, France); chloranbucil; GEMZAR gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE. vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (Camptosar, CPT-11) (including the treatment regimen of irinotecan with 5-FU and leucovorin); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine;

combretastatin; leucovorin (LV); oxaliplatin, including the oxaliplatin treatment regimen (FOLFOX); lapatinib (Tykerb); inhibitors of PKC-α, Raf, H-Ras, EGFR (*e.g.*, erlotinib (Tarceva)) and VEGF-A that reduce cell proliferation and pharmaceutically acceptable salts, acids or derivatives of any of the above. In addition, the methods of treatment can further include the use of radiation. In addition, the methods of treatment can further include the use of photodynamic therapy.

Accordingly, in some embodiments, the present invention relates to combination therapies using the Fc-based chimeric protein complex and a chemotherapeutic agent. In some embodiments, the present invention relates to administration of the Fc-based chimeric protein complex to a patient undergoing treatment with a chemotherapeutic agent. In some embodiments, the chemotherapeutic agent is a DNA-intercalating agent such as, without limitation, doxorubicin, cisplatin, daunorubicin, and epirubicin. In an embodiment, the DNA-intercalating agent is doxorubicin.

In illustrative embodiments, the Fc-based chimeric protein complex acts synergistically when co-administered with doxorubicin. In an illustrative embodiment, the Fc-based chimeric protein complex acts synergistically when co-administered with doxorubicin for use in treating tumor or cancer. For example, co-administration of the Fc-based chimeric protein complex and doxorubicin may act synergistically to reduce or eliminate the tumor or cancer, or slow the growth and/or progression and/or metastasis of the tumor or cancer. In illustrative embodiments, the combination of the Fc-based chimeric protein complex and doxorubicin may exhibit improved safety profiles when compared to the agents used alone in the context of monotherapy. In illustrative embodiments, the Fc-based chimeric protein complex and doxorubicin may be administered at doses that are lower than the doses employed when the agents are used in the context of monotherapy. In some embodiments, the Fc-based chimeric protein complex comprises a mutated interferon such as a mutated IFNα2. In illustrative embodiments, the mutated IFNα2 comprises one or more mutations at positions 148, 149, and 153 with reference to SEQ ID NO: 1 or SEQ ID NO: 2, such as the substitutions M148A, R149A, and L153A.

In some embodiments, the present invention relates to combination therapy with one or more immune-modulating agents, for example, without limitation, agents that modulate immune checkpoint. In various embodiments, the immune-modulating agent targets one or more of PD-1, PD-L1, and PD-L2. In various embodiments, the immune-modulating agent is PD-1 inhibitor. In various embodiments, the immune-modulating agent is an antibody specific for one or more of PD-1, PD-L1, and PD-L2. For instance, in some embodiments, the immune-modulating agent is an antibody such as, by way of non-limitation, nivolumab, (ONO-4538/BMS-936558, MDX1106, OPDIVO, BRISTOL MYERS SQUIBB), pembrolizumab (KEYTRUDA, MERCK), pidilizumab (CT-011, CURE TECH), MK-3475 (MERCK), BMS 936559 (BRISTOL MYERS SQUIBB), MPDL328OA (ROCHE). In some embodiments, the immune-modulating agent targets one or more of CD137 or CD137L. In various embodiments, the immune-modulating agent is an antibody specific for one or more of CD137 or CD137L. For instance, in some embodiments, the immune-modulating agent is an antibody such as, by way of non-limitation, urelumab (also known as BMS-663513 and anti-4-1BB antibody). In some embodiments, the present Fc-based chimeric protein complex is combined with urelumab (optionally with one or more of nivolumab, lirilumab, and urelumab) for the treatment of

solid tumors and/or B-cell non-Hodgkins lymphoma and/or head and neck cancer and/or multiple myeloma. In some embodiments, the immune-modulating agent is an agent that targets one or more of CTLA-4, AP2M1, CD80, CD86, SHP-2, and PPP2R5A. In various embodiments, the immune-modulating agent is an antibody specific for one or more of CTLA-4, AP2M1, CD80, CD86, SHP-2, and PPP2R5A. For instance, in some embodiments, the immune-modulating agent is an antibody such as, by way of non-limitation, ipilimumab (MDX-010, MDX-101, Yervoy, BMS) and/or tremelimumab (Pfizer). In some embodiments, the present Fc-based chimeric protein complexis combined with ipilimumab (optionally with bavituximab) for the treatment of one or more of melanoma, prostate cancer, and lung cancer. In various embodiments, the immune-modulating agent targets CD20. In various embodiments, the immune-modulating agent is an antibody specific CD20. For instance, in some embodiments, the immune-modulating agent is an antibody such as, by way of non-limitation, Ofatumumab (GENMAB), obinutuzumab (GAZYVA), AME-133v (APPLIED MOLECULAR EVOLUTION), Ocrelizumab (GENENTECH), TRU-015 (TRUBION/EMERGENT), veltuzumab (IMMU-106).

In some embodiments, the present invention relates to combination therapy using the Fc-based chimeric protein complex and a checkpoint inhibitor. In some embodiments, the present invention relates to administration of the Fc-based chimeric protein complex to a patient undergoing treatment with a checkpoint inhibitor. In some embodiments, the checkpoint inhibitor is an agent that targets one or more of PD-1, PD-L1, PD-L2, and CTLA-4 (including any of the anti-PD-1, anti-PD-L1, anti-PD-L2, and anti-CTLA-4 agents described herein). In some embodiment, the checkpoint inhibitor is one or more of nivolumab, (ONO-4538/BMS-936558, MDX1106, OPDIVO, BRISTOL MYERS SQUIBB), pembrolizumab (KEYTRUDA, MERCK), pidilizumab (CT-011, CURE TECH), MK-3475 (MERCK), BMS 936559 (BRISTOL MYERS SQUIBB), MPDL328OA (ROCHE), ipilimumab (MDX-010, MDX-101, Yervoy, BMS) and tremelimumab (Pfizer). In an embodiment, the checkpoint inhibitor is an antibody against PD-L1.

In illustrative embodiments, the Fc-based chimeric protein complex acts synergistically when co-administered with the anti-PD-L1 antibody. In an illustrative embodiment, the Fc-based chimeric protein complex acts synergistically when co-administered with the anti-PD-L1 antibody for use in treating tumor or cancer. For example, co-administration of the Fc-based chimeric protein complex and the anti-PD-L1 antibody may act synergistically to reduce or eliminate the tumor or cancer, or slow the growth and/or progression and/or metastasis of the tumor or cancer. In some embodiments, the combination of the Fc-based chimeric protein complex and the anti-PD-L1 antibody may exhibit improved safety profiles when compared to the agents used alone in the context of monotherapy. In some embodiments, the Fc-based chimeric protein complex and the anti-PD-L1 antibody may be administered at doses that are lower than the doses employed when the agents are used in the context of monotherapy. In some embodiments, the Fc-based chimeric protein complex comprises a mutated interferon such as a mutated IFNα2. In illustrative embodiments, the mutated IFNα2 comprises one or more mutations at positions 148, 149, and 153 with reference to SEQ ID NO: 1 or SEQ ID NO: 2, such as the substitutions M148A, R149A, and L153A.

In some embodiments, the present invention relates to combination therapies using the Fc-based chimeric protein complex and an immunosuppressive agent. In some embodiments, the present invention relates to administration of the Fc-based chimeric protein complex to a patient undergoing treatment with an immunosuppressive agent. In an embodiment, the immunosuppressive agent is TNF.

In illustrative embodiments, the Fc-based chimeric protein complex acts synergistically when co-administered with TNF. In an illustrative embodiment, the Fc-based chimeric protein complex acts synergistically when co-administered with TNF for use in treating tumor or cancer. For example, co-administration of the Fc-based chimeric protein complex and TNF may act synergistically to reduce or eliminate the tumor or cancer, or slow the growth and/or progression and/or metastasis of the tumor or cancer. In some embodiments, the combination of the Fc-based chimeric protein complex and TNF may exhibit improved safety profiles when compared to the agents used alone in the context of monotherapy. In some embodiments, the Fc-based chimeric protein complex and TNF may be administered at doses that are lower than the doses employed when the agents are used in the context of monotherapy. In some embodiments, the Fc-based chimeric protein complex comprises a mutated interferon such as a mutated IFNα2. In illustrative embodiments, the mutated IFNα2 comprises one or more mutations at positions 148, 149, and 153 with reference to SEQ ID NO: 1 or SEQ ID NO: 2, such as the substitutions M148A, R149A, and L153A.

In some embodiments, the Fc-based chimeric protein complex acts synergistically when used in combination with Chimeric Antigen Receptor (CAR) T-cell therapy. In an illustrative embodiment, the Fc-based chimeric protein complex acts synergistically when used in combination with CAR T-cell therapy in treating tumor or cancer. In an embodiment, the Fc-based chimeric protein complex acts synergistically when used in combination with CAR T-cell therapy in treating blood-based tumors. In an embodiment, the Fc-based chimeric protein complex acts synergistically when used in combination with CAR T-cell therapy in treating solid tumors. For example, use of the Fc-based chimeric protein complex and CAR T-cells may act synergistically to reduce or eliminate the tumor or cancer, or slow the growth and/or progression and/or metastasis of the tumor or cancer. In various embodiments, the Fc-based chimeric protein complex of the invention induces CAR T-cell division. In various embodiments, the Fc-based chimeric protein complex of the invention induces CAR T-cell proliferation. In various embodiments, the Fc-based chimeric protein complex of the invention prevents anergy of the CAR T cells.

In various embodiments, the CAR T-cell therapy comprises CAR T cells that target antigens (*e.g.*, tumor antigens) such as, but not limited to, carbonic anhydrase IX (CAIX), 5T4, CD19, CD20, CD22, CD30, CD33, CD38, CD47, CS1, CD138, Lewis-Y, L1-CAM, MUC16, ROR-1, IL13Rα2, gp100, prostate stem cell antigen (PSCA), prostate-specific membrane antigen (PSMA), B-cell maturation antigen (BCMA), human papillomavirus type 16 E6 (HPV-16 E6), CD171, folate receptor alpha (FR-α), GD2, human epidermal growth factor receptor 2 (HER2), mesothelin, EGFRvIII, fibroblast activation protein (FAP), carcinoembryonic antigen (CEA), and vascular endothelial growth factor receptor 2 (VEGF-R2), as well as other tumor antigens well known in the art. Additional illustrative tumor antigens include, but are not limited to MART-1/Melan-A, gp100, Dipeptidyl peptidase IV (DPPIV), adenosine deaminase-binding protein (ADAbp), cyclophilin b, Colorectal associated antigen (CRC)-0017-1A/GA733,

Carcinoembryonic Antigen (CEA) and its immunogenic epitopes CAP-1 and CAP-2, etv6, aml1, Prostate Specific Antigen (PSA) and its immunogenic epitopes PSA-1, PSA-2, and PSA-3, T-cell receptor/CD3-zeta chain, MAGE-family of tumor antigens (*e.g.*, MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A4, MAGE-A5, MAGE-A6, MAGE-A7, MAGE-A8, MAGE-A9, MAGE-A10, MAGE-A11, MAGE-A12, MAGE-Xp2 (MAGE-B2), MAGE-Xp3 (MAGE-B3), MAGE-Xp4 (MAGE-B4), MAGE-C1, MAGE-C2, MAGE-C3, MAGE-C4, MAGE-C5), GAGE-family of tumor antigens (*e.g.*, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, GAGE-8, GAGE-9), BAGE, RAGE, LAGE-1, NAG, GnT-V, MUM-1, CDK4, tyrosinase, p53, MUC family, HER2/neu, p21ras, RCAS1, α-fetoprotein, E-cadherin, α-catenin, β-catenin and γ-catenin, p120ctn, gp100 Pmel117, PRAME, NY-ESO-1, cdc27, adenomatous polyposis coli protein (APC), fodrin, Connexin 37, Ig-idiotype, p15, gp75, GM2 and GD2 gangliosides, viral products such as human papilloma virus proteins, Smad family of tumor antigens, Imp-1, NA, EBV-encoded nuclear antigen (EBNA)-1, brain glycogen phosphorylase, SSX-1, SSX-2 (HOM-MEL-40), SSX-1, SSX-4, SSX-5, SCP-1 CT-7, c-erbB-2, CD19, CD37, CD56, CD70, CD74, CD138, AGS16, MUC1 , GPNMB, Ep-CAM, PD-L1, and PD-L2.

Exemplary CAR T-cell therapy include, but are not limited to, JCAR014 (Juno Therapeutics), JCAR015 (Juno Therapeutics), JCAR017 (Juno Therapeutics), JCAR018 (Juno Therapeutics), JCAR020 (Juno Therapeutics), JCAR023 (Juno Therapeutics), JCAR024 (Juno Therapeutics), CTL019 (Novartis), KTE-C19 (Kite Pharma), BPX-401 (Bellicum Pharmaceuticals), BPX-501 (Bellicum Pharmaceuticals), BPX-601 (Bellicum Pharmaceuticals), bb2121 (Bluebird Bio), CD-19 Sleeping Beauty cells (Ziopharm Oncology), UCART19 (Cellectis), UCART123 (Cellectis), UCART38 (Cellectis), UCARTCS1 (Cellectis), OXB-302 (Oxford BioMedica, MB-101 (Mustang Bio) and CAR T-cells developed by Innovative Cellular Therapeutics.

In some embodiments, the Fc-based chimeric protein complex is used in a method of treating multiple sclerosis (MS) in combination with one or more MS therapeutics including, but not limited to, 3-interferons, glatiramer acetate, T-interferon, IFN-ß-2 (U. S. Patent Publication No. 2002/0025304), spirogermaniums (*e.g.*, N-(3-dimethylaminopropyl)-2-aza-8,8-dimethyl-8-germanspiro [4:5] decane, N-(3-dimethylaminopropyl)-2-aza-8,8-diethyl-8- germaspiro [4:5] decane, N-(3-dimethylaminopropyl)-2-aza-8,8-dipropyl-8-germaspiro [4:5] decane, and N-(3-dimethylaminopropyl)-2-aza-8, 8-dibutyl-8-germaspiro [4:5] decane), vitamin D analogs (*e.g.*, 1,25 (OH) 2D3, (see, *e.g.*, U.S. Patent No. 5,716,946)), prostaglandins (*e.g.*, latanoprost, brimonidine, PGE1, PGE2 and PGE3, see, *e.g.*, U. S. Patent Publication No. 2002/0004525), tetracycline and derivatives (*e.g.*, minocycline and doxycycline, see, *e.g.*, U.S. Patent Publication No. 20020022608), a VLA-4 binding antibody (see, *e.g.*, U.S. Patent Publication No. 2009/0202527), adrenocorticotrophic hormone, corticosteroid, prednisone, methylprednisone, 2-chlorodeoxyadenosine, mitoxantrone, sulphasalazine, methotrexate, azathioprine, cyclophosphamide, cyclosporin, fumarate, anti-CD20 antibody (*e.g.*, rituximab), and tizanidine hydrochloride.

In some embodiments, the Fc-based chimeric protein complex is used in combination with one or more therapeutic agents that treat one or more symptoms or side effects of MS. Such agents include, but are not limited to, amantadine, baclofen, papaverine, meclizine, hydroxyzine, sulfamethoxazole, ciprofloxacin, docusate, pemoline, dantrolene, desmopressin, dexamethasone, tolterodine, phenyloin, oxybutynin, bisacodyl, venlafaxine,

amitriptyline, methenamine, clonazepam, isoniazid, vardenafil, nitrofurantoin, psyllium hydrophilic mucilloid, alprostadil, gabapentin, nortriptyline, paroxetine, propantheline bromide, modafinil, fluoxetine, phenazopyridine, methylprednisolone, carbamazepine, imipramine, diazepam, sildenafil, bupropion, and sertraline.

In some embodiments, the Fc-based chimeric protein complex is used in a method of treating multiple sclerosis in combination with one or more of the disease modifying therapies (DMTs) described herein (*e.g.* the agents of Table A). In some embodiments, the present invention provides an improved therapeutic effect as compared to use of one or more of the DMTs described herein (*e.g.* the agents listed in the Table below) without the one or more disclosed binding agent. In an embodiment, the combination of the Fc-based chimeric protein complex and the one or more DMTs produces synergistic therapeutic effects.

Illustrative Disease Modifying Therapies

Generic Name	Branded Name/Company	Frequency/Route of Delivery/Usual Dose
teriflunomide	AUBAGIO (GENZYME)	Every day; pill taken orally; 7 mg or 14 mg.
interferon beta-1a	AVONEX (BIOGEN IDEC)	Once a week; intramuscular (into the muscle) injection; 30 mcg
interferon beta-1b	BETASERON (BAYER HEALTHCARE PHARMACEUTICALS, INC.)	Every other day; subcutaneous (under the skin) injection; 250 mcg.
glatiramer acetate	COPAXONE (TEVA NEUROSCIENCE)	Every day; subcutaneous (under the skin) injection; 20 mg (20,000 mcg) OR Three times a week; subcutaneous (under the skin) injection; 40 mg (40,000 mcg)
interferon beta-1b	EXTAVIA (NOVARTIS PHARMACEUTICALS CORP.)	Every other day; subcutaneous (under the skin) injection; 250 mcg.
fingolimod	GILENYA (NOVARTIS PHARMACEUTICALS CORP.)	Every day; capsule taken orally; 0.5 mg.
Alemtuzumab (anti-CD52 monoclonal antibody)	LEMTRADA (GENZYME)	Intravenous infusion on five consecutive days, followed by intravenous infusion on three consecutive days one year later (12 mg)
mitoxantrone	NOVANTRONE (EMD SERONO)	Four times a year by IV infusion in a medical facility. Lifetime cumulative dose limit of approximately 8–12 doses over 2–3 years (140 mg/m2).
pegylated interferon beta-1a	PLEGRIDY (BIOGEN IDEC)	Every 14 days; subcutaneous (under the skin) injection; 125 mcg
interferon beta-1a	REBIF (EMD SERONO, INC.)	Three times a week; subcutaneous (under the skin) injection; 44 mcg
dimethyl fumarate (BG-12)	TECFIDERA (BIOGEN IDEC)	Twice a day; capsule taken orally; 120 mg for one week and 240 mg therafter
Natalizumab (humanized monoclonal antibody VLA-4 antagonist)	TYSABRI (BIOGEN IDEC)	Every four weeks by IV infusion in a registered infusion facility; 300 mg
DMTs in Development		
Amiloride (targets Acid-sensing ion channel-1 Epithelial sodium channel Na+/H+ exchanger)	PAR PHARMACEUTICAL, PERRIGO COMPANY , SIGMAPHARM LABORATORIES	Oral

Generic Name	Branded Name/Company	Frequency/Route of Delivery/Usual Dose
ATX-MS-1467 (targets Major histocompatibility complex class II T cell responses to myelin basic protein)	APITOPE / MERCK SERONO	Intradermal Subcutaneous
BAF312 (targets Sphingosine 1-phosphate (S1P) receptor subtypes S1P1 and S1P5 B cell distrubution T cell distribution)	NOVARTIS PHARMA	Oral
BGC20-0134 (targets Proinflammatory and anti-inflammatory cytokines)	BTG PLC	Oral
BIIB033 (targets LINGO-1 ("leucine-rich repeat and immunoglobulin-like domain-containing, Nogo receptor-interacting protein"))	BIOGEN	Intravenous infusion used in Phase I and Phase II trials Subcutaneous injection used in Phase I trial
Cladribine (targets CD4+ T cells DNA synthesis and repair E-selectin Intracellular adhesion molecule-1 Pro-inflammatory cytokines interleukin 2 and interleukin 2R Pro-inflammatory cytokines interleukin 8 and RANTES Cytokine secretion Monocyte and lymphocyte migration)	MERCK SERONO	Oral
Cyclophosphamide (targets T cells, particularly CD4+ helper T cells B cells)	BAXTER HEALTHCARE CORPORATION	Oral, monthly intravenous pulses
Daclizumab (humanized monoclonal antibody targeting CD25 Immune modulator of T cells)	BIOGEN IDEC/ABBVIE BIOTHERAPEUTICS	Projected to be IM injection once monthly
Dalfampridine (targets Voltage-gated potassium channels Degenerin/epithelial sodium channels L-type calcium channels that contain subunit Cavbeta3)	ACORDA THERAPEUTICS / BIOGEN IDEC	One tablet every 12 hours (extended release), 10 mg twice a day
Dronabinol (targets Cannabinoid receptor CB1 Cannabinoid receptor CB2)	ABBVIE INC.	Oral
Firategrast (targets Alpha4beta1 integrin)	GLAXOSMITHKLINE	Oral
GNbAC1MSRV-Env (targets envelope protein of the MS-associated retrovirus)	GENEURO SA / SERVIER	Intravenous infusion
Idebenone (targets Reactive oxygen species)	SANTHERA PHARMACEUTICALS	Oral Dose in clinical trial for PPMS is 2250 mg per day (750 mg dose, 3 times per day)

Generic Name	Branded Name/Company	Frequency/Route of Delivery/Usual Dose
Imilecleucel-T (targets Myelin-specific, autoreactive T cells)	OPEXA THERAPEUTICS / MERCK SERONO	Subcutaneous Given 5 times per year, according to information from the manufacturer
Laquinimod	TEVA	Projected to be 0.6 mg or 1.2 mg oral tablet taken daily
Masitinib (targets KIT (a stem cell factor, also called c-KIT) receptor as well as select other tyrosine kinases Mast cells)	AB SCIENCE	Oral
MEDI-551 (targets CD19, a B cell-specific antigen that is part of the B cell receptor complex and that functions in determining the threshold for B cell activation B cells Plasmablasts, B cells that express CD19 (but not CD20) and that secrete large quantities of antibodies; depletion of plasmablasts may be useful in autoimmune diseases involving pathogenic autoantibodies)	MEDIMMUNE	Intravenous Subcutaneous
Minocycline (targets T cells Microglia Leukocyte migration Matrix metalloproteinases)	VARIOUS	Oral Available as pellet-filled capsules and an oral suspension
MIS416 (targets Innate immune system Pathogen-associated molecular pattern recognition receptors of the innate immune system Myeloid cells of the innate immune system, which might be able to remodel the deregulated immune system activity that occurs in SPMS)	INNATE IMMUNOTHERAPEUTICS	Intravenous
Mycophenolate mofetil (targets Purine synthesis)	MANUFACTURED BY GENENTECH	Oral
Naltrexone (targets Opioid receptors Toll-like receptor 4)	VARIOUS	Given at low doses (3 to 4.5 mg per day) in oral form as"Low-dose naltrexone" (or "LDN")
Ocrelizumab and Ofatumumab (humanized monoclonal antibodies targeting CD20 B cell suppression	ROCHE / GSK	Projected to be IV infusion
ONO-4641 (targets Sphingosine 1-phosphate receptor)	ONO PHARMACEUTICAL CO.	Oral

Generic Name	Branded Name/Company	Frequency/Route of Delivery/Usual Dose
Phenytoin (targets Sodium channels)	PFIZER	Intravenous Intramuscular (less favored option) Oral
Ponesimod	ACTELION	To be determined
Raltegravir (targets Retroviral integrase Herpesvirus DNA packaging terminase)	MERCK	Oral 400 mg tablet twice daily, according to information from the manufacturer
RHB-104	REDHILL BIOPHARMA LIMITED	95 mg clarithromycin, 45 mg rifabutin, and 10 mg clofazimine
Riluzole (targets Glutamatergic neurotransmission Glutamate uptake and release Voltage-gated sodium channels Protein kinase C)	COVIS PHARMA / SANOFI	Oral

MS disease progression may be most intensive, and most damaging, at the earliest stages of disease progression. Accordingly, counter to many reimbursement policies and physician practice in light of, for example, costs and side effect mitigation, it may be most beneficial for a patient's long term disease status to begin treatment with the most intensive DMTs, for instance so-called second-line therapies. In some embodiments, a patient is treated with a regimen of the Fc-based chimeric protein complex in combination with a second-line therapy. Such a combination is used to reduce the side effect profile of one or more second-line therapies. In some embodiments, the combination is used to reduce dose of frequency of administration of one or more second-line therapies. For example, the doses of agents listed in the Table provided above may be reduced by about 50%, or about 40%, or about 30%, or about 25% in the context of the combination and the/or the frequency of dosing may be decreased to be half as often, or a third as often or may be reduced from, for example, daily to every other day or weekly, every other day to weekly or bi-weekly, weekly to bi-weekly or monthly, *etc.* Accordingly, in some embodiments, the Fc-based chimeric protein complex increase patient adherence by allowing for more convenient treatment regimens. Further, some DMTs have a suggested lifetime dose limitation *e.g.* for mitoxantrone, the lifetime cumulative dose should be strictly limited to 140 mg/m^2, or 2 to 3 years of therapy. In some embodiments, supplementation with the Fc-based chimeric protein complex preserves patient's access to mitoxantrone by allowing for lower or less frequent dosing with this DMT.

In some embodiments, the patient is a naive patient, who has not received treatment with one or more DMTs, and the Fc-based chimeric protein complex is used to buffer the side effects of a second-line therapy. Accordingly, the naive patient is able to benefit from the long-term benefits of a second-line therapy at disease outset. In some embodiments, the Fc-based chimeric protein complex is used as an entry therapy that precedes the use of a second-line therapy. For example, the Fc-based chimeric protein complex may be administered for an initial treatment period of about 3 months to stabilize disease and then the patient may be transitioned to a maintenance therapy of a second line agent.

It is generally believed that naive patients are more likely to respond to therapy as compared to patients that have received, and perhaps failed one or more DMT. In some embodiments, the Fc-based chimeric protein complex finds use in patients that have received, and perhaps failed one or more DMT. For example, in some embodiments, the Fc-based chimeric protein complex increases the therapeutic effect in patients that have received, and perhaps failed one or more DMT and may allow these patients to respond like naive patients.

In some embodiments, the patient has received or is receiving treatment with one or more DMTs and is not responding well. For example, the patient may be refractory or poorly responsive to one or more DMTs. In some embodiments, the patient is refractory, or poorly responsive to one or more of teriflunomide (AUBAGIO (GENZYME)); interferon beta-1a (AVONEX (BIOGEN IDEC); interferon beta-1b (BETASERON (BAYER HEALTHCARE PHARMACEUTICALS, INC.); glatiramer acetate (COPAXONE (TEVA NEUROSCIENCE); interferon beta-1b (EXTAVIA (NOVARTIS PHARMACEUTICALS CORP.); fingolimod (GILENYA (NOVARTIS PHARMACEUTICALS CORP.); alemtuzumab (LEMTRADA (GENZYME); mitoxantrone (NOVANTRONE (EMD SERONO); pegylated interferon beta-1a (PLEGRIDY (BIOGEN IDEC); interferon beta-1a (REBIF (EMD SERONO, INC.); dimethyl fumarate (BG-12) (TECFIDERA (BIOGEN IDEC); and natalizumab (TYSABRI (BIOGEN IDEC). In some embodiments, the one or more disclosed binding agent results in a therapeutic benefit of one or more DMTs in the patient and therefore reduces or eliminates the non-responsiveness to the DMT. For instance, this may spare the patient therapy with one or more DMTs at a higher dosing or frequency.

In patients with more aggressive disease, one approach is an induction treatment model, where a therapy with strong efficacy but strong safety concerns would be given first, followed by a maintenance therapy. An example of such a model might include initial treatment with alemtuzumab, followed by IFN-β, GA, or BG-12. In some embodiments, the one or more disclosed binding agent is used to prevent the need to switch therapies for maintenance. In some embodiments, the one or more disclosed binding agent is used to as maintenance therapy to one or more DMTs, including second line therapies. In some embodiments, the one or more disclosed binding agent is used to as first therapy in an induction, followed by another DMT as a maintenance therapy- such as, for example, a first line therapy.

In some embodiments, the one or more disclosed binding agent may be administered for an initial treatment period of about 3 months to stabilize disease and then the patient may be transitioned to a maintenance therapy of a first line agent.

In various embodiments, the one or more disclosed binding agent is used to reduce one or more side effects of a DMT, including without limitation any agent disclosed herein. For example, the one or more disclosed binding agent may be used in a regimen that allows dose sparing for one or more DMTs and therefore results in fewer side effects. For example, in some embodiments, the one or more disclosed binding agent may reduce one or more side effects of AUBAGIO or related agents, which may include hair thinning, diarrhea, flu, nausea, abnormal liver tests and unusual numbness or tingling in the hands or feet (paresthesias), levels of white blood cells, which can increase the risk of infections; increase in blood pressure; and severe liver damage. In some embodiments, the one or more disclosed binding agent may reduce one or more side effects of AVONEX or related agents which

include flu-like symptoms following injection, depression, mild anemia, liver abnormalities, allergic reactions, and heart problems. In some embodiments, the one or more disclosed binding agent may reduce one or more side effects of BETASERON or related agents which include flu-like symptoms following injection, injection site reactions, allergic reactions, depression, liver abnormalities, and low white blood cell counts. In some embodiments, the one or more disclosed binding agent may reduce one or more side effects of COPAXONE or related agents which include injection site reactions, vasodilation (dilation of blood vessels); chest pain; a reaction immediately after injection, which includes anxiety, chest pain, palpitations, shortness of breath, and flushing. In some embodiments, the one or more disclosed binding agent may reduce one or more side effects of EXTAVIA or related agents which include flu-like symptoms following injection, injection site reactions, allergic reactions, depression, liver abnormalities, and low white blood cell counts. In some embodiments, the one or more disclosed binding agent may reduce one or more side effects of GILENYA or related agents which include headache, flu, diarrhea, back pain, liver enzyme elevations, cough, slowed heart rate following first dose, infections, and swelling in the eye. In some embodiments, the one or more disclosed binding agent may reduce one or more side effects of LEMTRADA or related agents which include rash, headache, fever, nasal congestion, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, hives, itching, thyroid gland disorders, fungal Infection, pain in joints, extremities and back, diarrhea, vomiting, flushing, and infusion reactions (including nausea, hives, itching, insomnia, chills, flushing, fatigue, shortness of breath, changes in the sense of taste, indigestion, dizziness, pain). In some embodiments, the one or more disclosed binding agent may reduce one or more side effects of NOVANTRONE or related agents which include blue-green urine 24 hours after administration; infections, bone marrow suppression (fatigue, bruising, low blood cell counts), nausea, hair thinning, bladder infections, mouth sores, and serious liver and heart damage. In some embodiments, the one or more disclosed binding agent may reduce one or more side effects of PLEGRIDY or related agents which include flu-like symptoms following injection, injection site reactions, depression, mild anemia, liver abnormalities, allergic reactions, and heart problems. In some embodiments, the one or more disclosed binding agent may reduce one or more side effects of REBIF or related agents which include flu-like symptoms following injection, injection site reactions, liver abnormalities, depression, allergic reactions, and low red or white blood cell counts. In some embodiments, one or more disclosed binding agent may reduce one or more side effects of TECFIDERA or related agents which include flushing (sensation of heat or itching and a blush on the skin), gastrointestinal issues (nausea, diarrhea, abdominal pain), rash, protein in the urine, elevated liver enzymes; and reduction in blood lymphocyte (white blood cell) counts. In some embodiments, the one or more disclosed binding agent may reduce one or more side effects of TYSABRI or related agents which include headache, fatigue, urinary tract infections, depression, respiratory tract infections, joint pain, upset stomach, abdominal discomfort, diarrhea, vaginitis, pain in the arms or legs, rash, allergic or hypersensitivity reactions within two hours of infusion (dizziness, fever, rash, itching, nausea, flushing, low blood pressure, difficulty breathing, chest pain).

In some embodiments, the present invention relates to combination therapy with one or more chimeric agents described in WO 2013/10779, WO 2015/007536, WO 2015/007520, WO 2015/007542, and WO 2015/007903, the entire contents of which are hereby incorporated by reference in their entireties.

In some embodiments, inclusive of, without limitation, infectious disease applications, the present invention pertains to anti-infectives as additional therapeutic agents. In some embodiments, the anti-infective is an anti-viral agent including, but not limited to, Abacavir, Acyclovir, Adefovir, Amprenavir, Atazanavir, Cidofovir, Darunavir, Delavirdine, Didanosine, Docosanol, Efavirenz, Elvitegravir, Emtricitabine, Enfuvirtide, Etravirine, Famciclovir, and Foscarnet. In some embodiments, the anti-infective is an anti-bacterial agent including, but not limited to, cephalosporin antibiotics (cephalexin, cefuroxime, cefadroxil, cefazolin, cephalothin, cefaclor, cefamandole, cefoxitin, cefprozil, and ceftobiprole); fluoroquinolone antibiotics (cipro, Levaquin, floxin, tequin, avelox, and norflox); tetracycline antibiotics (tetracycline, minocycline, oxytetracycline, and doxycycline); penicillin antibiotics (amoxicillin, ampicillin, penicillin V, dicloxacillin, carbenicillin, vancomycin, and methicillin); monobactam antibiotics (aztreonam); and carbapenem antibiotics (ertapenem, doripenem, imipenem/cilastatin, and meropenem). In some embodiments, the anti-infectives include anti-malarial agents (*e.g.*, chloroquine, quinine, mefloquine, primaquine, doxycycline, artemether/lumefantrine, atovaquone/proguanil and sulfadoxine/pyrimethamine), metronidazole, tinidazole, ivermectin, pyrantel pamoate, and albendazole.

In some embodiments, inclusive, without limitation, of autoimmmune applications, the additional therapeutic agent is an immunosuppressive agent. In some embodiments, the immunosuppressive agent is an anti-inflammatory agent such as a steroidal anti-inflammatory agent or a non-steroidal anti-inflammatory agent (NSAID). Steroids, particularly the adrenal corticosteroids and their synthetic analogues, are well known in the art. Examples of corticosteroids useful in the present invention include, without limitation, hydroxyltriamcinolone, alpha-methyl dexamethasone, beta-methyl betamethasone, beclomethasone dipropionate, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, clobetasol valerate, desonide, desoxymethasone, dexamethasone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, clocortelone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate. (NSAIDS) that may be used in the present invention, include but are not limited to, salicylic acid, acetyl salicylic acid, methyl salicylate, glycol salicylate, salicylmides, benzyl-2,5-diacetoxybenzoic acid, ibuprofen, fulindac, naproxen, ketoprofen, etofenamate, phenylbutazone, and indomethacin. In some embodiments, the immunosupressive agent may be cytostatics such as alkylating agents, antimetabolites (*e.g.*, azathioprine, methotrexate), cytotoxic antibiotics, antibodies (*e.g.*, basiliximab, daclizumab, and muromonab), anti-immunophilins (*e.g.*, cyclosporine, tacrolimus, sirolimus), inteferons, opioids, TNF binding proteins, mycophenolates, and small biological agents (*e.g.*, fingolimod, myriocin). Additional anti-inflammatory agents are described, for example, in U.S. Patent No. 4,537,776, the entire contents of which is incorporated by reference herein.

In some embodiments, the Fc-based chimeric protein complex described herein, include derivatives that are modified, *i.e.*, by the covalent attachment of any type of molecule to the composition such that covalent attachment does not prevent the activity of the composition. For example, but not by way of limitation, derivatives include composition that have been modified by, *inter alia*, glycosylation, lipidation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, *etc*. Any of numerous chemical modifications can be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, *etc.*

In still other embodiments, the Fc-based chimeric protein complex described herein further comprise a cytotoxic agent, comprising, in illustrative embodiments, a toxin, a chemotherapeutic agent, a radioisotope, and an agent that causes apoptosis, necrosis or any other form of cell death. Such agents may be conjugated to a composition described herein.

The Fc-based chimeric protein complex described herein may thus be modified post-translationally to add effector moieties such as chemical linkers, detectable moieties such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, and chemiluminescent moieties, or functional moieties such as for example streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, and radioactive materials.

Illustrative cytotoxic agents include, but are not limited to, methotrexate, aminopterin, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine; alkylating agents such as mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU), mitomycin C, lomustine (CCNU), 1-methylnitrosourea, cyclothosphamide, mechlorethamine, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II) (DDP) cisplatin and carboplatin (paraplatin); anthracyclines include daunorubicin (formerly daunomycin), doxorubicin (adriamycin), detorubicin, carminomycin, idarubicin, epirubicin, mitoxantrone and bisantrene; antibiotics include dactinomycin (actinomycin D), bleomycin, calicheamicin, mithramycin, and anthramycin (AMC); and antimytotic agents such as the vinca alkaloids, vincristine and vinblastine. Other cytotoxic agents include paclitaxel (taxol), ricin, pseudomonas exotoxin, gemcitabine, cytochalasin B, gramicidin D, ethidium bromide, emetine, etoposide, tenoposide, colchicin, dihydroxy anthracin dione, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, procarbazine, hydroxyurea, asparaginase, corticosteroids, mytotane (O,P'-(DDD)), interferons, and mixtures of these cytotoxic agents.

Further cytotoxic agents include, but are not limited to, chemotherapeutic agents such as carboplatin, cisplatin, paclitaxel, gemcitabine, calicheamicin, doxorubicin, 5-fluorouracil, mitomycin C, actinomycin D, cyclophosphamide, vincristine, bleomycin, VEGF antagonists, EGFR antagonists, platins, taxols, irinotecan, 5-fluorouracil, gemcytabine, leucovorine, steroids, cyclophosphamide, melphalan, vinca alkaloids (*e.g.*, vinblastine, vincristine, vindesine and vinorelbine), mustines, tyrosine kinase inhibitors, radiotherapy, sex hormone antagonists, selective androgen receptor modulators, selective estrogen receptor modulators, PDGF antagonists, TNF antagonists, IL-1β antagonists, interleukins (*e.g.* IL-12 or IL-2), IL-12R antagonists, Toxin conjugated monoclonal antibodies, tumor antigen specific monoclonal antibodies, Erbitux, Avastin, Pertuzumab, anti-CD20

antibodies, Rituxan, ocrelizumab, ofatumumab, DXL625, HERCEPTIN®, or any combination thereof. Toxic enzymes from plants and bacteria such as ricin, diphtheria toxin and Pseudomonas toxin may be conjugated to the therapeutic agents (*e.g.* antibodies) to generate cell-type-specific-killing reagents (Youle, *et al.*, Proc. Nat'l Acad. Sci. USA 77:5483 (1980); Gilliland, *et al.*, Proc. Nat'l Acad. Sci. USA 77:4539 (1980); Krolick, *et al.*, Proc. Nat'l Acad. Sci. USA 77:5419 (1980)).

Other cytotoxic agents include cytotoxic ribonucleases as described by Goldenberg in U.S. Pat. No. 6,653,104. Embodiments of the invention also relate to radioimmunoconjugates where a radionuclide that emits alpha or beta particles is stably coupled to the Fc-based chimeric protein complex, with or without the use of a complex-forming agent. Such radionuclides include beta-emitters such as Phosphorus-32, Scandium-47, Copper-67, Gallium-67, Yttrium-88, Yttrium-90, Iodine-125, Iodine-131, Samarium-153, Lutetium-177, Rhenium-186 or Rhenium-188, and alpha-emitters such as Astatine-211, Lead-212, Bismuth-212, Bismuth-213 or Actinium-225.

Illustrative detectable moieties further include, but are not limited to, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, beta-galactosidase and luciferase. Further illustrative fluorescent materials include, but are not limited to, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin and dansyl chloride. Further illustrative chemiluminescent moieties include, but are not limited to, luminol. Further illustrative bioluminescent materials include, but are not limited to, luciferin and aequorin. Further illustrative radioactive materials include, but are not limited to, Iodine-125, Carbon-14, Sulfur-35, Tritium and Phosphorus-32.

Methods of Treatment

Methods and compositions described herein have application to treating various diseases and disorders, including, but not limited to cancer, infections, immune disorders, and inflammatory diseases or conditions.

Further, any of the present agents may be for use in the treating, or the manufacture of a medicament for treating, various diseases and disorders, including, but not limited to cancer, infections, immune disorders, inflammatory diseases or conditions, and autoimmune diseases.

In some embodiments, the present invention relates to the treatment of, or a patient having cancer. As used herein, cancer refers to any uncontrolled growth of cells that may interfere with the normal functioning of the bodily organs and systems, and includes both primary and metastatic tumors. Primary tumors or cancers that migrate from their original location and seed vital organs can eventually lead to the death of the subject through the functional deterioration of the affected organs. A metastasis is a cancer cell or group of cancer cells, distinct from the primary tumor location, resulting from the dissemination of cancer cells from the primary tumor to other parts of the body. Metastases may eventually result in death of a subject. For example, cancers can include benign and malignant cancers, polyps, hyperplasia, as well as dormant tumors or micrometastases.

Illustrative cancers that may be treated include, but are not limited to, basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and central nervous system cancer; breast cancer; cancer of the peritoneum; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer

(including gastrointestinal cancer); glioblastoma; hepatic carcinoma; hepatoma; intra-epithelial neoplasm; kidney or renal cancer; larynx cancer; leukemia; liver cancer; lung cancer (*e.g.*, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung); melanoma; myeloma; neuroblastoma; oral cavity cancer (lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; salivary gland carcinoma; sarcoma; skin cancer; squamous cell cancer; stomach cancer; testicular cancer; thyroid cancer; uterine or endometrial cancer; cancer of the urinary system; vulval cancer; lymphoma including Hodgkin's and non-Hodgkin's lymphoma, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia; chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); acute myeloid leukemia (AML); Hairy cell leukemia; chronic myeloblastic leukemia; as well as other carcinomas and sarcomas; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (*e.g.* that associated with brain tumors), and Meigs' syndrome.

In various embodiments, the present invention provides Fc-based chimeric protein complexes which comprise wild type or modified signaling agents for the treatment of cancer. In some embodiments, the Fc-based chimeric protein complexes of the invention significantly reduce and/or eliminate tumors. In some embodiments, the present Fc-based chimeric protein complexes significant reduce and/or eliminate tumors when administered to a subject in combination with other anti-cancer agents such as chemotherapeutic agents, checkpoint inhibitors, and immunosuppressive agents. In various embodiments, the combination of Fc-based chimeric protein complexes and other anti-cancer agents synergistically reduced tumor size and/or eliminated tumor cells.

In various embodiments, the present invention relates to cancer combination therapies with an Fc-based chimeric protein complex comprising one or more targeting moieties and one or more wild type or modified signaling agents. Accordingly, the present invention provides for an Fc-based chimeric protein complex that include, for example, a targeting moiety and one or more signaling agents and uses thereof in combination with anti-cancer agents.

For instance, in various embodiments, the present invention pertains to combination therapies for cancer involving Fc-based chimeric protein complex and a wild type or modified signaling agent, including, without limitation a mutated human interferon, such as IFN alpha, including human interferon alpha 2.

In other embodiments, the present Fc-based chimeric protein complex comprises multiple targeting moieties and therefore be present in bispecific or trispecific formats. For instance, in various embodiments, the present invention pertains to combination therapies for cancer involving an Fc-based chimeric protein complex and a checkpoint inhibitor binding agent (*e.g.* anti-PD-L1, anti-PD-1, anti-PD-L2, or anti-CTLA) described herein and a modified signaling agent, including, without limitation a mutated human interferon, such as IFN alpha, including human interferon alpha 2.

In various embodiments, the signaling agent is wild type or modified to have reduced affinity or activity for one or more of its receptors, which allows for attenuation of activity (inclusive of agonism or antagonism) and/or prevents non-specific signaling or undesirable sequestration of the chimeric protein. In some embodiments, the reduced affinity or activity at the receptor is restorable by inclusion in the present complex having one or more of the targeting moieties as described herein.

In some embodiments, the present invention relates to the treatment of, or a patient having a microbial infection and/or chronic infection. Illustrative infections include, but are not limited to, HIV/AIDS, tuberculosis, osteomyelitis, hepatitis B, hepatitis C, Epstein-Barr virus or parvovirus, T cell leukemia virus, bacterial overgrowth syndrome, fungal or parasitic infections.

In some embodiments, the present invention relates to the treatment of, or a patient having one or more of chronic granulomatous disease, osteopetrosis, idiopathic pulmonary fibrosis, Friedreich's ataxia, atopic dermatitis, Chagas disease, cancer, heart failure, autoimmune disease, sickle cell disease, thalassemia, blood loss, transfusion reaction, diabetes, vitamin B12 deficiency, collagen vascular disease, Shwachman syndrome, thrombocytopenic purpura, Celiac disease, endocrine deficiency state such as hypothyroidism or Addison's disease, autoimmune disease such as Crohn's Disease, systemic lupus erythematosis, rheumatoid arthritis or juvenile rheumatoid arthritis, ulcerative colitis immune disorders such as eosinophilic fasciitis, hypoimmunoglobulinemia, or thymoma/thymic carcinoma, graft versus host disease, preleukemia, Nonhematologic syndrome (*e.g.* Down's, Dubowwitz, Seckel), Felty syndrome, hemolytic uremic syndrome, myelodysplasic syndrome, nocturnal paroxysmal hemoglobinuria, osteomyelofibrosis, pancytopenia, pure red-cell aplasia, Schoenlein-Henoch purpura, malaria, protein starvation, menorrhagia, systemic sclerosis, liver cirrhosis, hypometabolic states, and congestive heart failure.

In some embodiments, the present invention relates to the treatment of, or a patient having one or more of chronic granulomatous disease, osteopetrosis, idiopathic pulmonary fibrosis, Friedreich's ataxia, atopic dermatitis, Chagas disease, mycobacterial infections, cancer, scleroderma, hepatitis, hepatitis C, septic shock, and rheumatoid arthritis.

In various embodiments, the present compositions are used to treat or prevent one or more inflammatory diseases or conditions, such as inflammation, acute inflammation, chronic inflammation, respiratory disease, atherosclerosis, restenosis, asthma, allergic rhinitis, atopic dermatitis, septic shock, rheumatoid arthritis, inflammatory bowel disease, inflammatory pelvic disease, pain, ocular inflammatory disease, celiac disease, Leigh Syndrome, Glycerol Kinase Deficiency, Familial eosinophilia (FE), autosomal recessive spastic ataxia, laryngeal inflammatory disease; Tuberculosis, Chronic cholecystitis, Bronchiectasis, Silicosis and other pneumoconioses.

In various embodiments, the present invention has application to treating autoimmune and/or neurodegenerative diseases.

In various embodiments, the present compositions are used to treat or prevent one or more conditions characterized by undesirable CTL activity, and/or a conditions characterized by high levels of cell death. For

instance, in various embodiments, the present compositions are used to treat or prevent one or more conditions associated with uncontrolled or overactive immune response.

In various embodiments, the present compositions are used to treat or prevent one or more autoimmune and/or neurodegenerative diseases or conditions, such as MS, diabetes mellitus, lupus, celiac disease, Crohn's disease, ulcerative colitis, Guillain-Barre syndrome, scleroderms, Goodpasture's syndrome, Wegener's granulomatosis, autoimmune epilepsy, Rasmussen's encephalitis, Primary biliary sclerosis, Sclerosing cholangitis, Autoimmune hepatitis, Addison's disease, Hashimoto's thyroiditis, Fibromyalgia, Menier's syndrome; transplantation rejection (*e.g.*, prevention of allograft rejection) pernicious anemia, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, Sjogren's syndrome, lupus erythematosus, myasthenia gravis, Reiter's syndrome, Grave's disease, and other autoimmune diseases.

In various embodiments, the present invention is used to treat or prevent various autoimmune and/or neurodegenerative diseases. In some embodiments, the autoimmune and/or neurodegenerative diseases selected from MS (including without limitation the subtypes described herein), Alzheimer's disease (including, without limitation, Early-onset Alzheimer's, Late-onset Alzheimer's, and Familial Alzheimer's disease (FAD), Parkinson's disease and parkinsonism (including, without limitation, Idiopathic Parkinson's disease, Vascular parkinsonism, Drug-induced parkinsonism, Dementia with Lewy bodies, Inherited Parkinson's, Juvenile Parkinson's), Huntington's disease, Amyotrophic lateral sclerosis (ALS, including, without limitation, Sporadic ALS, Familial ALS, Western Pacific ALS, Juvenile ALS, Hiramaya Disease).

In an embodiment, the present invention provides methods for the treatment or prevention of one or more liver disorders, selected from viral hepatitis, alcohol hepatitis, autoimmune hepatitis, alcohol liver disease, fatty liver disease, steatosis, steatohepatitis, non-alcohol fatty liver disease, drug-induced liver disease, cirrhosis, fibrosis, liver failure, drug induced liver failure, metabolic syndrome, hepatocellular carcinoma, cholangiocarcinoma, primary biliary cirrhosis (primary biliary cholangitis), bile capillaries, Gilbert's syndrome, jaundice, and any other liver toxicity-associated indication. In some embodiments, the present invention provides methods for the treatment or prevention of liver fibrosis. In some embodiments, the present invention provides methods for the treatment or prevention of primary sclerosing cholangitis (PSC), chronic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatitis C infection, alcoholic liver disease, liver damage, optionally due to progressive fibrosis and liver fibrosis.In some embodiments, the present invention provides methods for the treatment or prevention of nonalcoholic steatohepatitis (NASH).In some embodiments, the present invention provides methods that reduce or prevent fibrosis.In some embodiments, the present invention provides methods that reduce or prevent cirrhosis. In some embodiments, the present invention provides methods that reduce or prevent hepatocellular carcinoma.

In various embodiments, the present invention provides methods for the treatment or prevention of cardiovascular disease, such as a disease or condition affecting the heart and vasculature, including but not limited to, coronary heart disease (CHD), cerebrovascular disease (CVD), aortic stenosis, peripheral vascular disease, atherosclerosis, arteriosclerosis, myocardial infarction (heart attack), cerebrovascular diseases (stroke), transient ischaemic

attacks (TIA), angina (stable and unstable), atrial fibrillation, arrhythmia, valvular disease, and/or congestive heart failure. In various embodiments, the present invention provides methods for the treatment or prevention of cardiovascular disease which involves inflammation.

In various embodiments, the present invention provides methods for the treatment or prevention of one or more respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, allergic rhinitis, sinusitis, pulmonary vasoconstriction, inflammation, allergies, impeded respiration, respiratory distress syndrome, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, Hantavirus pulmonary syndrome (HPS), Loeffler's syndrome, Goodpasture's syndrome, Pleurisy, pneumonitis, pulmonary edema, pulmonary fibrosis, Sarcoidosis, complications associated with respiratory syncitial virus infection, and other respiratory diseases.

In various embodiments, the present invention is used to treat or prevent MS. In various embodiments, the Fc-based chimeric protein complexes as described herein are used to eliminate and reduce multiple MS symptoms. Illustrative symptoms associated with multiple sclerosis, which can be prevented or treated with the compositions and methods described herein, include: optic neuritis, diplopia, nystagmus, ocular dysmetria, internuclear ophthalmoplegia, movement and sound phosphenes, afferent pupillary defect, paresis, monoparesis, paraparesis, hemiparesis, quadraparesis, plegia, paraplegia, hemiplegia, tetraplegia, quadraplegia, spasticity, dysarthria, muscle atrophy, spasms, cramps, hypotonia, clonus, myoclonus, myokymia, restless leg syndrome, footdrop, dysfunctional reflexes, paraesthesia, anaesthesia, neuralgia, neuropathic and neurogenic pain, l'hermitte's sign, proprioceptive dysfunction, trigeminal neuralgia, ataxia, intention tremor, dysmetria, vestibular ataxia, vertigo, speech ataxia, dystonia, dysdiadochokinesia, frequent micturation, bladder spasticity, flaccid bladder, detrusor-sphincter dyssynergia, erectile dysfunction, anorgasmy, frigidity, constipation, fecal urgency, fecal incontinence, depression, cognitive dysfunction, dementia, mood swings, emotional lability, euphoria, bipolar syndrome, anxiety, aphasia, dysphasia, fatigue, Uhthoff's symptom, gastroesophageal reflux, and sleeping disorders. Mitigation or amelioration or one more of these symptoms in a subject can be achieved by the one or more agent as described herein.

In various embodiments, the Fc-based chimeric protein complexes as described herein is used to treat or prevent clinically isolated syndrome (CIS). A clinically isolated syndrome (CIS) is a single monosymptomatic attack compatible with MS, such as optic neuritis, brain stem symptoms, and partial myelitis. Patients with CIS that experience a second clinical attack are generally considered to have clinically definite multiple sclerosis (CDMS). Over 80 percent of patients with CIS and MRI lesions go on to develop MS, while approximately 20 percent have a self-limited process. Patients who experience a single clinical attack consistent with MS may have at least one lesion consistent with multiple sclerosis prior to the development of clinically definite multiple sclerosis. In various embodiments, the presently described Fc-based chimeric protein complexes is used to treat CIS so it does not develop into MS, including, for example RRMS.

In various embodiments, the Fc-based chimeric protein complexes as described herein are used to treat or prevent radiologically isolated syndrome (RIS). In RIS, incidental imaging findings suggest inflammatory demyelination in

the absence of clinical signs or symptoms. In various embodiments, the Fc-based chimeric protein complex is used to treat RIS so it does not develop into MS, including, for example RRMS.

In various embodiments, the Fc-based chimeric protein complexes as described herein are used to treat one or more of benign multiple sclerosis; relapsing-remitting multiple sclerosis (RRMS); secondary progressive multiple sclerosis (SPMS); progressive relapsing multiple sclerosis (PRMS); and primary progressive multiple sclerosis (PPMS).

Benign multiple sclerosis is a retrospective diagnosis which is characterized by 1-2 exacerbations with complete recovery, no lasting disability and no disease progression for 10-15 years after the initial onset. Benign multiple sclerosis may, however, progress into other forms of multiple sclerosis. In various embodiments, the Fc-based chimeric protein complex is used to treat benign multiple sclerosis so it does not develop into MS.

Patients suffering from RRMS experience sporadic exacerbations or relapses, as well as periods of remission. Lesions and evidence of axonal loss may or may not be visible on MRI for patients with RRMS. In various embodiments, the Fc-based chimeric protein complexes as described herein are used to treat RRMS. In some embodiments, RRMS includes patients with RRMS; patients with SPMS and superimposed relapses; and patients with CIS who show lesion dissemination on subsequent MRI scans according to McDonald's criteria. A clinical relapse, which may also be used herein as “relapse,” “confirmed relapse,” or “clinically defined relapse,” is the appearance of one or more new neurological abnormalities or the reappearance of one or more previously observed neurological abnormalities. This change in clinical state must last at least 48 hours and be immediately preceded by a relatively stable or improving neurological state of at least 30 days. In some embodiments, an event is counted as a relapse when the subject's symptoms are accompanied by observed objective neurological changes, consistent with an increase of at least 1.00 in the Expanded Disability Status Scale (EDSS) score or one grade in the score of two or more of the seven FS or two grades in the score of one of FS as compared to the previous evaluation.

SPMS may evolve from RRMS. Patients afflicted with SPMS have relapses, a diminishing degree of recovery during remissions, less frequent remissions and more pronounced neurological deficits than RRMS patients. Enlarged ventricles, which are markers for atrophy of the corpus callosum, midline center and spinal cord, are visible on MRI of patients with SPMS. In various embodiments, the Fc-based chimeric protein complexes as described herein is used to treat RRMS so it does not develop into SPMS.

PPMS is characterized by a steady progression of increasing neurological deficits without distinct attacks or remissions. Cerebral lesions, diffuse spinal cord damage and evidence of axonal loss are evident on the MRI of patients with PPMS. PPMS has periods of acute exacerbations while proceeding along a course of increasing neurological deficits without remissions. Lesions are evident on MRI of patients suffering from PRMS. In various embodiments, the Fc-based chimeric protein complex as described herein is used to treat RRMS and/or SPMS so it does not develop into PPMS.

In some embodiments, the Fc-based chimeric protein complexes as described herein are used in a method of treatment of relapsing forms of MS. In some embodiments, the Fc-based chimeric protein complex is used in a

method of treatment of relapsing forms of MS to slow the accumulation of physical disability and/or reduce the frequency of clinical exacerbations, and, optionally, for patients who have experienced a first clinical episode and have MRI features consistent with MS. In some embodiments, the Fc-based chimeric protein complexes as described herein are used in a method of treatment of worsening relapsing-remitting MS, progressive-relapsing MS or secondary-progressive MS to reduce neurologic disability and/or the frequency of clinical exacerbations. In some embodiments, the Fc-based chimeric protein complexes reduce the frequency and/or severity of relapses.

In some embodiments, the Fc-based chimeric protein complexes are used in a method of treatment of relapsing forms of MS in patients who have had an inadequate response to (or are refractory to) one, or two, or three, or four, or five, or six, or seven, or eight, or nine, or ten or more disease modifying therapies (DMTs).

In various embodiments, the subject's symptoms may be assessed quantitatively, such as by EDSS, or decrease in the frequency of relapses, or increase in the time to sustained progression, or improvement in the magnetic resonance imaging (MRI) behavior in frequent, serial MRI studies and compare the patient's status measurement before and after treatment. In a successful treatment, the patient status will have improved (*e.g.*, the EDSS measurement number or frequency of relapses will have decreased, or the time to sustained progression will have increased, or the MRI scans will show less pathology).

In some embodiments, the patient can be evaluated, *e.g.*, before, during or after receiving the Fc-based chimeric protein complexes *e.g.*, for indicia of responsiveness. Various clinical or other indicia of effectiveness of treatment, *e.g.*, EDSS score; MRI scan; relapse number, rate, or severity; multiple sclerosis functional composite (MSFC); multiple sclerosis quality of life inventory (MSQLI); Paced Serial Addition Test (PASAT); symbol digit modalities test (SDMT); 25-foot walk test; 9-hole peg test; low contrast visual acuity; Modified Fatigue Impact Scale; expanded disability status score (EDSS); multiple sclerosis functional composite (MSFC); Beck Depression Inventory; and 7/24 Spatial Recall Test can be used. In various embodiments, the Fc-based chimeric protein complexes cause an improvement in one or more of these measures. Further, the patient can be monitored at various times during a regimen. In some embodiments, the Fc-based chimeric protein complexes cause a disease improvement as assessed by MacDonald dissemination in space and time. For example, for dissemination in space, lesion imaging, such as, by way of illustration, Barkhof-Tintore MR imaging criteria, may be used, including at least one gadolinium-enhancing lesion or 9 T2 hyperintense lesions; at least one infratentorial lesion; at least one juxtacortical lesion; at least about three periventricular lesions; and a spinal cord lesion. For dissemination in time, MRI can also be used; for example, if an MRI scan of the brain performed at ≥3 months after an initial clinical event demonstrates a new gadolinium-enhancing lesion, this may indicate a new CNS inflammatory event, because the duration of gadolinium enhancement in MS is usually less than 6 weeks. If there are no gadolinium-enhancing lesions but a new T2 lesion (presuming an MRI at the time of the initial event), a repeat MR imaging scan after another 3 months may be needed with demonstration of a new T2 lesion or gadolinium-enhancing lesion.

In some embodiments, disease effects are assessed using any of the measures described in Lavery, *et al.* Multiple Sclerosis International, Vol 2014 (2014), Article ID 262350, the entire contents of which are hereby incorporated by reference.

In some embodiments, the Fc-based chimeric protein complex results in one or more of: (a) prevention of worsening in disability defined as deterioration by 1.0 point on EDSS, (b) increase in time to relapse, (c) reduction or stabilization of number and/or volume of gadolinium enhancing lesions, (d) decreased annualized relapse rate, (e) increased relapse duration and severity by NRS score, (f) decrease in disease activity as measured by MRI (annual rate of new or enlarging lesions), (g) lower average number of relapses at 1 year, or 2 years, (h) sustained disease progression as measured by the EDSS at 3 months, (i) prevention of conversion to CDMS, (j) no or few new or enhancing T2 lesions, (k) minimal change in hyperintense T2 lesion volume, (l) increased time to McDonald defined MS, (m) prevention of progression of disability as measured by sustained worsening of EDSS at 12 weeks, (n) reduction in time to relapse at 96 weeks, and (o) reduction or stabilization of brain atrophy (*e.g.* percentage change from baseline).

In one embodiment, the Fc-based chimeric protein complexes are administered and is effective to result in a decreased rate of relapse (*e.g.*, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or greater reduction in rate of relapse) compared to the rate of relapse before administration (*e.g.*, compared to the rate of relapse following administration for 12 months or for less than 12 months, *e.g.*, about 10, or about 8, or about 4, or about 2 or less months) of treatment, or before commencement of treatment, when measured between 3-24 months (*e.g.*, between 6-18 months, *e.g.*, 12 months) after a previous relapse.

In one embodiment, the Fc-based chimeric protein complexes are administered and are effective to result in a prevention of an increase in EDSS score from a pre-treatment state. The Kurtzke Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis. The EDSS replaced the previous Disability Status Scales which used to bunch people with MS in the lower brackets. The EDSS quantifies disability in eight Functional Systems (FS) and allows neurologists to assign a Functional System Score (FSS) in each of these. The Functional Systems are: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual and cerebral.

In one embodiment, the Fc-based chimeric protein complexes are administered and is effective to result in a decreased EDSS score (*e.g.*, a decrease of 1, 1.5, 2, 2.5, 3 points or more, *e.g.*, over at least three months, six months, one year, or longer) compared to the EDSS score following administration of the Fc-based chimeric protein complexes (*e.g.* for 12 months or for less than 12 months, *e.g.*, less than 10, 8, 4 or less months, or before the commencement of treatment).

In one embodiment, the Fc-based chimeric protein complexes are administered and is effective to result in a decreased number of new lesions overall or of any one type (*e.g.*, at least 10%, 20%, 30%, 40% decrease), compared to the number of new lesions following administration of the Fc-based chimeric protein complexes for 12 months or for less than 12 months, *e.g.*, less than 10, 8, 4 or less months, or before commencement of treatment;

In one embodiment, the Fc-based chimeric protein complexes are administered and is effective to result in a decreased number of lesions overall or of any one type (*e.g.*, at least 10%, 20%, 30%, 40% decrease), compared to the number of lesions following administration of the Fc-based chimeric protein complexes for 12 months or for less than 12 months, *e.g.*, less than 10, 8, 4 or less months, or before commencement of treatment;

In one embodiment, the Fc-based chimeric protein complexes are administered and is effective to result in a reduced rate of appearance of new lesions overall or of any one type (*e.g.*, at least 10%, 20%, 30%, 40% reduced rate), compared to the rate of appearance of new lesions following administration for 12 months or for less than 12 months, *e.g.*, less than 10, 8, 4 or less months, or before commencement of treatment;

In one embodiment, the Fc-based chimeric protein complexes are administered and is effective to result in a reduced increase in lesion area overall or of any one type (*e.g.*, at least 10%, 20%, 30%, 40% decreased increase), compared to an increase in lesion area following administration for 12 months or less than 12 months, *e.g.*, less than 10, 8, 4 or less months, or before commencement of treatment.

In one embodiment, the Fc-based chimeric protein complexes are administered and is effective to result in a reduced incidence or symptom of optic neuritis (*e.g.*, improved vision), compared to the incidence or symptom of optic neuritis following administration for 12 months or for less than 12 months, *e.g.*, less than 10, 8, 4 or less months, or before commencement of treatment.

In various embodiments, methods of the invention are useful in treatment a human subject. In some embodiments, the human is a pediatric human. In other embodiments, the human is an adult human. In other embodiments, the human is a geriatric human. In other embodiments, the human may be referred to as a patient. In some embodiments, the human is a female. In some embodiments, the human is a male.

In certain embodiments, the human has an age in a range of from about 1 to about 18 months old, from about 18 to about 36 months old, from about 1 to about 5 years old, from about 5 to about 10 years old, from about 10 to about 15 years old, from about 15 to about 20 years old, from about 20 to about 25 years old, from about 25 to about 30 years old, from about 30 to about 35 years old, from about 35 to about 40 years old, from about 40 to about 45 years old, from about 45 to about 50 years old, from about 50 to about 55 years old, from about 55 to about 60 years old, from about 60 to about 65 years old, from about 65 to about 70 years old, from about 70 to about 75 years old, from about 75 to about 80 years old, from about 80 to about 85 years old, from about 85 to about 90 years old, from about 90 to about 95 years old or from about 95 to about 100 years old. In various embodiments, the human has an age of more than 30 years old.

Immune Modulation

In various embodiments, the present compositions are capable of, or find use in methods of, immune modulation. For instance, in various embodiments, the present methods of treatment may involve the immune modulation described herein. In some embodiments, the immune modulation involves IFN signaling, including modified IFN signaling, in the context of a dendritic cell (DC).

In various embodiments, a multi-specific Fc-based chimeric protein complex is provided. In some embodiments, such multi-specific Fc-based chimeric protein complex of the invention recognizes and binds to a first target and one or more antigens found on one or more immune cells, which can include, without limitation, megakaryocytes, thrombocytes, erythrocytes, mast cells, basophils, neutrophils, eosinophils, monocytes, macrophages, natural killer cells, T lymphocytes (*e.g.*, cytotoxic T lymphocytes, T helper cells, natural killer T cells), B lymphocytes,

plasma cells, dendritic cells, or subsets thereof. In some embodiments, the Fc-based chimeric protein complex specifically binds to an antigen of interest and effectively directly or indirectly recruits one of more immune cells.

In some embodiments, the Fc-based chimeric protein complex specifically binds to an antigen of interest and effectively directly or indirectly recruits one of more immune cells to cause an immunosuppressive effect, *e.g.* the Fc-based chimeric protein complex directly or indirectly recruits an immunosuppressive immune cell. In some embodiments, the immunosuppressive immune cell is a regulatory T cell (or "Tregs" which, as used herein, refers to a subpopulation of T cells which modulate the immune system, abrogate autoimmune disease, maintain tolerance to self-antigens and thwart anti-tumor immune responses). Other immunosuppressive immune cells include myeloid suppressor cells (or "MSC," which, as used herein, refers to a heterogeneous population of cells, defined by their myeloid origin, immature state, and ability to potently suppress T cell responses); tumor associated neutrophils (or "TANs" which, as used herein, refers to a subset of neutrophils that are capable of suppressing immune responses); tumor associated macrophages (or "TAMs" which, as used herein, refers to a subset of macrophages that may reduce an immune response), M2 macrophages, and/or tumor-inducing mast cells (which as used herein, refers to a subset of bone marrow-derived, long-lived, heterogeneous cellular population). Also, immunosuppressive immune cells include Th2 cells and Th17 cells. Additionally, immunosuppressive immune cells include immune cells, *e.g.*, CD4+ and/or CD8+ T cells, expressing one or more checkpoint inhibitory receptors (*e.g.* receptors, including CTLA-4, B7-H3, B7-H4, TIM-3, expressed on immune cells that prevent or inhibit uncontrolled immune responses). *See* Stagg, J. *et. al.,* Immunotherapeutic approach in triple-negative breast cancer. Ther Adv Med Oncol. (2013) 5(3):169-181).

In some embodiments, the Fc-based chimeric protein complex stimulates regulatory T cell (Treg) proliferation. Treg cells are characterized by the expression of the Foxp3 (Forkhead box p3) transcription factor. Most Treg cells are CD4+ and CD25+, and can be regarded as a subset of helper T cells, although a small population may be CD8+. Thus the immune response, which is to be modulated by a method of the invention, may comprise inducing proliferation of Treg cells, optionally in response to an antigen. Thus the method may comprise administering to the subject an Fc-based chimeric protein complex comprising the antigen. The antigen may be administered with an adjuvant which promotes proliferation of Treg cells.

Insofar as this method involves stimulating proliferation and differentiation of Treg cells in response to a specific antigen, it can be considered to be a method of stimulating an immune response. However, given that Treg cells may be capable of modulating the response of other cells of the immune system against an antigen in other ways, *e.g.* inhibiting or suppressing their activity, the effect on the immune system as a whole may be to modulate (*e.g.* suppress or inhibit) the response against that antigen. Thus the methods of this aspect of the invention can equally be referred to as methods of modulating (*e.g.* inhibiting or suppressing) an immune response against an antigen.

In some embodiments, the methods therapeutically or prophylactically inhibit or suppress an undesirable immune response against a particular antigen, even in a subject with pre-existing immunity or an on-going immune response to that antigen. This may be particularly useful, for example, in the treatment of autoimmune disease.

Under certain conditions, it may also be possible to tolerize a subject against a particular antigen by targeting the antigen to an antigen presenting cell expressing a target of the targeting moiety of the Fc-based chimeric protein complex. The invention thus provides a method for inducing tolerance in a subject towards an antigen, comprising administering to the subject a composition comprising the antigen, wherein the antigen is associated with a binding agent having affinity for the targeting moiety of the Fc-based chimeric protein complex and wherein the antigen is administered in the absence of an adjuvant. Tolerance in this context typically involves depletion of immune cells which would otherwise be capable of responding to that antigen, or inducing a lasting reduction in responsiveness to an antigen in such immune cells.

It may be particularly desirable to raise a Treg response against an antigen to which the subject exhibits, or is at risk of developing, an undesirable immune response. For example, it may be a self-antigen against which an immune response occurs in an autoimmune disease. Examples of autoimmune diseases in which specific antigens have been identified as potentially pathogenically significant include multiple sclerosis (myelin basic protein), insulin-dependent diabetes mellitus (glutamic acid decarboxylase), insulin-resistant diabetes mellitus (insulin receptor), celiac disease (gliadin), bullous pemphigoid (collagen type XVII), auto-immune haemolytic anaemia (Rh protein), auto-immune thrombocytopenia (GpIIb/IIIa), myaesthenia gravis (acetylcholine receptor), Graves' disease (thyroid-stimulating hormone receptor), glomerulonephritis, such as Goodpasture's disease (alpha3(IV)NC1 collagen), and pernicious anaemia (intrinsic factor). Alternatively, the target antigen may be an exogenous antigen which stimulates a response which also causes damage to host tissues. For example, acute rheumatic fever is caused by an antibody response to a Streptococcal antigen which cross-reacts with a cardiac muscle cell antigen. Thus these antigens, or particular fragments or epitopes thereof, may be suitable antigens for use in the present invention.

In various embodiments, the present agents, or methods using these agents, reduce or suppress autoreactive T cells. In some embodiments, the multi-specific Fc-based chimeric protein complex, optionally through an interferon signaling in the context of an Fc-based chimeric protein complex, causes this immunosuppression. In some embodiments, the multi-specific Fc-based chimeric protein complex stimulates PD-L1 or PD-L2 signaling and/or expression which may suppress autoreactive T cells. In some embodiments, the Fc-based chimeric protein complex, optionally through an interferon signaling in the context of an Fc-based chimeric protein complex, causes this immunosuppression. In some embodiments, the Fc-based chimeric protein complex stimulates PD-L1 or PD-L2 signaling and/or expression, which may suppress autoreactive T cells.

In various embodiments, the present methods comprise modulating the ratio of regulatory T cells to effector T cells in favor of immunosuppression, for instance, to treat autoimmune diseases. For instance, the present methods, in some embodiments, reduce and/or suppress one or more of cytotoxic T cells; effector memory T cells; central memory T cells; $CD8^+$ stem cell memory effector cells; TH1 effector T-cells; TH2 effector T cells; TH9 effector T cells; TH17 effector T cells. For instance, the present methods, in some embodiments, increase and/or stimulate one or more of $CD4^+CD25^+FOXP3^+$ regulatory T cells, $CD4^+CD25^+$ regulatory T cells, $CD4^+CD25^-$ regulatory T cells, CD4+CD25high regulatory T cells, $TIM\text{-}3^+PD\text{-}1^+$ regulatory T cells, lymphocyte activation gene-3 $(LAG\text{-}3)^+$

regulatory T cells, CTLA-4/CD152$^+$ regulatory T cells, neuropilin-1 (Nrp-1)$^+$ regulatory T cells, CCR4$^+$CCR8$^+$ regulatory T cells, CD62L (L-selectin)$^+$ regulatory T cells, CD45RBlow regulatory T cells, CD127low regulatory T cells, LRRC32/GARP$^+$ regulatory T cells, CD39$^+$ regulatory T cells, GITR$^+$ regulatory T cells, LAP$^+$ regulatory T cells, 1B11$^+$ regulatory T cells, BTLA$^+$ regulatory T cells, type 1 regulatory T cells (Tr1 cells),T helper type 3 (Th3) cells, regulatory cell of natural killer T cell phenotype (NKTregs), CD8$^+$ regulatory T cells, CD8$^+$CD28$^-$ regulatory T cells and/or regulatory T-cells secreting IL-10, IL-35, TGF-β, TNF-α, Galectin-1, IFN-γ and/or MCP1.

In some embodiments, the present methods favor immune inhibitory signals over immune stimulatory signals. In some embodiments, the present methods allow for reversing or suppressing immune activating or co-stimulatory signals. In some embodiments, the present methods allow for providing immune inhibitory signals. For instance, in some embodiments, the present agents and methods reduce the effects of an immune stimulatory signal, which, without limitation, is one or more of 4-1BB, OX-40, HVEM, GITR, CD27, CD28, CD30, CD40, ICOS ligand; OX-40 ligand, LIGHT (CD258), GITR ligand, CD70, B7-1, B7-2, CD30 ligand, CD40 ligand, ICOS, ICOS ligand, CD137 ligand and TL1A. Further, in some embodiments, the present agents and methods increase the effects of an immune inhibitory signal, which, without limitation, is one or more of CTLA-4, PD-L1, PD-L2, PD-1, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160 (also referred to as BY55), CGEN-15049, CHK 1 and CHK2 kinases, A2aR, CEACAM (*e.g.*, CEACAM-1, CEACAM-3 and/or CEACAM-5), and various B-7 family ligands (including, but are not limited to, B7-1, B7-2, B7-DC, B7-H1, B7-H2, B7-H3, B7-H4, B7-H5, B7-H6 and B7-H7.

Kits

The present invention also provides kits for the administration of any Fc-based chimeric protein complex described herein (*e.g.* with or without additional therapeutic agents). The kit is an assemblage of materials or components, including at least one of the inventive pharmaceutical compositions described herein. Thus, in some embodiments, the kit contains at least one of the pharmaceutical compositions described herein.

The exact nature of the components configured in the kit depends on its intended purpose. In one embodiment, the kit is configured for the purpose of treating human subjects.

Instructions for use may be included in the kit. Instructions for use typically include a tangible expression describing the technique to be employed in using the components of the kit to effect a desired therapeutic outcome, such as to treat cancer. Optionally, the kit also contains other useful components, such as, diluents, buffers, pharmaceutically acceptable carriers, syringes, catheters, applicators, pipetting or measuring tools, bandaging materials or other useful paraphernalia as will be readily recognized by those of skill in the art.

The materials and components assembled in the kit can be provided to the practitioner stored in any convenience and suitable ways that preserve their operability and utility. For example, the components can be provided at room, refrigerated or frozen temperatures. The components are typically contained in suitable packaging materials. In various embodiments, the packaging material is constructed by well-known methods, preferably to provide a sterile, contaminant-free environment. The packaging material may have an external label which indicates the contents and/or purpose of the kit and/or its components.

Definitions

As used herein, “a,” “an,” or “the” can mean one or more than one.

Further, the term “about” when used in connection with a referenced numeric indication means the referenced numeric indication plus or minus up to 10% of that referenced numeric indication. For example, the language “about 50” covers the range of 45 to 55.

As used herein, the term “effective amount” refers to a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, *e.g.*, an amount which results in the prevention of, or a decrease in a disease or disorder or one or more signs or symptoms associated with a disease or disorder. In the context of therapeutic or prophylactic applications, the amount of a composition administered to the subject will depend on the degree, type, and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. The compositions can also be administered in combination with one or more additional therapeutic compounds. In the methods described herein, the therapeutic compounds may be administered to a subject having one or more signs or symptoms of a disease or disorder. As used herein, something is “decreased” if a read-out of activity and/or effect is reduced by a significant amount, such as by 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%, at least about 95%, at least about 97%, at least about 98%, or more, up to and including at least about 100%, in the presence of an agent or stimulus relative to the absence of such modulation. As will be understood by one of ordinary skill in the art, in some embodiments, activity is decreased and some downstream read-outs will decrease but others can increase.

Conversely, activity is “increased” if a read-out of activity and/or effect is increased by a significant amount, for example by 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%, at least about 95%, at least about 97%, at least about 98%, or more, up to and including at least about 100% or more, at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 6-fold, at least about 7-fold, at least about 8-fold, at least about 9-fold, at least about 10-fold, at least about 50-fold, at least about 100-fold, in the presence of an agent or stimulus, relative to the absence of such agent or stimulus.

As referred to herein, all compositional percentages are by weight of the total composition, unless otherwise specified. As used herein, the word “include,” and its variants, is intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that may also be useful in the compositions and methods of this technology. Similarly, the terms “can” and “may” and their variants are intended to be non-limiting, such that recitation that an embodiment can or may comprise certain elements or features does not exclude other embodiments of the present technology that do not contain those elements or features.

Although the open-ended term “comprising,” as a synonym of terms such as including, containing, or having, is used herein to describe and claim the invention, the present invention, or embodiments thereof, may alternatively be described using alternative terms such as “consisting of” or “consisting essentially of.”

As used herein, the words "preferred" and "preferably" refer to embodiments of the technology that afford certain benefits, under certain circumstances. However, other embodiments may also be preferred, under the same or other circumstances. Furthermore, the recitation of one or more preferred embodiments does not imply that other embodiments are not useful, and is not intended to exclude other embodiments from the scope of the technology.

The amount of compositions described herein needed for achieving a therapeutic effect may be determined empirically in accordance with conventional procedures for the particular purpose. Generally, for administering therapeutic agents for therapeutic purposes, the therapeutic agents are given at a pharmacologically effective dose. A "pharmacologically effective amount," "pharmacologically effective dose," "therapeutically effective amount," or "effective amount" refers to an amount sufficient to produce the desired physiological effect or amount capable of achieving the desired result, particularly for treating the disorder or disease. An effective amount as used herein would include an amount sufficient to, for example, delay the development of a symptom of the disorder or disease, alter the course of a symptom of the disorder or disease (*e.g.*, slow the progression of a symptom of the disease), reduce or eliminate one or more symptoms or manifestations of the disorder or disease, and reverse a symptom of a disorder or disease. Therapeutic benefit also includes halting or slowing the progression of the underlying disease or disorder, regardless of whether improvement is realized.

Effective amounts, toxicity, and therapeutic efficacy can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to about 50% of the population) and the ED50 (the dose therapeutically effective in about 50% of the population). The dosage can vary depending upon the dosage form employed and the route of administration utilized. The dose ratio between toxic and therapeutic effects is the therapeutic index and can be expressed as the ratio LD50/ED50. In some embodiments, compositions and methods that exhibit large therapeutic indices are preferred. A therapeutically effective dose can be estimated initially from in vitro assays, including, for example, cell culture assays. Also, a dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 as determined in cell culture, or in an appropriate animal model. Levels of the described compositions in plasma can be measured, for example, by high performance liquid chromatography. The effects of any particular dosage can be monitored by a suitable bioassay. The dosage can be determined by a physician and adjusted, as necessary, to suit observed effects of the treatment.

In certain embodiments, the effect will result in a quantifiable change of at least about 10%, at least about 20%, at least about 30%, at least about 50%, at least about 70%, or at least about 90%. In some embodiments, the effect will result in a quantifiable change of about 10%, about 20%, about 30%, about 50%, about 70%, or even about 90% or more. Therapeutic benefit also includes halting or slowing the progression of the underlying disease or disorder, regardless of whether improvement is realized.

As used herein, "methods of treatment" are equally applicable to use of a composition for treating the diseases or disorders described herein and/or compositions for use and/or uses in the manufacture of a medicaments for treating the diseases or disorders described herein.

EXAMPLES

In some Examples, two variants of the knob-in-hole technology are used: Ridgway (derived from Ridgway et al., Protein Engineering 1996;9:617-621 and used *e.g.* in Examples 1-6) and Merchant (derived from Merchant et al., Nature Biotechnology 1998;16:677-681 and used in most examples as of Example 7). Sequences are referred to as Fc1 and Fc2 (Ridgway hole and knob, respectively) and Fc3 and Fc4 (Merchant hole and knob, respectively). The 'standard' effector-mutation in the Ridgway constructs is LALA-PG (P329G), unless stated otherwise (see Example 4). For the Merchant constructs the LALA-KQ (K322Q) mutation is used (based on the data of Example 4) to this end.

Fc1: **Ridgway hole**: hIgG1 Fc_L234A_L235A_P329G_Y407T having the following amino acid sequence:

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1565)

Fc2: Ridgway knob: hIgG1 Fc_L234A_L235A_P329G_T366Y having the following amino acid sequence:

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1566)

Fc3: **Merchant hole**: hIgG1 Fc_L234A_L235A_K322Q_Y349C_T366S_L368A_Y407V having the following amino acid sequence:

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDE LTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1567)

Fc4: **Merchant knob**: hIgG1 Fc_L234A_L235A_K322Q_S354C_T366W having the following amino acid sequence:

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDE LTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1568)

Throughout the Examples, two Clec9A VHHs are used: R1CHCL50 (SEQ ID NO: 289) and 3LEC89 (SEQ ID NO: 391). Both are used in the original sequence or in a mutated form as follows:

- R1CHCL50_opt4: R1CHCL50_E1D-A74S-K83R-Q108L-H13Q-T64K (where E1D, A74S, K83R, Q108L, H13Q, and T64K refer to mutations in R1CHCL50 VHH having the amino acid sequence of SEQ ID NO: 289). R1CHCL50_opt4 has the following amino acid sequence:

DVQLVESGGGLVQPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRF TISRDNSKNTVYLQMNSLRPEDTAVYYCYLVALKAEYWGQGTLVTVSS (SEQ ID NO: 1569)

- 3LEC89_opt4: 3LEC89_E1D-Q5V-A74S-Q108L-G75K (where E1D, Q5V, A74S, Q108L, and G75K refer to mutations in 3LEC89 VHH having the amino acid sequence of SEQ ID NO: 391).
- 3LEC89_opt4 has the following amino acid sequence:

DVQLVESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRF TISRDNSKNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTLVTVSS (SEQ ID NO: 1570)

Example 1: Fc-based Chimeric Protein Complex Construction

Chimeric proteins with a targeting moiety and signaling agent were cloned into a human IgG1 Fc-fusion format mutated for reduced FcγR and C1q binding (LALA-PG mutations). A total of 5 combinations (see **FIGs. 20A-E**): two homodimeric and three heterodimeric (based on the knob-in-hole mutations; see Ridgway *et al.*, Protein Engineering, Design and Selection, Volume 9, Issue 7, 1 July 1996, Pages 617–621,) were constructed. In these fusion proteins the anti-human Clec9A VHH 3LEC89 was the targeting moiety and human IFNa2 with a R149A mutation was the signaling agent; these reagents were used for illustration of the general concept.

The relevant sequences (see **FIGs. 20A-E** for the identifiers) were:

P-956: pcDNA3.4-mouse light chain kappa-**hIgG1-LALA-PG**-*20*GGS*-3LEC89-*20*GGS+G*-IFNa2_R149A

MKLPVRLLVLMFWIPASSS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK***GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGS*QVQLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITN QGAPTYADSVKGRFTISRDNAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSS*GGSGGSGGSG GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG*CDLPQTHSLGSRRTLMLL AQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLN DLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1435)

P-957: pcDNA3.4-mouse Ig heavy chain-3LEC89-*20*GGS*-**hIgG1-LALA-PG**-*20*GGS+G*-IFNa2_R149A

MGWSCIIFFLVATATGVHS*QVQLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQ GAPTYADSVKGRFTISRDNAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSS**GGSGGSGGSGG SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS*DKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*GGSGGSGGS*

*GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG*CDLPQTHSLGSRRTLML LAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLN DLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1436)

P-958: pcDNA3.4-mouse Ig heavy chain-3LEC89-*20*GGS*-**hIgG1-LALA-PG-YT (hole)**

MGWSCIIFFLVATATGVHSQVQLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQ GAPTYADSVKGRFTISRDNAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSS*GGSGGSGGSGG SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS***DKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK** (SEQ ID NO: 1437)

P-959: pcDNA3.4-mouse light chain kappa-**hIgG1-LALA-PG-TY (knob)**-*20*GGS+G*-IFNa2_R149A

MKLPVRLLVLMFWIPASSS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK***GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGSG*CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIP VLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLK EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1438)

P-960: pcDNA3.4-mouse light chain kappa-**hIgG1-LALA-PG-YT (hole)**-*20*GGS*-3LEC89-20*GGS+G-IFNa2_R149A

MKLPVRLLVLMFWIPASSS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK***GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGS*QVQLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITN QGAPTYADSVKGRFTISRDNAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSS*GGSGGSGGSG GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG*CDLPQTHSLGSRRTLMLL AQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLN DLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1439)

P-961: pcDNA3.4-mouse Ig heavy chain-3LEC89-*20*GGS*-**hIgG1-LALA-PG-YT (hole)**-*20*GGS+G*-IFNa2_R149A

MGWSCIIFFLVATATGVHSQVQLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQ GAPTYADSVKGRFTISRDNAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSS*GGSGGSGGSGG SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS***DKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*GGSGGSGGS GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG*CDLPQTHSLGSRRTLML LAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLN DLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1440)

P-962: pcDNA3.4-mouse light chain kappa-**hIgG1-LALA-PG-TY** (knob)

MKLPVRLLVLMFWIPASSS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK** (SEQ ID NO: 1441)

Different constructs were made by GeneArt (Thermo Fisher) and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. Ten days after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the medium using the rProtein A Sepharose Fast Flow resin (GE Healthcare) according to the manufacturer's guidelines. Average yields ranged from 70 to 200 mg per liter (see table below). SDS-PAGE under reducing (with added β-mercaptoethanol (β-mEtOH)) and non-reducing conditions (without β-mEtOH) (see **FIG. 21**, protein loaded in lanes A-E of the gels are described in table below) clearly showed that proteins are expressed as disulfide-linked complexes. Aberrant clustering (combination of two knob or two hole chains; extra bands on the gel, as shown by *, **, or *** in lanes D and E of gels without β-mEtOH) is observed in the heterodimeric Fc-based chimeric protein complexes D and E. Under reducing conditions, the two parts of the heterodimeric Fc-based chimeric protein complexes are nicely separated.

Heterodimeric Fc-based chimeric protein complexes appeared more soluble than the homodimeric proteins. In the latter case, even at concentrations below 1 mg/ml proteins tended to aggregate and precipitate. Protein melting analysis using SYPRO Orange (Sigma-Aldrich) on a LightCycler 480 System (Roche) illustrated that the melting temperatures of the different proteins were very comparable and ranged from 66 to 70°C.

				Yield (mg) per liter

Homodimeric	A	P-956	Fc-3LEC89-IFNa2_R149A	73,2
	B	P-957	3LEC89-Fc-IFNa2_R149A	176,8
Heterodimeric	C	P-958 + P-959	3LEC89-Fc + Fc-IFNa2_R149A	199,2
	D	P-960 + P-962	Fc-3LEC89-IFNa2_R149A + Fc	174,8
	E	P-961 + P-962	3LEC89-Fc-IFNa2_R149A + Fc	156

To further estimate the stability of the proteins, the heterodimeric Fc-based chimeric protein complexes "C," "D," and "E" (see **FIGS. 20A-E**) were subjected to five cycles of freezing and thawing. Protein aggregates were removed by centrifugation just after thawing and protein concentrations were measured and plotted (see **FIG. 22**). Proteins C and D seemed more resistant to freezing-thawing than protein E.

Example 2: Fc-based Chimeric Protein Complex Characterization

Affinity of the heterodimeric Fc-based chimeric protein complexes for human Clec9A was determined using the bio-layer interferometry (BLI) technology on an Octet instrument (ForteBio). Recombinant Clec9A was biotinylated and trapped on Streptavidin sensors. Loaded tips were incubated with a serial dilution Fc-fusion. Shifts in the interference pattern were used to quantify the association and dissociation rates and thus the affinity. Data in the table below illustrates that the affinity is comparable in proteins C and E, while that in protein D was 10-fold lower.

Sample ID	KD (M)	kon(1/Ms)	kdis(1/s)
958 + 959 (C)	2.61E-09	1.29E+05	3.37E-04
960 + 962 (D)	3.16E-08	3.12E+04	9.88E-04
961 + 962 (E)	3.88E-09	1.07E+05	4.16E-04

To study biological activity of the heterodimeric Fc-based chimeric protein complexes, 6-16 reporter activity was measured in parental and HL116-hClec9A cell-lines. The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells were transfected with an expression vector encoding the human Clec9A sequence. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hClec9A cells were seeded overnight at 20,000 cells per 96-well, before stimulation with a serial dilution of IFNa2 as a positive control and Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in **FIG. 23** illustrate that homodimeric Fc-based chimeric protein complexes are slightly more active than the heterodimeric Fc-based chimeric protein complexes. In all cases activity on targeted cells vs activity on parental cells was observed at over a 10,000-fold difference.

Example 3: Pharmacokinetic Study in Mouse

To evaluate the pharmacokinetic behavior of the Fc-based Actaferons (Fc-AFNs), the molecules P957 and P958/P959 (Example 1) were dosed intravenously at 1.5 mg/kg in 12 mice for each construct. K-EDTA blood was taken from a first group of 3 mice at 5 minutes, 8 hours and 2 days, from a second group of 3 mice at 15 minutes,

1 day and 4 days, from a third group of 3 mice at 1, 7 and 14 days and from a fourth group of 3 mice at 3 hours, 21 and 28 days. The concentration of intact Fc-AFN was measured by ELISA. In brief the MAXISORP Nunc Immune plates (Thermo Scientific) were coated overnight with anti-human interferon alpha mAb (clone MMHA-13; PBL Assay Science) at 0,5 µg/ml in PBS. After washing the plates four times with PBS + 0,05% Tween-20, they were blocked with 0.1% Casein in PBS for at least 1 hour at room temperature. Subsequently, diluted samples and standards were incubated in 0.1% Casein in PBS for 2 hours at room temperature. After another wash cycle a custom made rabbit-anti-VHH (diluted 1/20000 in 0.1% Casein in PBS) was incubated for 2 hours at room temperature followed by an additional wash cycle and incubation with HRP-conjugated goat anti-rabbit (Jackson – 111-035-144; 1:5000 in 0.1% Casein) for 1 hour at room temperature. After a final washing cycle, peroxidase activity was measured using KPL substrate (5120-0047; SeraCare) according to the manufacturer's instructions. Concentrations from samples were calculated using GraphPad Prism. Measured concentrations are plotted **in FIG. 24**. Terminal half-life was estimated on average at about 4.5 days P958/P959 and at about 3.25 days for P957.

Example 4: Efficacy Study in Humanized Mouse

To evaluate the in vivo efficacy of Fc-based AFNs the molecules P957 and P958/P959 (Example 1; targeted to human CLEC9A, a highly specific conventional dendritic cell 1 (cDC1) marker) were tested in a tumor model in a humanized mouse. In brief, newborn NSG mice (1-2 days of age) were sublethal irradiated with 100 cGy prior to intrahepatic delivery of $1x10^5$ CD34+ human stem cells (from HLA-A2 positive cord bloods). At week 13 after stem cell transfer mice were subcutaneously inoculated with $25x10^5$ human RL follicular lymphoma cells (ATCC CRL-2261; not sensitive to the direct anti-proliferative effect of interferons (IFN)). Mice were treated daily intraperitoneally with 30 µg of human FMS-like tyrosine kinase 3 ligand (Flt3L) protein, from day 6 to day 17 after tumor inoculation. Weekly intravenous injection with buffer or Fc-AFN (25 µg) was initiated at day 10 after tumor inoculation, when a palpable tumor was visible (n=6 mice per group). Tumor size (caliper measurements), body weight and temperature were assessed daily. **FIG. 25** shows the tumor growth until 7 days after the second treatment (mice received weekly injections with either PBS or AFN, the data show tumor growth up to 7 days after the second weekly treatment) and demonstrates that all constructs induced a similar level of tumor growth inhibition. Data on body weight and temperature did not show any major difference between buffer treatment and AFN treatment supporting that the AFN treatment was well tolerated.

Example 5: Linker Lengths Heterodimeric Constructs

In the heterodimeric Fc AFN configuration of Examples 1 and 2, 20*GGS linkers between VHH and Fc as well as between Fc and IFN were used. The effect on different lengths of these linkers on biological activity (HL116-hClec9A reporter) or affinity for Clec9A in bio-layer interferometry (BLI) was evaluated.

In this and following Examples, various Fc variants are as follows (amino acids numbers refer to EU convention (PNAS, Edelman et al., 1969; 63 (1) 78-85)):

- Fc: hIgG1 Fc_L234A_L235A_P329G (where L234A, L235A, and P329G are mutations in the hIgG1 Fc sequence)

- Fc1: Ridgway hole: hIgG1 Fc_L234A_L235A_P329G_Y407T (where L234A, L235A, P329G, and Y407T are mutations in the hIgG1 Fc1 sequence)
- Fc2: Ridgway knob: hIgG1 Fc_L234A_L235A_P329G_T366Y (where L234A, L235A, P329G and T366Y are mutations in the hIgG1 Fc sequence)

The leader sequences used for expression are identical as those in Example 1 and not further detailed in any of the constructs as of this Example.

The linkers used consist of a number of GGS repeats optionally followed by an additional single glycine residue. They are referred to a nGGS where n represents the number of GGS repeats, the optional additional G is not separately indicated in the construct name.

Constructs:

- R1CHCL50_opt4-**5*GGS**-Fc1 (**P-1105**)

DVQLVESGGGLVQPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTIS RDNSKNTVYLQMNSLRPEDTAVYYCYLVALKAEYWGQGTLVTVSS**GGSGGSGGSGGSGGS**DKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK (SEQ ID NO: 1442)

- R1CHCL50_opt4-**3*GGS**-Fc1 (**P-1106**)

DVQLVESGGGLVQPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTIS RDNSKNTVYLQMNSLRPEDTAVYYCYLVALKAEYWGQGTLVTVSS**GGSGGSGGS**DKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K (SEQ ID NO: 1443)

- 3LEC89_opt4-**5*GGS**-Fc1 (**P-1107**)

DVQLVESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS RDNSKNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTLVTVSS**GGSGGSGGSGGSGGS**DKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK (SEQ ID NO: 1444)

- 3LEC89_opt4-**3*GGS**-Fc1 (**P-1108**)

DVQLVESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS RDNSKNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTLVTVSS**GGSGGSGGS**DKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS

VLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
GK (SEQ ID NO: 1445)

- Fc2-**10*GGS**-IFNa2_R149A (**P-1109**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQ
MRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQL
NDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE
(SEQ ID NO: 1446)

- Fc2-**5*GGS**-IFNa2_R149A (**P-1110**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGKG**GSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFG
FPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETP
LMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1447)

- Fc2-**3*GGS**-IFNa2_R149A (**P-1111**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFG
NQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSIL
AVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1448)

Production and purification of linker-length variants

Different constructs were made by GeneArt (Thermo Fisher) and combinations of hole (Fc1-based) and knob (Fc2-based) were combined to a heterodimeric configuration similar to the construct P958/959 of Example 1 as outlined in **FIG. 7B**, and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher). Variations in linker-lengths appeared not to affect the production (yields ranging from 100 to 300 mg per liter) and stability of the resulting proteins.

Biological activity on HL116 reporter cell lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells were transfected with an expression vector encoding the human Clec9A sequence. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hClec9A cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in the **FIG. 26** and Table 6 illustrate that variations in linker-length had no major effects on biological activity in targeted cells (HL116-hClec9A cells). Of note the biological activity measured for any of the 3LEC89-5*GGS-Fc1 based constructs is also comparable to the biological activity measured for 3LEC89-20*GGS-Fc1/Fc2-20*GGS-IFNa2_R149A as measured in Example 2.

Table 6: Biological activity of linker-length variants on HL116 cells. Summary of EC_{50} (ng/ml) values of the biological activity measured in **FIG. 26**.

	EC_{50} (ng/ml)			
	R1CHCL50-5*GGS-Fc1	R1CHCL50-3*GGS-Fc1	3LEC89-5*GGS-Fc1	3LEC89-3*GGS-Fc1
Fc2-10*GGS-IFNa2_R149A	2.04	3.37	1.52	3.11
Fc2-5*GGS-IFNa2_R149A	1.89	4.33	1.14	3.22
Fc2-3*GGS-IFNa2_R149A	2.42	3.63	1.15	2.35

Affinity for hClec9A

Affinity of the linker-length variants for human Clec9A was determined using the bio-layer interferometry (BLI) technology on an Octet instrument (ForteBio). Recombinant Clec9A was therefore biotinylated and trapped on a Streptavidin sensors (ForteBio). Loaded tips were incubated with a serial dilution Fc-fusions. In this experiment, 3LEC89 and R1CHCL50 hole constructs were combined with 5*GGS or 3*GGS linkers with the 10*GGS knob construct and compared with the original 3LEC89 configuration with two 20*GGS linkers. Shifts in the interference pattern were used to quantify the association and dissociation rates (and thus the affinity). Data, summarized in Table 7, show that shortening of the linkers does not have a negative impact on the affinity for hClec9A.

Table 7: Affinity of linker-length variants for hClec9A

	KD (M)	KD Error	ka (1/Ms)	ka Error	kdis (1/s)	kdis Error
3LEC89-20*GGS-Fc1 + Fc2-20*GGS-IFNa2_R149A	7.50E-09	3.72E-11	1.07E+05	3.26E+02	8.00E-04	3.15E-06
3LEC89-5*GGS-Fc1 + Fc2-10*GGS-IFNa2_R149A	8.42E-09	5.76E-11	1.23E+05	5.82E+02	1.00E-03	5.10E-06
3LEC89-3*GGS-Fc1 + Fc2-10*GGS-IFNa2_R149A	3.12E-09	2.20E-11	1.67E+05	4.86E+02	5.00E-04	3.35E-06
R1CHCL50-5*GGS-Fc1 + Fc2-10*GGS-IFNa2_R149A	7.46E-09	3.76E-11	1.60E+05	5.76E+02	1.20E-03	4.20E-06
R1CHCL50-3*GGS-Fc1 + Fc2-10*GGS-IFNa2_R149A	1.20E-08	9.07E-11	1.39E+05	8.59E+02	1.70E-03	7.26E-06

Example 6: Linker Lengths Homodimeric Constructs

In the homodimeric Fc AFN configuration of Examples 1 and 2, 20*GGS linkers between VHH and Fc as well as between Fc and IFN were used. The effect on different lengths of these linkers on biological activity (HL116-hClec9A reporter) was evaluated.

Constructs:

- 3LEC89_opt4-**10*GGS**-Fc-**10*GGS-**IFNa2_R149A (**P-1144**)

DVQLVESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS RDNSKNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTLVTVSS**GGSGGSGGSGGSGGSGGSGGSG GSGGSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPP SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**CDLPQTHSLGSR RTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKF YTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNL QESLRSKE (SEQ ID NO: 1449)

- 3LEC89_opt4-**5*GGS**-Fc-**5*GGS-**IFNa2_R149A (**P-1145**)

DVQLVESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS RDNSKNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTLVTVSS**GGSGGSGGSGGSGGS**DKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK**GGSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFG NQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSIL AVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1450)

- 3LEC89_opt4-**3*GGS**-Fc-**3*GGS-**IFNa2_R149A (**P-1146**)

DVQLVESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS RDNSKNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTLVTVSS**GGSGGSGGS**DKTHTCPPCPAPEA

AGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
GK**GGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE
MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLK
EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1451)

- 3LEC89_opt4-**AAA**-Fc-**AAA+G**-IFNa2_R149A (**P-1147**)

DVQLVESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS
RDNSKNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTLVTVSS**AAA**DKTHTCPPCPAPEAAGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES
NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**AAAG**C
DLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSS
AAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRA
EIMASFSLSTNLQESLRSKE (SEQ ID NO: 1452)

Production and purification of linker-length variants

The different constructs were made by GeneArt (Thermo Fisher) similar to the construct P957 of Example 1 as outlined in **FIG. 1A**, and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells were transfected with an expression vector encoding the human Clec9A sequence. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hClec9A cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in Table 8 illustrate that variations in linker-length had no major effects on biological activity in targeted cells (HL116-hClec9A cells).

Table 8: Biological activity of linker-length homodimeric variants on HL116 cells

	EC_{50} (ng/ml)
3LEC89(opt4)-10*GGS-Fc-10*GGS-IFNa2_R149A	1.77
3LEC89(opt4)-5*GGS-Fc-5*GGS-IFNa2_R149A	2.80
3LEC89(opt4)-3*GGS-Fc-3*GGS-IFNa2_R149A	2.33
3LEC89(opt4)-AAA-Fc-AAA-IFNa2_R149A	2.79

Example 7: Alternative Effector Mutations

To diminish the effector functions, *i.e.* complement dependent cytotoxicity (CDC) or antibody dependent cellular cytotoxicity (ADCC), of the Fc domain, the L234A_L235A mutations which mainly affect Fc-gamma receptor binding were combined with four extra Fc effector-mutations (P329G, K322Q, K322A or P331S) to further reduce complement binding. These mutations were applied to the 3LEC89-based heterodimeric Fc format with 20*GGS linkers. Resulting proteins were tested for biological activity (HL116-hClec9A reporter) and complement binding (BLI; Octet).

Constructs:

- 3LEC89-**20*GGS**-Fc1_*P329G* (**P-958**)

QVQLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS
RDNAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1453)

- Fc2_*P329G*-**20*GGS**-IFNa2_R149A (**P-959**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE
MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLK
EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1454)

- 3LEC89-20*GGS-Fc1_*K322Q* (**P-1074**)

QVQLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS
RDNAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY

KCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1455)

- Fc2_*K322Q*-20*GGS-IFNa2_R149A (**P-1077**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYQCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE
MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLK
EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1456)

- 3LEC89-**20*GGS**-Fc1_*K322A* (**P-1073**)

QVQLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS
RDNAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KC*A*VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1457)

- Fc2_*K322A*-**20*GGS**-IFNa2_R149A (**P-1076**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKC*A*VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE
MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLK
EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1458)

- 3LEC89-**20*GGS**-Fc1_*P331S* (**P-1075**)

QVQLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS
RDNAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPA*S*IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1459)

- Fc2_*P331S*-**20*GGS**-IFNa2_R149A (**P-1078**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA*S*IEKTISKAKGQPREPQVYTLPPSRDELTKN

QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE
MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLK
EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1460)

Production and purification of effector mutations variants

3LEC89-based Fc AFNs with different effector-mutations were produced in ExpiCHO cells as heterodimeric AFNs outlined in **FIG. 7B**, and as described in previous Examples. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher) according to the manufacturer's guidelines. No major difference in production yields (between 50 and 150 µg/ml) and stability were observed among the different mutants.

Biological activity on HL116 reporter cell lines

Biological activities of the alternative effector-mutants were measured as described in previous Examples. In brief, parental HL116 and the derived HL116-hClec9A were stimulated for 6 hours with a serial dilution of Fc-AFNs. Luciferase activity was measured and plotted in **FIG. 27**. Data clearly illustrate that resulting mutants show a very comparable biological activation profile on targeted (HL116-hClec9A) and untargeted (parental HL116) cells with EC_{50} values varying from 0.3 to 0.65 ng/ml.

Affinity for complement (C1q)

The effect of the different effector-mutations on the affinity for Complement Component C1q (C1q) was determined using the bio-layer interferometry (BLI) technology on an Octet instrument (ForteBio). Fc AFNs with the different mutations or a hIgG1 as a positive control were loaded onto a Protein A bio-sensor (ForteBio) and subsequently incubated with recombinant C1q (100 nM; ProSpec). Data in **FIG. 28** clearly illustrate that all effector-variants greatly lost their ability to bind to C1q, and that no significant differences between mutants could be observed.

Example 8: IFNa2 Variants

Here, we evaluate the effect of mutation of the hIFNa2 O-glycosylation site on position 106 (T106) and compare biological activity of two natural IFNa2 variants: IFNa2A and IFNa2B.

Constructs:

- R1CHCL50_opt4-**5*GGS**-Fc1 (**P-1105**)

DVQLVESGGGLVQPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTIS
RDNSKNTVYLQMNSLRPEDTAVYYCYLVALKAEYWGQGTLVTVSS**GGSGGSGGSGGSGGS**DKTHTCPP
CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 1461)

- 3LEC89_opt4-**5*GGS**-Fc1 (**P-1077**)

DVQLVESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS
RDNSKNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTLVTVSS**GGSGGSGGSGGSGGS**DKTHTCPP
CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 1462)

- Fc2-**10*GGS**-IFNa2A_R149A (**P-1109**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQ
MRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQL
NDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE
(SEQ ID NO: 1463)

- Fc2-**10*GGS**-IFNa2A_*T106A*-R149A (**P-1302**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQ
MRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQL
NDLEACVIQGVGV*A*ETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSK
E (SEQ ID NO: 1464)

- Fc2-**10*GGS**-IFNa2A_*T106E*-R149A (**P-1303**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQ
MRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQL
NDLEACVIQGVGV*E*ETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSK
E (SEQ ID NO: 1465)

- Fc2-**10*GGS**-IFNa2B_R149A (**P-1304**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQ

MRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQL
NDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE
(SEQ ID NO: 1466)

- Fc2-**10*GGS**-IFNa2B_*T106A*-R149A (**P-1305**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQ
MRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQL
NDLEACVIQGVGV*A*ETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSK
E (SEQ ID NO: 1467)

- Fc2-**10*GGS**-IFNa2B_*T106E*-R149A (**P-1306**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQ
MRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQL
NDLEACVIQGVGV*E*ETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSK
E (SEQ ID NO: 1468)

Production and purification of IFNα2 variants

R1CHCL50-5*GGS-Fc1 or 3LEC89-5*GGS-Fc1 were combined with the R149A mutant of IFNa2A or IFNa2B with or without mutated O-glycosylation site (T106, T106A or T106E) fused to Fc2 via a 10*GGS linker resulting in heterodimeric ActaFerons (AFNs) with a configuration outlined in **FIG. 7B.** Combinations were transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher) according to the manufacturer's guidelines. Production-levels of different combinations were comparable and varied between 170 and 420 µg/ml. The loss of O-glycosylation was confirmed using SDS-PAGE.

Biological activity on HL116 reporter cell-lines

Biological activities of the alternative IFNa2 mutants were measured as described in previous Examples. In brief, parental HL116 and the derived HL116-hClec9A were stimulated for six hours with a serial dilution of Fc-AFNs. Luciferase activity was measured and plotted in **FIG. 29** and summarized in Table 9. Data suggest that AFNs based on IFNa2B are only slightly more potent than those with IFNa2A, while mutation of the IFNa2 O-glycosylation site T106 (to A or E) does not affect signaling.

Table 9: Effect of IFNa2 mutations on biological activity. Summary of EC50 (ng/ml) values of the biological activity measured in **FIG. 29**

	EC_{50} (ng/ml)			
	3LEC89		R1CHCL50	
	IFNa2A	IFNa2B	IFNa2A	IFNa2B
wild type	0.98	0.58	1.68	1.07
T106A	0.58	0.37	1.49	0.61
T106E	1.04	0.38	1.58	1.18

Affinity for IFNAR2

Here the effect of the IFNa2 mutations on affinity for its receptor IFNAR2 in BLI was evaluated on an Octet instrument. R1CHCL50-based Fc variants with sequence variations in IFNa2 were loaded onto Protein A bio-sensors (Pall) and subsequently incubated with a serial dilution recombinant IFNAR2 (SinoBiological). Shifts in the interference pattern were used to quantify the association and dissociation rates and thus the affinity. These experiments showed that the mutations don't have a major impact on the affinity for IFNAR2 (data not shown).

Example 9: Additional Fc Formats

In previous Examples, a heteromeric Fc format was used in which the VHH (R1CHCL50 or 3LEC89) is cloned N- and the IFNa2 mutant C-terminally of the Fc portion. In this Example, formats with VHH and IFNa2 mutant on the same side (N- or C-terminally) of the molecule were generated. Resulting AFNs were tested for biological activity (HL116-hClec9A reporter) and hClec9A affinity (bio-layer interferometry (BLI) technology on an Octet instrument).

Constructs:

- 3LEC89-**20*GGS**-Fc1 (**P-958**)

QVQLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS
RDNAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1469)

- Fc2-**20*GGS**-IFNa2_R149A (**P-959**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE

MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLK EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1470)

- R1CHCL50_opt4-**20*GGS**-Fc1 (**P-1213**)

DVQLVESGGGLVQPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTIS RDNSKNTVYLQMNSLRPEDTAVYYCYLVALKAEYWGQGTLVTVSS**GGSGGSGGSGGSGGSGGSGGSG GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1471)

- IFNa2_R149A-**20*GGS**-Fc2 (**P-1214**)

CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDS SAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVR AEIMASFSLSTNLQESLRSKE**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1472)

- Fc1-**20*GGS**-R1CHCL50_opt4 (**P-1215**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG GSGGSGGSGGS**DVQLVESGGGLVQPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPN YADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCYLVALKAEYWGQGTLVTVSS (SEQ ID NO: 1473)

- Fc1-**20*GGS**-3LEC89_opt4 (**P-1216**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG GSGGSGGSGGS**DVQLVESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAP TYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTLVTVSS (SEQ ID NO: 1474)

Production and purification of different Fc formats

Hole (with the VHH C- or N-terminal) and knob (with the mutant IFNa2 C- or N-terminal) sequence were combined as follows:

- 3LEC89-20*GGS-Fc1 + Fc2-20*GGS-IFNa2_R149A (configuration: **FIG. 7B**);
- R1CHCL50-20*GGS-Fc1 + Fc2-20*GGS-IFNa2_R149A (configuration: **FIG. 7B**);
- 3LEC89-20*GGS-Fc1 + IFNa2_R149A-20*GGS-Fc2 (configuration: **FIG. 7C**);
- R1CHCL50-20*GGS-Fc1 + IFNa2_R149A-20*GGS-Fc2 (configuration: **FIG. 7C**);
- Fc1-20*GGS -3LEC89 + Fc2-20*GGS-IFNa2_R149A (configuration: **FIG. 7D**);
- Fc1-20*GGS -R1CHCL50 + Fc2-20*GGS-IFNa2_R149A (configuration: **FIG. 7D**);

These sequences were produced in ExpiCHO cells. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher) according to the manufacturer's guidelines. Yields of different Fc formats were comparable and ranged from 100 to 250 µg/ml.

Biological activity on HL116 reporter cell-lines

Biological activities of the different Fc-formats were measured as described in previous Examples. In brief, parental HL116 and the derived HL116-hClec9A were stimulated for 6 hours with a serial dilution of Fc-AFNs. Luciferase activity was measured and plotted in **FIG. 30** and summarized in Table 10. Data suggest that Fc formats with both VHH and IFNa2_R149A cloned C-terminally are somewhat less active on targeted cells compared to the other two formats. Of note, no signaling was observed in the untargeted cells (parental HL116) for any of the constructs and hence all constructs retain a very high targeting index.

Table 10: Biological activity of different Fc formats. Summary of EC50 (ng/ml) values of the biological activity measured in **FIG. 30.**

	EC50 (ng/ml)	
	R1CHCL50	3LEC89
VHH-20*GGS-Fc1 + Fc2-20*GGS-IFNa2_R149A	0.63	0.79
VHH-20*GGS-Fc1 + IFNa2_R149A-20*GGS-Fc2	0.66	0.53
Fc1-20*GGS-VHH + Fc2-20*GGS-IFNa2_R149A	1.28	1.47

Affinity for hClec9A

Affinity of different Fc formats for human Clec9A was determined as described in Example 1. Data, summarized in Table 11, illustrate that differences in association and dissociation (and thus KD) between the different formats are only marginal.

Table 11: Affinity of different Fc formats for Clec9A

	KD (M)	KD Error	kon (1/Ms)	kon Error	koff (1/s)	koff Error
3LEC89-Fc + Fc-IFN	1,56E-09	*1,17E-11*	3,75E+05	*1,22E+03*	5,85E-04	*3,92E-06*
R1CHCL50-Fc + Fc-IFN	2,55E-09	*2,41E-11*	3,12E+05	*1,70E+03*	7,96E-04	*6,13E-06*
3LEC89-Fc + IFN-Fc	1,61E-09	*1,72E-11*	2,85E+05	*1,13E+03*	4,61E-04	*4,55E-06*
R1CHCL50-Fc + IFN-Fc	2,15E-09	*2,39E-11*	2,84E+05	*1,54E+03*	6,09E-04	*5,92E-06*
Fc-3LEC89 + Fc-IFN	3,23E-09	*2,77E-11*	2,85E+05	*1,55E+03*	9,19E-04	*6,13E-06*
Fc-R1CHCL50 + Fc-IFN	1,83E-09	*1,48E-11*	2,96E+05	*1,02E+03*	5,42E-04	*3,95E-06*

Example 10: Comparison of Two Different Knob-In-Hole (KiH) Mutations

Here, two variants of the knob-in-hole technology: Ridgway (as used in previous Examples) and Merchant were compared. Sequences are referred to as Fc1 and Fc2 (Ridgway hole and knob, respectively) and Fc3 and Fc4 (Merchant hole and knob, respectively). Fc constructs, with a configuration outlined in **FIG. 7B**, with both KiHs were made based on VHHs R1CHCL50 and 3LEC89.

- **Fc1**: **Ridgway hole**: hIgG1 Fc_L234A_L235A_P329G_Y407T
- **Fc2**: **Ridgway knob**: hIgG1 Fc_L234A_L235A_P329G_T366Y
- **Fc3**: **Merchant hole**: hIgG1 Fc_L234A_L235A_K322Q_Y349C_T366S_L368A_Y407V
- **Fc4**: **Merchant knob**: hIgG1 Fc_L234A_L235A_K322Q_S354C_T366W

Constructs:

- 3LEC89-**20*GGS**-Fc1 (**P-958**)

QVQLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS RDNAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSG GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1475)

- Fc2-**20*GGS**-IFNa2_R149A (**P-959**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG GSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLK EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1476)

- R1CHCL50_opt4-**5*GGS**-Fc1 (**P-1105**)

DVQLVESGGGLVQPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTIS
RDNSKNTVYLQMNSLRPEDTAVYYCYLVALKAEYWGQGTLVTVSS**GGSGGSGGSGGSGGS**DKTHTCPP
CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 1477)

- 3LEC89-**20*GGS-Fc3** (**P-1411**)

QLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTISRD
NAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
QVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1478)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKN
QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE
MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLK
EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1479)

- R1CHCL50-Fc3-20*GGS-IFNa2_R149A (**P-1451**)

QVQLVESGGGLVHPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGRFTIS
RDNAKNTVYLQMNSLKPEDTAVYYCYLVALKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1480)

Production and purification of different Fc formats

Combinations of knob and hole constructs were produced in ExpiCHO cells as described above. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher) according to

the manufacturer's guidelines. Use of different knob in holes (KiH's) did not have a major influence on production levels, which varied from 250 to 400 µg/ml.

Biological activity on HL116 reporter cell-lines

Biological activities of the different KiH Fc AFNs were measured as described in previous Examples. In brief, parental HL116 and the derived HL116-hClec9A were stimulated for six hours with a serial dilution of Fc-AFNs. Luciferase activity was measured and plotted in **FIG. 31.** Data suggest that the different KiH variations do not affect biological activity in targeted cells (*i.e.* Clec9A expressing) significantly.

Example 11: Mono- vs. Bi-valent Targeted Fc Formats

In this Example, the biological activity and relative binding of a mono- and bivalent targeted (*i.e.* molecules with one or two VHHs, respectively) format of R1CHCL50 Fc AFN was compared.

Constructs:

- R1CHCL50- **20*GGS**-Fc3 (**P-1451**)

QVQLVESGGGLVHPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGRFTIS
RDNAKNTVYLQMNSLKPEDTAVYYCYLVALKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1481)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKN
QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE
MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLK
EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1482)

- R1CHCL50-**20*GGS**-Fc4-20*GGS-IFNa2_R149A (**P-1459**)

QVQLVESGGGLVHPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGRFTIS
RDNAKNTVYLQMNSLKPEDTAVYYCYLVALKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGSGGSGGSGGS
GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSCDLPQTHSLGSRRTLMLL
AQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQ

QLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLR SKE (SEQ ID NO: 1483)

Production and purification of different Fc formats

A mono- (schematic: **FIG. 7B**) or bivalent (schematic: **FIG. 16A**) targeted variants of R1CHCL50 Fc AFN was made by combining the corresponding knob and a hole constructs and express them in ExpiCHO cells as described above. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher) according to the manufacturer's guidelines.

Biological activity on HL116 reporter cell-lines

Biological activities of mono- and bivalent targeted Fc AFNs were measured as described in previous Examples. In brief, parental HL116 and the derived HL116-hClec9A were stimulated for six hours with a serial dilution of Fc-AFNs. Luciferase activity was measured and plotted in **FIG. 32**. Data show that the bivalent targeted AFN is approximately five-fold more active on target cells (HL116-hClec9A). Signaling in non-target cells (parental HL116 cells) was comparable for both variants.

Relative affinity in FACS

To measure relative affinities for Clec9A of the mono- and bivalent targeted Fc AFNs, HL116-hClec9A cells were incubated with a serial dilution of AFN. Binding was detected by subsequent incubation with an FITC-coupled anti-human secondary Ab, measured on a MACSQuant X instrument (Miltenyi Biotech) and analysed using the FlowLogic software (Miltenyi Biotech). Data in **FIG. 33** illustrates that the bivalent targeted AFN has an about 15-fold lower binding EC50 when compared to the monovalent variant.

Example 12: Variant Bivalent Targeted Fc Formats

In this Example, additional bivalent but heterodimeric variant Fc formats were generated and the biological activity was tested.

Constructs:

- R1CHCL50-**20*GGS**-R1CHCL50-**20*GGS**-Fc3

QVQLVESGGGLVHPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGRFTIS RDNAKNTVYLQMNSLKPEDTAVYYCYLVALKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSG GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**QVQLVESGGGLVHPGGSLRLSCAASGSF SSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCYLVA LKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG GSGGSGGSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVC TLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1484)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKN
QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE
MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLK
EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1485)

Production and purification of different Fc formats

The bivalent (schematic: FIG. 8B) targeted variant of our R1CHCL50 Fc AFN was made by combining the corresponding knob and a hole constructs and expressing them in ExpiCHO cells as described above. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher) according to the manufacturer's guidelines.

Biological activity on HL116 reporter cell-lines

The biological activity of the bivalent targeted Fc AFNs was measured as described in previous Examples. In brief, parental HL116 and the derived HL116-hClec9A were stimulated for six hours with a serial dilution of Fc-AFNs.

Example 13: Pharmacokinetic Study in Mouse

To evaluate the pharmacokinetic behavior of the Fc-based AFNs, 4 different molecules were selected all carrying the K322Q mutation:

- R1CHCL50(opt)4 combined with IFNa2_R149A using a Ridgway KiH Fc with LALA-K322Q mutation (combining construct 1 and 2)
- R1CHCL50(opt)4 combined with IFNa2_R149A-T106E using a Ridgway KiH Fc with LALA-K322Q mutation (combining construct 1 and 3)
- R1CHCL50(opt)4 combined with IFNa2_R149A using a Merchant KiH Fc with LALA-K322Q mutation (combining construct 4 and 5)
- R1CHCL50(opt)4 combined with IFNa2_R149A-T106E using a Merchant KiH Fc with LALA-K322Q mutation (combining construct 5 and 6)

Constructs:

1. R1CHCL50(opt4)-**5*GGS**-Fc1 (P329; K322Q) (**P-1477**)

DVQLVESGGGLVQPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTIS
RDNSKNTVYLQMNSLRPEDTAVYYCYLVALKAEYWGQGTLVTVSS**GGSGGSGGSGGSGGS**DKTHTCPP
CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 1486)

2. Fc2 (P329; K322Q)-**10*GGS**- IFNa2_R149A (P-1481)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQ
MRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQL
NDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE
(SEQ ID NO: 1487)

3. Fc2 (P329; K322Q)-**10*GGS**- IFNa2_R149A_T106E (P-1482)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQ
MRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQL
NDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSK
E (SEQ ID NO: 1488)

4. R1CHCL50(opt4)-**5*GGS**-Fc3 (P-1479)

DVQLVESGGGLVQPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTIS
RDNSKNTVYLQMNSLRPEDTAVYYCYLVALKAEYWGQGTLVTVSS**GGSGGSGGSGGSGGS**DKTHTCPP
CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 1489)

5. Fc4-**10*GGS**- IFNa2_R149A (P-1483)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKN
QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLA
QMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQ
LNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSK
E (SEQ ID NO: 1490)

6. Fc4-**10*GGS**- IFNa2_R149A_T106E (P-1484)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKN
QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE

ALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLA QMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQ LNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSK E (SEQ ID NO: 1491)

Production and purification of different Fc formats

Production was performed in ExpiCHO cells as described above. Recombinant proteins were purified from the supernatant on a HiTrap Protein A HP (GE Healthcare) and eluted proteins were, after neutralization, desalted on a G25 column (GE Healthcare) followed by final and 0.22 µm filtration.

Biological activity on HL116 reporter cell-lines

Biological activities of purified Fc-AFNs were measured as described in previous Examples. In brief, parental HL116 and the derived HL116-hClec9A were stimulated for six hours with a serial dilution of Fc-AFNs. Luciferase activity was measured and plotted in **FIG. 34**. Data show that all 4 constructs have a similar potency and specificity for target cells only.

PK study in mouse

In total 9 mice were dosed intravenously at 1 mg/kg with each construct. K-EDTA blood was taken from a first group of 3 mice at 5 minutes, 8 hours and 6 days, from a second group of 3 mice at 15 minutes, 1 day and 10 days and from a third group of 3 mice at 2 hours, 3 days and 14 days. The concentration of intact Fc-AFN was measured by ELISA. In brief the MAXISORP Nunc Immune plates (Thermo Scientific) were coated overnight with anti-human interferon alpha mAb (clone MMHA-13; PBL Assay Science) at 0.5 µg/ml in PBS. After washing the plates four times with PBS + 0,05% Tween-20, they were blocked with 0.1% Casein in PBS for at least 1 hour at room temperature. Subsequently, diluted samples and standards were incubated in 0.1% Casein in PBS for 2 hours at room temperature. After another wash cycle a custom made rabbit-anti-VHH (diluted 1/20000 in 0.1% Casein in PBS) was incubated for 2 hours at room temperature followed by an additional wash cycle and incubation with HRP-conjugated goat anti-rabbit (Jackson – 111-035-144; 1:5000 in 0.1% Casein) for 1 hour at room temperature. After a final washing cycle, peroxidase activity was measured using KPL substrate (5120-0047; SeraCare) according to the manufacturer's instructions. Concentrations from samples were calculated using GraphPad Prism. Measured concentrations are plotted in **FIG. 35** and show that all 4 constructs have a similar PK profile except for a somewhat faster clearance of the Ridgway based Fc-construct at the last sampling time point. Terminal half-life was estimated on average at about 3 days for the Ridgway constructs and 4.5 days for the Merchant constructs.

Example 14: Efficacy Study in Humanized Mouse

To evaluate the in vivo efficacy of the Fc-based AFNs the same 4 molecules as selected in Example 12 (targeted to human CLEC9A, a highly specific cDC1 marker) were tested in a tumor model in a humanized mouse. In brief, newborn NSG mice (1-2 days of age) were sublethal irradiated with 100 cGy prior to intrahepatic delivery of $1x10^5$ CD34+ human stem cells (from HLA-A2 positive cord bloods). At week 13 after stem cell transfer mice were subcutaneously inoculated with $25x10^5$ human RL follicular lymphoma cells (ATCC CRL-2261; not sensitive to the

direct anti-proliferative effect of IFN). Mice were treated daily intraperitoneally with 30 µg of human Flt3L protein, from day 10 to day 19 after tumor inoculation. Weekly intravenous injection with buffer or Fc-AFN (8 or 75 µg) was initiated at day 11 after tumor inoculation, when a palpable tumor was visible (n=5 mice per group). Tumor size (caliper measurements), body weight and temperature were assessed daily. Data in **FIG. 36** and **FIG. 37** show the tumor growth until 6 days after the second treatment (mice received weekly injections with either PBS or AFN, the data show tumor growth up to 7 days after the second weekly treatment). **FIG. 36** demonstrates that all constructs induced a similar level of tumor growth inhibition at the lower dose of 8 µg. **FIG. 37** shows the result of higher doses for a Merchant construct resulting in increasing tumor growth inhibition. Data on body weight and temperature did not show any major difference between buffer treatment and AFN treatment supporting that all AFN treatments were well tolerated.

Example 15: PD-L1 VHH-based Fc AFNs

In this Example, PD-L1 (programmed death-ligand 1) targeted Fc AFNs based on a human PD-L1 specific VHH (clone 2LIG99; blocks interaction with PD-1) for targeting to tumour cells or activated immune cells were generated and evaluated.

Constructs:

- 2LIG99-_*HA-tag*_**20*GGS**-Fc-**20*GGS**-IFNa2_R149A_*H6* (**P-991**)

QVQLQESGGGLVQAGGSLRLSCTASGTIFSINRMDWFRQAPGKQRELVALITSDGTPAYADSAKGRF TISRDNTKKTVSLQMNSLKPEDTAVYYCHVSSGVYNYWGQGTQVTVSS*AAAYPYDVPDY***GSGGSGG SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTC PPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGSG**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQ FQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSI LAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE*HHHHHH* (SEQ ID NO: 1492)

- 2LIG99-20*GGS-Fc1 (**P-1040**)

QVQLQESGGGLVQAGGSLRLSCTASGTIFSINRMDWFRQAPGKQRELVALITSDGTPAYADSAKGRF TISRDNTKKTVSLQMNSLKPEDTAVYYCHVSSGVYNYWGQGTQVTVSS**GGSGGSGGSGGSGGSGG SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK (SEQ ID NO: 1493)

- Fc2-**20*GGS**- IFNa2_R149A (**P-959**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPS
RDELTKNQVSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSGGSGGSGGSGGSGCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQ
EEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETP
LMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1494)

- 2LIG99-**20*GGS**-Fc3 (**P-1415**)

QVQLQESGGGLVQAGGSLRLSCTASGTIFSINRMDWFRQAPGKQRELVALITSDGTPAYADSAKGRF
TISRDNTKKTVSLQMNSLKPEDTAVYYCHVSSGVYNYWGQGTQVTVSS**GGSGGSGGSGGSGGSGG**
SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPS
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 1495)

- 2LIG99-**20*GGS**-Fc4-**20*GGS**-IFNa2_R149A (**P-1412**)

QVQLQESGGGLVQAGGSLRLSCTASGTIFSINRMDWFRQAPGKQRELVALITSDGTPAYADSAKGRF
TISRDNTKKTVSLQMNSLKPEDTAVYYCHVSSGVYNYWGQGTQVTVSS**GGSGGSGGSGGSGGSGG**
SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPS
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQ
QIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLK
EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1496)

Production and purification of PD-L1 VHH-based AFN

Homodimeric (2LIG99-20*GGS-Fc-20*GGS-IFNa2_R149A; scheme: **FIG. 1A**), monovalent heterodimeric (2LIG99-20*GGS-Fc1 + Fc2-20*GGS-IFNa2_R149A; scheme: **FIG. 7B**), or the bivalent targeted heterodimeric (2LIG99-20*GGS-Fc3 + 2LIG99-20*GGS-Fc4-20*GGS-IFNa2_R149A; **FIG. 16A**) variants of the 2LIG99 Fc AFN (for a schematic representation, see **FIG. 38**) were produced in ExpiCHO cells by transient transfection of the corresponding constructs according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher). The homodimeric 2LIG99-20*GGS-Fc-20*GGS-IFNa2_R149A

was considerably less stable after purification with a high tendency to aggregate, while the two other constructs showed good solubility.

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells express PD-L1 endogenously, so targeting was evaluated in the absence or presence of an excess of the corresponding free PD-L1 VHH (2LIG99). Parental HL116 were seeded overnight at 20,000 cells per 96-well, pre-incubated with 2LIG99 (20 µg/ml) and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in the **FIG. 38** illustrate that the homodimeric and monovalent heterodimeric variants are comparably active (EC_{50} values of 2.98 and 2.14 ng/ml respectively), while the bivalent targeted heterodimeric variant is 40 – 50 times more active. In all three cases, excess of free VHH is sufficient to block signaling thereby illustrating the PD-L1 dependence of the signaling.

Example 16: Efficacy Study in Humanized Mouse

To evaluate the in vivo efficacy of Fc-based PD-L1 targeted AFNs, the homodimer variant (2LIG99-20*GGS-Fc-20*GGS-IFNa2_R149A) as described in Example 15 was tested in a tumor model in a humanized mouse. Protein production was performed in ExpiCHO cells as described above. Recombinant proteins were purified from the supernatant on a HiTrap Protein A HP (GE Healthcare). Low pH-eluted proteins were after neutralization desalted on a G25 column (GE Healthcare) and 0.22 µm filtered. Newborn NSG mice (1-2 days of age) were sublethal irradiated with 100 cGy prior to intrahepatic delivery of $1x10^5$ CD34+ human stem cells (from HLA-A2 positive cord bloods). At week 13 after stem cell transfer mice were subcutaneously inoculated with $25x10^5$ human RL follicular lymphoma cells (ATCC CRL-2261; not sensitive to the direct anti-proliferative effect of IFN). Mice were treated daily intraperitoneally with 30 µg of human Flt3L protein, from day 5 to day 18 after tumor inoculation. Weekly perilesional injection with PBS or Fc-AFN (27 µg) or the PD-L1 blocking monoclonal antibody atezolizumab (30 µg; InVivoGen Catalog No.: hpdl1-mab12) was initiated at day 9 after tumor inoculation, when a palpable tumor was present (n=6 mice per group). Tumor size (caliper measurements), body weight and temperature were assessed daily. Data in **FIG. 39** show the tumor growth until 7 days after the second treatment (mice received weekly injections with either PBS or AFN, the data show tumor growth up to 7 days after the second weekly treatment), demonstrating the superiority of PD-L1 targeted Fc-AFN versus PBS or even atezolizumab treatment. Data on body weight and temperature did not show any major difference between buffer treatment of AFN treatment supporting that all AFN treatments were well tolerated.

Example 17: Clec4C VHH-based Fc AFNs

In this Example, Clec4C targeted Fc AFNs based on a human Clec4C specific VHH (clone 2CL92) for targeting to plasmacytoid dendritic cell were generated and evaluated.

Constructs:

- Clec4C VHH-**20*GGS**-Fc3 (**P-1571**)

QVQLQESGGGSVQAGDSLRLSCAASGRTFSGYAMGWFRQAPGKEREFVATISTSGSSTYYADSVK GRFTISRDNAKKSVYLQINSLKTEDAAVYYCAARLSFDNTAFYTSAIRYSYWGQGTQVTVSS**GGSGG SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTC PPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTK NQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1497)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPC RDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGSGGSGGS**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQE EFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPL MKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1498)

Production and purification of Clec4C VHH-based AFN

Constructs Clec4C VHH-20*GGS-Fc3 and Fc4-20*GGS-IFNa2_R149A were combined to a heterodimeric AFN (for a schematic representation, see **FIG. 7B**) and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells were transfected with an expression vector encoding the human Clec4C sequence. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hClec4C cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in the **FIG. 40** illustrate that both cell-lines are comparably sensitive to wild type IFNa2, while the Clec4C Fc AFN is much more active on targeted cells (HL116-hClec4C) compared to untargeted cells (parental HL116).

Example 18: CD20 VHH-based Fc AFNs

In this Example, CD20 targeted Fc AFNs based on a human CD20 specific VHH (clone 2HCD25) for targeting to B-cells and/or B-cell derived tumour cells were generated and evaluated.

Constructs:

- CD20 VHH-**20*GGS**-Fc3 (**P-1570**)

QVQLQESGGGLAQAGGSLRLSCAASGRTFSMGWFRQAPGKEREFVAAITYSGGSPYYASSVRGRF
TISRDNAKNTVYLQMNSLKPEDTAVYYCAANPTYGSDWNAENWGQGTQVTVSS**GGSGGSGGSGGS**
GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEA
AGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 1499)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPC
RDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSGGSGGSGGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQE
EFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPL
MKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1500)

Production and purification of CD20 VHH-based AFN

Constructs CD20 VHH-20*GGS-Fc3 and Fc4-20*GGS-IFNa2_R149A were combined to a heterodimeric AFN (for a schematic representation, see **FIG. 7B**) and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells were transfected with an expression vector encoding the human CD20 sequence. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hCD20 cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in the **FIG. 41** illustrate that both cell-lines are comparably sensitive to wild type IFNa2, while the CD20 Fc AFN is much more active on targeted cells (HL116-hCD20) compared to untargeted cells (parental HL116).

Example 19: CD13 VHH-based Fc AFNs

In this Example, CD13 targeted Fc AFNs based on a human CD13 specific VHH for targeting to tumour stromal cells were generated and evaluated.

Constructs:

- CD13 VHH-20*GGS-Fc3 (**P-1569**)
- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPC
RDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSGGSGGSGGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQE
EFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPL
MKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1501)

Production and purification of CD13 VHH-based AFN

Constructs CD13 VHH-20*GGS-Fc3 and Fc4-20*GGS-IFNa2_R149A were combined to a heterodimeric AFN (for a schematic representation, see **FIG. 7B**) and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells express CD13 endogenously, so targeting will be evaluated in the absence or presence of an excess of the corresponding free CD13 VHH. Parental HL116 were therefor seeded overnight at 20,000 cells per 96-well, pre-incubated with CD13 VHH and subsequently stimulated with a serial dilution of Fc AFNs with excess for 6 hours. Luciferase activity was measured in cell lysates. Data in the **FIG. 42** illustrate that stimulation in the presence of an excess CD13 VHH lowers biological activity 60-fold, thereby illustrating that the reconstitution of the IFN signaling is indeed depending on CD13 targeting.

Example 20: FAP VHH-based Fc AFNs

In this Example, FAP (fibroblast activation protein) targeted Fc AFNs based on three human FAP specific VHHs (clones 2PE14, 3PE12 and 3PE42) for targeting to tumour stromal cells were generated and evaluated.

Constructs:

- 2PE14 VHH-**20*GGS**-Fc3 (**P-1781**)

QVQLQESGGGLVQPGGSLRLSCAASGSTFSINAVAWYRQAPGKRRELVAGISGGGVTNYPDSVKGR
FTISRDNAKNTVYLQMSSLKPEDTAVYYCNLWPPRASPGGRVYWGQGTQVTVSS**GGSGGSGGSGG**
SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPE
AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCA
VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK (SEQ ID NO: 1502)

- 3PE12 VHH-**20*GGS**-Fc3 (**P-1782**)

QVQLQESGGGLVQPGGSLRLSCAASGSTFSGNAMAWYRQAPGKRRELVAGISGGGVTNYPDSVKG
RFTISRDNAKNTVYLQMSSLKPEDTAVYYCNLWPPRVSPGGGVYWGQGTQVTVSS**GGSGGSGGSG**
GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAP
EAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSC
AVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSLSPGK (SEQ ID NO: 1503)

- 3PE42 VHH-**20*GGS**-Fc3 (**P-1783**)

QVQLQESGGGLVQPGESLRLSCAVSGSTSSMNAMAWYRQAPGKRRELVAGISGGGATNYPDSVKG
RFTISRDNAKNTVYLQMSSLKPEDTAVYYCNLWPPRASPGGGVYWGQGTQVTVSS**GGSGGSGGSG**
GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAP
EAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSC
AVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALH
NHYTQKSLSLSPGK (SEQ ID NO: 1504)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPC
RDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSGGSGGSGGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQE
EFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPL
MKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1505)

Production and purification of FAP VHH-based AFN

Constructs 2PE14-20*GGS-Fc3, 3PE12-20*GGS-Fc3, or 3PE42-20*GGS-Fc3 were combined with construct Fc4-20*GGS-IFNa2_R149A to heterodimeric AFNs (for a schematic representation, see **FIG. 7B**) and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells were transfected with an expression vector encoding the human FAP sequence. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hFAP cells were seeded overnight at 20,000 cells per 96-well and subsequently

stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in the **FIG. 43** illustrates that both cell-lines are comparably sensitive to wild type IFNa2, while the FAP Fc AFNs is much more active on targeted cells (HL116-hFAP) compared to untargeted cells (parental HL116).

Example 21: CD8 VHH-based Fc AFNs

In this Example, CD8 targeted Fc AFNs based on a human CD8 specific VHH (clone 1CDA65) for targeting to cytotoxic T-cells were generated and evaluated.

Constructs:

- CD8 VHH-**20*GGS**-Fc3 (**P-1568**)

QVQLQESGGGLVHPGGSLRLSCAASGRSFSSYFMGWFRQAPGKEREFVAGIGWNDGSINYADSVK GRFTISRDNAKNTGYLQMNSLKPEDTAVYYCAASVSLYGLEKSSAYTSWGQGTQVTVSS**GGSGGSG GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQ VSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 1506)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPC RDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGSGGSGGS**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQE EFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPL MKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1507)

Production and purification of CD8 VHH-based AFN

Constructs CD8 VHH-20*GGS-Fc3 and Fc4-20*GGS-IFNa2_R149A were combined to a heterodimeric AFN (for a schematic representation, see **FIG. 7B**) and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells were transfected with an expression vector encoding the human CD8 sequence. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hCD8 cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in

the **FIG. 44** illustrate that both cell-lines are comparably sensitive to wild type IFNa2, while the CD8 Fc AFN is much more active on targeted cells (HL116-hCD8) compared to untargeted cells (parental HL116).

Example 22: Monovalent Clec9A and PD-L1 Targeted Fc AFNs

In this Example, we generated and evaluated Fc AFNs targeting both Clec9A (marker for cDC1 dendritic cells) and PD-L1 (expressed on tumour cells and activated immune cells). For targeting, we used two VHHs: R1CHCL50 (human Clec9A specific) and 2LIG99 (human PD-L1 specific).

Constructs:

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPC RDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGSGGSGGS**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQE EFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPL MKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1508)

- R1CHCL50-**20*GGS**-2LIG99-**20*GGS**-Fc3 (**P-1467**)

QVQLVESGGGLVHPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGR FTISRDNAKNTVYLQMNSLKPEDTAVYYCYLVALKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSG GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**QVQLQESGGGLVQAGGSL RLSCTASGTIFSINRMDWFRQAPGKQRELVALITSDGTPAYADSAKGRFTISRDNTKKTVSLQMNSLK PEDTAVYYCHVSSGVYNYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQV SNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1509)

- 2LIG99-**20*GGS**-R1CHCL50-**20*GGS**-Fc3 (**P-1469**)

QVQLQESGGGLVQAGGSLRLSCTASGTIFSINRMDWFRQAPGKQRELVALITSDGTPAYADSAKGRF TISRDNTKKTVSLQMNSLKPEDTAVYYCHVSSGVYNYWGQGTQVTVSS**GGSGGSGGSGGSGGSGG SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**QVQLVESGGGLVHPGGSLR LSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGRFTISRDNAKNTVYLQMNSLK PEDTAVYYCYLVALKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG GSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVS NKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNY

KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1510)

Production and purification of Clec9A and PD-L1 VHH-based AFN

The following combinations were transiently transfected in ExpiCHO cells:

i. R1CHCL50-2LIG99-Fc3 + Fc4-IFNa2_R149A (bispecific; monovalent targeting; scheme: **FIG. 8B**);

ii. 2LIG99-R1CHCL50-Fc3 + Fc4-IFNa2_R149A (bispecific; monovalent targeting; scheme: **FIG. 8B**).

One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Relative affinity in FACS

To measure relative affinities for Clec9A and PD-L1 the bispecific targeted Fc AFNs, and HL116-hClec9A cells were incubated with a serial dilution of AFN in the absence or presence of an excess of the competing free VHH 2LIG99. Binding was detected by subsequent incubation with an FITC-coupled anti-human secondary Ab, measured on a MACSQuant X instrument (Miltenyi Biotech) and analysed using the FlowLogic software (Miltenyi Biotech). Data in **FIG. 45** illustrates that both bispecific targeted AFNs can bind to both targets simultaneously resulting in increased affinity for cells expressing both targets.

Example 23: Monovalent and Bivalent Clec9A and PD-L1 Targeted Fc AFNs

In this Example, we generated and evaluated Fc AFNs targeting both Clec9A (marker for cDC1 dendritic cells) and PD-L1 (expressed on tumour cells and activated immune cells). For targeting, we used two VHHs: R1CHCL50 (human Clec9A specific) and 2LIG99 (human PD-L1 specific). Two bispecific formats (one resulting in monovalent, the other in bivalent targeting) were compared with the monospecific Fc AFNs for biological activity. Bivalent-bispecific targeting is schematically represented in **FIGS. 46A-D**.

Constructs:

- R1CHCL50-**20*GGS**-Fc3 (**P-1451**)

QVQLVESGGGLVHPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGR FTISRDNAKNTVYLQMNSLKPEDTAVYYCYLVALKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSG GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO: 1511)

- 2LIG99-**20*GGS**-Fc3 (**P-1415**)

QVQLQESGGGLVQAGGSLRLSCTASGTIFSINRMDWFRQAPGKQRELVALITSDGTPAYADSAKGRF TISRDNTKKTVSLQMNSLKPEDTAVYYCHVSSGVYNYWGQGTQVTVSS**GGSGGSGGSGGSGGSGG SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPS

VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 1512)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPC
RDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSGGSGGSGGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQE
EFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPL
MKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1513)

- 2LIG99-**20*GGS**-Fc4**20*GGS**--IFNa2_R149A (**P-1412**)

QVQLQESGGGLVQAGGSLRLSCTASGTIFSINRMDWFRQAPGKQRELVALITSDGTPAYADSAKGRF
TISRDNTKKTVSLQMNSLKPEDTAVYYCHVSSGVYNYWGQGTQVTVSS**GGSGGSGGSGGSGGSGG**
SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPS
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQ
QIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLK
EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1514)

- 3LEC89-**20*GGS**-Fc3-**20*GGS**-2LIG99 (**P-1413**)

QVQLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKG
RFTISRDNAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSS**GGSGGSGGSGGSGGS**
GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGG
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
SGGSGGSQVQLQESGGGLVQAGGSLRLSCTASGTIFSINRMDWFRQAPGKQRELVALITSDGTPAY
ADSAKGRFTISRDNTKKTVSLQMNSLKPEDTAVYYCHVSSGVYNYWGQGTQVTVSS (SEQ ID NO:
1515)

- R1CHCL50-**20*GGS**-2LIG99-**20*GGS**-Fc3 (**P-1467**)

QVQLVESGGGLVHPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGR FTISRDNAKNTVYLQMNSLKPEDTAVYYCYLVALKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSG GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**QVQLQESGGGLVQAGGSL RLSCTASGTIFSINRMDWFRQAPGKQRELVALITSDGTPAYADSAKGRFTISRDNTKKTVSLQMNSLK PEDTAVYYCHVSSGVYNYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQV SNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1516)

- R1CHCL50-**20*GGS**-2LIG99-**20*GGS**-Fc4-**20*GGS**-IFNa2_R149A (**P-1468**)

QVQLVESGGGLVHPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGR FTISRDNAKNTVYLQMNSLKPEDTAVYYCYLVALKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSG GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**QVQLQESGGGLVQAGGSL RLSCTASGTIFSINRMDWFRQAPGKQRELVALITSDGTPAYADSAKGRFTISRDNTKKTVSLQMNSLK PEDTAVYYCHVSSGVYNYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQV SNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**GGSGGSGGS GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**CDLPQTHSLGS RRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDET LLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIM ASFSLSTNLQESLRSKE (SEQ ID NO: 1517)

Production and purification of Clec9A and PD-L1 VHH-based AFN

The following combinations were transiently transfected in ExpiCHO cells:

i. R1CHCL50-Fc3 + Fc4-IFNa2_R149A (mono-specific Clec9A; scheme: **FIG. 7B**);
ii. 2LIG99-Fc3 + Fc4-IFNa2_R149A (mono-specific PD-L1; scheme: **FIG. 7B**);
iii. R1CHCL50-Fc3 + 2LIG99-Fc4-IFNa2_R149A (bispecific; monovalent targeting; scheme: **FIG. 16A**);
iv. 3LEC89-Fc3-2LIG99 + Fc4-IFNa2_R149A (bispecific; monovalent targeting; scheme: **FIG. 8A**);
v. R1CHCL50-2LIG99-Fc3 + R1CHCL50-2LIG99-Fc4-IFNa2_R149A (bispecific and bi-valent targeting; **FIG. 46C**).

One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells express PD-L1 endogenously and were therefore used to evaluate signaling based on PD-L1 targeting. The 'untargeted' situation was mimicked by stimulating cells in the presence of an excess free PD-L1 VHH 2LIG99. Clec9A targeting was evaluated by comparing signaling in parental HL116 vs HL116-hClec9A cells. Parental and derived cells were seeded overnight at 20,000 cells per 96-well, pre-incubated with 2LIG99 (20 µg/ml) (where indicated) and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in **FIG. 47** and Table 12 illustrate, *inter alia*, that:

- 2LIG99 containing Fc AFNs are active on both cell lines as expected, specificity of targeting is demonstrated by the competition with free VHH 2LIG99;
- AFNs based on R1CHCL50 only are active only on HL116-hClec9A cells;
- Bispecific AFNs are significantly more active on HL116-hClec9A cells (expressing both targets) compared to the monospecific variants or compared to parental HL116 expressing only PD-L1; and
- The bispecific and bivalent targeting molecule has the lowest EC50 on the cell line expressing only PD-L1 confirming earlier findings of increased potency by bivalent targeting (Example 15).

Table 12: Biological activity of bi-specific Clec9A-PD-L1 Fc AFN variants as show in **FIG. 47**.

		EC50 (nM)	
		Parental HL116	HL116-hClec9A
(i)	R1CHCL50-Fc3 + Fc4-IFNa2_R149A	ND	0,14
(ii)	2LIG99-Fc3 + Fc4-IFNa2_R149A	3,76	1,94
(iii)	R1CHCL50-Fc3 + 2LIG99-Fc4-IFNa2_R149A	7,16	0,0005
(iv)	3LEC89-Fc3-2LIG99 +. Fc4-IFNa2_R149A	52,12	0,33
(v)	R1CHCL50-2LIG99-Fc3 + R1CHCL50-2LIG99-Fc4-IFNa2_R149A	0,76	0,012

Example 24: Efficacy Study in Humanized Mouse

To evaluate the in vivo efficacy of Fc-based PD-L1 and/or CLEC9A targeted AFNs, a molecules (i), (ii), and (iii) as well as the mixture of molecules (i) and (ii) as described in Example 23; Table 12 were tested in a tumor model in a humanized mouse. Protein production was performed in ExpiCHO cells as described above. Recombinant proteins were purified from the supernatant on a HiTrap Protein A HP (GE Healthcare). Bound proteins were eluted from the column at pH 3.5 (25 mM Na-citrate) and neutralized with 1 M Tris pH8.8. Finally, the proteins were desalted on a G25 or desalted and polished on a G200 column (GE Healthcare) to 10 mM NH4-acetate pH5 – 123.5 mM NaCl – 0.02% Tween20 and 0.22 µm filtered. Newborn NSG mice (1-2 days of age) were sublethal irradiated with 100 cGy prior to intrahepatic delivery of $1x10^5$ CD34+ human stem cells (from HLA-A2 positive cord bloods). At week 13 after stem cell transfer mice were subcutaneously inoculated with $25x10^5$ human RL follicular lymphoma cells (ATCC CRL-2261). Mice were treated daily intraperitoneally with 30 µg of human Flt3L protein,

from day 8 to day 15 after tumor inoculation. Intravenous injection with buffer or Fc-AFN was performed on at days 9 and 15 after tumor inoculation, when a palpable tumor was detected (n=4-5 mice per group). Animals were followed until 4 days after the second treatment. Tumor size (caliper measurements was assessed at regular intervals. **FIG. 48** demonstrates the superiority that both the CLEC9A and the PD-L1 targeted AFN reduced tumor growth compared to buffer treatment only. The bispecific AFN targeted to both PD-L1 and CLEC9A appears superior over the single targeted AFNs or the combination of the single-targeted AFNs.

Example 25: CD8 and Clec4C targeted Fc AFNs

In this Example, we generated and evaluated Fc AFNs targeting both Clec4C (marker for plasmacytoid dendritic cells) and CD8 (T cell subset). For targeting, we used two VHHs: 2CL92 (human Clec4C specific) and 1CDA65 (human CD8 specific). The bispecific format will be compared with the monospecific Fc AFNs for biological activity on target expressing HL116 cells.

Constructs:

- Clec4C VHH-**20*GGS**-Fc3 (**P-1571**)

QVQLQESGGGSVQAGDSLRLSCAASGRTFSGYAMGWFRQAPGKEREFVATISTSGSSTYYADSVK GRFTISRDNAKKSVYLQINSLKTEDAAVYYCAARLSFDNTAFYTSAIRYSYWGQGTQVTVSS**GGSGG SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTC PPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTK NQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1518)

- CD8 VHH-**20*GGS**-Fc3 (**P-1568**)

QVQLQESGGGLVHPGGSLRLSCAASGRSFSSYFMGWFRQAPGKEREFVAGIGWNDGSINYADSVK GRFTISRDNAKNTGYLQMNSLKPEDTAVYYCAASVSLYGLEKSSAYTSWGQGTQVTVSS**GGSGGSG GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQ VSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 1519)

- Fc4-20*GGS-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPC RDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGSGGSGGS**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQE

EFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPL
MKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1520)

- CD8 VHH-**20*GGS**-Fc4-**20*GGS**-IFNa2_R149A (**P-1628**)

QVQLQESGGGLVQPGGSLRLSCAASGSIFSINVMGWYRQTPGKERELVAKITNFGITSYADSAQGRFT
ISRGNAKNTVYLQMNSLKPEDTAVYYCNLDTTGWGPPPYQYWGQGTQVTVSS**GGSGGSGGSGGSG**
GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAA
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVK
GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE
MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITL
YLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1521)

Production and purification of Clec4C and CD8 VHH-based AFNs

The following combinations were transiently transfected in ExpiCHO cells:

(i) Clec4C VHH-Fc3 + Fc4-IFNa2_R149A (Clec4C specific AFN; scheme: **FIG. 7B**);

(ii) CD8 VHH-Fc3 + Fc4-IFNa2_R149A (Clec4C specific AFN; scheme: **FIG. 7B**);

(iii) Clec4C VHH-Fc3 + CD8 VHH-Fc4-IFNa2_R149A (bi-specific AFN; scheme: **FIG. 16A**).

One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Vectors encoding human Clec4C or human CD8 were stably transfected in these HL116 cells, resulting in the HL116-hClec4C and HL116-hCD8 cell lines. To measure biological activity, parental and derived cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in **FIG. 49** illustrate that mono-specific Fc AFNs are only active on the respective HL116-hClec4C and HL116-hCD8 cell lines, while the bi-specific Fc AFN induces signaling in both cell lines, but not in parental cells.

Example 26: scFv Xcr1 Ab AFNs

In this Example, we designed and evaluated AFNs based on a scFv variant of the human Xcr1 Ab 5G7 for targeting of conventional dendritic cells type 1 (cDC1) cells.

Constructs:

- scFv Xcr1 Ab-**20*GGS**-Fc3 (**P-1620**)

DVVMTQTPLSLPVTLGNQASIFCRSSLGLVHRNGNTYLHWYLQKPGQSPKLLIYKVSHRFSGVPDRFSGSG
SGTDFTLKISRVEAEDLGVYFCSQSTHVPWTFGGGTKLEIKGGGGSGGGGSGGGGSGGGGSQAYLQQS
GAELVRPGASVKMSCKASGYTFTSHNLHWVKQTPRQGLQWIGAIYPGNGNTAYNQKFKGKATLTVDKSSS
TAYMQLSSLTSDDSAVYFCARWGSVVGDWYFDVWGTGTTVTVSSS**GGSGGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1522)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKN
QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE
MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLK
EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1523)

Production and purification of scFv Xcr1 Ab-based AFN

Constructs scFv Xcr1 Ab-20*GGS-Fc3 and Fc4-20*GGS-IFNa2_R149A were combined to a heterodimeric AFN with a configuration outlined in **FIG. 7B**, and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells were transfected with an expression vector encoding the human Xcr1 sequence. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hXcr1 cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in the **FIG. 50** illustrate that both cell-lines are comparably sensitive to wild type IFNa2, while the hXcr1 Fc AFN is more active on targeted cells (HL116-hXcr1) compared to untargeted cells (parental HL116).

Example 28: Construction of scFv CD20 Ab AFNs

In this Example, we designed and evaluated AFNs based on a scFv variant of the human CD20 Ab Rituximab for targeting B- and tumor cells.

Constructs:

- scFv CD20 Ab-**20*GGS**-Fc3 (**P-1622**)

QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGSGTSYS
LTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRGSTGGGGSGGGGSGGGGSQVQLQQPGAELVKPG
ASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKGKATLTADKSSSTAYMQLSS
LTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKA
LPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1524)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKN
QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE
MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLK
EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1525)

Production and purification of scFv CD20 Ab-based AFN

Constructs scFv CD20 Ab-20*GGS-Fc3 and Fc4-20*GGS-IFNa2_R149A were combined to a heterodimeric AFN with a configuration outlined in **FIG. 7B,** and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Example 28: Characterization of scFv CD20 Ab AFNs

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells were transfected with an expression vector encoding the human CD20 sequence. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hCD20 cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in the **FIG. 51** illustrate that both cell-lines are comparably sensitive to wild type IFNa2, while the hCD20 Fc AFN is more active on targeted cells (HL116-hCD20) compared to untargeted cells (parental HL116).

Example 29: scFv CD20 Ab AFRs

In this Example, we target AcTafactors (AFRs) to B- or tumor cells using a scFv variant of the human CD20 Ab Rituximab. TNF, bearing the Y87F mutation, will be cloned as a single chain trimer (with GGGGS-linkers) on one Fc arm in the AFR.

Constructs:

- scFv CD20 Ab-**20*GGS**-Fc3 (**P-1622**)

QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGSGTSYS
LTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRGSTGGGGSGGGGSGGGGSQVQLQQPGAELVKPG
ASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKGKATLTADKSSSTAYMQLSS
LTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKA
LPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1526)

- Fc4-**20*GGS**-3*TNF_Y87F (**P-1545**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKN
QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSGGSSSRTPSDKPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS
QVLFKGQGCPSTHVLLTHTISRIAVSFQTKVNLLSAIKSPCQRETPEGAEAKPWYEPIYLGGVFQLEKGDRL
SAEINRPDYLDFAESGQVYFGIIALGGGGSSSRTPSDKPVAHVVANPQAEGQLQWLNRRANALLANGVELR
DNQLVVPSEGLYLIYSQVLFKGQGCPSTHVLLTHTISRIAVSFQTKVNLLSAIKSPCQRETPEGAEAKPWYEP
IYLGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGIIALGGGGSSSRTPSDKPVAHVVANPQAEGQLQWL
NRRANALLANGVELRDNQLVVPSEGLYLIYSQVLFKGQGCPSTHVLLTHTISRIAVSFQTKVNLLSAIKSPCQ
RETPEGAEAKPWYEPIYLGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGIIAL (SEQ ID NO: 1527)

Production and purification of AFRs

Constructs scFv CD20 Ab-20*GGS-Fc3 and Fc4-20*GGS-3*TNF_Y87F were combined to a heterodimeric AFR with a configuration outlined in **FIG. 7B**, and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HEK-Dual reporter cell-lines

HEK-Dual TNF-α cells (InvivoGen) were derived from the human embryonic kidney 293 (HEK 293) cell line by stable co-transfection of two NF-κB-inducible reporter constructs based on either secreted alkaline phosphatase (SEAP) or a secreted luciferase (Lucia). Parental cells were stably transfected with an expression vector encoding the human CD20 sequence. Stable transfected clones were selected in puromycin-containing medium. Parental HEK-Dual and HEK-Dual-hCD20 cells were seeded at 20,000 cells per 96-well and subsequently stimulated overnight with a serial dilution of Fc AFRs. Secreted Lucia luciferase activity was measured using QUANTI-Luc

(InvivoGen). Data in the **FIG. 52** illustrate that both cell-lines are comparably sensitive to wild type TNF, while the CD20 Fc AFR is more active on targeted cells (HEK-Dual-hCD20) compared to untargeted cells (HEK-Dual).

Example 30: FLT3L Fc AFNs

In this Example, we designed and evaluated AFNs based on FMS-like tyrosine kinase 3 ligand (FLT3L) for targeting of hematopoietic (blood) progenitors.

Constructs

- FLT3L-**20*GGS**-Fc3 (**P-1623**)

TQDCSFQHSPISSDFAVKIRELSDYLLQDYPVTVASNLQDEELCGGLWRLVLAQRWMERLKTVAGSKMQGL LERVNTEIHFVTKCAFQPPPSCLRFVQTNISRLLQETSEQLVALKPWITRQNFSRCLELQCQPDSSTLPPPW SPRPLEATAPTAPQPS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGG SGGSGGSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTL PPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1528)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKN QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGS**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLK EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1529)

Production and purification of FLT3L-based AFN

Constructs FLT3L-20*GGS-Fc3 and Fc4-20*GGS-IFNa2_R149A were combined to an AFN variant with a configuration outlined in **FIG. 7B**, and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity: STAT1 phosphorylation in transient transfected Hek293T cells

Hek293T cells were transiently transfected with a FLT3 expression plasmid or an empty vector (MOCK). Two days after transfection, cells were stimulated with a serial dilution (as indicated) wild type IFNa2 or FLT3L-Fc-AFN for 15 minutes at 37 °C. After fixation (10 minutes, 37°C, Fix Buffer I; BD Biosciences), permeabilization (30 minutes, on ice, Perm III Buffer I; BD Biosciences) and washing, cells were stained with anti-STAT1 pY701 Ab (BD Biosciences). Samples were acquired with a MACSQuant X instrument (Miltenyi Biotec) and analysed using the FlowLogic software (Miltenyi Biotec). Data in **FIG. 53** clearly illustrate that the FLT3L Fc AFN is only capable to

induce STAT1 phosphorylation in FLT3 and not MOCK transfected cells, thereby illustrating that targeting using this ligand is possible. Of note, FLT3 or MOCK transfected cells are equally sensitive to wild type IFNa2.

Example 31: PD-1ec Fc AFNs

In this Example, we designed and evaluated AFNs based on the extracellular (ec) portion of programmed cell death protein 1 (PD-1) for targeting to PD-L1 expressing T and pro-B cells.

Constructs:

- PD-1ec-**20*GGS**-Fc3 (**P-1829**)

PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDRSQP GQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSP RPAGQFQTLVS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSR DELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1530)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKN QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGS**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLK EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1531)

Production and purification of PD-1ec AFN

Constructs PD-1ec-20*GGS-Fc3 and Fc4-20*GGS-IFNa2_R149A were combined to a heterodimeric AFN with a configuration outlined in **FIG. 7B**, and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells express PD-L1 (the ligand for PD-1) endogenously, so targeting was evaluated in the absence or presence of an excess of the PD-L1 VHH (2LIG99) that interferes with the PD-1/PD-L1 interaction. Cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of PD-1 Fc AFNs for 6 hours in the presence or absence of 2LIG99 VHH (50 µg/ml). Luciferase activity was measured in cell lysates. Data in the **FIG. 54** illustrate that the VHH is able

to, at least in part, neutralize signaling by the PD-1ec Fc AFN, thereby illustrating that it is possible to target mutated cytokines based on the PD-1/PD-L1 interaction.

Example 32: PD-L1ec Fc AFNs

In this Example, we designed and evaluated AFNs based on the extracellular portion (ec) of programmed cell death ligand 1 (PD-L1) for targeting of tumor cells or activated immune cells.

Constructs:

- PD-L1ec-**20*GGS**-Fc3 (**P-1830**)

FTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKD QLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHELTCQAEGYPK AEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPN ERS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**D KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQ VSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK (SEQ ID NO: 1532)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKN QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGS**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLK EKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1533)

Production and purification of PD-L1ec-based AFN

Constructs PD-L1ec-20*GGS-Fc3 and Fc4-20*GGS-IFNa2_R149A were combined to a heterodimeric AFN with a configuration outlined in **FIG. 7B**, and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells were transfected with an expression vector encoding the human PD-1 sequence lacking its cytoplasmic tail. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hPD-1 cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in

cell lysates. Data in the **FIG. 55** illustrate that both cell-lines are comparably sensitive to wild type IFNa2, while the PD-L1ec Fc AFN is more active on targeted cells (HL116-PD-1) compared to untargeted cells (parental HL116).

Example 33: Bivalent Ligand Targeted AFNs

In this Example, we designed and evaluated AFNs based on the use of bivalent extracellular (ec) portions of programmed cell death protein 1 (PD-1) for targeting to PD-L1 expressing T and pro-B cells or programmed cell death ligand 1 (PD-L1) for targeting of tumor cells or activated immune cells.

Constructs:

- PD-1ec-**20*GGS**-Fc3 (**P-1829**)

PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDRSQP
GQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSP
RPAGQFQTLVS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSR
DELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSC
SVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1534)

- PD-1ec-**20*GGS**-Fc4-**20*GGS**-IFNa2_R149A

PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDRSQP
GQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSP
RPAGQFQTLVS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCR
DELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC
SVMHEALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGG**
SGGSGGSGGSGGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETI
PVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRI
TLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1535)

- PD-L1ec-**20*GGS**-Fc3 (**P-1830**)

FTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKD
QLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHELTCQAEGYPK
AEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPN
ERS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**D
KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQ
VSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPGK (SEQ ID NO: 1536)

- PD-L1ec-**20*GGS**-Fc4-**20*GGS**-IFNa2_R149A

FTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKD
QLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHELTCQAEGYPK
AEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPN
ERS**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**D
KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQ
VSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGG**
SGGSGGSGGSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMI
QQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLKEK
KYSPCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1537)

Production and purification of bivalent ec-AFNs

The following combinations were transiently transfected in ExpiCHO cells:

i. PD-1ec-20*GGS-Fc3 and PD-1ec-20*GGS-Fc4-20*GGS-IFNa2_R149A (bispecific; monovalent targeting; scheme: **FIG. 16A**);

ii. PD-L1ec-20*GGS-Fc3 and PD-L1ec-20*GGS-Fc4-20*GGS-IFNa2_R149A (bispecific; monovalent targeting; scheme: **FIG. 16A**).

One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells express PD-L1 (the ligand for PD-1) endogenously, so targeting was evaluated in the absence or presence of an excess of free PD-L1 VHH (2LIG99) that interferes with the PD-1/PD-L1 interaction. In addition, the HL116 cells transfected with the human PD-1 sequence lacking its cytoplasmic tail (Example 32) was used to test the PD-L1 based construct. Cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of PD-1 Fc AFNs for 6 hours in the presence or absence of 2LIG99 VHH (50 µg/ml). Luciferase activity was measured in cell lysates.

Example 34: NGR peptide based Fc-AFNs

In this example, we designed and evaluated AFNs targeted to CD13 in the tumor neovasculature with the NGR-peptide-motif as targeting agent. The sequence was cloned as a cyclic sgcNGRc peptide C-terminal of both Fc arms in the resulting NGR Fc AFN. Biological activity on parental HL116 cells was compared with that of a Clec9A-targeted Fc AFN.

Constructs:

- Fc1-**20*GGS**-R1CHCL50 (**P-1215**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DVQ
LVESGGGLVQPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTISRDNSKNT
VYLQMNSLRPEDTAVYYCYLVALKAEYWGQGTLVTVSS (SEQ ID NO: 1538)

- IFNa2_R149A-**20*GGS**-Fc2 (**P-1214**)

CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAA
WDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASF
SLSTNLQESLRSKE**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG
GSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 1539)

- Fc3-*sgcNGRc* (**P-1853**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS
LSPGK*SGCNGRC* (SEQ ID NO: 1540)

- IFNa2_R149A-**20*GGS**-Fc4-*sgcNGRc* (**P-1854**)

CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAA
WDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASF
SLSTNLQESLRSKE**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSG
GSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLYCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK*SGCNGRC* (SEQ ID NO: 1541)

Production and purification of AFNs

Constructs were combined as follows and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines:

(i) Clec9A VHH Fc AFN: Fc3-20*GGS-R1CHCL50 + IFNa2_R149A-20*GGS-Fc4 (configuration as outlined in **FIG. 7A**);

(ii) NGR Fc AFN: Fc3-sgNGRc + IFNa2_R149A-20*GGS-Fc4-sgcNGRc (configuration as outlined in **FIG. 16B**).

One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells endogenously express the NGR target CD13. Cells were seeded overnight at 20.000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in the **FIG. 56** illustrate that the NGR Fc AFN is clearly more potent in inducing IFN-like signaling when compared to a Clec9A targeted Fc AFN showing the specificity of the NGR targeting.

Example 35: Targeting of wild type IFNa2

In this Example, we compared signaling upon targeting of wild type IFNa2 or the AFN mutant IFNa2_R149A to specific populations within peripheral blood mononuclear cells (PBMCs). Cytokine, or mutant thereof, will be targeted using a CD20 VHH (clone 2HCD25), CD8 VHH (clone 1CDA65), or a Clec4C VHH (clone 2CL92) in an Fc context.

Constructs:

- CD20 VHH-**20*GGS**-Fc3 (**P-1570**)

QVQLQESGGGLAQAGGSLRLSCAASGRTFSMGWFRQAPGKEREFVAAITYSGGSPYYASSVRGRFTISR DNAKNTVYLQMNSLKPEDTAVYYCAANPTYGSDWNAENWGQGTQVTVSS**GGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1542)

- CD8 VHH-**20*GGS**-Fc 3 (**P-1568**)

QVQLQESGGGLVHPGGSLRLSCAASGRSFSSYFMGWFRQAPGKEREFVAGIGWNDGSINYADSVKGRFT ISRDNAKNTGYLQMNSLKPEDTAVYYCAASVSLYGLEKSSAYTSWGQGTQVTVSS**GGSGGSGGSGGSGG SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1543)

- Clec4C VHH-**20*GGS**-Fc3 (**P-1571**)

QVQLQESGGGSVQAGDSLRLSCAASGRTFSGYAMGWFRQAPGKEREFVATISTSGSSTYYADSVKGRFTI SRDNAKKSVYLQINSLKTEDAAVYYCAARLSFDNTAFYTSAIRYSYWGQGTQVTVSS**GGSGGSGGSGGSG GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPS

VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1544)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQ VSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGS**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQ IFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLKEKKYS PCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1545)

- Fc4-**20*GGS**-IFNa2 (**P-1538**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQ VSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGS**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQ IFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLKEKKYS PCAWEVVRAEIMRSFSLSTNLQESLRSKE (SEQ ID NO: 1546)

Production and purification of CD20 and Clec4C VHH-based AFN

Combinations of these constructs were transiently transfected in ExpiCHO cells and resulted in following AFNs (for a schematic outline, see **FIG. 7B**):

(i) CD20 VHH-20*GGS-Fc3 + Fc4-IFNa2_R149A

(ii) CD20 VHH-20*GGS-Fc3 + Fc4-IFNa2

(iii) CD8 VHH-20*GGS-Fc3 + Fc4-IFNa2_R149A

(iv) CD8 VHH-20*GGS-Fc3 + Fc4-IFNa2

(v) Clec4C VHH-20*GGS-Fc3 + Fc4-IFNa2_R149A

(vi) Clec4C VHH-20*GGS-Fc3 + Fc4-IFNa2

One week after transfection, supernatant was collected, and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity upon Clec4C targeting: STAT1 phosphorylation in PBMCs

Biological activity of Clec4C-targeted molecules was tested as follows: PBMCs from buffy coats of healthy donors were isolated using density gradient centrifugation with Ficoll-Paque (GE Healthcare). Dendritic cells were first

enriched using the pan-DC enrichment kit (Miltenyi Biotec). Enriched cells were washed twice with FACS buffer (2% FBS, 1 mM EDTA in PBS) and stained with FITC-coupled anti-hClec4C (Miltenyi Biotec) for 20 minutes at 4°C. After two washes, cells were stimulated with a serial dilution of wild type or mutants Fc AFNs for 15 minutes at 37°C. After fixation (10 minutes, 37°C, Fix Buffer I; BD Biosciences) and permeabilization (30 minutes, on ice, Perm III Buffer I; BD Biosciences) and washing, cells were stained with anti-STAT1 pY701 Ab (BD Biosciences). Samples were acquired with a Wacquant X instrument (Miltenyi Biotec) and analysed using the FlowLogic software (Miltenyi Biotec). Data are summarized in **FIG. 57**. Clec4C positive and negative cells respond with similar potency (ratio of EC50s: ≈1) to wild type IFNa2. On the other hand, wild type or mutant IFNa2 is much more active when targeted with a Clec4C VHH to CLEC4C positive cells. The respective EC50 ratios are about 40 and >40.

Biological activity upon CD8 targeting: STAT1 phosphorylation in PBMCs

Biological activity of CD8-targeted molecules was tested as follows: PBMCs from buffy coats of healthy donors were isolated using density gradient centrifugation with Ficoll-Paque (GE Healthcare). Cells were washed twice with FACS buffer (2% FBS, 1 mM EDTA in PBS) and stained with FITC-coupled anti-hCD8 (Miltenyi Biotec) for 20 minutes at 4°C. After two washes, cells were stimulated with a serial dilution of wild type or mutants Fc AFNs for 15 minutes at 37°C. After fixation (10 minutes, 37°C, Fix Buffer I; BD Biosciences) and permeabilization (30 minutes, on ice, Perm III Buffer I; BD Biosciences) and washing, cells were stained with anti-STAT1 pY701 Ab (BD Biosciences). Samples were acquired with a MACSQuant X instrument (Miltenyi Biotec) and analysed using the FlowLogic software (Miltenyi Biotec). Data are summarized in **FIG. 58**. CD8 positive and negative cells respond with similarly potency (ratio of EC50s: ≈1) to wild type IFNa2. On the other hand, wild type or mutant IFNa2 is much more active when targeted with a CD8 VHH to CD8 positive cells. The respective EC50 ratios are about 125 and >125.

Biological activity upon CD20 targeting: STAT1 phosphorylation in PBMCs

Biological activity of CD20-targeted molecules was tested as follows: PBMCs from buffy coats of healthy donors were isolated using density gradient centrifugation with Ficoll-Paque (GE Healthcare). Cells were washed twice with FACS buffer (2% FBS, 1 mM EDTA in PBS) and B-cells stained with FITC-coupled anti-hCD19 (SinoBiologics) for 20 minutes at 4°C. After two washes, cells were stimulated with a serial dilution of wild type or mutants Fc AFNs for 15 minutes at 37°C. After fixation (10 minutes, 37°C, Fix Buffer I; BD Biosciences) and permeabilization (30 minutes, on ice, Perm III Buffer I; BD Biosciences) and washing, cells were stained with anti-STAT1 pY701 Ab (BD Biosciences). Samples were acquired with a MACSQuant X instrument (Miltenyi Biotec) and analysed using the FlowLogic software (Miltenyi Biotec). Data are summarized in **FIG. 59**. CD19 positive (i.e. B-cells) and negative cells respond with similarly potency (ratio of EC50s: ≈1) to wild type IFNa2. On the other hand, wild type or mutant IFNa2 is much more active when targeted with a CD20 VHH to CD19 positive cells. The respective EC50 ratios are about 25 and >500.

Example 36: Alternative IFNa2 AFN Mutations

In this Example, several different residues in IFNa2 were mutated in a Clec9A targeted Fc AFN context to evaluate the effect on signaling in targeted and untargeted cells. The positions of the various mutations are shown in **FIG. 60** (here, wild type is SEQ ID NO: 2).

*Constructs (**FIG. 60**)*

```
30-LKDRHDFGFP-//-VVRAEIMRSFSLSTNLQESLRSKE-165: wild type IFNa2
30-...A......-//-.......................-165: P-1838: Fc4-hIFNa2_R33A
30-..........-//-..A....................-165: P-1839: Fc4-hIFNa2_R144A
30-..........-//-..I....................-165: P-1840: Fc4-hIFNa2_R144I
30-..........-//-..L....................-165: P-1841: Fc4-hIFNa2_R144L
30-..........-//-..S....................-165: P-1842: Fc4-hIFNa2_R144S
30-..........-//-..T....................-165: P-1843: Fc4-hIFNa2_R144T
30-..........-//-..Y....................-165: P-1844: Fc4-hIFNa2_R144Y
30-..........-//-...D...................-165: P-1845: Fc4-hIFNa2_A145D
30-..........-//-...G...................-165: P-1846: Fc4-hIFNa2_A145G
30-..........-//-...H...................-165: P-1847: Fc4-hIFNa2_A145H
30-..........-//-...K...................-165: P-1848: Fc4-hIFNa2_A145K
30-..........-//-...Y...................-165: P-1849: Fc4-hIFNa2_A145Y
30-..........-//-......A................-165: P-1850: Fc4-hIFNa2_M148A
30-..........-//-.......A...............-165: P-1414: Fc4-hIFNa2_R149A
30-..........-//-..........A............-165: P-1851: Fc4-hIFNa2_L153A
```

Production and purification of AFNs

Different mutation variants of Fc4-20*GGS-IFNa2 were combined with construct R1CHCL50-20*GGS-Fc3, resulting in an AFN with a structure outlined in **FIG. 7B**. Proteins were transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected, and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells were transfected with an expression vector encoding the human Clec9A sequence. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hClec9A cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with different concentrations of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in the **FIG. 61** illustrate that all mutations, result in an Fc AFN that preferentially signals in targeted cells (here hClec9A expressing HL116).

Example 37: Actakines Based On Interferon Alpha 1

This Example evaluates and generate AcTakines based on wild type interferon alpha 1 (IFNα1) and targeted via a human Clec9A specific VHH (clone R1CHCL50).

Constructs:

- R1CHCL50-**20*GGS**-Fc3 (**P-1451**)

QVQLVESGGGLVHPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGRFTISR DNAKNTVYLQMNSLKPEDTAVYYCYLVALKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSGGS**

GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC QVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1547)

- Fc4-**20*GGS**-IFNa1 (**P-1852**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQ VSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGS**CDLPETHSLDNRRTLMLLAQMSRISPSSCLMDRHDFGFPQEEFDGNQFQKAPAISVLHELIQ QIFNLFTTKDSSAAWDEDLLDKFCTELYQQLNDLEACVMQEERVGETPLMNADSILAVKKYFRRITLYLTEKK YSPCAWEVVRAEIMRSLSLSTNLQERLRRKE (SEQ ID NO: 1548)

Production and purification of IFNα1 AFN

Constructs R1CHCL50-20*GGS-Fc3 and Fc4-20*GGS-IFNa1 were combined, resulting in an AFN with a structure outlined in **FIG. 7B**, and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected, and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells were transfected with an expression vector encoding the human Clec9A sequence. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hClec9A cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in the **FIG. 62** illustrate that both cell-lines are comparably sensitive to wild type IFNa1. The EC50 of IFNa1-based Fc AFN signaling in targeted cells is 0.3 ng/ml, while no luciferase induction could be measured in parental HL116 cells.

Example 38: Actakines Based on Interferon ß

In this Example, we generated and evaluated AcTakines based on interferon beta with the W22G mutation (IFNb_W22G) and targeted via a human Clec9A specific VHH (clone R1CHCL50).

Constructs:

- R1CHCL50-**20*GGS**-Fc3 (**P-1451**)

QVQLVESGGGLVHPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGRFTISR DNAKNTVYLQMNSLKPEDTAVYYCYLVALKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTL

MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC QVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1549)

- Fc4-**20*GGS**-IFNb_W22G (**P-1855**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQ VSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGS**MSYNLLGFLQRSSNFQCQKLLGQLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIYEM LQNIFAIFRQDSSSTGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSLHLKRYYGRILHYLKAK EYSHCAWTIVRVEILRNFYFINRLTGYLRN (SEQ ID NO: 1550)

Production and purification of IFNb AFN

Constructs R1CHCL50-20*GGS-Fc3 and Fc4-20*GGS-IFNb_W22G were combined, resulting in an AFN with a structure outlined in **FIG. 7B,** and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. One week after transfection, supernatant was collected, and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells were transfected with an expression vector encoding the human Clec9A sequence. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hClec9A cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in the **FIG. 63** illustrate that both cell-lines are comparably sensitive to wild type IFNb, while the Clec9A-targeted Fc AFN is much more active on targeted cells (HL116-hClec9A) compared to untargeted cells (parental HL116).

Example 39: Actakines Based on Interleukin-1

In this Example, we generated and evaluated AcTakines based on human interleukin-1 with the Q148G (hIL1b_Q148G) mutation and targeted via a human CD8 specific VHH (clone 1CDA65). The resulting AcTakine will be referred to as the AcTaleukin (ALN) hereafter.

Constructs:

- CD8 VHH-**20*GGS**-Fc3 (**P-1568**)

QVQLQESGGGLVHPGGSLRLSCAASGRSFSSYFMGWFRQAPGKEREFVAGIGWNDGSINYADSVKGRFTI SRDNAKNTGYLQMNSLKPEDTAVYYCAASVSLYGLEKSSAYTSWGQGTQVTVSS**GGSGGSGGSGGSGG SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPSV

FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1551)

- Fc4-**20*GGS**-IL1b_Q148G (**P-1626**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSAPVRSLNCTLRDSQQKSLVMSGPYELKALHLGGQDMEQQVVFSMSFVQGEESNDKIPVALGLKEKNLYLSCVLKDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINNKLEFESAQFPNWYISTSQAENMPVFLGGTKGGQDITDFTMQFVSS (SEQ ID NO: 1552)

Production and purification of ALN

Constructs CD8 VHH-20*GGS-Fc3 and Fc4-20*GGS-IL1b_Q148G were combined and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. Resulting ALN has a structure as outlined in **FIG. 7B**. One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HEK-Blue IL-1β Cells

Biological activity of the resulting ALN was measured on HEK-Blue™ IL-1β Cells (InvivoGen) with an NF-κB/AP-1-inducible SEAP (secreted alkaline phosphatase) reporter. Therefore, cells were transiently transfected with an empty vector or an expression-plasmid encoding human CD8. 36 hours post transfection, cells were resuspended and stimulated overnight with a serial dilution wild type IL-1β or ALN. SEAP was measured using the Phospha-Light SEAP Reporter Gene Assay System (ThermoFisher) according to the manufacturer's guidelines. Data in **FIG. 64** illustrate that MOCK or hCD8 transfected cells are comparably sensitive to wild type IL-1β, while ALN is specifically signals in cells expressing the target (here hCD8).

Example 40: Actakines Based on Tumor Necrosis Factor

In this Example, we generated and evaluated AcTakines based on tumour necrosis factor with the Y87F mutation (TNF_Y87F) and targeted via a human Clec9A specific VHH (clone R1CHCL50). TNF_Y87F will be cloned as a single chain trimer (with GGGGS-linkers) on one Fc arm, and the resulting AcTakine will be referred to as the AcTafactor (AFR) hereafter.

Constructs:

- CD20 VHH-**20*GGS**-Fc3 (**P-1570**)

QVQLQESGGGLAQAGGSLRLSCAASGRTFSMGWFRQAPGKEREFVAAITYSGGSPYYASSVRGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAANPTYGSDWNAENWGQGTQVTVSS**GGSGGSGGSGGSGGSGGS**

GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1553)

- Fc4-**20*GGS**-3*TNF_Y87F (**P-1545**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKN QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSSS**RTPSDKPVAHVVANPQAEGQLQWLNRRANALLANGVELRDNQLVVPSEGLYLIYS QVLFKGQGCPSTHVLLTHTISRIAVSFQTKVNLLSAIKSPCQRETPEGAEAKPWYEPIYLGGVFQLEKGDRL SAEINRPDYLDFAESGQVYFGIIALGGGGSSSRTPSDKPVAHVVANPQAEGQLQWLNRRANALLANGVELR DNQLVVPSEGLYLIYSQVLFKGQGCPSTHVLLTHTISRIAVSFQTKVNLLSAIKSPCQRETPEGAEAKPWYEP IYLGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGIIALGGGGSSSRTPSDKPVAHVVANPQAEGQLQWL NRRANALLANGVELRDNQLVVPSEGLYLIYSQVLFKGQGCPSTHVLLTHTISRIAVSFQTKVNLLSAIKSPCQ RETPEGAEAKPWYEPIYLGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGIIAL (SEQ ID NO: 1554)

Production and purification of human CD20 VHH-based AFRs

Constructs were combined transiently expressed in the ExpiCHO expression system as follows:

(i) CD20 VHH-20*GGS-Fc3 + Fc4-20*GGS-3*TNF_Y87F (AFR; see scheme 7B)

One week after transfection, supernatant was collected and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HEK-Dual reporter cell-lines

HEK-Dual TNF-α cells (InvivoGen) were derived from the human embryonic kidney 293 cell line by stable co-transfection of two NF-κB-inducible reporter constructs. This allows the TNF-α-induced NF-κB activation by monitoring the activity of either secreted alkaline phosphatase (SEAP) or a secreted luciferase (Lucia). Parental cells were stably transfected with an expression vector encoding the human CD20 sequence. Stable transfected clones were selected in puromycin-containing medium. Parental HEK-Dual and HEK-Dual-hCD20 cells were seeded at 20,000 cells per 96-well and subsequently stimulated overnight with a serial dilution of Fc AFRs. Secreted Lucia luciferase activity was measured using QUANTI-Luc (InvivoGen). Data in the **FIG. 65** illustrate that both cell-lines are comparably sensitive to wild type TNF, while the CD20 Fc AFR is more active on targeted cells (HEK-Dual-hCD20) compared to untargeted cells (HEK-Dual).

Example 41: Bi-AcTakines

In this Example, we generated and evaluated a bi-AcTakine containing both IFNa2_R149A and hIL1b_Q148Q mutants and targeted via a human CD8 specific VHH (clone 1CDA65).

Constructs:

- Fc3-**20*GGS**-IL1b_Q148G (**P-1627**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQ
VSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**
GGSGGSGGSAPVRSLNCTLRDSQQKSLVMSGPYELKALHLGGQDMEQQVVFSMSFVQGEESNDKIPVAL
GLKEKNLYLSCVLKDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINNKLEFESAQFPNWYISTSQAENMPV
FLGGTKGGQDITDFTMQFVSS (SEQ ID NO: 1555)

- CD8 VHH-**20*GGS**-Fc4-20*GGS-IFNa2_R149A (**P-1628**)

QVQLQESGGGLVQPGGSLRLSCAASGSIFSINVMGWYRQTPGKERELVAKITNFGITSYADSAQGRFTISRG
NAKNTVYLQMNSLKPEDTAVYYCNLDTTGWGPPPYQYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSG**
GSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSDKTHTCPPCPAPEAAGGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGSGGSGGS
GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSCDLPQTHSLGSRRTL
MLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTEL
YQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESL
RSKE (SEQ ID NO: 1556)

Production and purification of the bi-AcTakine

Constructs Fc3-20*GGS-IL1b_Q148G and CD8 VHH-20*GGS-Fc4-20*GGS-IFNa2_R149A were combined and transiently expressed in the ExpiCHO expression system (Thermo Fisher) according to the manufacturer's guidelines. The resulting bi-AcTakine has a structure as outlined in **FIG. 6A**. One week after transfection, supernatant was collected, and cells removed by centrifugation. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity

The HL116 reporter cell-line was used to test the bi-AcTakine for IFN-like signaling. Parental HL116 cells were transfected with an expression vector encoding the human CD8 sequence. Stable transfected clones were selected in G418-containing medium. Parental HL116 and HL116-hCD8 cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in the **FIG. 66** illustrate that both cell-lines are comparably sensitive to wild type IFNa2, while the bi-AcTakine is much more active on targeted cells (HL116-hCD8) compared to untargeted cells (parental HL116).

IL-1β -like signaling of the bi-AcTakine was measured on HEK-Blue™ IL-1β Cells (InvivoGen) with an NF-κB/AP-1-inducible SEAP (secreted alkaline phosphatase) reporter. Therefore, cells were transiently transfected with an empty vector or an expression-plasmid encoding human CD8. 36 hours post transfection, cells were resuspended and stimulated overnight with a serial dilution wild type IL-1β or bi-AcTakine. SEAP was measured using the Phospha-Light SEAP Reporter Gene Assay System (ThermoFisher) according to the manufacturer's guidelines. Data in **FIG. 67** illustrate that MOCK or CD8 transfected HEK-Blue cells are comparably sensitive to wild type IL-1β, while the bi-AcTakine is specifically capable to induce signaling in target (here CD8) expressing cells and not in MOCK transfected cells.

Example 42: Clec9A Fc AFNs Based on Human IgG4

In this Example, we designed and evaluated Clec9A-targeted (via VHH R1CHCL50) AFNs based on human IgG1 or human IgG4. The human IgG4 used has a S228P mutation to avoid in vivo exchange of half-molecules. In addition, either a knob or hole was engineered in the respective Fc-chains.

Constructs:

- R1CHCL50-**20*GGS**-Fc3 (**P-1451**)

QVQLVESGGGLVHPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGRFTISR DNAKNTVYLQMNSLKPEDTAVYYCYLVALKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC QVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1557)

- Fc4-**20*GGS**-IFNa2_R149A (**P-1414**)

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQ VSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGS**CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQ IFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLKEKKYS PCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1558)

- R1CHCL50-**20*GGS**-hIgG4 Fc (**P-1754**) (hole)

SQVQLVESGGGLVHPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGRFTIS RDNAKNTVYLQMNSLKPEDTAVYYCYLVALKAEYWGQGTQVTVSS**GGSGGSGGSGGSGGSGGSGGSGG SGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS**DKTHTCPPCPAPEFLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLVSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 1559)

- hIgG4 Fc-**20*GGS**-IFNa2_R149A (**P-1755**) (knob)

DKTHTCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEAL HNHYTQKSLSLSLGK**GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGS GGSGGSGGSC**DLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQ IFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVEETPLMKEDSILAVRKYFQRITLYLKEKKYS PCAWEVVRAEIMASFSLSTNLQESLRSKE (SEQ ID NO: 1560)

Production and purification of Clec9A and PD-L1 VHH-based AFN

The following combinations were transiently transfected in ExpiCHO cells:

(i) R1CHCL50-Fc3 + Fc4-IFNa2_R149A (IgG1 based AFN)

(ii) R1CHCL50-hIgG4 Fc + hIgG4 Fc-IFNa2_R149A (IgG4 based AFN)

One week after transfection, supernatant was collected and cells removed by centrifugation. The resulting AcTakines have a structure as outlined in **FIG. 7B**. Recombinant proteins were purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Clec9A targeting was tested using the stable HL116-hClec9A cell-line. Parental and derived cells were seeded overnight at 20,000 cells per 96-well and subsequently stimulated with a serial dilution of Fc AFNs for 6 hours. Luciferase activity was measured in cell lysates. Data in **FIG. 68** show that both HL116 and HL116-hClec9A respond similarly to wild type IFNa2. Furthermore, Clec9A targeted Fc AFNs based on human IgG1 or IgG4 have comparable EC50 values on targeted HL116-hClec9A, while signaling on parental cells could only be observed at very high concentrations.

Example 43: Comparative PK Between Chimera Lacking an Fc and the Present PC-Based Chimeric Protein Complexes

This Example is related to the PK (pharmacokinetics) of an AFN without Fc (3LEC89-20*GGS-hulFNa2_R149A-his6) in mice. This chimera has the sequence of:

P-602 sequence

QVQLQESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAAITNQGAPTYADSVKGRFTIS RDNAGNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTQVTVSSVDGGSGGSGGSGGSGGSGGSRS GGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSGGSAAAMCDLPQTHSLGSRRTLMLLAQMRRI SLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLE ACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSTNLQESLRSKELEHH HHHH (SEQ ID NO: 1561)

Nine animals were dosed intravenously at 3 mg/kg. K-EDTA blood was taken from a first group of 3 mice at 5 minutes and 1 hour, from a second group of 3 mice at 15 minutes and 3 hours and finally from the last group at 8 hours. The concentration in the plasma samples was measured using the same ELISA as described for the Fc-fusion proteins. The measured concentration (**FIG. 69**) show a fast clearing of this type of molecules resulting in a concentration below detection limit (0.12 µg/ml) at the 8-hour time point. The estimated terminal half-life is in the range of 2 hours.

A comparable study with the same IFN and anti-Clec9A components – but now in the Fc-format (*i.e.* replacing the GGS linker with the described Fc) was described in Example 3 (See **FIG. 24**). The half-life was dramatically increased – to multiple days (**FIG. 24**).

Example 44: scFv PD-L1 -based Fc AFNs

In this Example, PD-L1 (programmed death-ligand 1) targeted Fc AFNs based on a human PD-L1 specific scFv for targeting to tumour cells or activated immune cells is generated and evaluated.

Several constructs including scFv directed to PD-L1 as the targeting agent and wild type IFNα2 as the signaling agent are constructed. Some illustrative configurations of these PD-L1 targeted constructs are shown, *e.g.*, in FIGs. 4A-D, where the targeting agent is a scFv directed towards PD-L1 and signaling agent is wild type IFNα2.

Production and purification of PD-L1 scFv-based AFN

The constructs are produced in ExpiCHO cells by transient transfection of the corresponding constructs according to the manufacturer's guidelines. One week after transfection, supernatant is collected and cells removed by centrifugation. Recombinant proteins are purified from the supernatant using the Pierce Protein A spin plates (Thermo Fisher).

Biological activity on HL116 reporter cell-lines

Biological activity of these constructs are studied in HL116 reporter cell-lines. The HL116 clone is derived from the human HT1080 cell line (ATCC CCL-121). It contains the firefly luciferase gene controlled by the IFN-inducible 6-16 promoter. Parental HL116 cells express PD-L1 endogenously, so targeting is evaluated in the absence or presence of an excess of the corresponding free PD-L1 scFv.

Construction and characterization of IFNα-armed anti-PD-L1 is performed. Flow cytometry is used to show binding of indicated protein in IFNAR1-/- A20 cells and PD-L1-/- A20 cells at the concentration of 80 nM.

Numbers indicate the mean fluorescent intensity (MFI). The bioactivity of scFv PD-L1 -based Fc AFNs was measured by an anti-viral infection biological assay. L929 cells were cultured with each protein overnight before

being infected with VSV-GFP virus. After another 30 h of culture, the percentage of virus-infected cells was determined by flow cytometry.

Balb/c mice (n = 5) are inoculated with $3x10^6$ A20 cells. After tumor is established, mice are treated with 20 μg of control, anti-PD-L1, IFNα-Fc, or scFv PD-L1-based Fc AFNs by i.t. or i.v. (day 11 and 15) injection.

Tumor size is measured twice per week. C57BL/6 mice (n = 4–8) are inoculated with $5x10^5$ MC38 cells. Mice are treated i.v. with 25 μg control or scFv PD-L1-based Fc AFNs on days 14 and 18. Mice are injected i.v. with 25 μg of indicated protein. Protein concentrations in tumor tissues or serum at different time points is measured by ELISA.

EQUIVALENTS

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth and as follows in the scope of the appended claims.

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

INCORPORATION BY REFERENCE

All patents and publications referenced herein are hereby incorporated by reference in their entireties.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention.

As used herein, all headings are simply for organization and are not intended to limit the disclosure in any manner. The content of any individual section may be equally applicable to all sections

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CLAIMS

What is claimed is:

1. An Fc-based chimeric protein complex comprising:

(a) a targeting moiety comprising a recognition domain that recognizes and/or binds to a target;

(b) a signaling agent, wherein the signaling agent is:

i) a wild type signaling agent; or

ii) a modified signaling agent that has one or more mutations that confer improved safety relative to the wild type signaling agent; and

(c) an Fc domain, the Fc domain comprising an Fc chain and optionally having one or more mutations that reduce or eliminate one or more effector functions of the Fc domain, promotes Fc chain pairing of the Fc domain, and/or stabilizes a hinge region in the Fc domain.

2. The Fc-based chimeric protein complex of claim 1, further comprising one or more linkers.

3. The Fc-based chimeric protein complex of claims 1 or 2, wherein the Fc domain is selected from IgG, IgA, IgD, IgM, or IgE.

4. The Fc-based chimeric protein complex of claim 3, wherein the IgG is selected from IgG1, IgG2, IgG3, or IgG4.

5. The Fc-based chimeric protein complex of claim 3, wherein the Fc domain is selected from human IgG, IgA, IgD, IgM, or IgE.

6. The Fc-based chimeric protein complex of claim 5, wherein the human IgG is selected from human IgG1, IgG2, IgG3, or IgG4.

7. The Fc-based chimeric protein complex of any one of claims 1-6, wherein the signaling agent is a modified signaling agent and has reduced affinity or activity at the signaling agent's receptor relative to a wild type signaling agent.

8. The Fc-based chimeric protein complex of claim 7, wherein the signaling agent is a modified signaling agent and the targeting moiety restores the modified signaling agent's affinity or activity at the signaling agent's receptor.

9. The Fc-based chimeric protein complex of any one of claims 1-8, wherein the Fc chain pairing is promoted by ionic pairing and/or a knob-in-hole pairing.

10. The Fc-based chimeric protein complex of any one of claims 1-9, wherein the one or more mutations to the Fc domain results in an ionic pairing between the Fc chains in the Fc domain.

11. The Fc-based chimeric protein complex of any one of claims 1-10, wherein the one or more mutations to the Fc domain results in a knob-in-hole pairing of the Fc domain.

12. The Fc-based chimeric protein complex of any one of claims 1-11, wherein the one or more mutations to the Fc domain results in the reduction or elimination of the effector function of the Fc domain.

13. The Fc-based chimeric protein complex of any one of claims 1-12, wherein the targeting moiety comprise a recognition domain that recognizes and/or binds an antigen or receptor on a tumor cell, and/or tumor stroma, and/or ECM, and/or immune cell.

14. The Fc-based chimeric protein complex of claim 13, wherein the immune cell is selected from a T cell, a B cell, a dendritic cell, a macrophage, a neutrophil, and a NK cell.

15. The Fc-based chimeric protein complex of any one of the above claims, wherein the targeting moiety comprises a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein, a darpin, an anticalin, an adnectin, an aptamer, a Fv, a Fab, a Fab', a $F(ab')_2$, a peptide mimetic molecule, a natural ligand for a receptor, or a synthetic molecule.

16. The Fc-based chimeric protein complex of any one of the above claims, wherein the targeting moiety comprises a VHH.

17. The Fc-based chimeric protein complex of any one of the above claims, wherein the targeting moiety recognizes and/or binds to its target without substantially neutralizing the target's activity or wherein the targeting moiety recognizes and/or binds to its target and substantially neutralizes the target's activity.

18. The Fc-based chimeric protein complex of any one of the above claims, wherein the targeting moiety directly or indirectly recruits immune cells to tumor cells or to the tumor microenvironment.

19. The Fc-based chimeric protein complex of any one of the above claims, wherein the targeting moiety enhances antigen presentation.

20. The Fc-based chimeric protein complex of any one of the above claims, wherein the targeting moiety enhances tumor antigen presentation, optionally by dendritic cells.

21. The Fc-based chimeric protein complex of any one of the above claims, wherein the targeting moiety binds to one of the following targets: CD8, CD13, CD20, Clec9A, Clec4c, PD-1, PD-L1, PD-L2, SIRP1α, FAP, XCR1, tenascin CA1, Flt3, or an ECM protein.

22. The Fc-based chimeric protein complex of any one of the above claims, wherein the signaling agent is a modified signaling agent and the mutations in the modified signaling agent allow for attenuation of activity.

23. The Fc-based chimeric protein complex of claim 22, wherein agonistic or antagonistic activity is attenuated.

24. The Fc-based chimeric protein complex of any one of the above claims, wherein the signaling agent is a modified signaling agent and the modified signaling agent is selected from an interferon, an interleukin, and a tumor necrosis factor.

25. The Fc-based chimeric protein complex of any one of the above claims, wherein the signaling agent is a modified signaling agent and the modified signaling agent is selected from human: IFNα2, IFNα1, IFNβ, IFNγ, consensus interferon, TNF, TNFR, TGF-α, TGF-β, VEGF, EGF, PDGF, FGF, TRAIL, IL-1β, IL-2, IL-3, IL-4, IL-6, IL-10, IL-12, IL-13, IL-15, IL-18, IL-33, IGF-1, or EPO.

26. The Fc-based chimeric protein complex of claim 25, wherein the human IFNα2 comprises one or more mutations selected from R33A, T106X_3, R120E, R144X_1 A145X_2, M148A, R149A, and L153A and with respect to the amino acid sequence of SEQ ID NO: 1 or 2, wherein X_1 is selected from A, S, T, Y, L, and I, wherein X_2 is selected from G, H, Y, K, and D, and wherein X_3 is selected from A and E.

27. The Fc-based chimeric protein complex of claim 25, wherein the human IFNβ comprises one or more mutations selected from W22G, R27G, L32A, L32G, R35A, R35G, V148G, L151G, R152A, and R152G with respect to the amino acid sequence of SEQ ID NO: 3.

28. The Fc-based chimeric protein complex of claim 25, wherein the human IL-1β comprises one or more mutations selected from A117G/P118G, R120G, R120A, L122A, T125G/L126G, R127G, Q130A, Q130W, Q131G, K132A, S137G/Q138Y, L145G, H146A, H146G, H146E, H146N, H146R, L145A/L147A, Q148E, Q148G, Q148L, Q148G/Q150G, Q150G/D151A, M152G, F162A, F162A/Q164E, F166A, Q164E/E167K, N169G/D170G, I172A, V174A, K208E, K209A, K209D, K209A/K210A, K219S, K219Q, E221S, E221K, E221S/N224A, N224S/K225S, E244K, and N245Q with respect to the amino acid sequence of SEQ ID NO: 17.

29. The Fc-based chimeric protein complex of claim 25, wherein the human IL-2 comprises one or more mutations selected from R38A, F42A, Y45A, E62A, N88R, N88I, N88G, D20H, Q126L, Q126F, D109, and C125 with respect to the amino acid sequence of SEQ ID NO: 18.

30. The Fc-based chimeric protein complex of claim 25, wherein the human TNFα comprises one or more mutations selected from R32G, N34G, Q67G, H73G, L75G, L75A, L75S, T77A, S86G, Y870, Y87L, Y87A, Y87F, V91G, V91A, I97A, I97Q, I97S, T105G, P106G, A109Y, P113G, Y115G, Y115A, E127G, N137G, D143N, A145G, A145T, and Y87Q/I97A with respect to the amino acid sequence of SEQ ID NO: 14.

31. The Fc-based chimeric protein complex of any one of claims 1-30, wherein the Fc domain is homodimeric.

32. The Fc-based chimeric protein complex of any one of claims 1, 2, and 7-30, wherein the Fc domain is heterodimeric.

33. The Fc-based chimeric protein complex of claim 25, wherein the signaling agent is a modified IFNα2, optionally having a R149A mutation with respect to the amino acid sequence of SEQ ID NO: 1 or 2.

34. The Fc-based chimeric protein complex of claim 26 or 33, wherein the targeting moiety binds to Clec9A and the signaling agent is modified IFNα2, optionally having one or more of the following mutations: R33A, R144A, R144I, R144L, R144S, R144T, R144Y, A145D, A145G, A145H, A145K, A145Y, M148A, and L153A.

35. The Fc-based chimeric protein complex of claim 33, wherein the targeting moiety binds to PD-L1 and the signaling agent is modified IFNα2.

36. The Fc-based chimeric protein complex of claim 33, wherein the targeting moiety binds to PD-1 and the signaling agent is modified IFNα2.

37. The Fc-based chimeric protein complex of claim 33, wherein:

(i) the targeting moiety binds to Clec4c and the signaling agent is modified IFNα2, or

(ii) the targeting moiety binds to XCR1 and the signaling agent is modified IFNα2.

38. The Fc-based chimeric protein complex of claim 33, wherein the targeting moiety binds to CD20 and the signaling agent is modified IFNα2.

39. The Fc-based chimeric protein complex of claim 33, wherein the targeting moiety binds to CD13 and the signaling agent is modified IFNα2.

40. The Fc-based chimeric protein complex of claim 33, wherein the targeting moiety binds to FAP and the signaling agent is modified IFNα2.

41. The Fc-based chimeric protein complex of claim 33, wherein the targeting moiety binds to CD8 and the signaling agent is modified IFNα2.

42. The Fc-based chimeric protein complex of claim 33, wherein the targeting moiety binds to Flt3 and optionally comprises the extracellular domain of Flt3L, or a functional portion thereof and the signaling agent is modified IFNα2.

43. The Fc-based chimeric protein complex of claim 21, wherein the targeting moiety is an scFv against PD-L1 and the signaling agent is wild type IFNα2.

44. The Fc-based chimeric protein complex of claim 33, wherein the targeting moiety comprises the extracellular domain of PD-L1, or a functional portion thereof, and the signaling agent is modified IFNα2.

45. The Fc-based chimeric protein complex of claim 33, wherein the targeting moiety comprises the extracellular domain of PD-1, or a functional portion thereof, and the signaling agent is modified IFNα2.

46. The Fc-based chimeric protein complex of claim 33, wherein the targeting moiety comprises the NGR peptide and the signaling agent is modified IFNα2.

47. The Fc-based chimeric protein complex of claim 25, wherein the signaling agent is a wildtype IFNβ or a modified IFNβ.

48. The Fc-based chimeric protein complex of claim 47, wherein the targeting moiety binds to Clec9A and the signaling agent is modified IFNβ.

49. The Fc-based chimeric protein complex of claim 25, wherein the signaling agent is a wildtype IL-1β or a modified IL-1β.

50. The Fc-based chimeric protein complex of claim 49, wherein the targeting moiety binds to CD8 and the signaling agent is modified IL-1β.

51. The Fc-based chimeric protein complex of claim 25, wherein the signaling agent is a wildtype TNF or a modified TNF.

52. The Fc-based chimeric protein complex of claim 51, wherein the targeting moiety binds to CD20 and the signaling agent is modified TNF.

53. The Fc-based chimeric protein complex of any one of claims 1-52, wherein the chimeric protein complex further comprises a second targeting moiety.

54. The Fc-based chimeric protein complex of claim 53, wherein the second targeting moiety binds to one of the following targets: CD8, CD13, CD20, Clec9A, Clec4c, PD-1, PD-L1, PD-L2, SIRP1α, FAP, XCR1, tenascin CA1, Flt3, or an ECM protein.

55. The Fc-based chimeric protein complex of any one of claims 1-54, wherein the chimeric protein complex further comprises a second signaling agent.

56. The Fc-based chimeric protein complex of claim 55, wherein the second signaling agent is a wild type or modified signaling agent.

57. The Fc-based chimeric protein complex of claim 56, wherein the second signaling agent is selected from human: IFNα2, IFNα1, IFNβ, IFNγ, consensus interferon, TNF, TNFR, TGF-α, TGF-β, VEGF, EGF, PDGF, FGF, TRAIL, IL-1β, IL-2, IL-3, IL-4, IL-6, IL-10, IL-12, IL-13, IL-15, IL-18, IL-33, IGF-1, or EPO.

58. A method for treating or preventing cancer, comprising administering to a patient in need thereof an effective amount of the Fc-based chimeric protein complex of any one of claims 1-57.

59. A use of the Fc-based chimeric protein complex of any one of claims 1-57 for treating or preventing cancer.

60. A use of the Fc-based chimeric protein complex of any one of claims 1-57 for the preparation of a medicament for the treatment of prevention of cancer.

61. The method of claim 58 or the use of claim 59 or claim 60, wherein the cancer is selected form one or more of basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and central nervous system cancer; breast cancer; cancer of the peritoneum; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer (including gastrointestinal cancer); glioblastoma; hepatic carcinoma; hepatoma; intra-epithelial neoplasm; kidney or renal cancer; larynx cancer; leukemia; liver cancer; lung cancer (*e.g.*, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung); melanoma; myeloma; neuroblastoma; oral cavity cancer (lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; salivary gland carcinoma; sarcoma; skin cancer; squamous cell cancer; stomach cancer; testicular cancer; thyroid cancer; uterine or endometrial cancer; cancer of the urinary system; vulval cancer; lymphoma including Hodgkin's and non-Hodgkin's lymphoma, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia; chronic lymphocytic leukemia (CLL); acute

lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; as well as other carcinomas and sarcomas; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses; edema (*e.g.* that associated with brain tumors); and Meigs' syndrome.

62. A method for treating or preventing an autoimmune disease, neurodegenerative disease, metabolic disease, and/or cardiovascular disease, comprising administering to a patient in need thereof an effective amount of effective amount of the Fc-based chimeric protein complex of any one of claims 1-57.

63. A use of the Fc-based chimeric protein complex of any one of claims 1-57 for treating or preventing an autoimmune disease, neurodegenerative disease, metabolic disease, and/or cardiovascular disease.

64. A use of the Fc-based chimeric protein complex of any one of claims 1-57 for the preparation of a medicament for the treatment of prevention of an autoimmune disease, neurodegenerative disease, metabolic disease, and/or cardiovascular disease.

65. The method of claim 62 or the use of claim 63 or claim 64, wherein the autoimmune disease, neurodegenerative disease, metabolic disease, and/or cardiovascular disease is selected from multiple sclerosis, diabetes mellitus, lupus, celiac disease, Crohn's disease, ulcerative colitis, Guillain-Barre syndrome, scleroderms, Goodpasture's syndrome, Wegener's granulomatosis, autoimmune epilepsy, Rasmussen's encephalitis, Primary biliary sclerosis, Sclerosing cholangitis, Autoimmune hepatitis, Addison's disease, Hashimoto's thyroiditis, Fibromyalgia, Menier's syndrome; transplantation rejection (*e.g.*, prevention of allograft rejection) pernicious anemia, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, Sjogren's syndrome, lupus erythematosus, myasthenia gravis, Reiter's syndrome, and Grave's disease.

66. An Fc-based chimeric protein complex where the complex is a homodimer comprising:

(a) a targeting moiety comprising a recognition domain that recognizes and/or binds to a target;

(b) a signaling agent, wherein the signaling agent is:

i) a wild type signaling agent; or

ii) a modified signaling agent that has one or more mutations that confer improved safety relative to the wild type signaling agent; and

(c) an Fc domain, the Fc domain comprising an Fc chain and optionally having one or more mutations that reduce or eliminate one or more effector functions of the Fc domain and/or stabilizes a hinge region in the Fc domain.

67. The Fc-based chimeric protein complex of claim 66, further comprising one or more linkers.

68. The Fc-based chimeric protein complex of any one of claims 66 or 67, wherein the Fc domain is selected from IgG, IgA, IgD, IgM, or IgE.

69. The Fc-based chimeric protein complex of claim 68, wherein the IgG is selected from IgG1, IgG2, IgG3, or IgG4.

70. The Fc-based chimeric protein complex of claim 68, wherein the Fc domain is selected from human IgG, IgA, IgD, IgM, or IgE.

71. The Fc-based chimeric protein complex of claim 70, wherein the human IgG is selected from human IgG1, IgG2, IgG3, or IgG4.

72. The Fc-based chimeric protein complex of any one of claims 66-71, wherein the signaling agent is a modified signaling agent and the modified signaling agent has reduced affinity or activity at the signaling agent's receptor relative to a wild type signaling agent.

73. The Fc-based chimeric protein complex of claim 72, wherein signaling agent is a modified signaling agent and the targeting moiety restores the modified signaling agent's affinity or activity at the signaling agent's receptor.

74. The Fc-based chimeric protein complex of any one of claims 66-73, wherein the one or more mutations to the Fc domain results in the reduction or elimination of the effector function of the Fc domain.

75. The Fc-based chimeric protein complex of any one of claims 66-74, wherein the targeting moiety comprise a recognition domain that recognizes and/or binds an antigen or receptor on a tumor cell, and/or tumor stroma, and/or ECM, and/or immune cell.

76. The Fc-based chimeric protein complex of claim 75, wherein the immune cell is selected from a T cell, a B cell, a dendritic cell, a macrophage, a neutrophil, and a NK cell.

77. The Fc-based chimeric protein complex of any one of claims 66-76, wherein the targeting moiety comprises a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein, a darpin, an anticalin, an adnectin, an aptamer, a Fv, a Fab, a Fab', a $F(ab')_2$, a peptide mimetic molecule, a natural ligand for a receptor, or a synthetic molecule.

78. The Fc-based chimeric protein complex of any one of claims 66-77, wherein the targeting moiety comprises a VHH.

79. The Fc-based chimeric protein complex of any one of claims 66-78, wherein the targeting moiety recognizes and/or binds to its target without substantially neutralizing the target's activity or wherein the targeting moiety recognizes and/or binds to its target and substantially neutralizes the target's activity.

80. The Fc-based chimeric protein complex of any one of claims 66-79, wherein the targeting moiety directly or indirectly recruits immune cells to tumor cells or to the tumor microenvironment.

81. The Fc-based chimeric protein complex of any one of claims 66-80, wherein the targeting moiety enhances antigen presentation.

82. The Fc-based chimeric protein complex of any one of claims 66-81, wherein the targeting moiety enhances tumor antigen presentation, optionally by dendritic cells.

83. The Fc-based chimeric protein complex of any one of claims 66-82, wherein the targeting moiety binds to one of the following targets: CD8, CD13, CD20, Clec9A, Clec4c, PD-1, PD-L1, PD-L2, SIRP1α, FAP, XCR1, tenascin CA1, Flt3, or an ECM protein.

84. The Fc-based chimeric protein complex of any one of claims 66-83, wherein the signaling agent is a modified signaling agent and the mutations in the modified signaling agent allow for attenuation of activity.

85. The Fc-based chimeric protein complex of claim 84, wherein agonistic or antagonistic activity is attenuated.

86. The Fc-based chimeric protein complex of any one of claims 66-85, wherein the modified signaling agent is selected from an interferon, an interleukin, and a tumor necrosis factor.

87. The Fc-based chimeric protein complex of any one of claims 66-86, wherein the modified signaling agent is selected from human: IFNα2, IFNα1, IFNβ, IFNγ, consensus interferon, TNF, TNFR, TGF-α, TGF-β, VEGF, EGF, PDGF, FGF, TRAIL, IL-1β, IL-2, IL-3, IL-4, IL-6, IL-10, IL-12, IL-13, IL-15, IL-18, IL-33, IGF-1, or EPO.

88. The Fc-based chimeric protein complex of claim 87, wherein the human IFNα2 comprises one or more mutations selected from R33A, T106X_3, R120E, R144X_1 A145X_2, M148A, R149A, and L153A and with respect to the amino acid sequence of SEQ ID NO: 1 or 2, wherein X_1 is selected from A, S, T, Y, L, and I, wherein X_2 is selected from G, H, Y, K, and D, and wherein X_3 is selected from A and E.

89. The Fc-based chimeric protein complex of claim 87, wherein the human IFNβ comprises one or more mutations selected from W22G, R27G, L32A, L32G, R35A, R35G, V148G, L151G, R152A, and R152G with respect to the amino acid sequence of SEQ ID NO: 3.

90. The Fc-based chimeric protein complex of claim 87, wherein the human IL-1β comprises one or more mutations selected from A117G/P118G, R120G, R120A, L122A, T125G/L126G, R127G, Q130A, Q130W, Q131G, K132A, S137G/Q138Y, L145G, H146A, H146G, H146E, H146N, H146R, L145A/L147A, Q148E, Q148G, Q148L, Q148G/Q150G, Q150G/D151A, M152G, F162A, F162A/Q164E, F166A, Q164E/E167K, N169G/D170G, I172A, V174A, K208E, K209A, K209D, K209A/K210A, K219S, K219Q, E221S, E221K, E221S/N224A, N224S/K225S, E244K, and N245Q with respect to the amino acid sequence of SEQ ID NO: 17.

91. The Fc-based chimeric protein complex of claim 87, wherein the human IL-2 comprises one or more mutations selected from R38A, F42A, Y45A, E62A, N88R, N88I, N88G, D20H, Q126L, Q126F, D109, and C125 with respect to the amino acid sequence of SEQ ID NO: 18.

92. The Fc-based chimeric protein complex of claim 87, wherein the human TNFα comprises one or more mutations selected from R32G, N34G, Q67G, H73G, L75G, L75A, L75S, T77A, S86G, Y870, Y87L, Y87A, Y87F, V91G, V91A, I97A, I97Q, I97S, T105G, P106G, A109Y, P113G, Y115G, Y115A, E127G, N137G, D143N, A145G, A145T, and Y87Q/I97A with respect to the amino acid sequence of SEQ ID NO: 14.

93. The Fc-based chimeric protein complex of claim 87, wherein the signaling agent is a modified IFNα2, optionally with a R149A mutation with respect to the amino acid sequence of SEQ ID NO: 1 or 2.

94. The Fc-based chimeric protein complex of claim 88 or 93, wherein the targeting moiety binds to Clec9A and the signaling agent is modified IFNα2, optionally having one or more of the following mutations: R33A, R144A, R144I, R144L, R144S, R144T, R144Y, A145D, A145G, A145H, A145K, A145Y, M148A, and L153A.

95. The Fc-based chimeric protein complex of claim 93, wherein the targeting moiety binds to PD-L1 and the signaling agent is modified IFNα2.

96. The Fc-based chimeric protein complex of claim 93, wherein the targeting moiety binds to PD-1 and the signaling agent is modified IFNα2.

97. The Fc-based chimeric protein complex of claim 93, wherein:

(i) the targeting moiety binds to Clec4c and the signaling agent is modified IFNα2, or

(ii) the targeting moiety binds to XCR1 and the signaling agent is modified IFNα2.

98. The Fc-based chimeric protein complex of claim 93, wherein the targeting moiety binds to CD20 and the signaling agent is modified IFNα2.

99. The Fc-based chimeric protein complex of claim 93, wherein the targeting moiety binds to CD13 and the signaling agent is modified IFNα2.

100. The Fc-based chimeric protein complex of claim 93, wherein the targeting moiety binds to FAP and the signaling agent is modified IFNα2.

101. The Fc-based chimeric protein complex of claim 93, wherein the targeting moiety binds to CD8 and the signaling agent is modified IFNα2.

102. The Fc-based chimeric protein complex of claim 93, wherein the targeting moiety binds to Flt3 and optionally comprises the extracellular domain of Flt3L, or a functional portion thereof, and the signaling agent is modified IFNα2.

103. The Fc-based chimeric protein complex of claim 83, wherein the targeting moiety is an scFv against PD-L1 and the signaling agent is wild type IFNα2.

104. The Fc-based chimeric protein complex of claim 93, wherein the targeting moiety comprises the extracellular domain of PD-L1, or a functional portion thereof, and the signaling agent is modified IFNα2.

105. The Fc-based chimeric protein complex of claim 93, wherein the targeting moiety comprises the extracellular domain of PD-1, or a functional portion thereof, and the signaling agent is modified IFNα2.

106. The Fc-based chimeric protein complex of claim 93, wherein the targeting moiety comprises the NGR peptide and the signaling agent is modified IFNα2.

107. The Fc-based chimeric protein complex of claim 87, wherein the signaling agent is a wildtype IFNβ or a modified IFNβ.

108. The Fc-based chimeric protein complex of claim 107, wherein the targeting moiety binds to Clec9A and the signaling agent is modified IFNβ.

109. The Fc-based chimeric protein complex of claim 87, wherein the signaling agent is a wildtype IL-1β or a modified IL-1β.

110. The Fc-based chimeric protein complex of claim 109, wherein the targeting moiety binds to CD8 and the signaling agent is modified IL-1β.

111. The Fc-based chimeric protein complex of claim 87, wherein the signaling agent is a wildtype TNFα or a modified TNFα.

112. The Fc-based chimeric protein complex of claim 111, wherein the targeting moiety binds to CD20 and the signaling agent is modified TNFα.

113. The Fc-based chimeric protein complex of any one of claims 66-112, wherein the chimeric protein complex further comprises a second targeting moiety.

114. The Fc-based chimeric protein complex of claim 113, wherein the second targeting moiety binds to one of the following targets: CD8, CD13, CD20, Clec9A, Clec4c, PD-1, PD-L1, PD-L2, SIRP1α, FAP, XCR1, tenascin CA1, Flt3, or an ECM protein.

115. The Fc-based chimeric protein complex of any one of claims 66-114, wherein the chimeric protein complex further comprises a second signaling agent.

116. The Fc-based chimeric protein complex of claim 115, wherein the second signaling agent is a wild type or modified signaling agent.

117. The Fc-based chimeric protein complex of claim 116, wherein the second signaling agent is selected from human: IFNα2, IFNα1, IFNβ, IFNγ, consensus interferon, TNFα, TNFR, TGF-α, TGF-β, VEGF, EGF, PDGF, FGF, TRAIL, IL-1β, IL-2, IL-3, IL-4, IL-6, IL-10, IL-12, IL-13, IL-15, IL-18, IL-33, IGF-1, or EPO.

118. A method for treating or preventing cancer, comprising administering to a patient in need thereof an effective amount of the Fc-based chimeric protein complex of any one of claims 66-117.

119. A use of the Fc-based chimeric protein complex of any one of claims 66-117 for treating or preventing cancer.

120. A use of the Fc-based chimeric protein complex of any one of claims 66-117 for the preparation of a medicament for the treatment of prevention of cancer.

121. The method of claim 118 or the use of claim 119 or claim 120, wherein the cancer is selected form one or more of basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and central nervous system cancer; breast cancer; cancer of the peritoneum; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer (including gastrointestinal cancer); glioblastoma; hepatic carcinoma; hepatoma; intra-epithelial neoplasm; kidney or renal cancer; larynx cancer; leukemia; liver cancer; lung cancer (*e.g.*, small-cell lung cancer, non-small cell lung cancer,

adenocarcinoma of the lung, and squamous carcinoma of the lung); melanoma; myeloma; neuroblastoma; oral cavity cancer (lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; salivary gland carcinoma; sarcoma; skin cancer; squamous cell cancer; stomach cancer; testicular cancer; thyroid cancer; uterine or endometrial cancer; cancer of the urinary system; vulval cancer; lymphoma including Hodgkin's and non-Hodgkin's lymphoma, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia; chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; as well as other carcinomas and sarcomas; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses; edema (*e.g.* that associated with brain tumors); and Meigs' syndrome.

122. A method for treating or preventing an autoimmune disease, neurodegenerative disease, metabolic disease, and/or cardiovascular disease, comprising administering to a patient in need thereof an effective amount of effective amount of the Fc-based chimeric protein complex of any one of claims 66-117.

123. The use of the Fc-based chimeric protein complex of any one of claims 66-117 for treating or preventing an autoimmune disease, neurodegenerative disease, metabolic disease, and/or cardiovascular disease.

124. The use of the Fc-based chimeric protein complex of any one of claims 66-117 for the preparation of a medicament for the treatment of prevention of an autoimmune disease, neurodegenerative disease, metabolic disease, and/or cardiovascular disease.

125. The method of claim 122 or the use of claim 123 or claim 124, wherein the autoimmune disease, neurodegenerative disease, metabolic disease, and/or cardiovascular disease is selected from multiple sclerosis, diabetes mellitus, lupus, celiac disease, Crohn's disease, ulcerative colitis, Guillain-Barre syndrome, scleroderms, Goodpasture's syndrome, Wegener's granulomatosis, autoimmune epilepsy, Rasmussen's encephalitis, Primary biliary sclerosis, Sclerosing cholangitis, Autoimmune hepatitis, Addison's disease, Hashimoto's thyroiditis, Fibromyalgia, Menier's syndrome; transplantation rejection (*e.g.*, prevention of allograft rejection) pernicious anemia, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, Sjogren's syndrome, lupus erythematosus, myasthenia gravis, Reiter's syndrome, and Grave's disease.

126. An Fc-based chimeric protein complex, where the complex is a heterodimer comprising:

(a) a targeting moiety comprising a recognition domain that recognizes and/or binds to a target;

(b) a signaling agent, wherein the signaling agent is:

i) a wild type signaling agent; or

ii) a modified signaling agent that has one or more mutations that confer improved safety relative to the wild type signaling agent; and

(c) an Fc domain, the Fc domain comprising an Fc chain and optionally having one or more mutations promoting Fc chain pairing of the Fc domain and optionally further having one or more mutations that reduce or eliminate one or more effector functions of the Fc domain, and/or stabilizes a hinge region in the Fc domain.

127. The Fc-based chimeric protein complex of claim 126, further comprising one or more linkers.

128. The Fc-based chimeric protein complex of any one of claims 126 or 127, wherein the Fc chains of the Fc domain are selected from IgG, IgA, IgD, IgM, or IgE.

129. The Fc-based chimeric protein complex of claim 128, wherein the IgG is selected from IgG1, IgG2, IgG3, or IgG4.

130. The Fc-based chimeric protein complex of claim 128, wherein the Fc chains of the Fc domain are selected from human IgG, IgA, IgD, IgM, or IgE.

131. The Fc-based chimeric protein complex of claim 130, wherein the human IgG is selected from human IgG1, IgG2, IgG3, or IgG4.

132. The Fc-based chimeric protein complex of any one of claims 126-131, wherein the signaling agent is a modified signaling agent and the modified signaling agent has reduced affinity or activity at the signaling agent's receptor relative to a wild type signaling agent.

133. The Fc-based chimeric protein complex of claim 132, wherein the signaling agent is a modified signaling agent and the targeting moiety restores the modified signaling agent's affinity or activity at the signaling agent's receptor.

134. The Fc-based chimeric protein complex of any one of claims 126-133, wherein the Fc chain pairing is promoted by ionic pairing and/or a knob-in-hole pairing.

135. The Fc-based chimeric protein complex of any one of claims 126-134 wherein the one or more mutations to the Fc domain results in an ionic pairing between the Fc chains in the Fc domain.

136. The Fc-based chimeric protein complex of any one of claims 126-135, wherein the one or more mutations to the Fc domain results in a knob-in-hole pairing of the Fc domain.

137. The Fc-based chimeric protein complex of any one of claims 126-136, wherein the one or more mutations to the Fc domain results in the reduction or elimination of the effector function of the Fc domain.

138. The Fc-based chimeric protein complex of any one of claims 126-137, wherein the targeting moiety comprise a recognition domain that recognizes and/or binds an antigen or receptor on a tumor cell, and/or tumor stroma, and/or ECM, and/or immune cell.

139. The Fc-based chimeric protein complex of claim 138, wherein the immune cell is selected from a T cell, a B cell, a dendritic cell, a macrophage, a neutrophil, and a NK cell.

140. The Fc-based chimeric protein complex of any one of claims 126-139, wherein the targeting moiety comprises a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein, a darpin, an anticalin, an adnectin, an aptamer, a Fv, a Fab, a Fab', a $F(ab')_2$, a peptide mimetic molecule, a natural ligand for a receptor, or a synthetic molecule.

141. The Fc-based chimeric protein complex of any one of claims 126-140, wherein the targeting moiety comprises a VHH.

142. The Fc-based chimeric protein complex of any one of claims 126-141, wherein the targeting moiety recognizes and/or binds to its target without substantially neutralizing the target's activity or wherein the targeting moiety recognizes and/or binds to its target and substantially neutralizes the target's activity.

143. The Fc-based chimeric protein complex of any one of claims 126-142, wherein the targeting moiety directly or indirectly recruits immune cells to tumor cells or to the tumor microenvironment.

144. The Fc-based chimeric protein complex of any one of claims 126-143, wherein the targeting moiety enhances antigen presentation.

145. The Fc-based chimeric protein complex of any one of claims 126-144, wherein the targeting moiety enhances tumor antigen presentation, optionally by dendritic cells.

146. The Fc-based chimeric protein complex of any one of claims 126-145, wherein the targeting moiety binds to one of the following targets: CD8, CD13, CD20, Clec9A, Clec4c, PD-1, PD-L1, PD-L2, SIRP1α, FAP, XCR1, tenascin CA1, Flt3, or an ECM protein.

147. The Fc-based chimeric protein complex of any one of claims 126-146, wherein the signaling agent is a modified signaling agent and the mutations in the modified signaling agent allows for attenuation of activity.

148. The Fc-based chimeric protein complex of claim 147, wherein agonistic or antagonistic activity is attenuated.

149. The Fc-based chimeric protein complex of any one of claims 126-148, wherein the signaling agent is a modified signaling agent and the modified signaling agent is selected from an interferon, an interleukin, and a tumor necrosis factor.

150. The Fc-based chimeric protein complex of any one of claims 126-149, wherein the modified signaling agent is selected from human: IFNα2, IFNα1, IFNβ, IFNγ, consensus interferon, TNFα, TNFR, TGF-α, TGF-β, VEGF, EGF, PDGF, FGF, TRAIL, IL-1β, IL-2, IL-3, IL-4, IL-6, IL-10, IL-12, IL-13, IL-15, IL-18, IL-33, IGF-1, or EPO.

151. The Fc-based chimeric protein complex of claim 150, wherein the human IFNα2 comprises one or more mutations selected from R33A, $T106X_3$, R120E, $R144X_1$ $A145X_2$, M148A, R149A, and L153A and with respect to the amino acid sequence of SEQ ID NO: 1 or 2, wherein X_1 is selected from A, S, T, Y, L, and I, wherein X_2 is selected from G, H, Y, K, and D, and wherein X_3 is selected from A and E.

152. The Fc-based chimeric protein complex of claim 150, wherein the human IFNβ comprises one or more mutations selected from W22G, R27G, L32A, L32G, R35A, R35G, V148G, L151G, R152A, and R152G with respect to the amino acid sequence of SEQ ID NO: 3.

153. The Fc-based chimeric protein complex of claim 150, wherein the human IL-1β comprises one or more mutations selected from A117G/P118G, R120G, R120A, L122A, T125G/L126G, R127G, Q130A, Q130W, Q131G, K132A, S137G/Q138Y, L145G, H146A, H146G, H146E, H146N, H146R, L145A/L147A, Q148E, Q148G, Q148L, Q148G/Q150G, Q150G/D151A, M152G, F162A, F162A/Q164E, F166A, Q164E/E167K, N169G/D170G, I172A, V174A, K208E, K209A, K209D, K209A/K210A, K219S, K219Q, E221S, E221K, E221S/N224A, N224S/K225S, E244K, and N245Q with respect to the amino acid sequence of SEQ ID NO: 17.

154. The Fc-based chimeric protein complex of claim 150, wherein the human IL-2 comprises one or more mutations selected from R38A, F42A, Y45A, E62A, N88R, N88I, N88G, D20H, Q126L, Q126F, D109, and C125 with respect to the amino acid sequence of SEQ ID NO: 18.

155. The Fc-based chimeric protein complex of claim 150, wherein the human TNFα comprises one or more mutations selected from R32G, N34G, Q67G, H73G, L75G, L75A, L75S, T77A, S86G, Y870, Y87L, Y87A, Y87F, V91G, V91A, I97A, I97Q, I97S, T105G, P106G, A109Y, P113G, Y115G, Y115A, E127G, N137G, D143N, A145G, A145T, and Y87Q/I97A with respect to the amino acid sequence of SEQ ID NO: 14.

156. The Fc-based chimeric protein complex of claim 150, wherein the signaling agent is a modified IFNα2, optionally with a R149A mutation with respect to the amino acid sequence of SEQ ID NO: 1 or 2.

157. The Fc-based chimeric protein complex of claim 151 or 156, wherein the targeting moiety binds to Clec9A and the signaling agent is modified IFNα2, optionally having one or more of the following mutations: R33A, R144A, R144I, R144L, R144S, R144T, R144Y, A145D, A145G, A145H, A145K, A145Y, M148A, and L153A.

158. The Fc-based chimeric protein complex of claim 156, wherein the targeting moiety binds to PD-L1 and the signaling agent is modified IFNα2.

159. The Fc-based chimeric protein complex of claim 156, wherein the targeting moiety binds to PD-1 and the signaling agent is modified IFNα2.

160. The Fc-based chimeric protein complex of claim 156, wherein:

(i) the targeting moiety binds to Clec4c and the signaling agent is modified IFNα2, or

(ii) the targeting moiety binds to XCR1 and the signaling agent is modified IFNα2.

161. The Fc-based chimeric protein complex of claim 156, wherein the targeting moiety binds to CD20 and the signaling agent is modified IFNα2.

162. The Fc-based chimeric protein complex of claim 156, wherein the targeting moiety binds to CD13 and the signaling agent is modified IFNα2.

163. The Fc-based chimeric protein complex of claim 156, wherein the targeting moiety binds to FAP and the signaling agent is modified IFNα2.

164. The Fc-based chimeric protein complex of claim 156, wherein the targeting moiety binds to CD8 and the signaling agent is modified IFNα2.

165. The Fc-based chimeric protein complex of claim 156, wherein the targeting moiety binds to Flt3 and optionally comprises the extracellular domain of Flt3L, or a functional portion thereof, and the signaling agent is modified IFNα2.

166. The Fc-based chimeric protein complex of claim 146, wherein the targeting moiety is an scFv against PD-L1 and the signaling agent is wild type IFNα2.

167. The Fc-based chimeric protein complex of claim 156, wherein the targeting moiety comprises the extracellular domain of PD-L1, or a functional portion thereof, and the signaling agent is modified IFNα2.

168. The Fc-based chimeric protein complex of claim 156, wherein the targeting moiety comprises the extracellular domain of PD-1, or a functional portion thereof, and the signaling agent is modified IFNα2.

169. The Fc-based chimeric protein complex of claim 156, wherein the targeting moiety binds comprises the NGR peptide and the signaling agent is modified IFNα2.

170. The Fc-based chimeric protein complex of claim 150, wherein the signaling agent is a wildtype IFNβ or a modified IFNβ.

171. The Fc-based chimeric protein complex of claim 170, wherein the targeting moiety binds to Clec9A and the signaling agent is modified IFNβ.

172. The Fc-based chimeric protein complex of claim 150, wherein the signaling agent is a wildtype IL-1β or a modified IL-1β.

173. The Fc-based chimeric protein complex of claim 172, wherein the targeting moiety binds to CD8 and the signaling agent is modified IL-1β.

174. The Fc-based chimeric protein complex of claim 150, wherein the signaling agent is a wildtype TNFα or a modified TNFα.

175. The Fc-based chimeric protein complex of claim 174, wherein the targeting moiety binds to CD20 and the signaling agent is modified TNFα.

176. The Fc-based chimeric protein complex of any one of claims 126-175, wherein the chimeric protein complex further comprises a second targeting moiety.

177. The Fc-based chimeric protein complex of claim 176, wherein the second targeting moiety binds to one of the following targets: CD8, CD13, CD20, Clec9A, Clec4c, PD-1, PD-L1, PD-L2, SIRP1α, FAP, XCR1, tenascin CA1, Flt3, or an ECM protein.

178. The Fc-based chimeric protein complex of any one of claims 126-177, wherein the chimeric protein complex further comprises a second signaling agent.

179. The Fc-based chimeric protein complex of claim 178, wherein the second signaling agent is a wild type or modified signaling agent.

180. The Fc-based chimeric protein complex of claim 179, wherein the second signaling agent is selected from human: IFNα2, IFNα1, IFNβ, IFNγ, consensus interferon, TNFα, TNFR, TGF-α, TGF-β, VEGF, EGF, PDGF, FGF, TRAIL, IL-1β, IL-2, IL-3, IL-4, IL-6, IL-10, IL-12, IL-13, IL-15, IL-18, IL-33, IGF-1, or EPO.

181. A method for treating or preventing cancer, comprising administering to a patient in need thereof an effective amount of the Fc-based chimeric protein complex of any one of claims 126-180.

182. A use of the Fc-based chimeric protein complex of any one of claims 126-180 for treating or preventing cancer.

183. A use of the Fc-based chimeric protein complex of any one of claims 126-180 for the preparation of a medicament for the treatment of prevention of cancer.

184. The method of claim 181 or the use of claim 182 or claim 183, wherein the cancer is selected form one or more of basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and central nervous system cancer; breast cancer; cancer of the peritoneum; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer (including gastrointestinal cancer); glioblastoma; hepatic carcinoma; hepatoma; intra-epithelial neoplasm; kidney or renal cancer; larynx cancer; leukemia; liver cancer; lung cancer (*e.g.*, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung); melanoma; myeloma; neuroblastoma; oral cavity cancer (lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; salivary gland carcinoma; sarcoma; skin cancer; squamous cell cancer; stomach cancer; testicular cancer; thyroid cancer; uterine or endometrial cancer; cancer of the urinary system; vulval cancer; lymphoma including Hodgkin's and non-Hodgkin's lymphoma, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia; chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; as well as other carcinomas and sarcomas; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses; edema (*e.g.* that associated with brain tumors); and Meigs' syndrome.

185. A method for treating or preventing an autoimmune disease, neurodegenerative disease, metabolic disease, and/or cardiovascular disease, comprising administering to a patient in need thereof an effective amount of effective amount of the Fc-based chimeric protein complex of any one of claims 126-180.

186. A use of the Fc-based chimeric protein complex of any one of claims 126-180 for treating or preventing an autoimmune disease, neurodegenerative disease, metabolic disease, and/or cardiovascular disease.

187. A use of the Fc-based chimeric protein complex of any one of claims 126-180 for the preparation of a medicament for the treatment of prevention of an autoimmune disease, neurodegenerative disease, metabolic disease, and/or cardiovascular disease.

188. The method of claim 185 or the use of claim 186 or claim 187, wherein the autoimmune disease, neurodegenerative disease, metabolic disease, and/or cardiovascular disease is selected from multiple sclerosis, diabetes mellitus, lupus, celiac disease, Crohn's disease, ulcerative colitis, Guillain-Barre syndrome, scleroderms, Goodpasture's syndrome, Wegener's granulomatosis, autoimmune epilepsy, Rasmussen's encephalitis, Primary biliary sclerosis, Sclerosing cholangitis, Autoimmune hepatitis, Addison's disease, Hashimoto's thyroiditis, Fibromyalgia, Menier's syndrome; transplantation rejection (*e.g.*, prevention of allograft rejection) pernicious anemia, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, Sjogren's syndrome, lupus erythematosus, myasthenia gravis, Reiter's syndrome, and Grave's disease.

189. A nucleic acid encoding an Fc-based chimeric protein complex of any one of claims 1-57, 66-117, or 126-180, or a constituent thereof.

190. The Fc-based chimeric protein complex of any one claims 1-57, 66-117, or 126-180, wherein the Fc-based chimeric protein complex is a complex of two proteins.

191. The Fc-based chimeric protein complex of claim 190, wherein the complex comprises one or more fusion proteins.

192. The Fc-based chimeric protein complex of any one claims 1-57, 66-117, 126-180, or 190-191, wherein Fc-based chimeric protein complex has a configuration and/or orientation as shown in any one of **FIGs. 1A-F, 2A-H, 3A-H, 4A-D, 5A-F, 6A-J, 7A-D, 8A-F, 9A-J, 10A-F, 11A-L, 12A-L, 13A-F, 14A-L, 15A-L, 16A-J, 17A-J, 18A-F, 19A-F, 20A-E, 38, 46A-D, 47**, and **49**.

193. The Fc-based chimeric protein complex of claim 192, wherein Fc-based chimeric protein complex has a configuration and/or orientation as shown in **FIG. 7B**.

194. The Fc-based chimeric protein complex of any one claims 1-57 or 126-180, wherein the Fc-based chimeric protein complex has a trans orientation/configuration, as relates to any targeting moiety and signaling agent, relative to each other, and/or any targeting moieties relative to each other, and/or any signaling agents relative to each other.

195. The Fc-based chimeric protein complex of any one claims 1-57 or 126-180, wherein the Fc-based chimeric protein complex has a cis orientation/configuration, as relates to any targeting moiety and signaling agent, relative to each other, and/or any targeting moieties relative to each other, and/or any signaling agents relative to each other.

196. The Fc-based chimeric protein complex of any one claims 1-57, 66-117, 126-180, or 190-195, wherein the Fc comprises L234A, L235A, and one additional mutation selected from K322A, K322Q, D265A, P32G, and P331S substitutions in human IgG1, wherein the numbering is based on the EU convention.

197. The Fc-based chimeric protein complex of any one claims 1-57, 66-117, 126-180, or 190-195, wherein the Fc comprises a S228P substitution in human IgG4, wherein the numbering is based on the EU convention.

FIG. 1A FIG. 1B FIG. 1C FIG. 1D FIG. 1E FIG. 1F

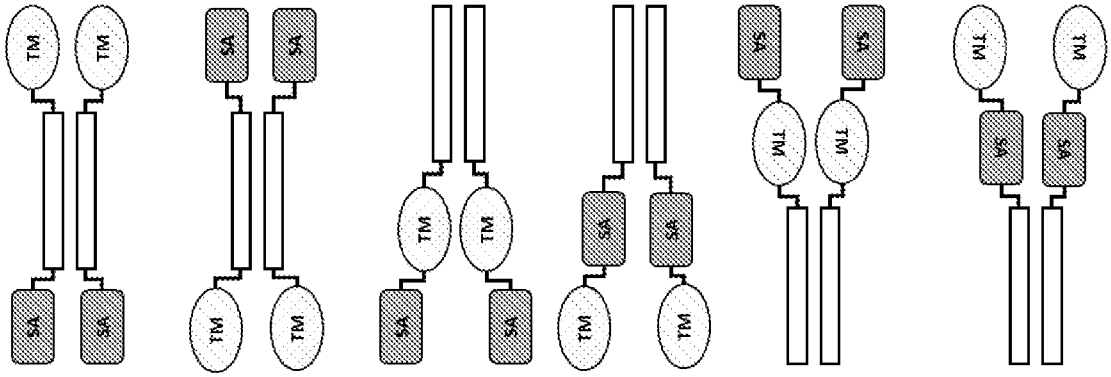


FIG. 2A FIG. 2B FIG. 2C FIG. 2D

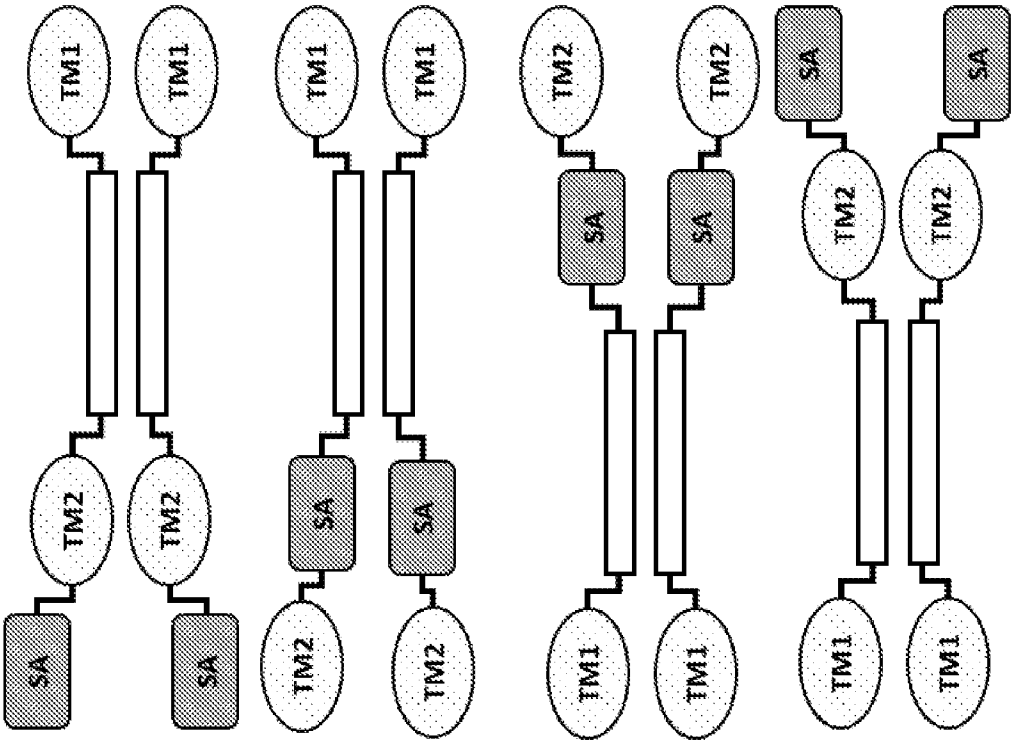


FIG. 2E

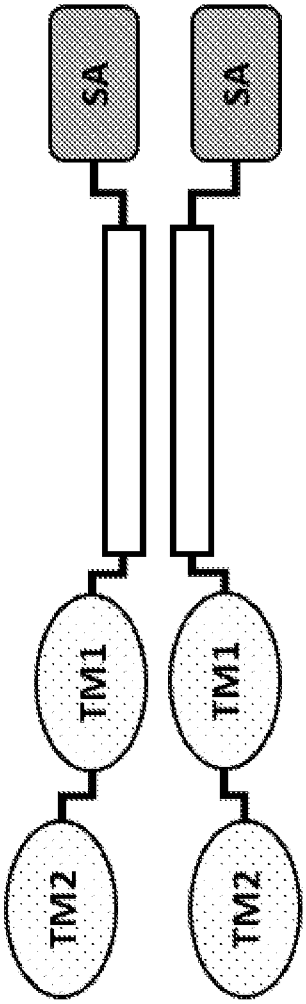


FIG. 2F

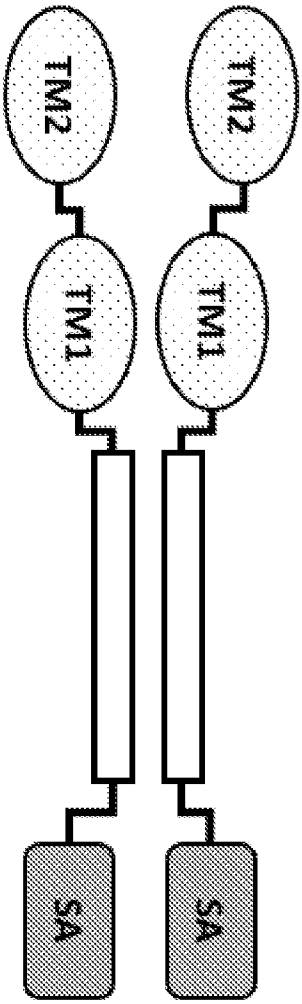


FIG. 2G

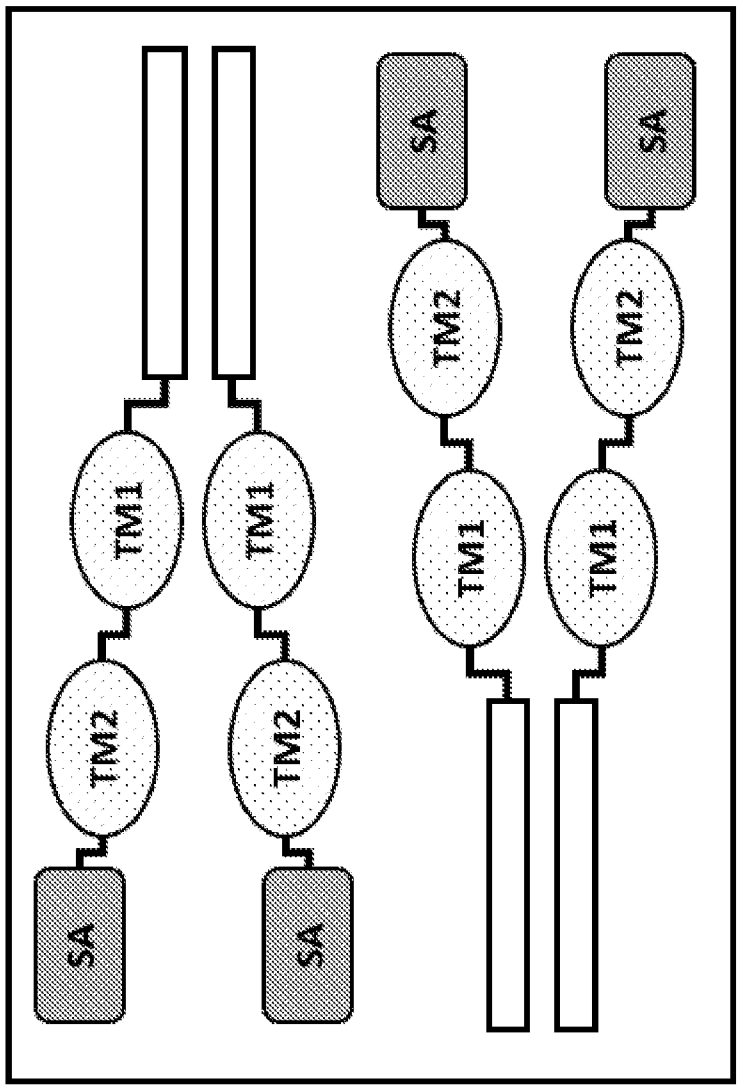


FIG. 2H

FIG. 3A FIG. 3B FIG. 3C FIG. 3D

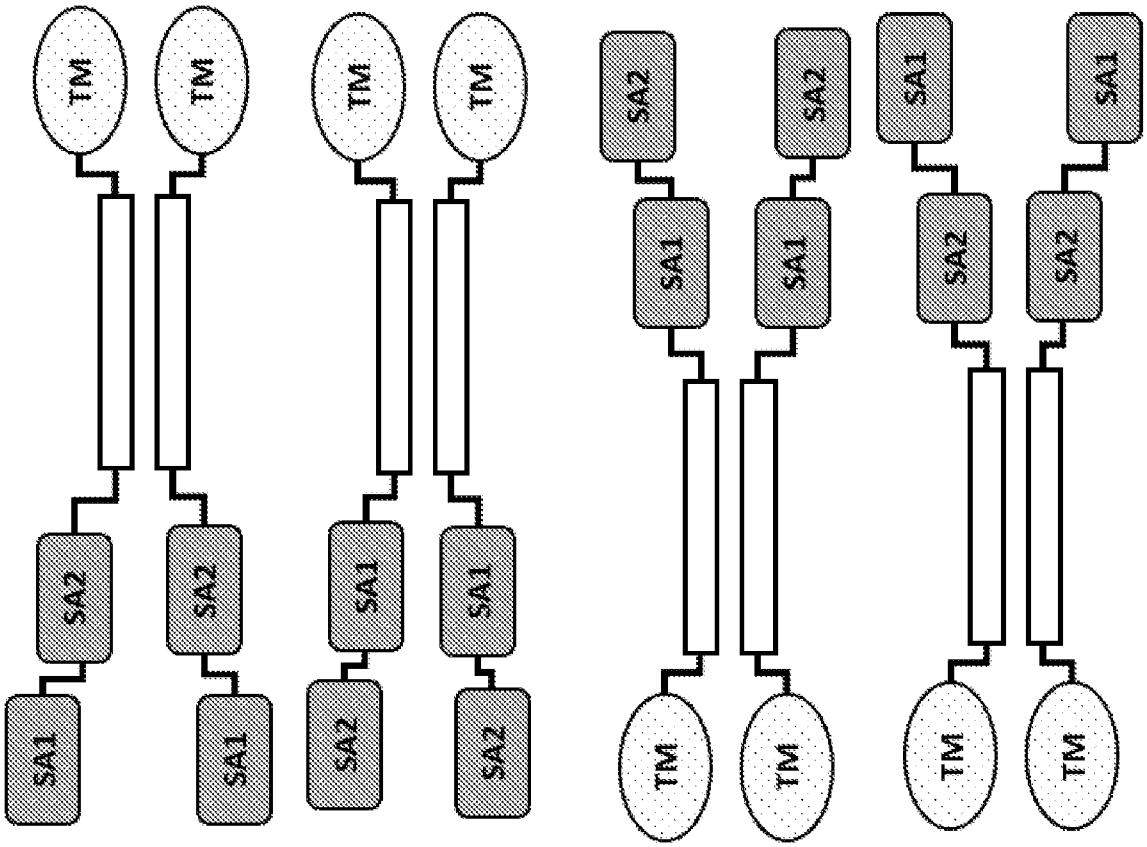


FIG. 3E

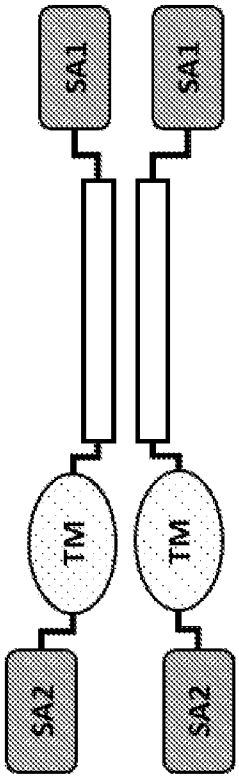


FIG. 3F

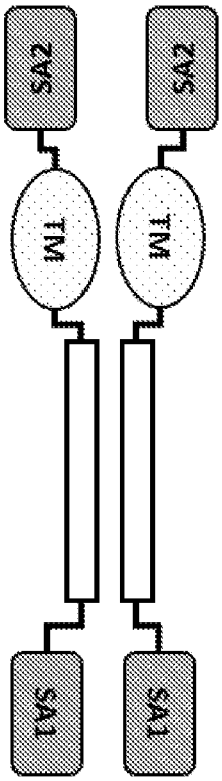


FIG. 3G

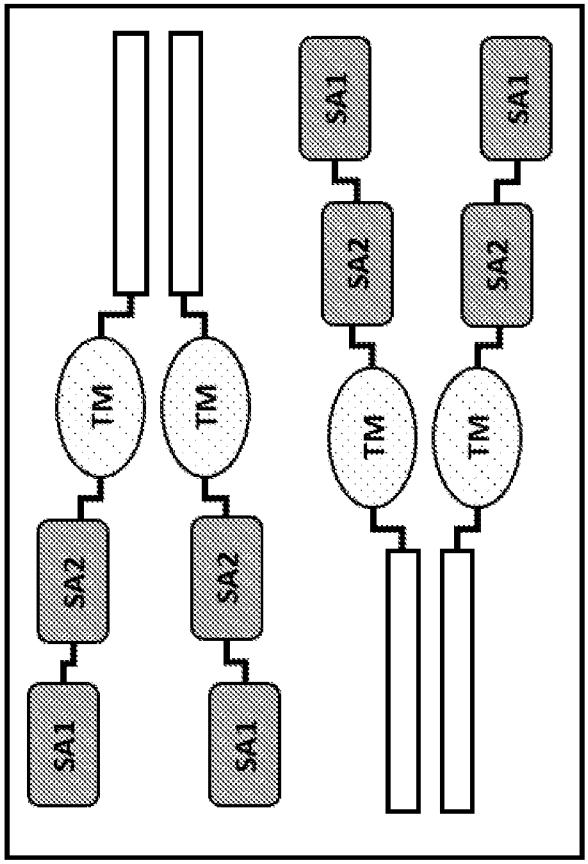


FIG. 3H

FIG. 4A FIG. 4B FIG. 4C FIG. 4D

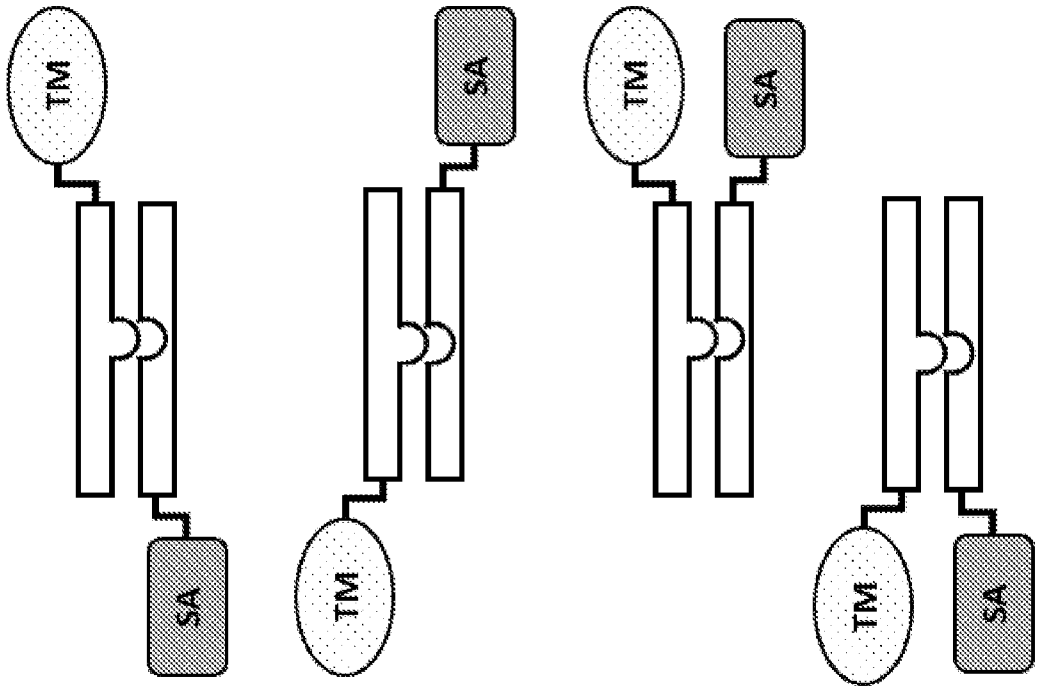


FIG. 5A FIG. 5B FIG. 5C FIG. 5D FIG. 5E FIG. 5F

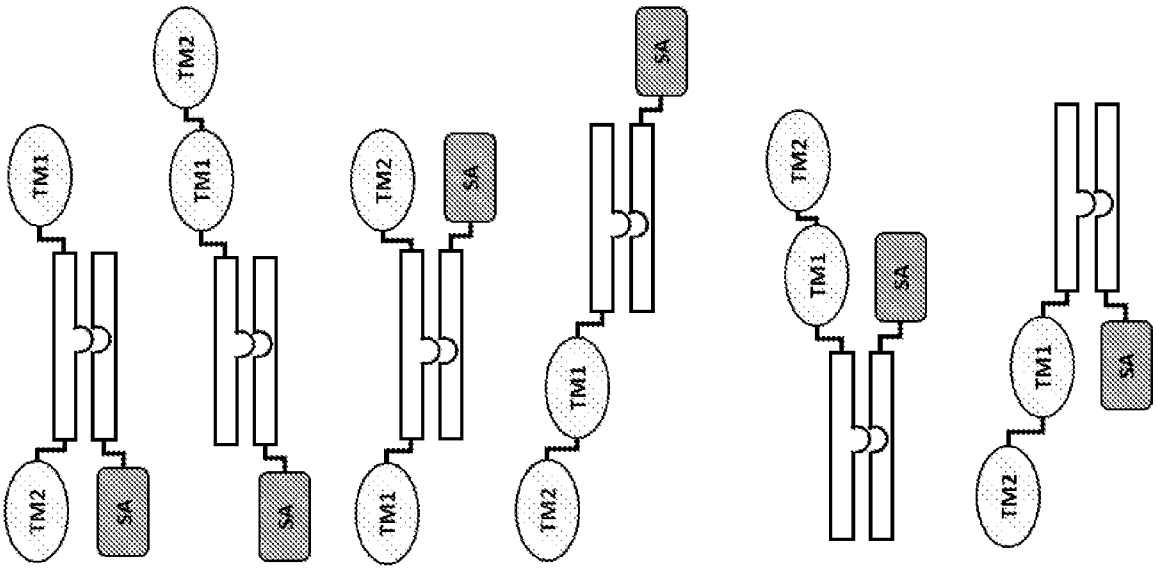


FIG. 6A FIG. 6B FIG. 6C FIG. 6D FIG. 6E FIG. 6F

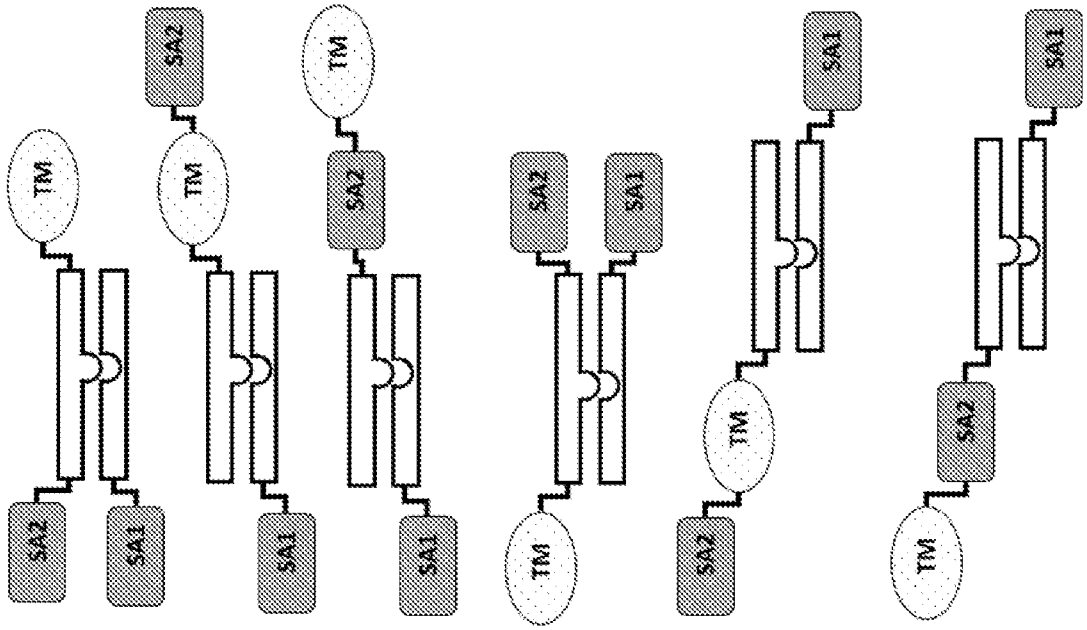


FIG. 6G

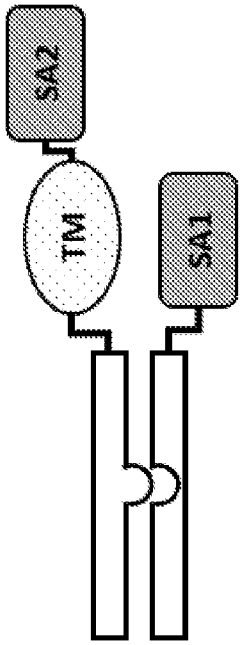


FIG. 6H

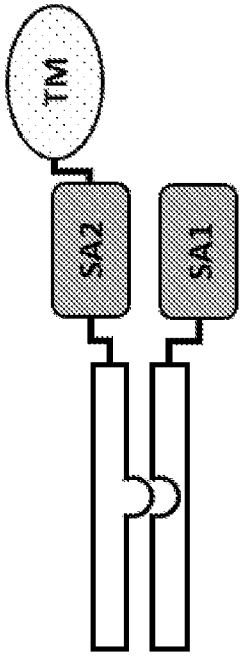


FIG. 6I

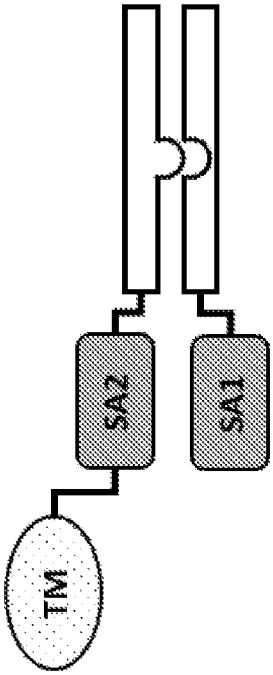


FIG. 6J

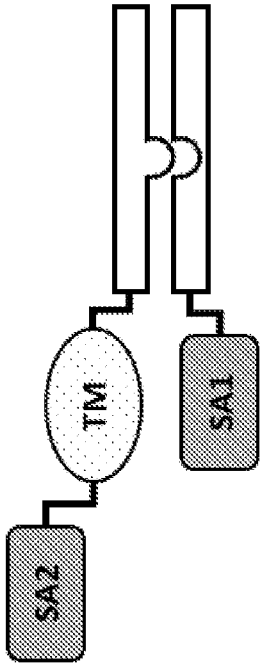


FIG. 7A FIG. 7B FIG. 7C FIG. 7D

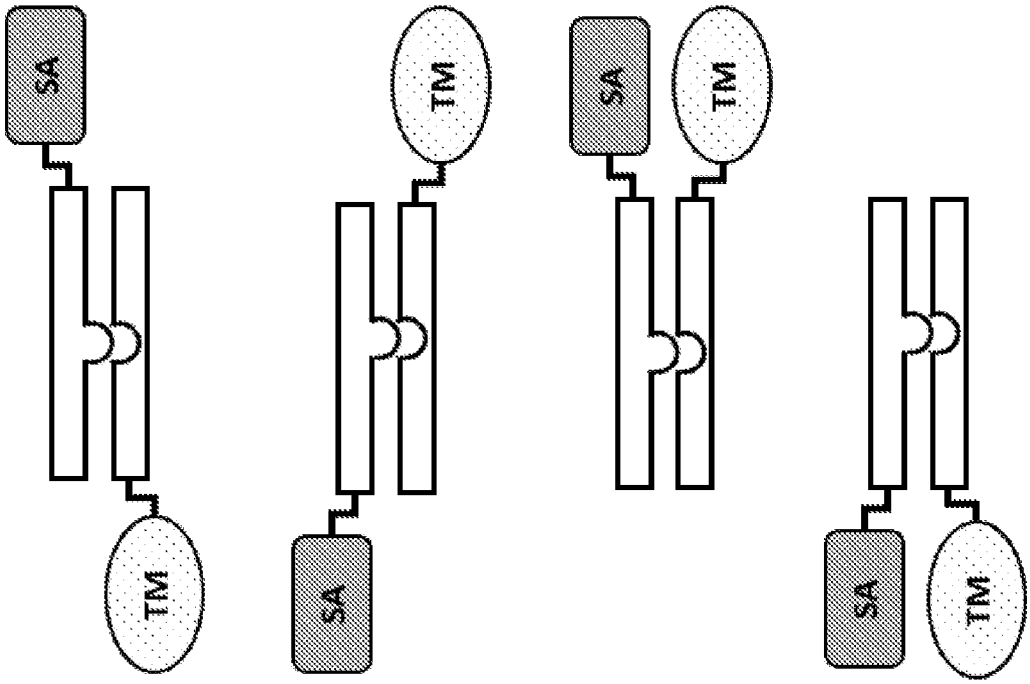


FIG. 8A FIG. 8B FIG. 8C FIG. 8D FIG. 8E FIG. 8F

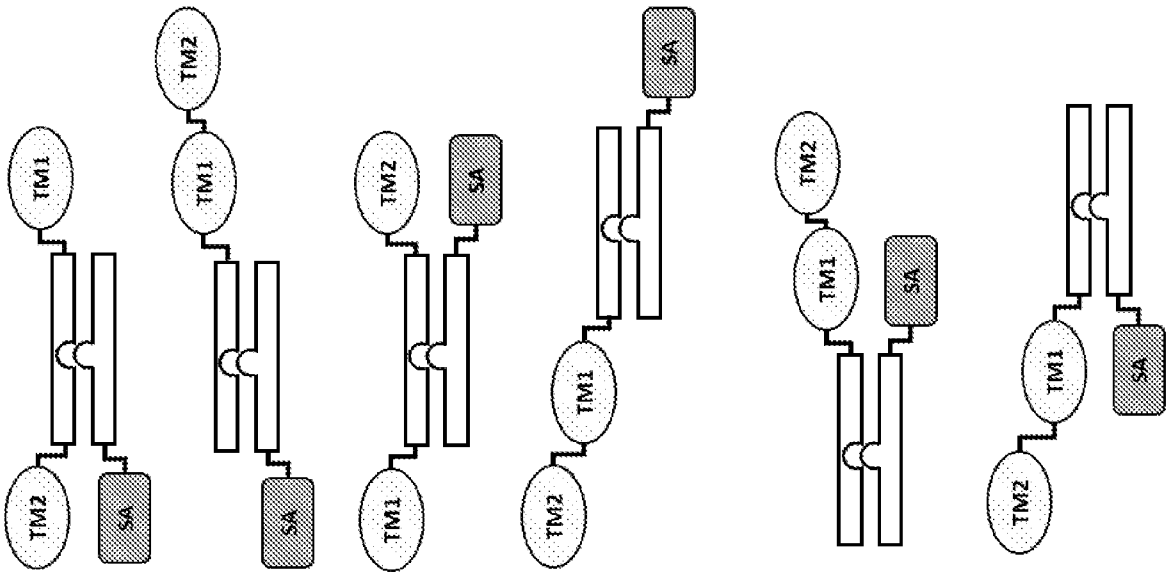


FIG. 9A FIG. 9B FIG. 9C FIG. 9D FIG. 9E

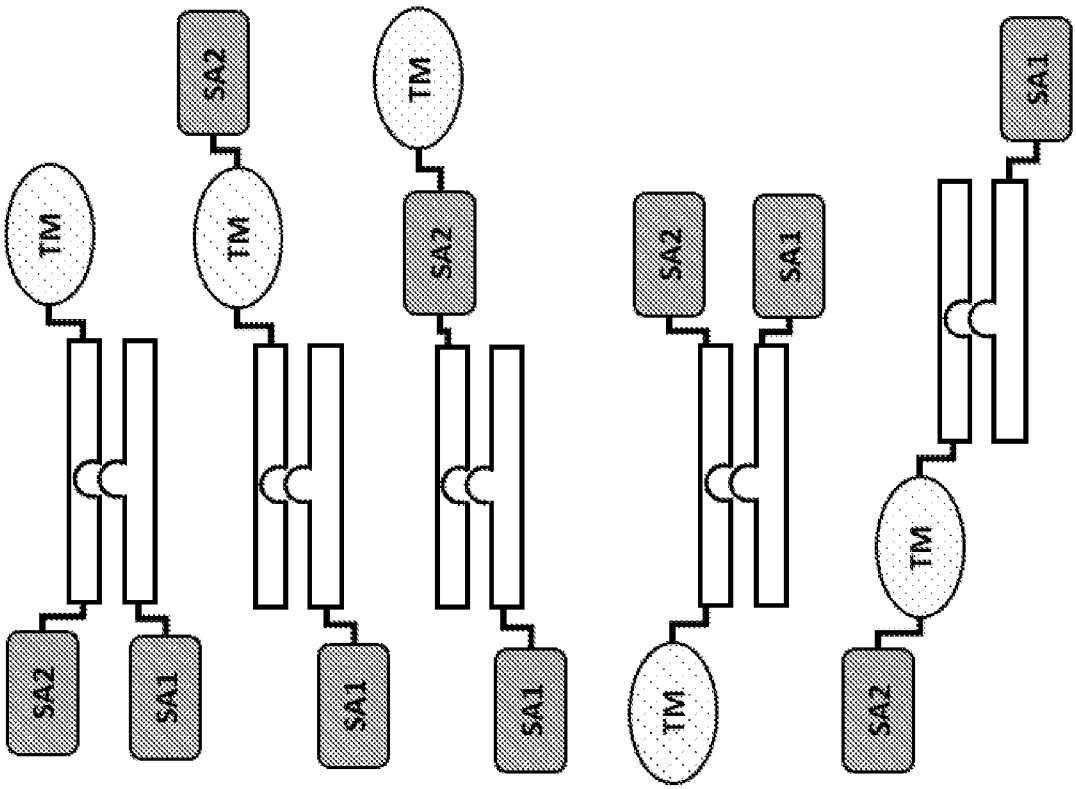


FIG. 9F FIG. 9G FIG. 9H FIG. 9I FIG. 9J

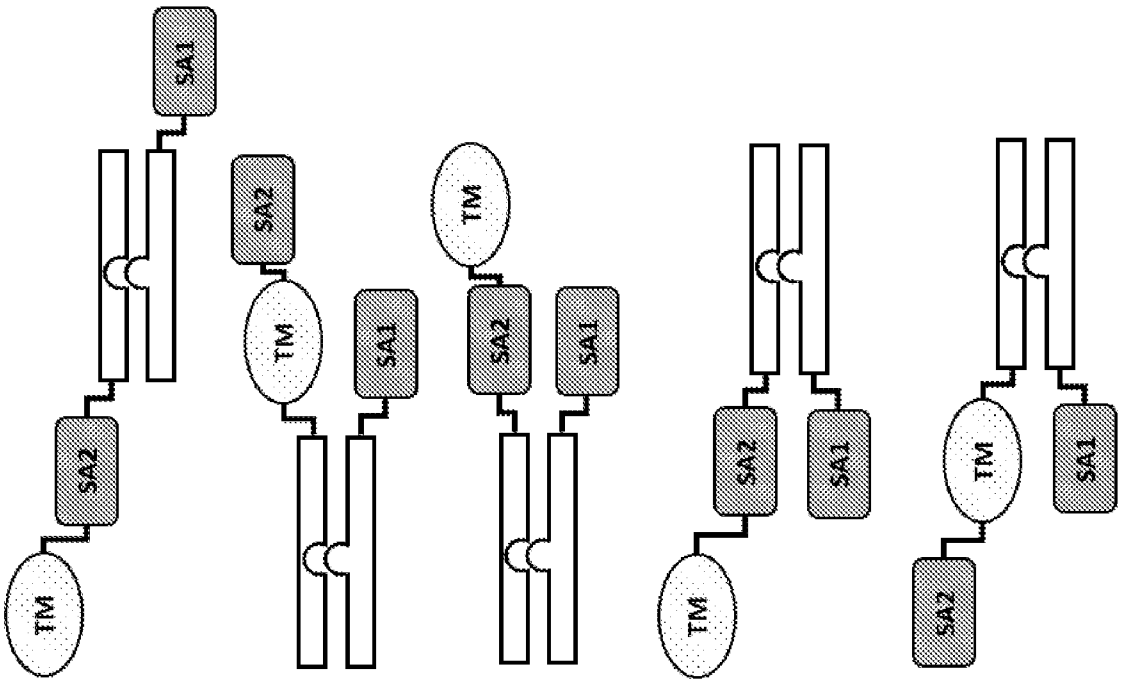


FIG. 10A FIG. 10B FIG. 10C FIG. 10D FIG. 10E FIG. 10F

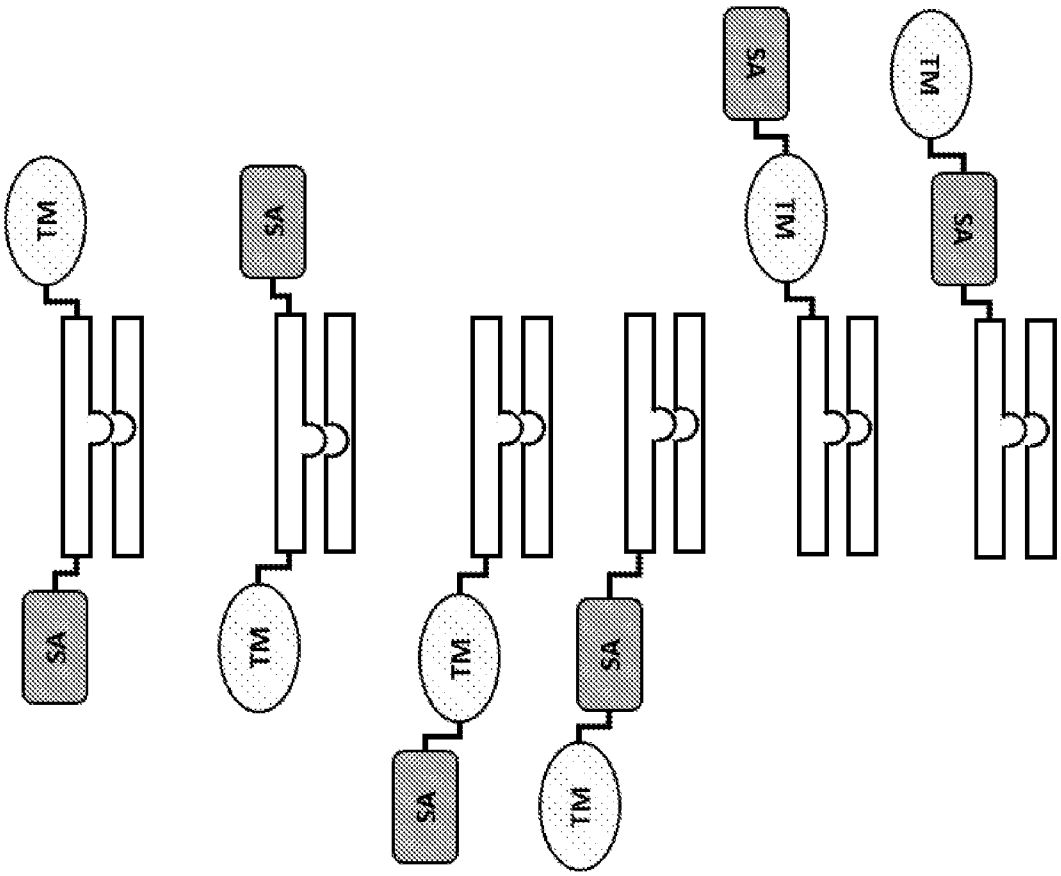


FIG. 11A FIG. 11B FIG. 11C FIG. 11D FIG. 11E

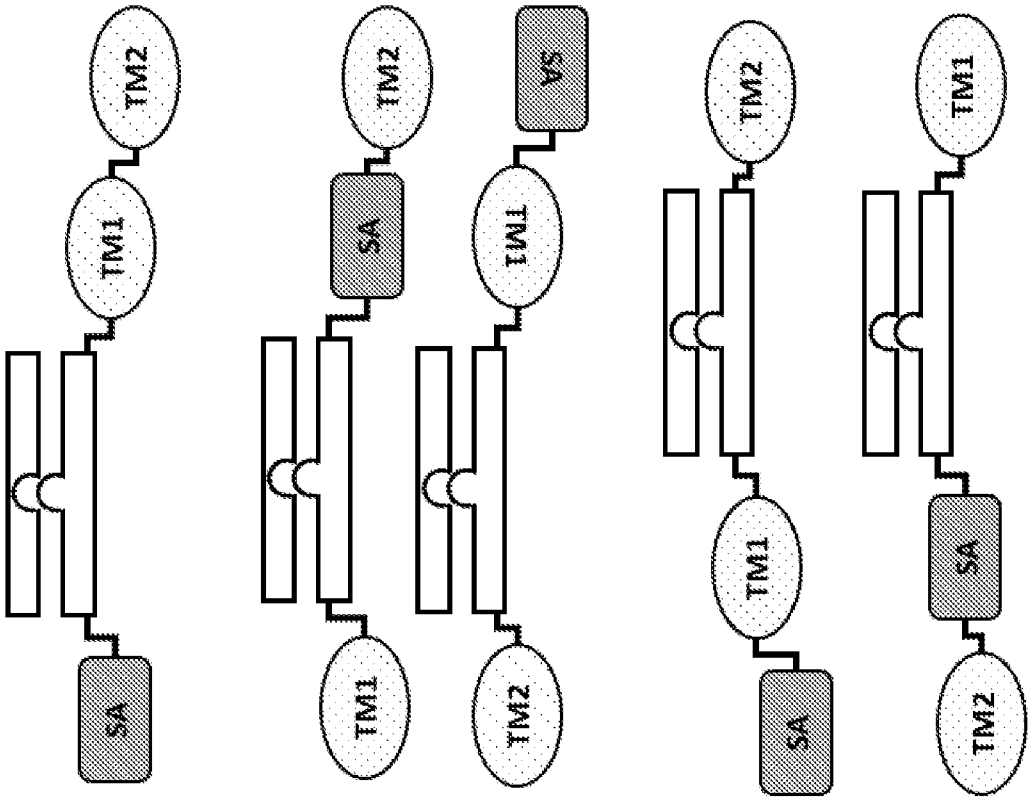


FIG. 11F FIG. 11G FIG. 11H FIG. 11I FIG. 11J FIG. 11K FIG. 11L

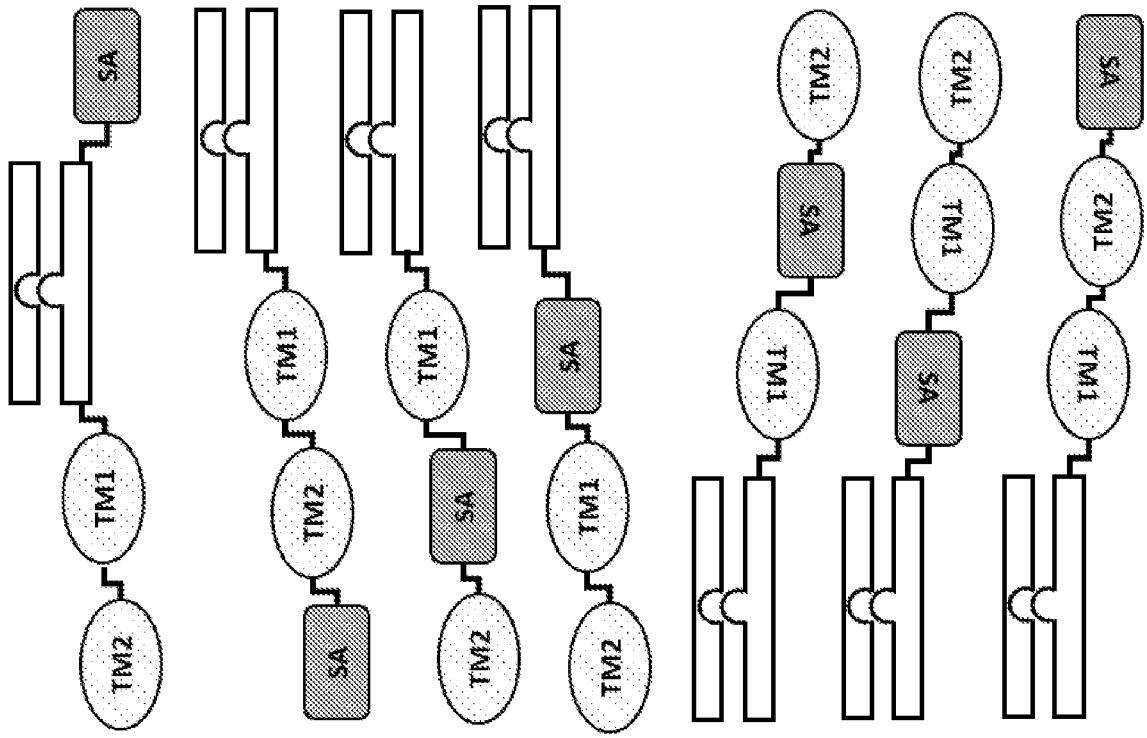


FIG. 12A FIG. 12B FIG. 12C FIG. 12D FIG. 12E FIG. 12F

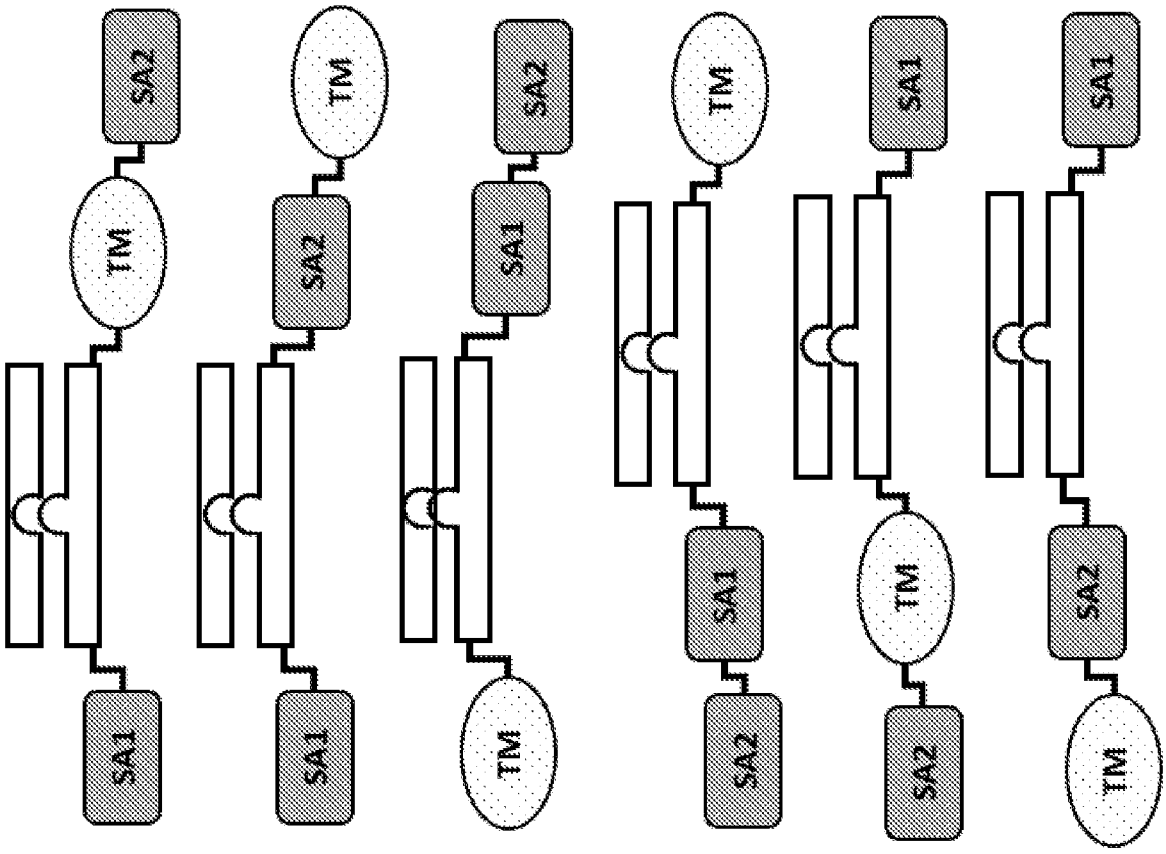


FIG. 12G FIG. 12H FIG. 12I FIG. 12J FIG. 12K FIG. 12L

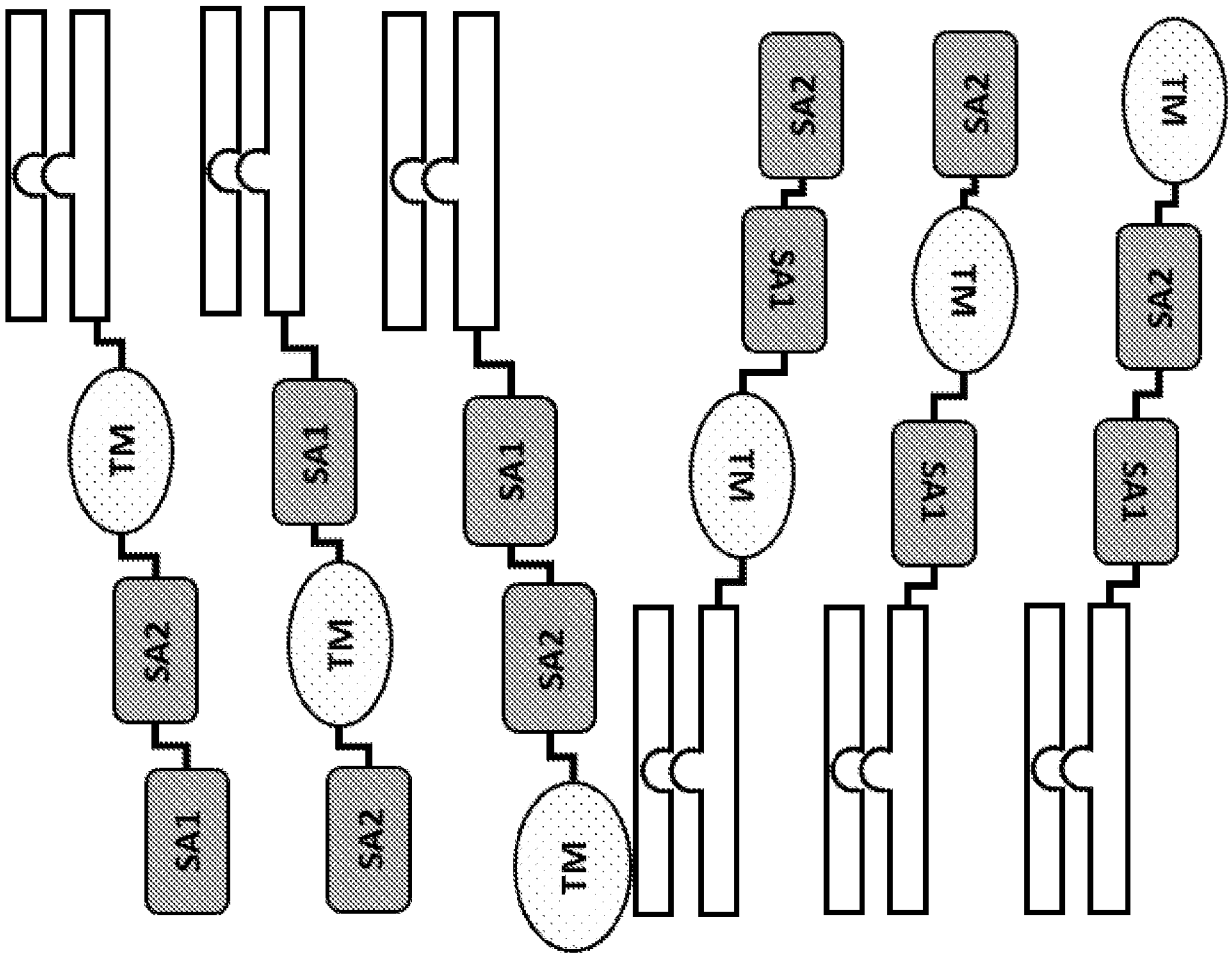


FIG. 13A FIG. 13B FIG. 13C FIG. 13D FIG. 13E FIG. 13F

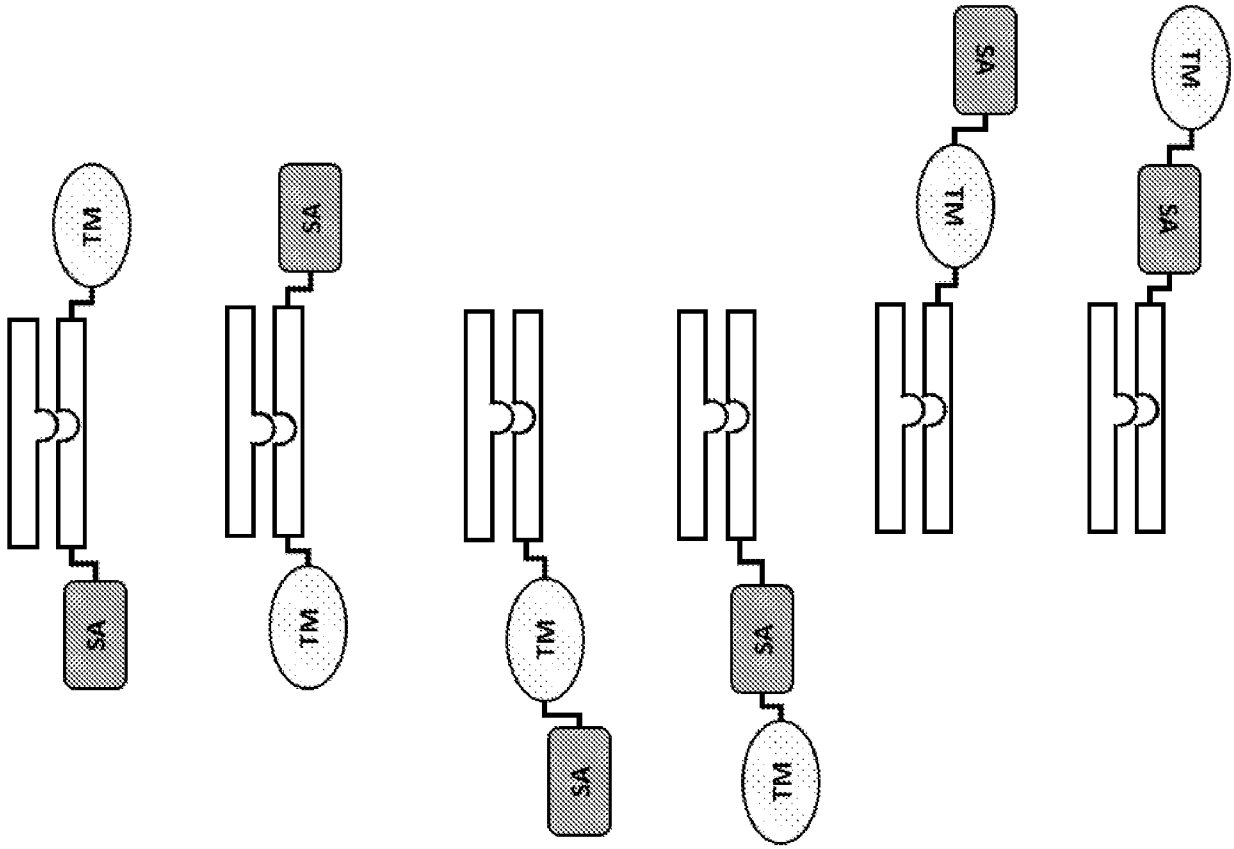


FIG. 14A FIG. 14B FIG. 14C FIG. 14D FIG. 14E FIG. 14F

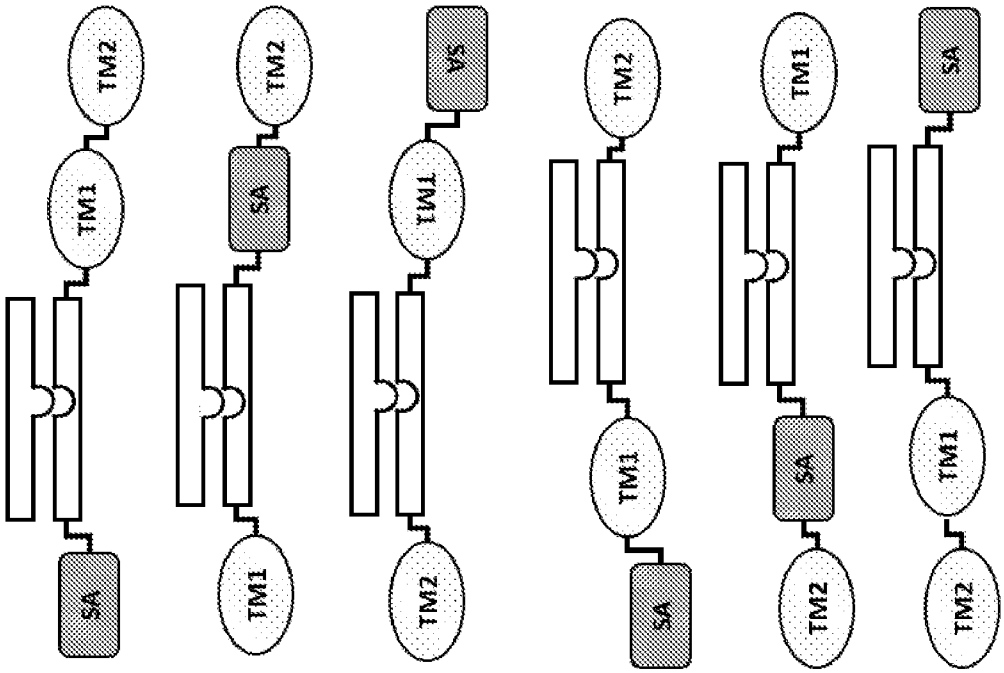


FIG. 14G FIG. 14H FIG. 14I FIG. 14J FIG. 14K FIG. 14L

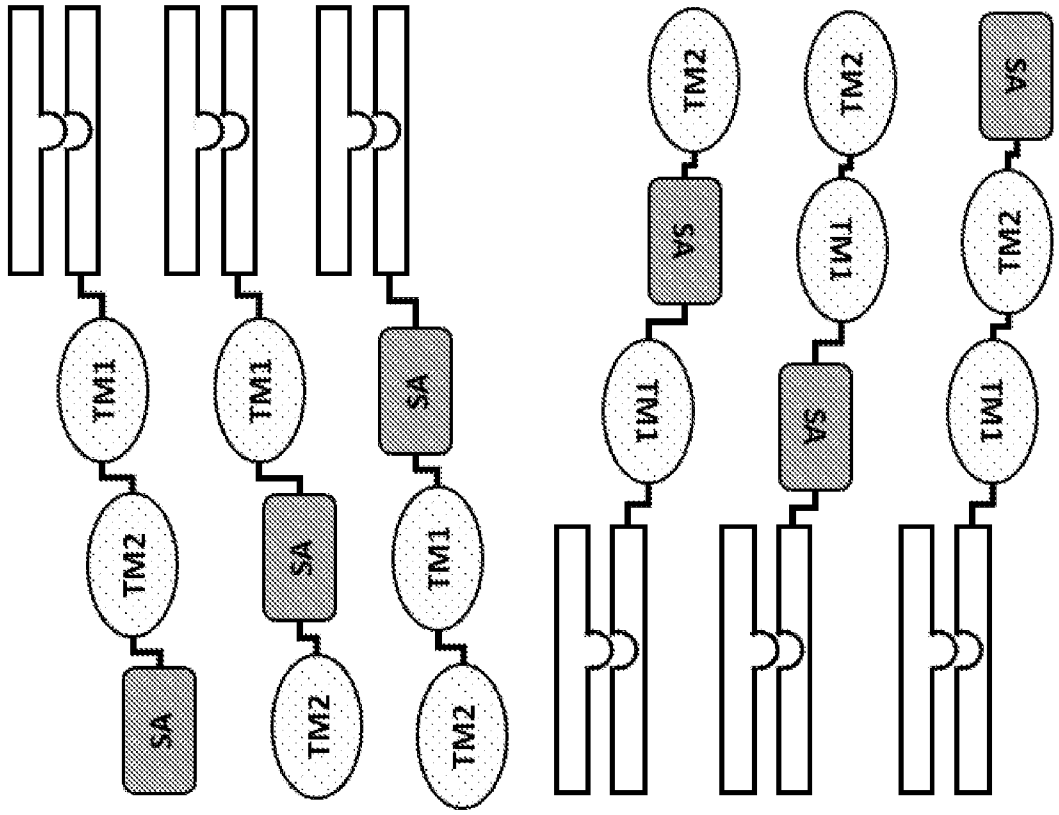


FIG. 15A FIG. 15B FIG. 15C FIG. 15D FIG. 15E FIG. 15F

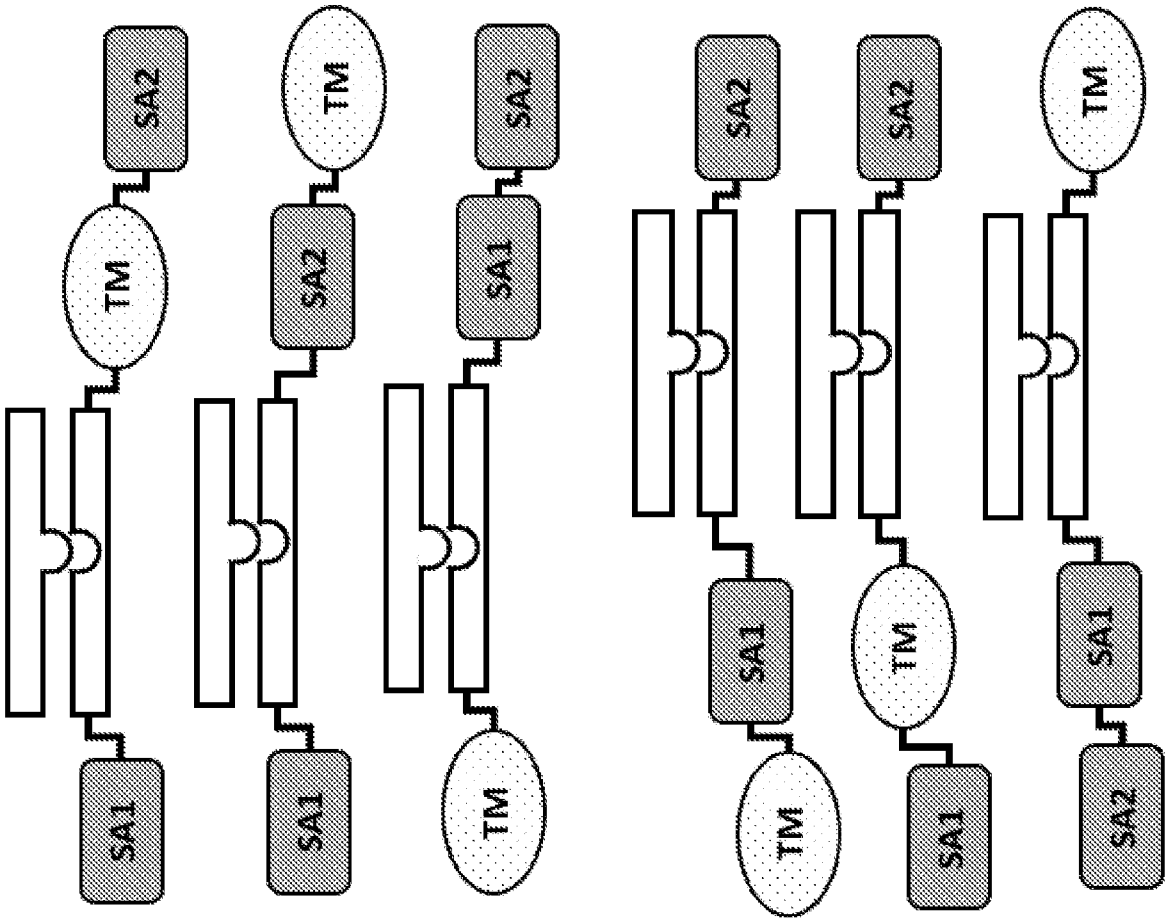


FIG. 15G FIG. 15H FIG. 15I FIG. 15J FIG. 15K FIG. 15L

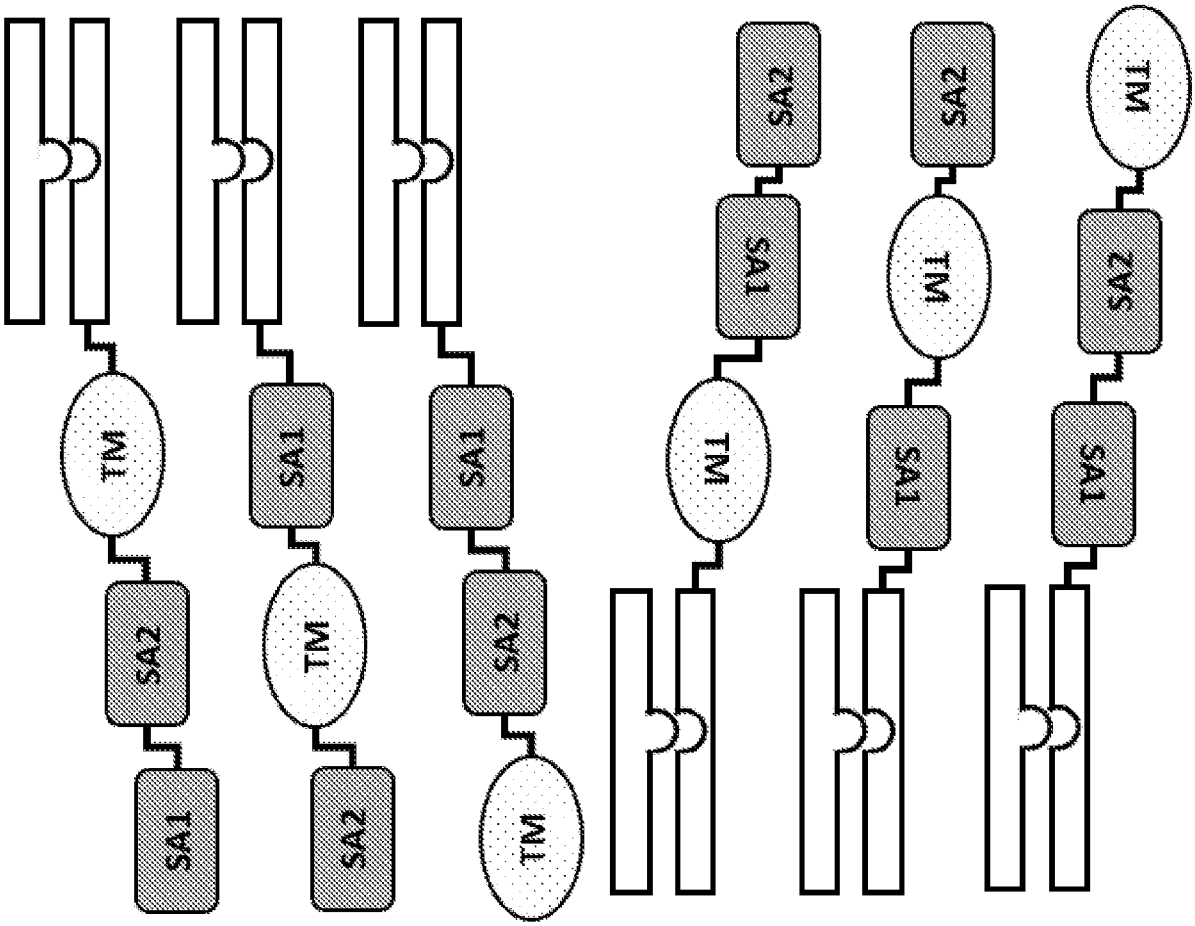


FIG. 16A FIG. 16B FIG. 16C FIG. 16D FIG. 16E

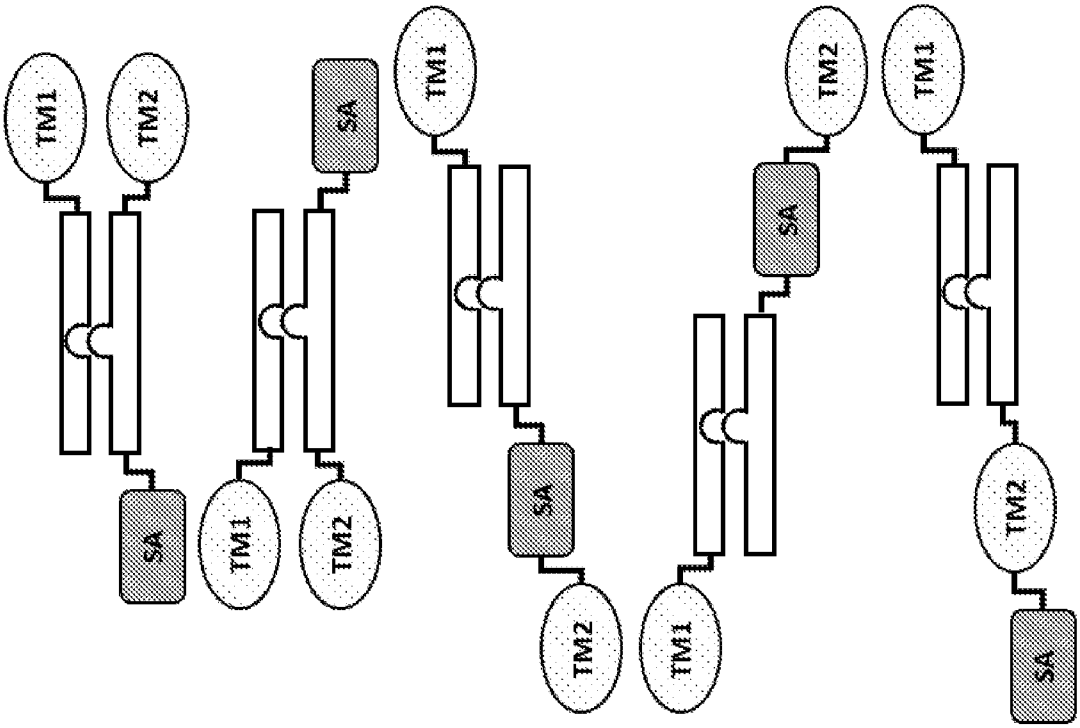


FIG. 16F FIG. 16G FIG. 16H FIG. 16I FIG. 16J

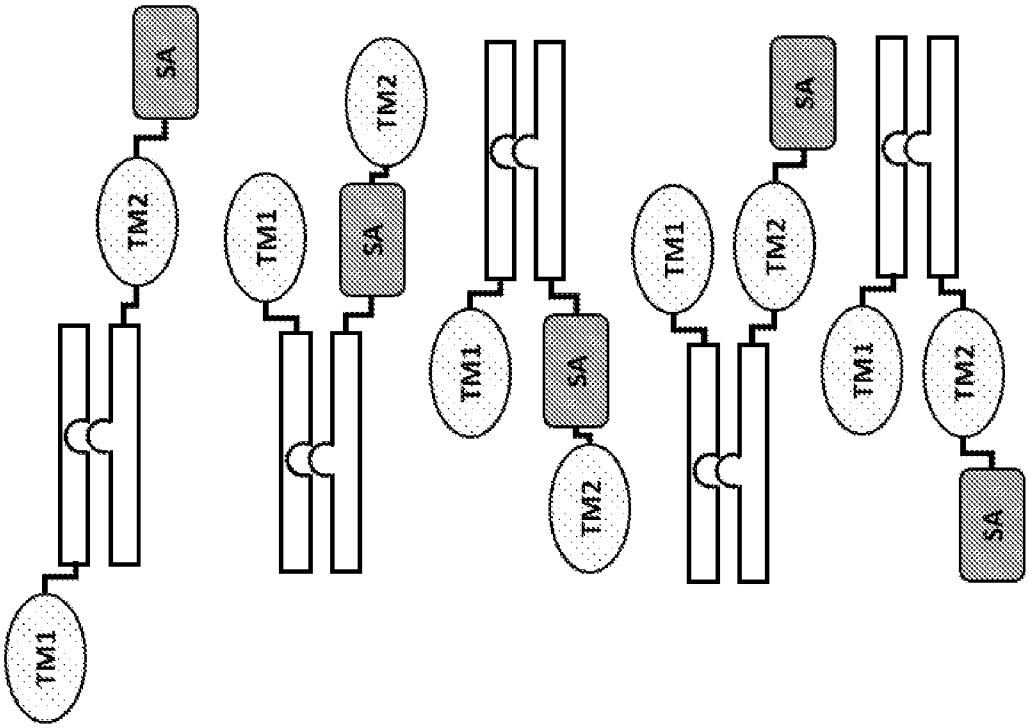


FIG. 17A FIG. 17B FIG. 17C FIG. 17D FIG. 17E

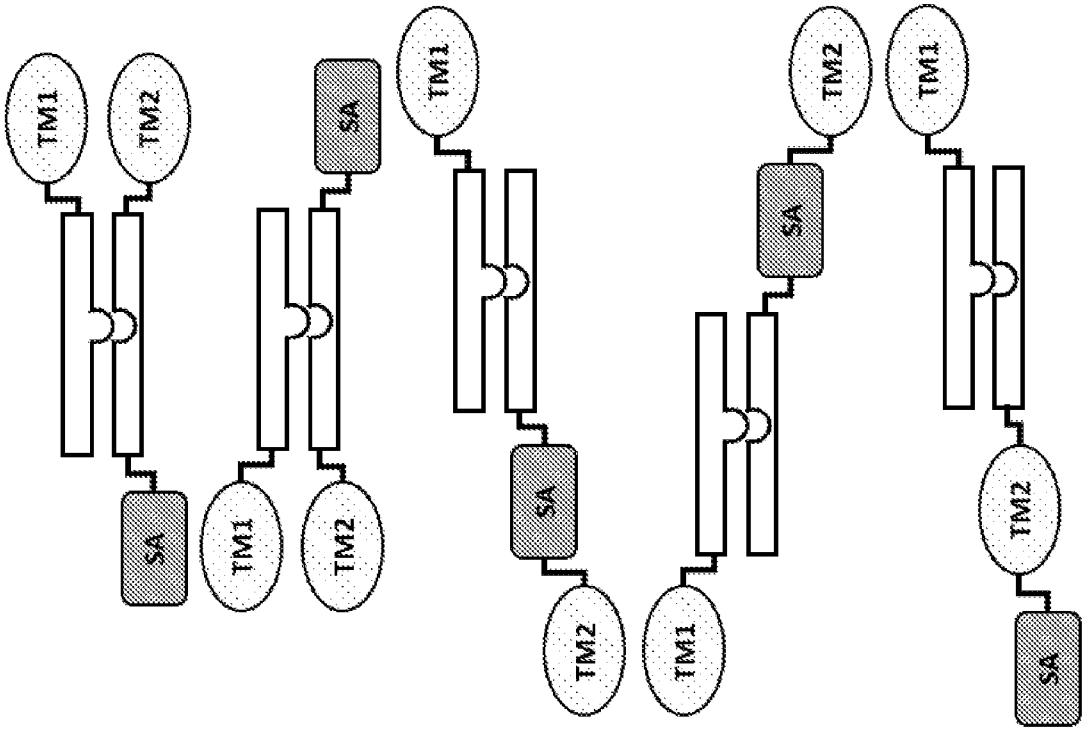


FIG. 17F FIG. 17G FIG. 17H FIG. 17I FIG. 17J

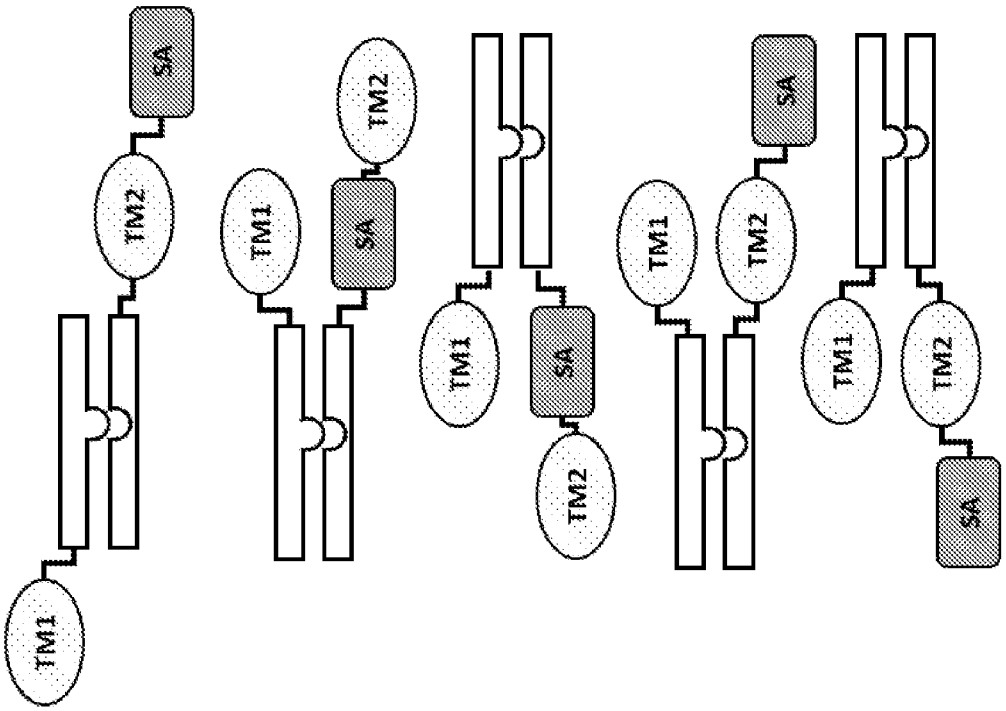


FIG. 18A FIG. 18B FIG. 18C FIG. 18D FIG. 18E FIG. 18F

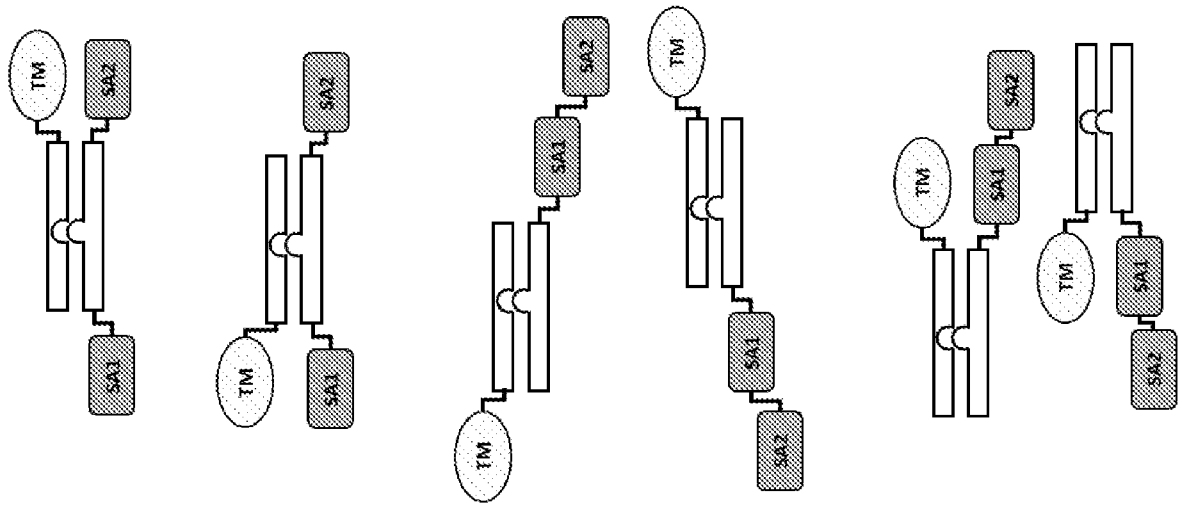


FIG. 19A FIG. 19B FIG. 19C FIG. 19D FIG. 19E FIG. 19F

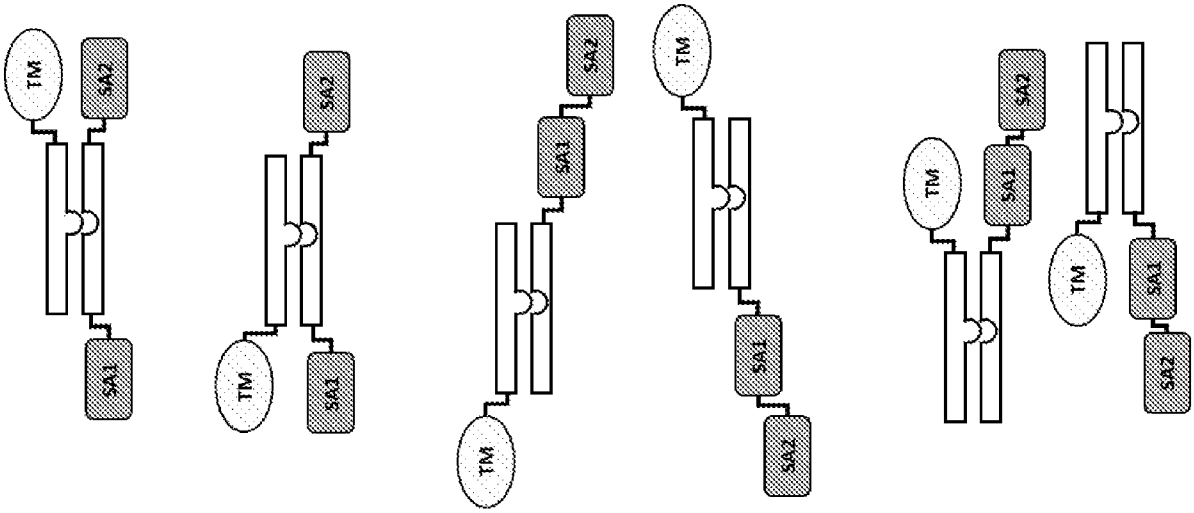


FIG. 20A FIG. 20B FIG. 20C FIG. 20D FIG. 20E

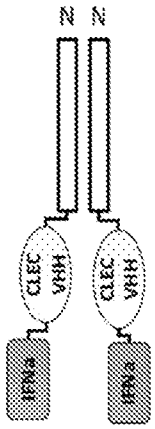
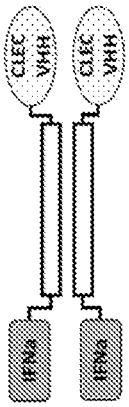
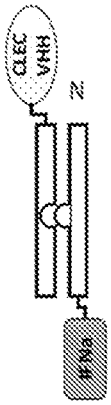
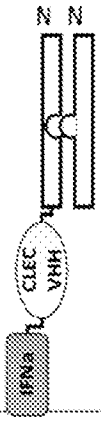
Homodimeric		Heterodimeric		
MW 130.1 kD; pI 7.13 (monomer 65 kDa)		MW 90.5 kD (41.8/48.7)	MW 90.5 kD (65/25.5)	MW 90.5 kD (65/25.5)
		Variants Mw 83.5 or 97.5 kD Single chain pI 8.05 / 6.40	Variants Mw 51 or 130 kD Single chain pI 7.13 / 7.20	Variants Mw 51 or 130 kD Single chain pI 7.13 / 7.20
				
P-956	P-957	P-958 + P-959	P-960 + P-962	P-961 + P-962

FIG. 21

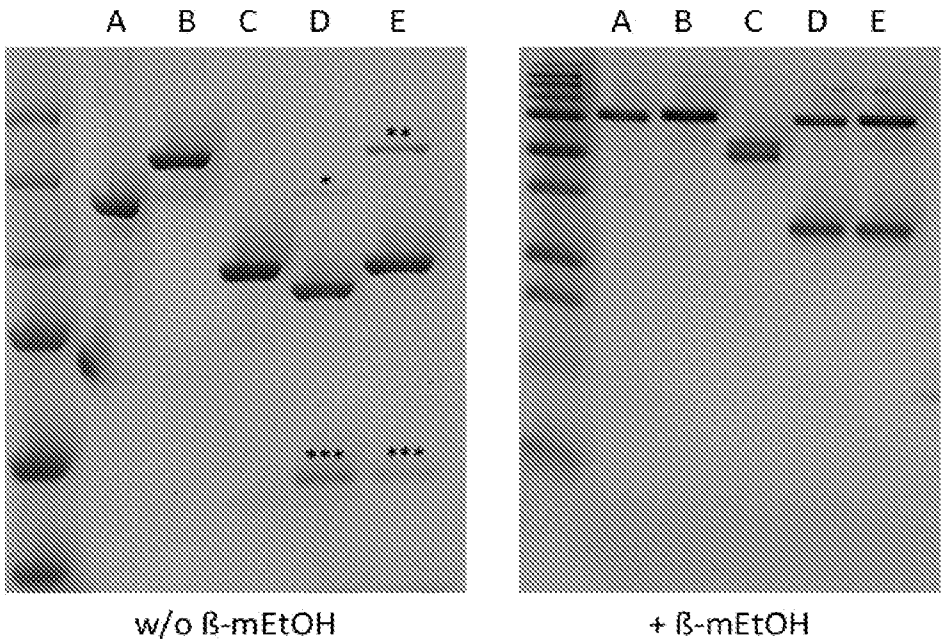

A B C D E
A B C D E
w/o ß-mEtOH
+ ß-mEtOH

FIG. 22

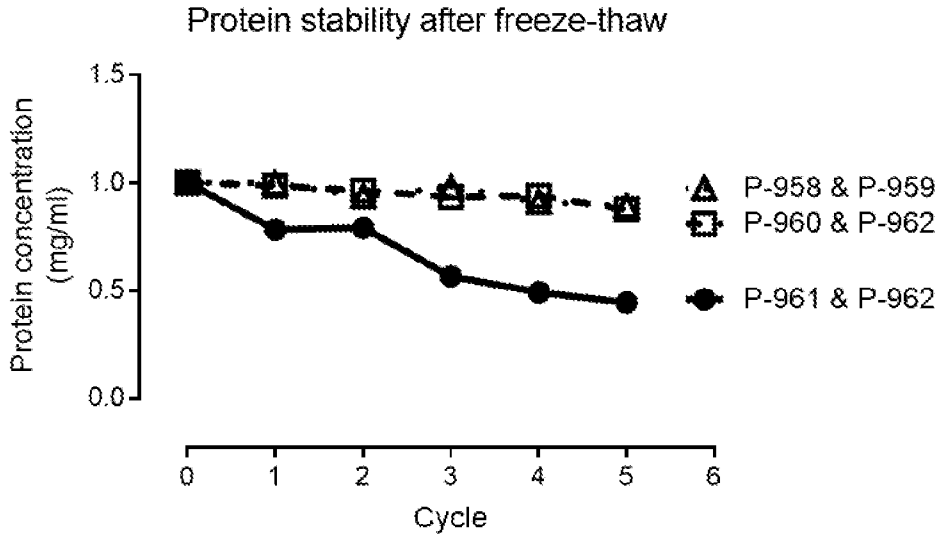

Protein stability after freeze-thaw
Protein concentration (mg/ml)
1.5
1.0
0.5
0.0
0
1
2
3
4
5
6
Cycle
P-958 & P-959
P-960 & P-962
P-961 & P-962

FIG. 23

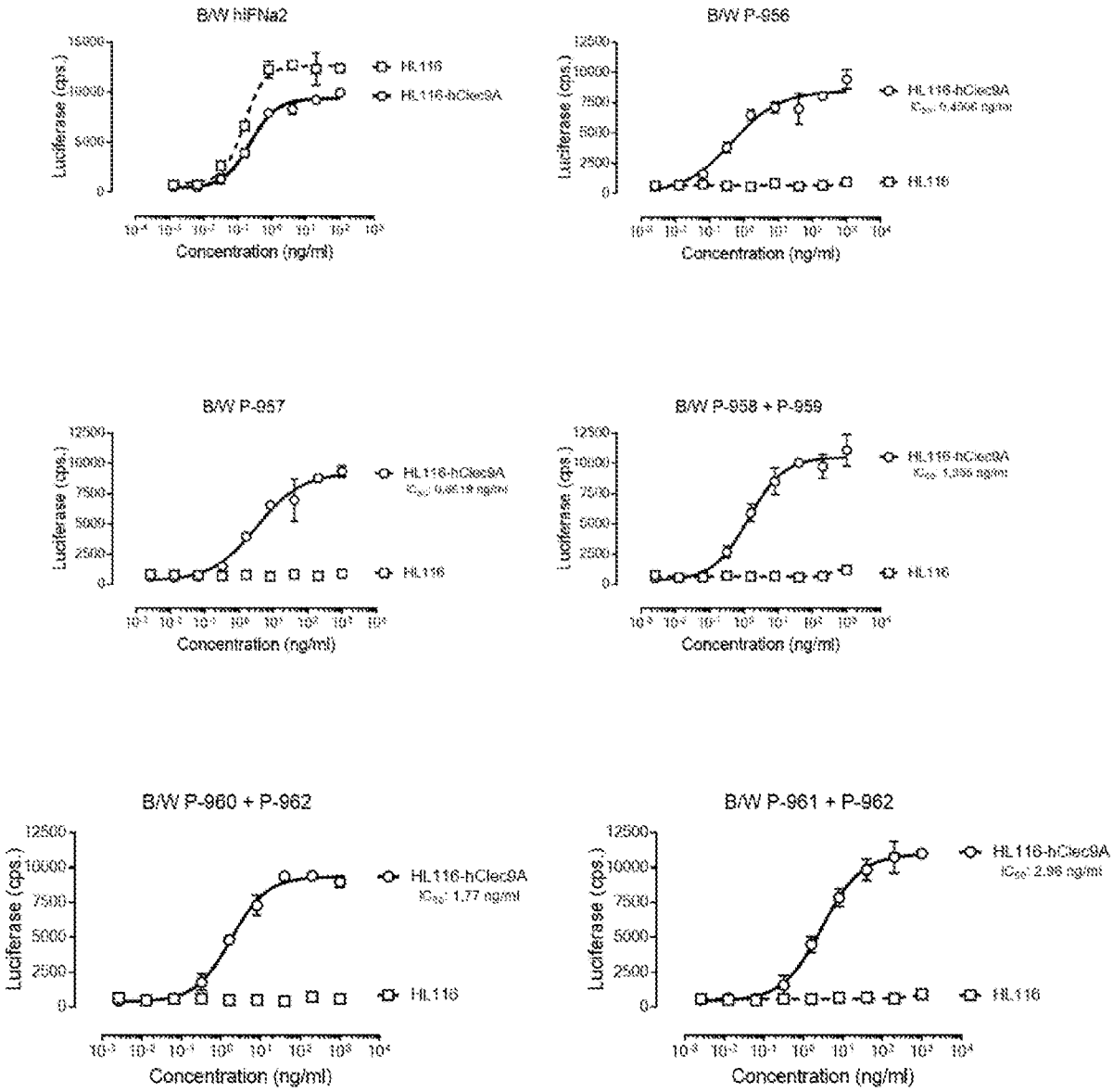

B/W hIFNa2
Luciferase (cps.)
Concentration (ng/ml)
HL116
HL116-hClec9A
B/W P-956
HL116-hClec9A
HL116
B/W P-957
HL116-hClec9A
HL116
B/W P-958 + P-959
HL116-hClec9A
HL116
B/W P-960 + P-962
HL116-hClec9A
HL116
B/W P-961 + P-962
HL116-hClec9A
HL116

FIG. 24

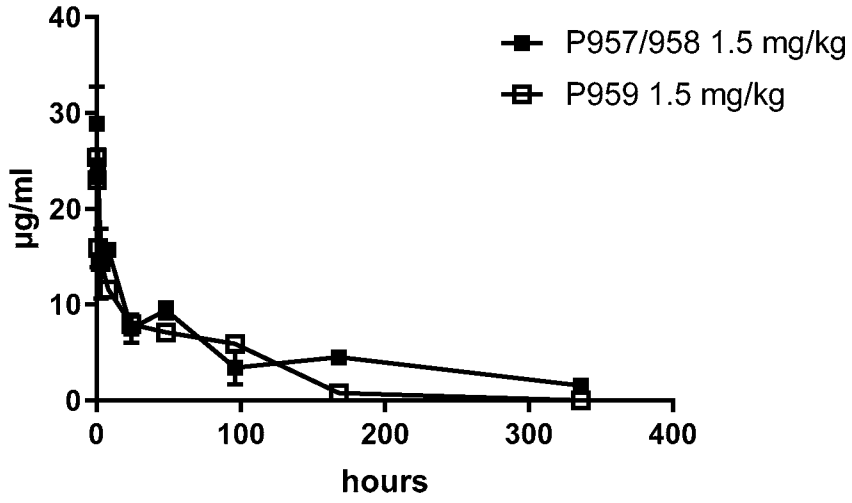

40
30
20
10
0
µg/ml
0
100
200
300
400
hours
P957/958 1.5 mg/kg
P959 1.5 mg/kg

FIG. 25

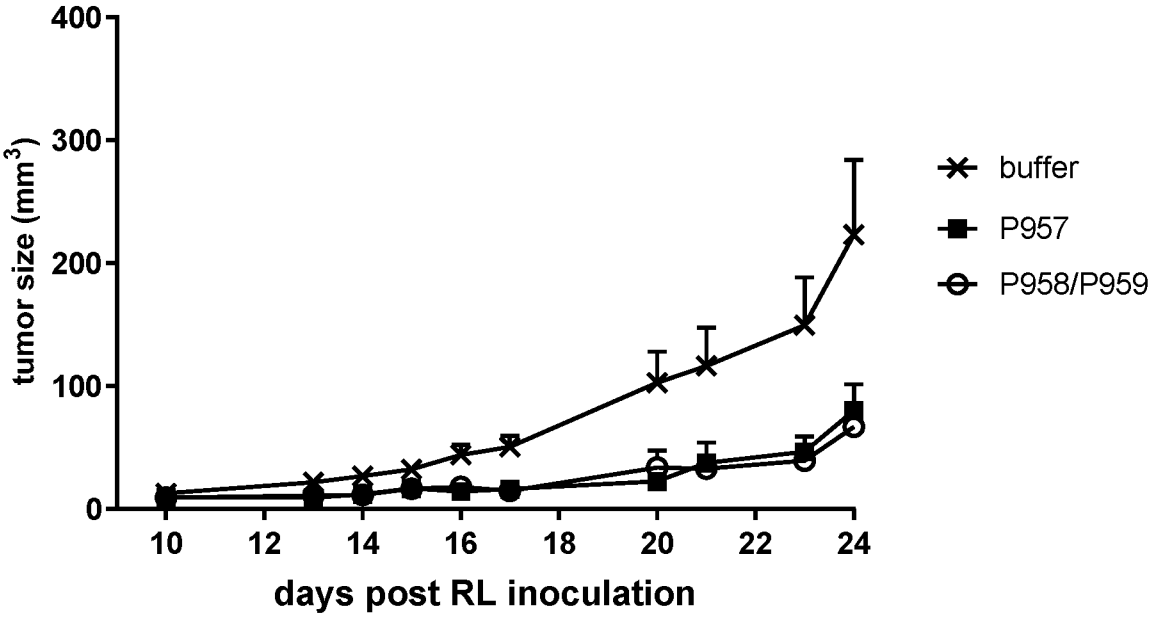

400
300
200
100
0
tumor size (mm3)
10
12
14
16
18
20
22
24
days post RL inoculation
buffer
P957
P958/P959

FIG. 26

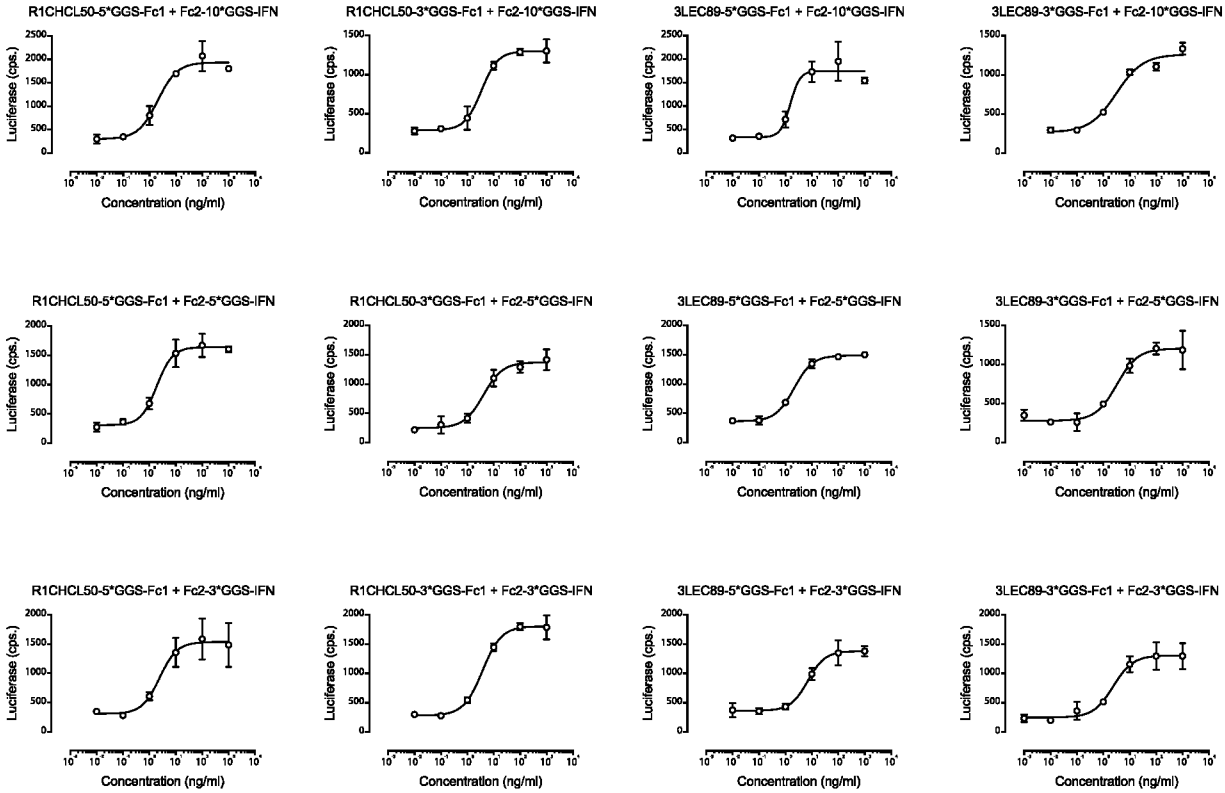

R1CHCL50-5*GGS-Fc1 + Fc2-10*GGS-IFN
R1CHCL50-3*GGS-Fc1 + Fc2-10*GGS-IFN
3LEC89-5*GGS-Fc1 + Fc2-10*GGS-IFN
3LEC89-3*GGS-Fc1 + Fc2-10*GGS-IFN
R1CHCL50-5*GGS-Fc1 + Fc2-5*GGS-IFN
R1CHCL50-3*GGS-Fc1 + Fc2-5*GGS-IFN
3LEC89-5*GGS-Fc1 + Fc2-5*GGS-IFN
3LEC89-3*GGS-Fc1 + Fc2-5*GGS-IFN
R1CHCL50-5*GGS-Fc1 + Fc2-3*GGS-IFN
R1CHCL50-3*GGS-Fc1 + Fc2-3*GGS-IFN
3LEC89-5*GGS-Fc1 + Fc2-3*GGS-IFN
3LEC89-3*GGS-Fc1 + Fc2-3*GGS-IFN
Luciferase (cps.)
Concentration (ng/ml)

FIG. 27

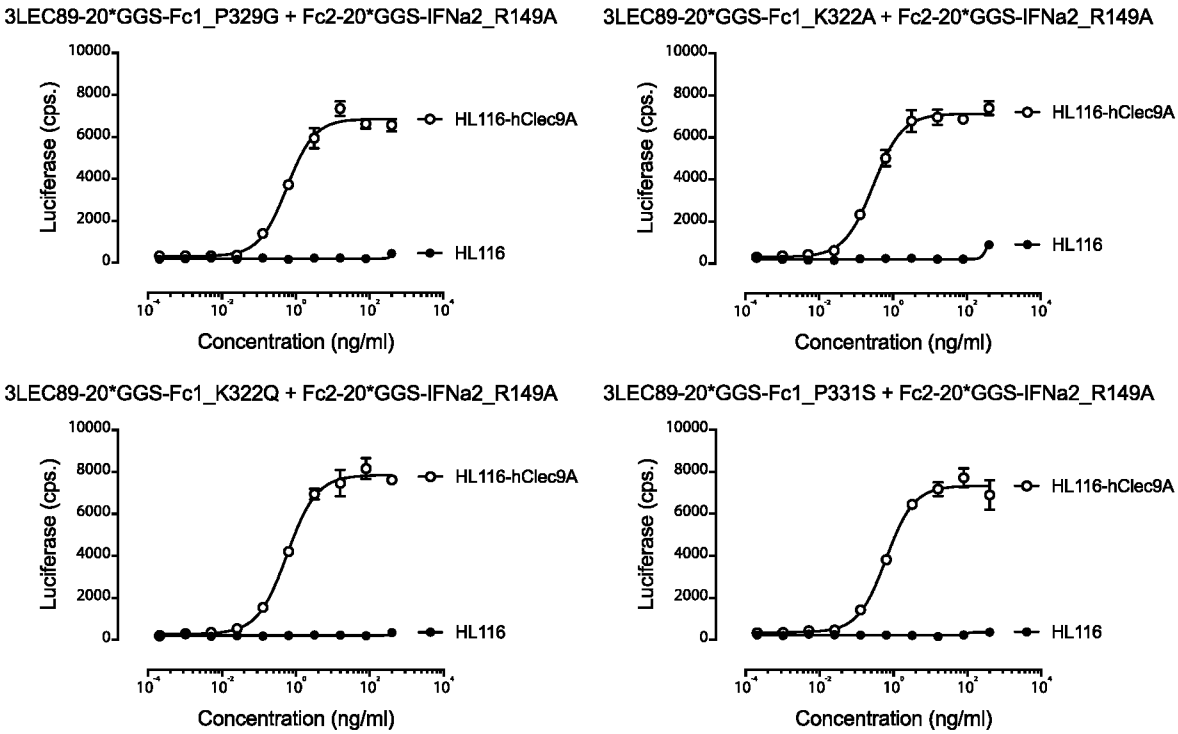

3LEC89-20*GGS-Fc1_P329G + Fc2-20*GGS-IFNa2_R149A
3LEC89-20*GGS-Fc1_K322A + Fc2-20*GGS-IFNa2_R149A
3LEC89-20*GGS-Fc1_K322Q + Fc2-20*GGS-IFNa2_R149A
3LEC89-20*GGS-Fc1_P331S + Fc2-20*GGS-IFNa2_R149A
Luciferase (cps.)
Concentration (ng/ml)
HL116-hClec9A
HL116

FIG. 28

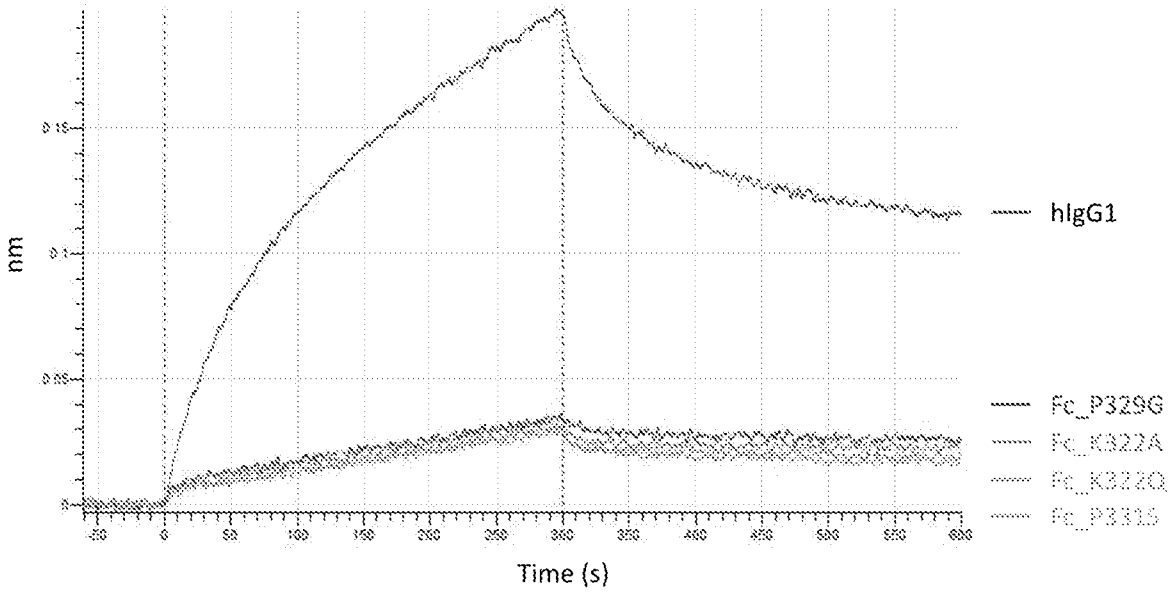


FIG. 29

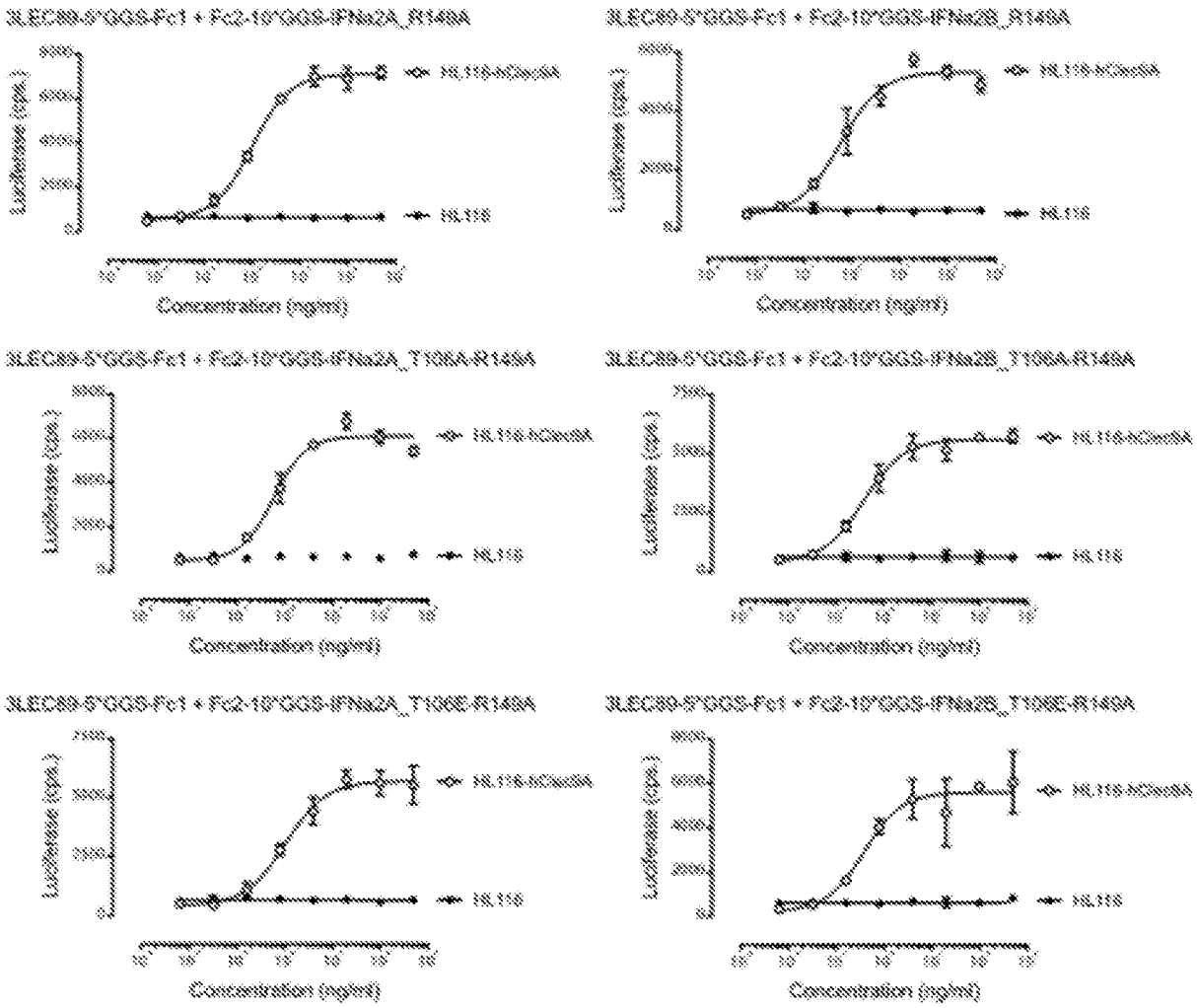
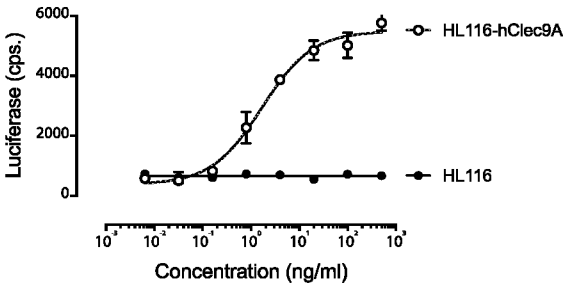
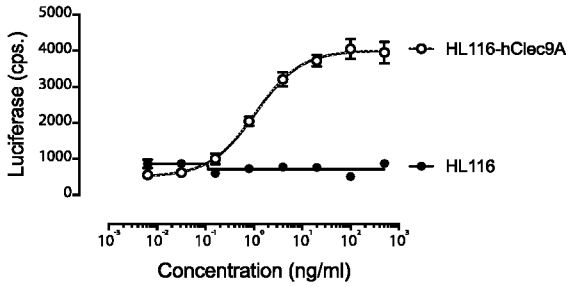

3LEC89-5'GGS-Fc1 + Fc2-10'GGS-IFNα2A_R149A
3LEC89-5'GGS-Fc1 + Fc2-10'GGS-IFNα2B_R149A
3LEC89-5'GGS-Fc1 + Fc2-10'GGS-IFNα2A_T106A-R149A
3LEC89-5'GGS-Fc1 + Fc2-10'GGS-IFNα2B_T106A-R149A
3LEC89-5'GGS-Fc1 + Fc2-10'GGS-IFNα2A_T106E-R149A
3LEC89-5'GGS-Fc1 + Fc2-10'GGS-IFNα2B_T106E-R149A
Luciferase (cps)
Concentration (ng/ml)
IL116-hCleavSite
IL116

FIG. 29 (Continued)

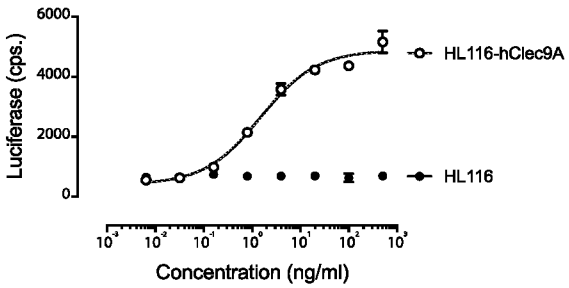
R1CHCL50-5*GGS-Fc1 + Fc2-10*GGS-IFNa2A_R149A



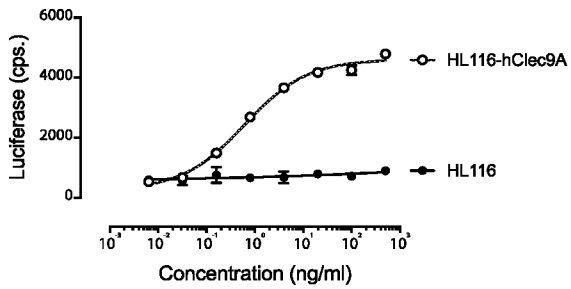
R1CHCL50-5*GGS-Fc1 + Fc2-10*GGS-IFNa2B_R149A



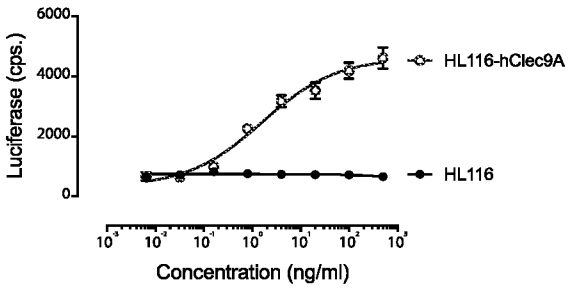
R1CHCL50-5*GGS-Fc1 + Fc2-10*GGS-IFNa2A_T106A-R149A



R1CHCL50-5*GGS-Fc1 + Fc2-10*GGS-IFNa2B_T106A-R149A



R1CHCL50-5*GGS-Fc1 + Fc2-10*GGS-IFNa2A_T106E-R149A



R1CHCL50-5*GGS-Fc1 + Fc2-10*GGS-IFNa2B_T106E-R149A

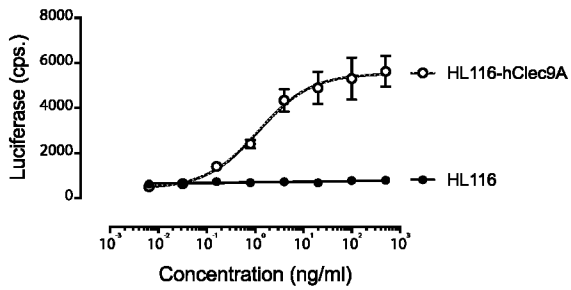


FIG. 30

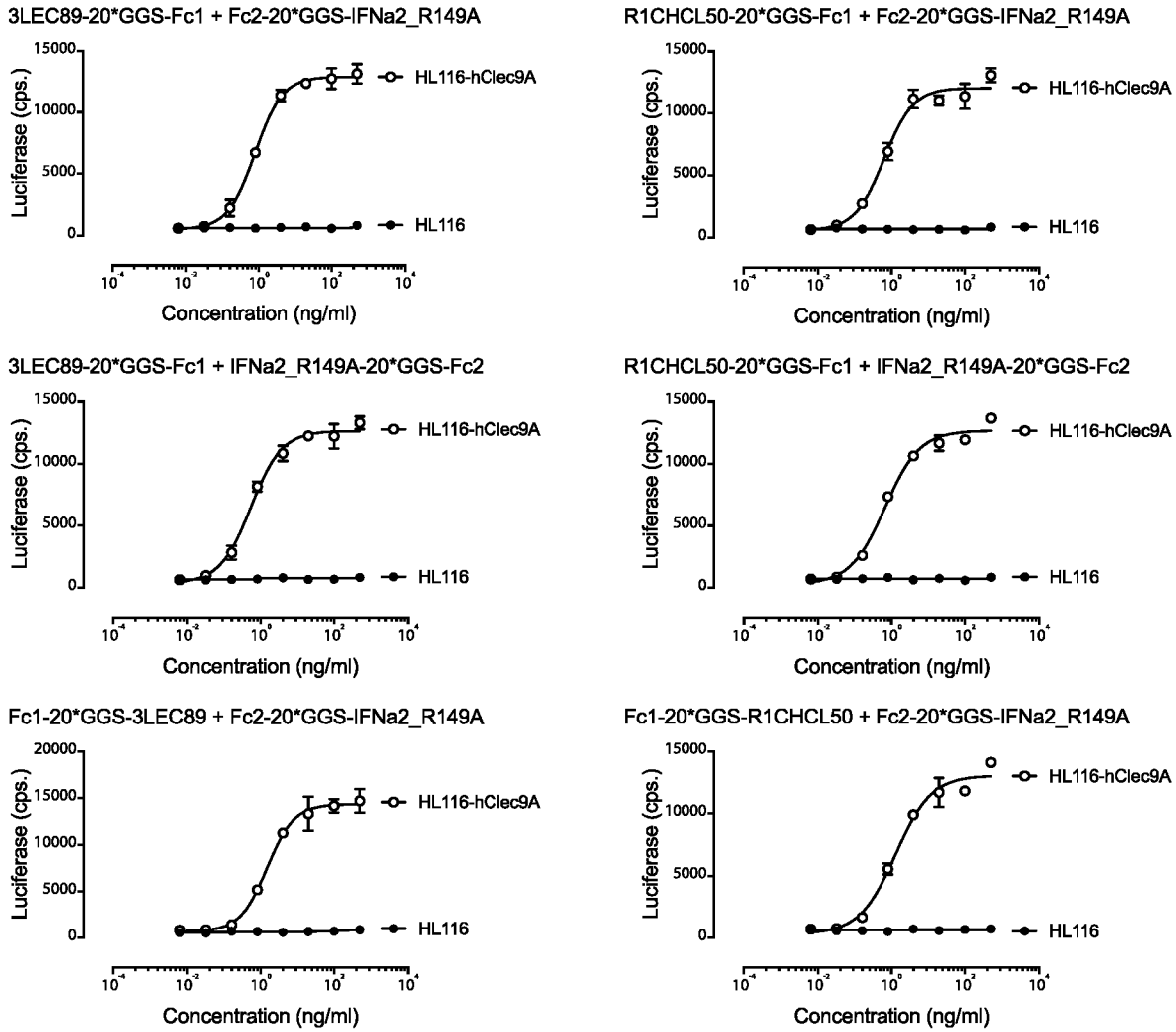

3LEC89-20*GGS-Fc1 + Fc2-20*GGS-IFNa2_R149A
R1CHCL50-20*GGS-Fc1 + Fc2-20*GGS-IFNa2_R149A
3LEC89-20*GGS-Fc1 + IFNa2_R149A-20*GGS-Fc2
R1CHCL50-20*GGS-Fc1 + IFNa2_R149A-20*GGS-Fc2
Fc1-20*GGS-3LEC89 + Fc2-20*GGS-IFNa2_R149A
Fc1-20*GGS-R1CHCL50 + Fc2-20*GGS-IFNa2_R149A
Luciferase (cps.)
Concentration (ng/ml)
HL116-hClec9A
HL116

FIG. 31

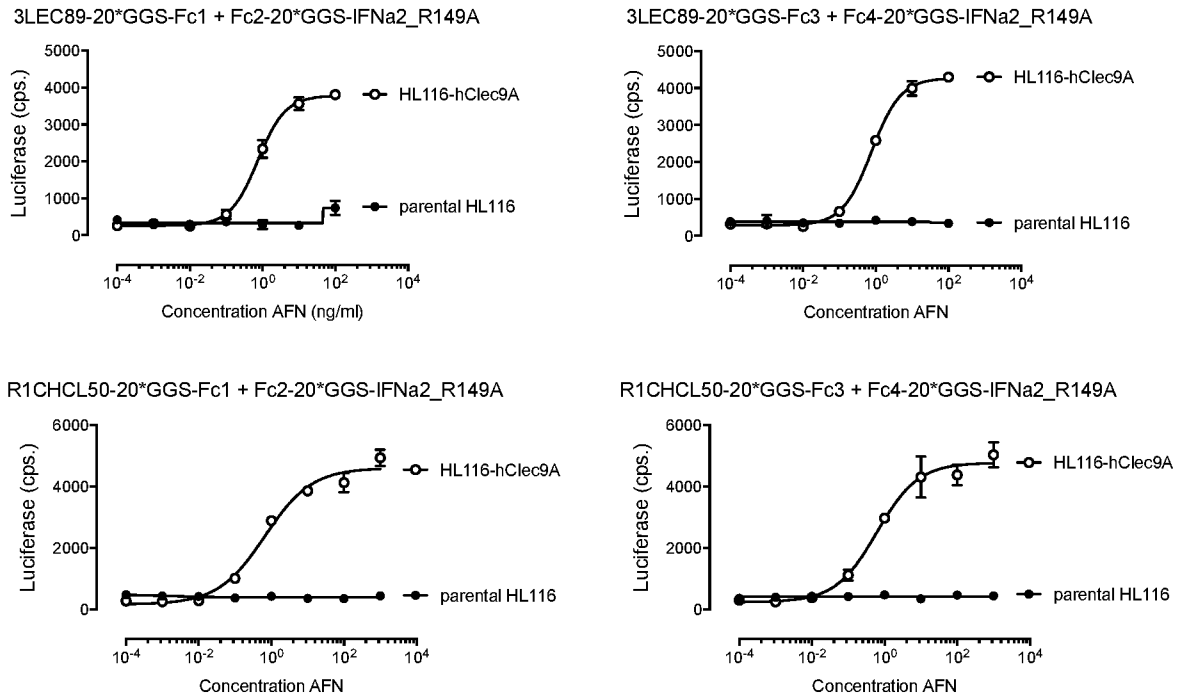

3LEC89-20*GGS-Fc1 + Fc2-20*GGS-IFNa2_R149A
Luciferase (cps.)
5000
4000
3000
2000
1000
0
HL116-hClec9A
parental HL116
10-4
10-2
100
102
104
Concentration AFN (ng/ml)
3LEC89-20*GGS-Fc3 + Fc4-20*GGS-IFNa2_R149A
Luciferase (cps.)
5000
4000
3000
2000
1000
0
HL116-hClec9A
parental HL116
10-4
10-2
100
102
104
Concentration AFN
R1CHCL50-20*GGS-Fc1 + Fc2-20*GGS-IFNa2_R149A
Luciferase (cps.)
6000
4000
2000
0
HL116-hClec9A
parental HL116
10-4
10-2
100
102
104
Concentration AFN
R1CHCL50-20*GGS-Fc3 + Fc4-20*GGS-IFNa2_R149A
Luciferase (cps.)
6000
4000
2000
0
HL116-hClec9A
parental HL116
10-4
10-2
100
102
104
Concentration AFN

FIG. 32

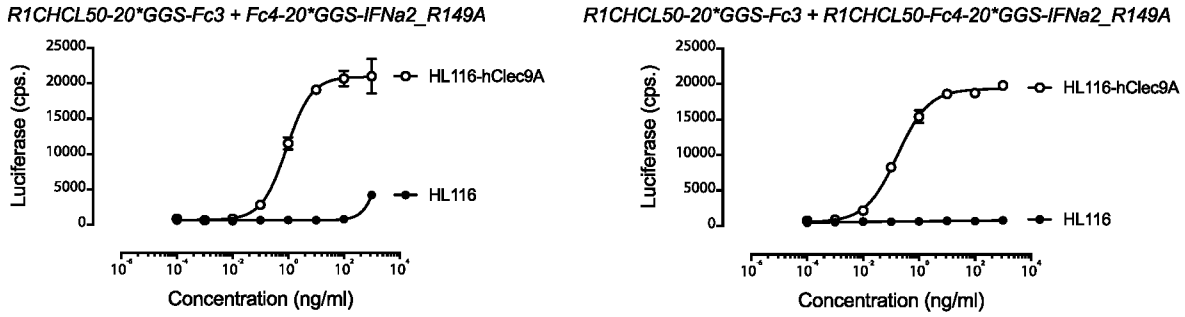

R1CHCL50-20*GGS-Fc3 + Fc4-20*GGS-IFNa2_R149A
Luciferase (cps.)
25000
20000
15000
10000
5000
0
HL116-hClec9A
HL116
Concentration (ng/ml)
R1CHCL50-20*GGS-Fc3 + R1CHCL50-Fc4-20*GGS-IFNa2_R149A
Luciferase (cps.)
25000
20000
15000
10000
5000
0
HL116-hClec9A
HL116
Concentration (ng/ml)

FIG. 33

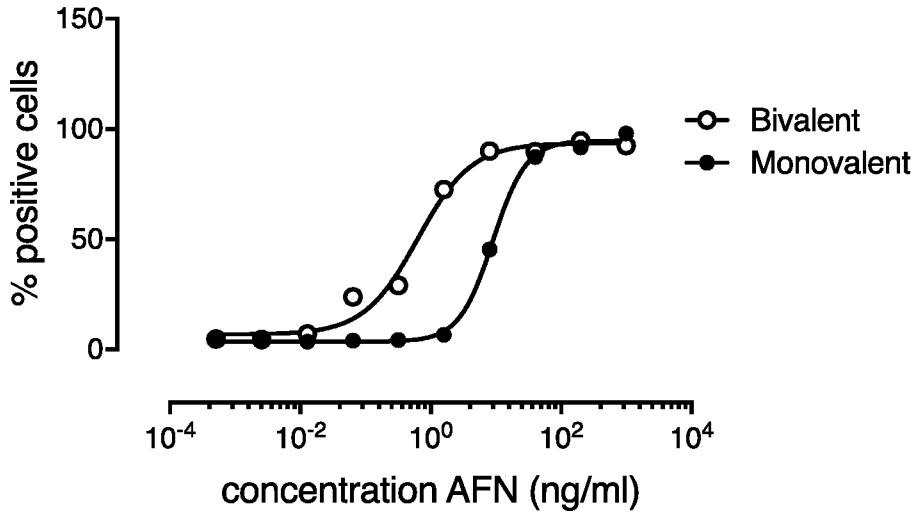

% positive cells
150
100
50
0
Bivalent
Monovalent
10-4
10-2
100
102
104
concentration AFN (ng/ml)

FIG. 34

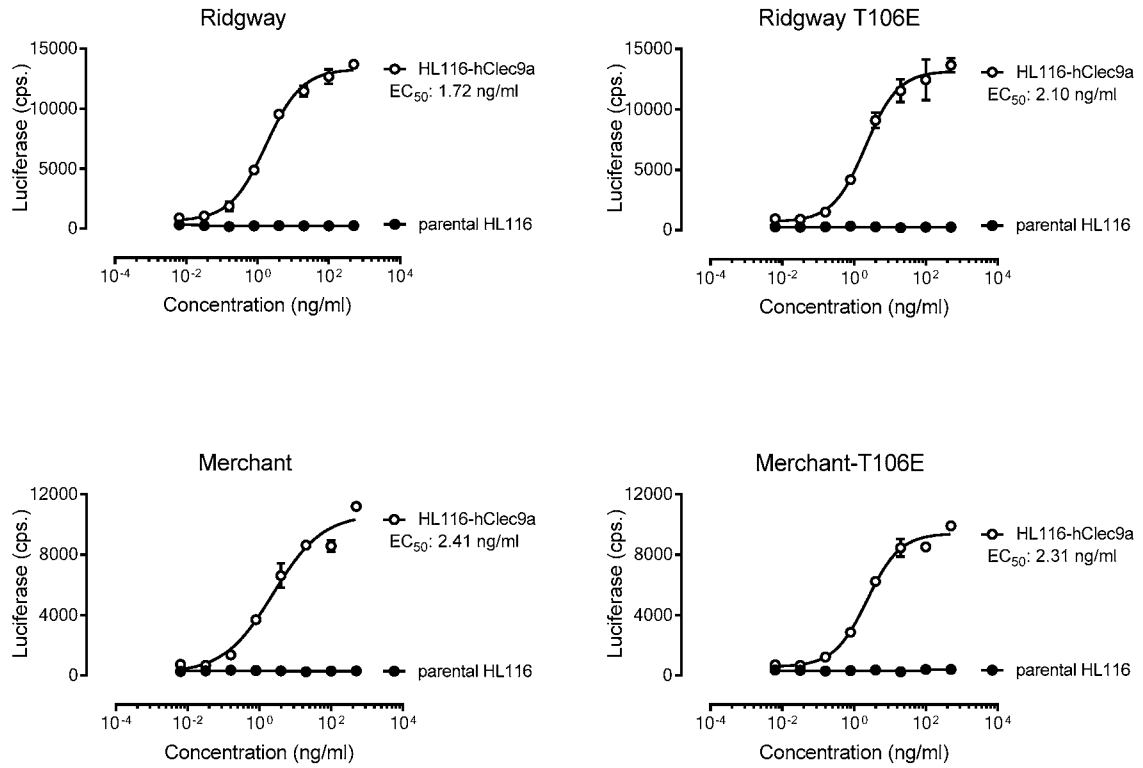

Ridgway
Luciferase (cps.)
15000
10000
5000
0
HL116-hClec9a
EC50: 1.72 ng/ml
parental HL116
10-4 10-2 100 102 104
Concentration (ng/ml)
Ridgway T106E
Luciferase (cps.)
15000
10000
5000
0
HL116-hClec9a
EC50: 2.10 ng/ml
parental HL116
10-4 10-2 100 102 104
Concentration (ng/ml)
Merchant
Luciferase (cps.)
12000
8000
4000
0
HL116-hClec9a
EC50: 2.41 ng/ml
parental HL116
10-4 10-2 100 102 104
Concentration (ng/ml)
Merchant-T106E
Luciferase (cps.)
12000
8000
4000
0
HL116-hClec9a
EC50: 2.31 ng/ml
parental HL116
10-4 10-2 100 102 104
Concentration (ng/ml)

FIG. 35

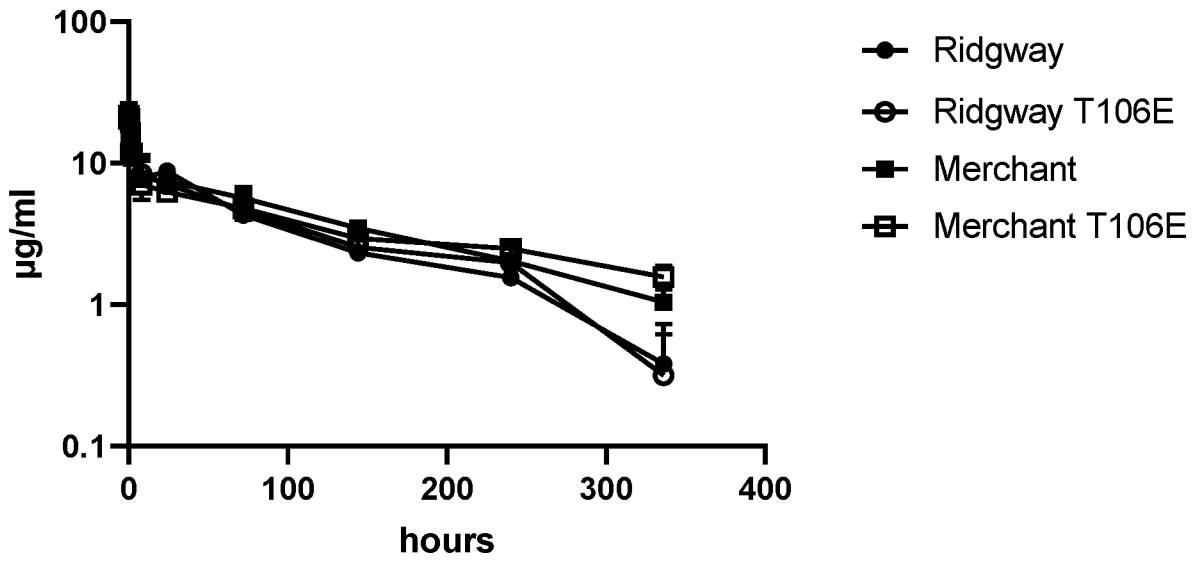

100
10
1
0.1
µg/ml
0
100
200
300
400
hours
Ridgway
Ridgway T106E
Merchant
Merchant T106E

FIG. 36

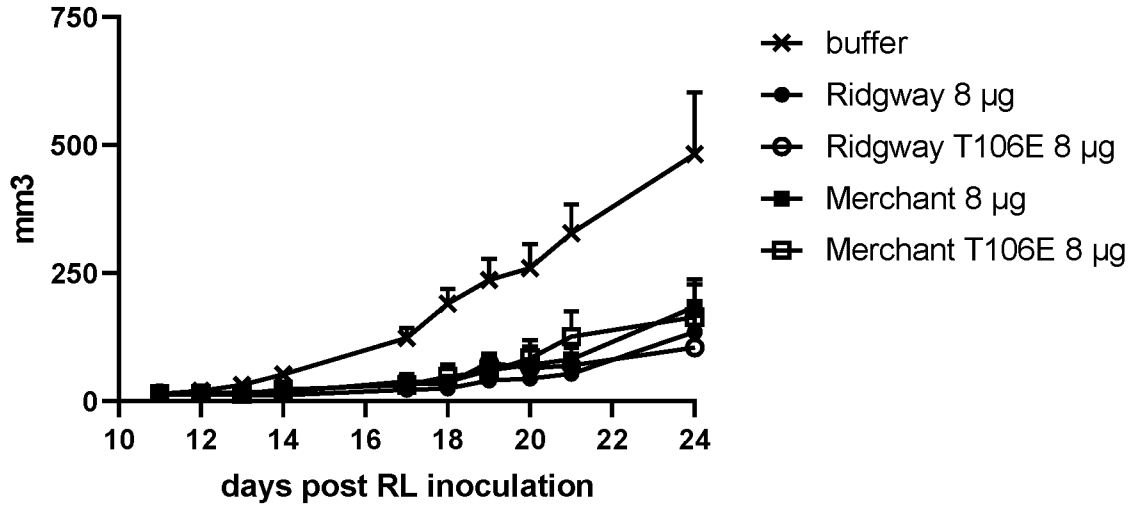

750
500
250
0
mm3
10
12
14
16
18
20
22
24
days post RL inoculation
buffer
Ridgway 8 µg
Ridgway T106E 8 µg
Merchant 8 µg
Merchant T106E 8 µg

FIG. 37

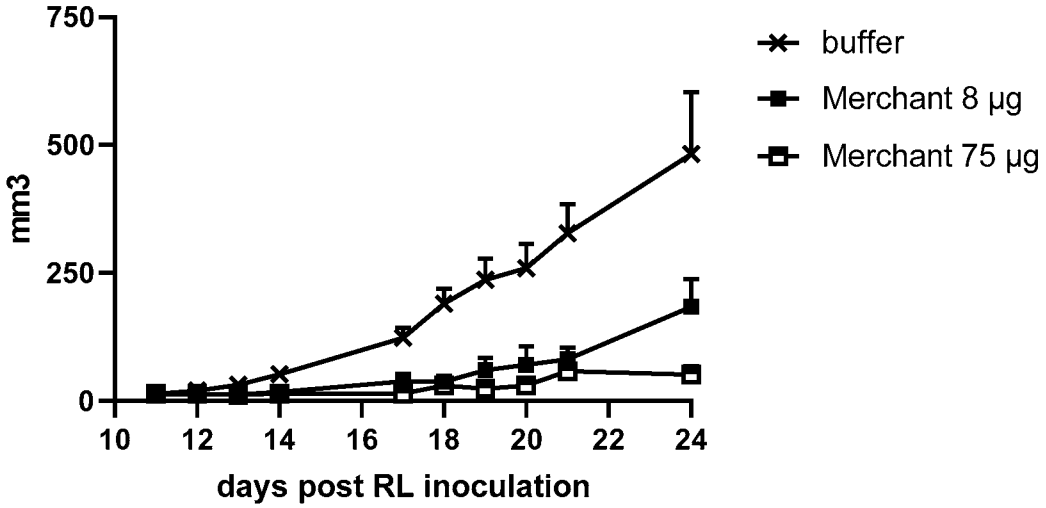

750
500
250
0
mm3
10
12
14
16
18
20
22
24
days post RL inoculation
buffer
Merchant 8 µg
Merchant 75 µg

FIG. 38

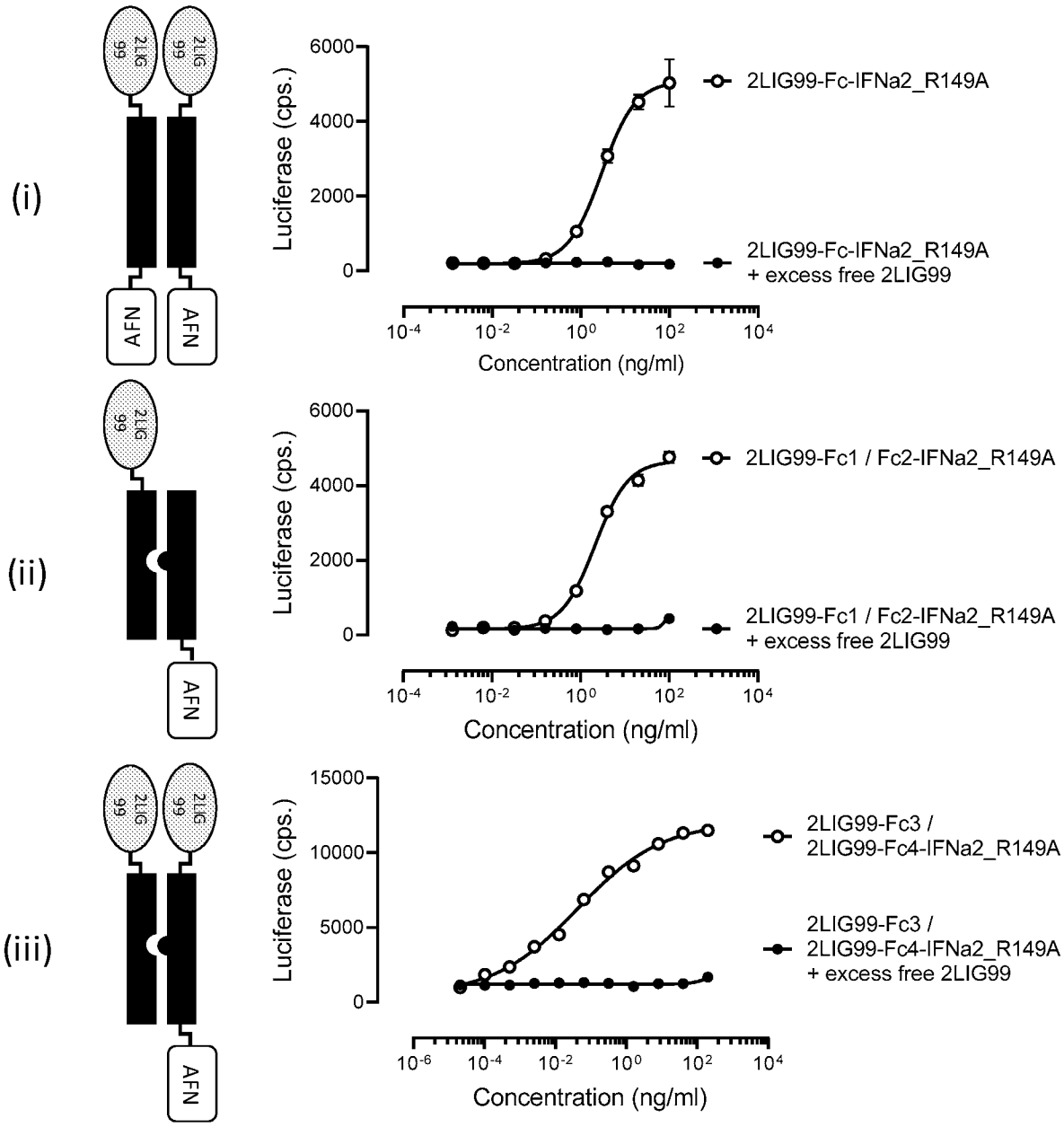

(i)
2LIG 99
2LIG 99
AFN
AFN
Luciferase (cps.)
6000
4000
2000
0
10-4
10-2
100
102
104
Concentration (ng/ml)
2LIG99-Fc-IFNa2_R149A
2LIG99-Fc-IFNa2_R149A
+ excess free 2LIG99
(ii)
2LIG 99
AFN
Luciferase (cps.)
6000
4000
2000
0
10-4
10-2
100
102
104
Concentration (ng/ml)
2LIG99-Fc1 / Fc2-IFNa2_R149A
2LIG99-Fc1 / Fc2-IFNa2_R149A
+ excess free 2LIG99
(iii)
2LIG 99
2LIG 99
AFN
Luciferase (cps.)
15000
10000
5000
0
10-6
10-4
10-2
100
102
104
Concentration (ng/ml)
2LIG99-Fc3 /
2LIG99-Fc4-IFNa2_R149A
2LIG99-Fc3 /
2LIG99-Fc4-IFNa2_R149A
+ excess free 2LIG99

FIG. 39

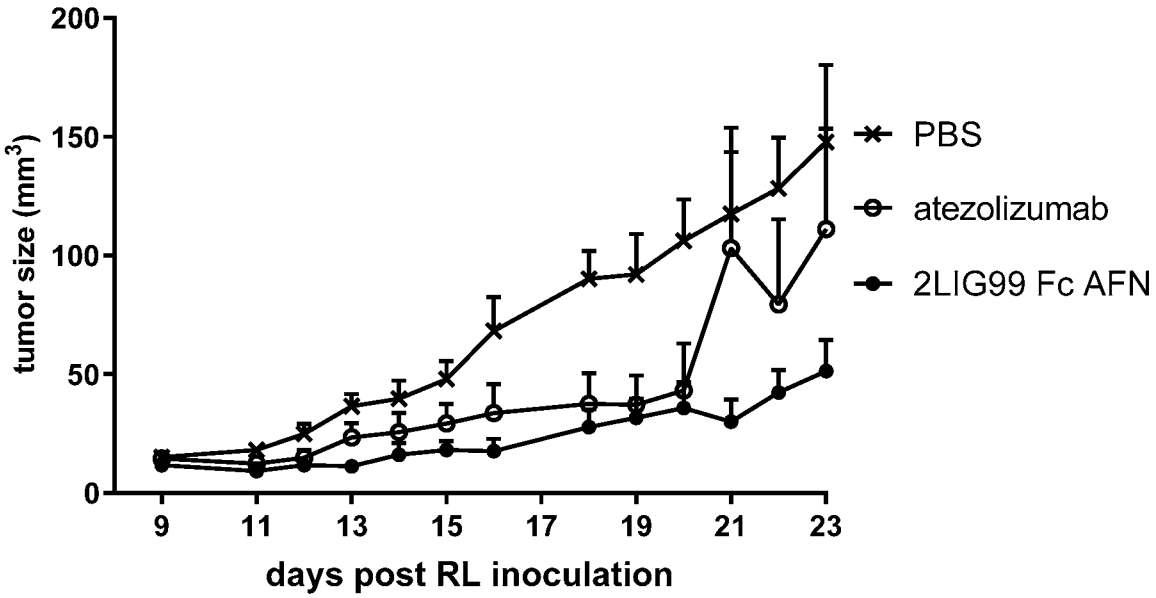

200
150
100
50
0
tumor size (mm3)
9
11
13
15
17
19
21
23
days post RL inoculation
PBS
atezolizumab
2LIG99 Fc AFN

FIG. 40

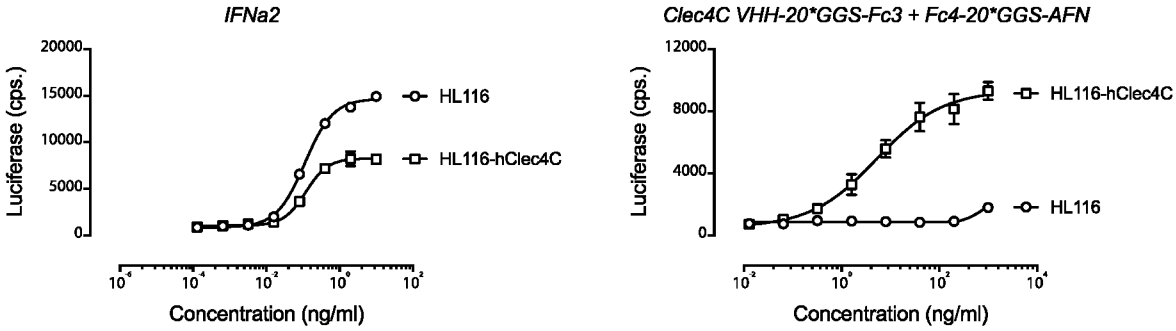

IFNa2
Luciferase (cps.)
20000
15000
10000
5000
0
HL116
HL116-hClec4C
Concentration (ng/ml)
Clec4C VHH-20*GGS-Fc3 + Fc4-20*GGS-AFN
Luciferase (cps.)
12000
8000
4000
0
HL116-hClec4C
HL116
Concentration (ng/ml)

FIG. 41

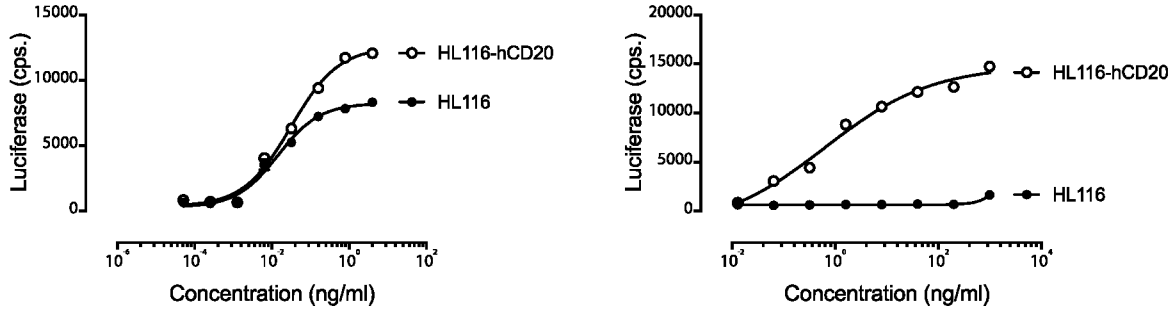

Luciferase (cps.)
15000
10000
5000
0
HL116-hCD20
HL116
Concentration (ng/ml)
Luciferase (cps.)
20000
15000
10000
5000
0
HL116-hCD20
HL116
Concentration (ng/ml)

FIG. 42

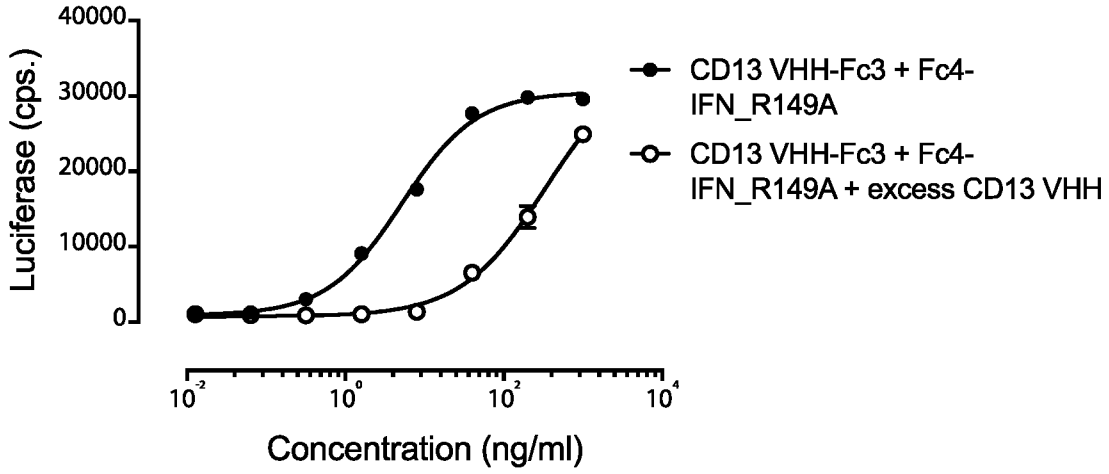

40000
30000
20000
10000
0
Luciferase (cps.)
CD13 VHH-Fc3 + Fc4-IFN_R149A
CD13 VHH-Fc3 + Fc4-IFN_R149A + excess CD13 VHH
Concentration (ng/ml)

FIG. 43

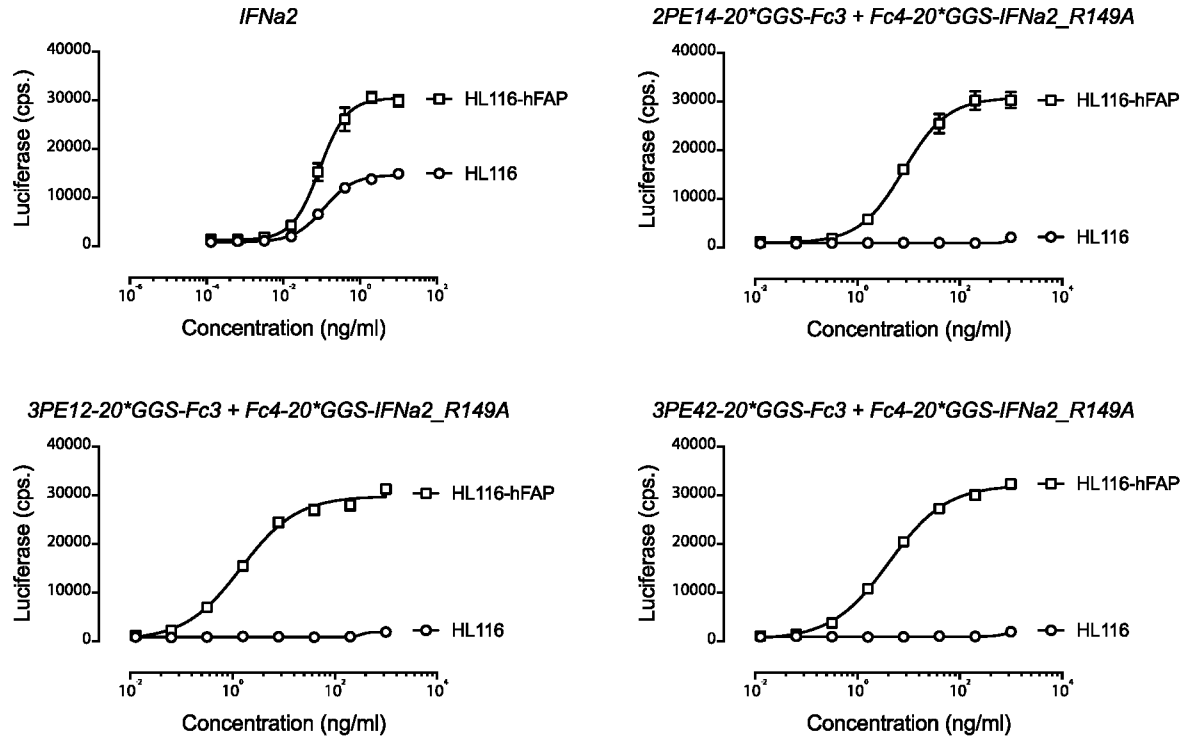

IFNa2
2PE14-20*GGS-Fc3 + Fc4-20*GGS-IFNa2_R149A
3PE12-20*GGS-Fc3 + Fc4-20*GGS-IFNa2_R149A
3PE42-20*GGS-Fc3 + Fc4-20*GGS-IFNa2_R149A
Luciferase (cps.)
HL116-hFAP
HL116
Concentration (ng/ml)

FIG. 44

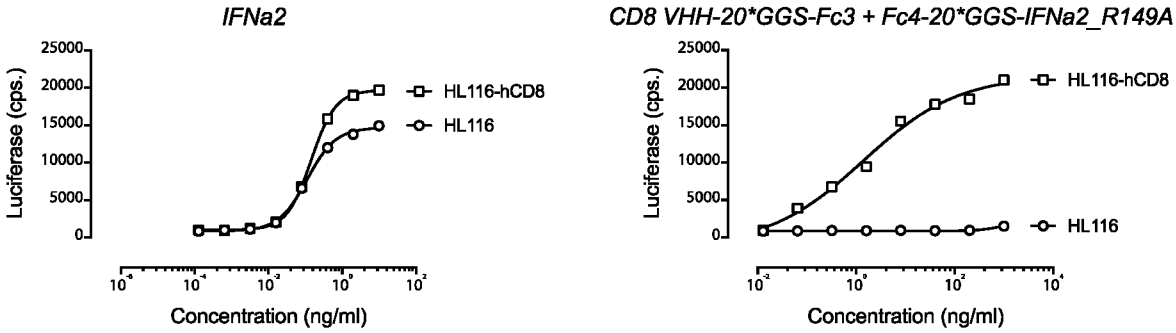

IFNa2
Luciferase (cps.)
25000
20000
15000
10000
5000
0
HL116-hCD8
HL116
Concentration (ng/ml)
CD8 VHH-20*GGS-Fc3 + Fc4-20*GGS-IFNa2_R149A
Luciferase (cps.)
HL116-hCD8
HL116
Concentration (ng/ml)

FIG. 45

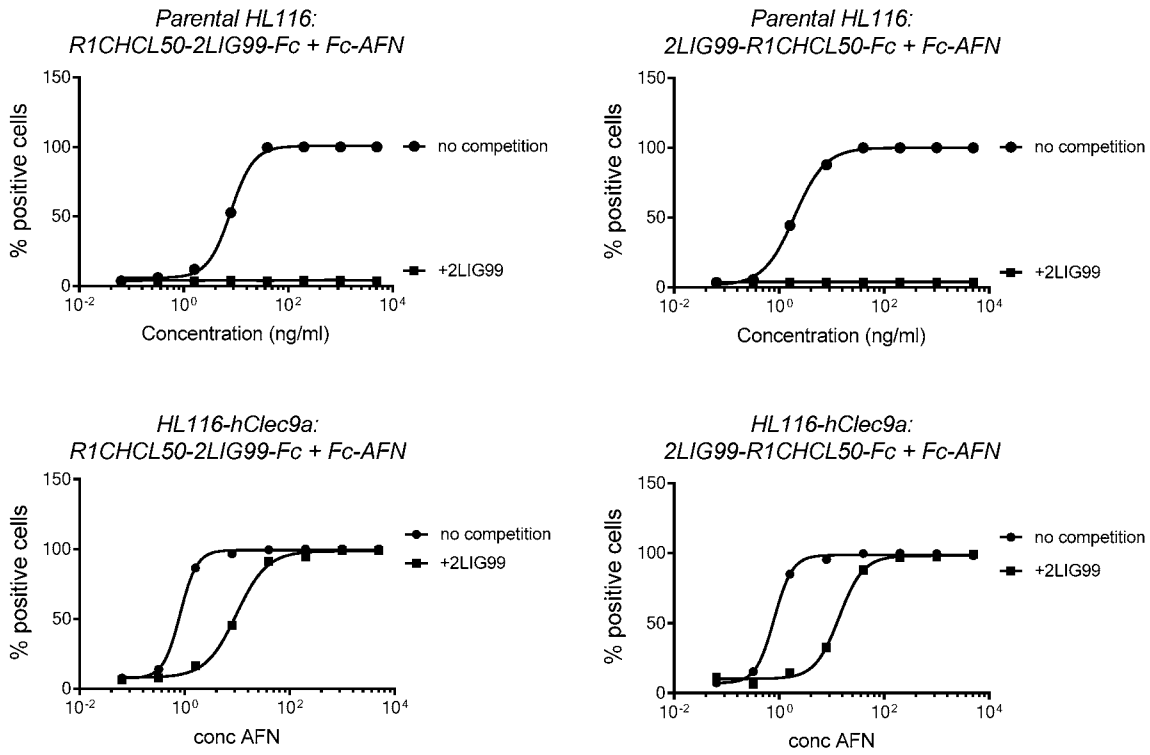

Parental HL116:
R1CHCL50-2LIG99-Fc + Fc-AFN
% positive cells
150
100
50
0
no competition
+2LIG99
Concentration (ng/ml)
Parental HL116:
2LIG99-R1CHCL50-Fc + Fc-AFN
% positive cells
no competition
+2LIG99
Concentration (ng/ml)
HL116-hClec9a:
R1CHCL50-2LIG99-Fc + Fc-AFN
% positive cells
no competition
+2LIG99
conc AFN
HL116-hClec9a:
2LIG99-R1CHCL50-Fc + Fc-AFN
% positive cells
no competition
+2LIG99
conc AFN

FIG. 46A

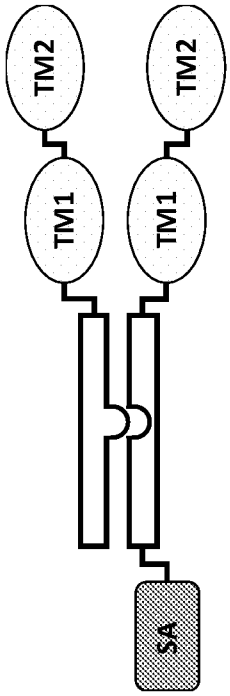


FIG. 46B

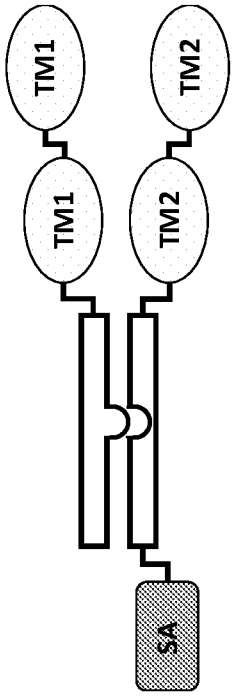


FIG. 46C

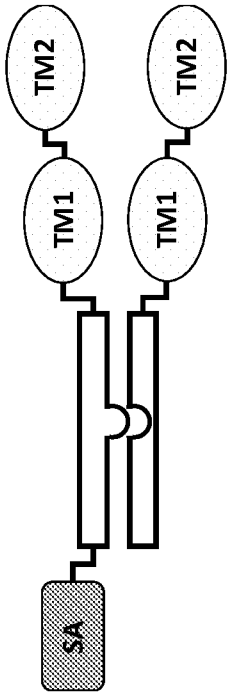


FIG. 46D

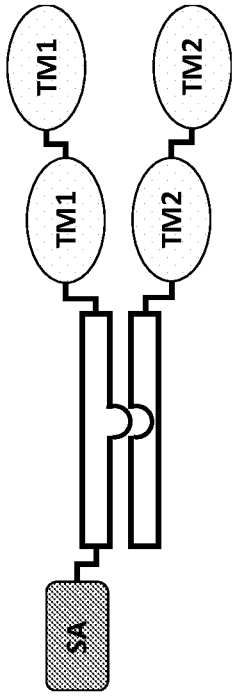


FIG. 47

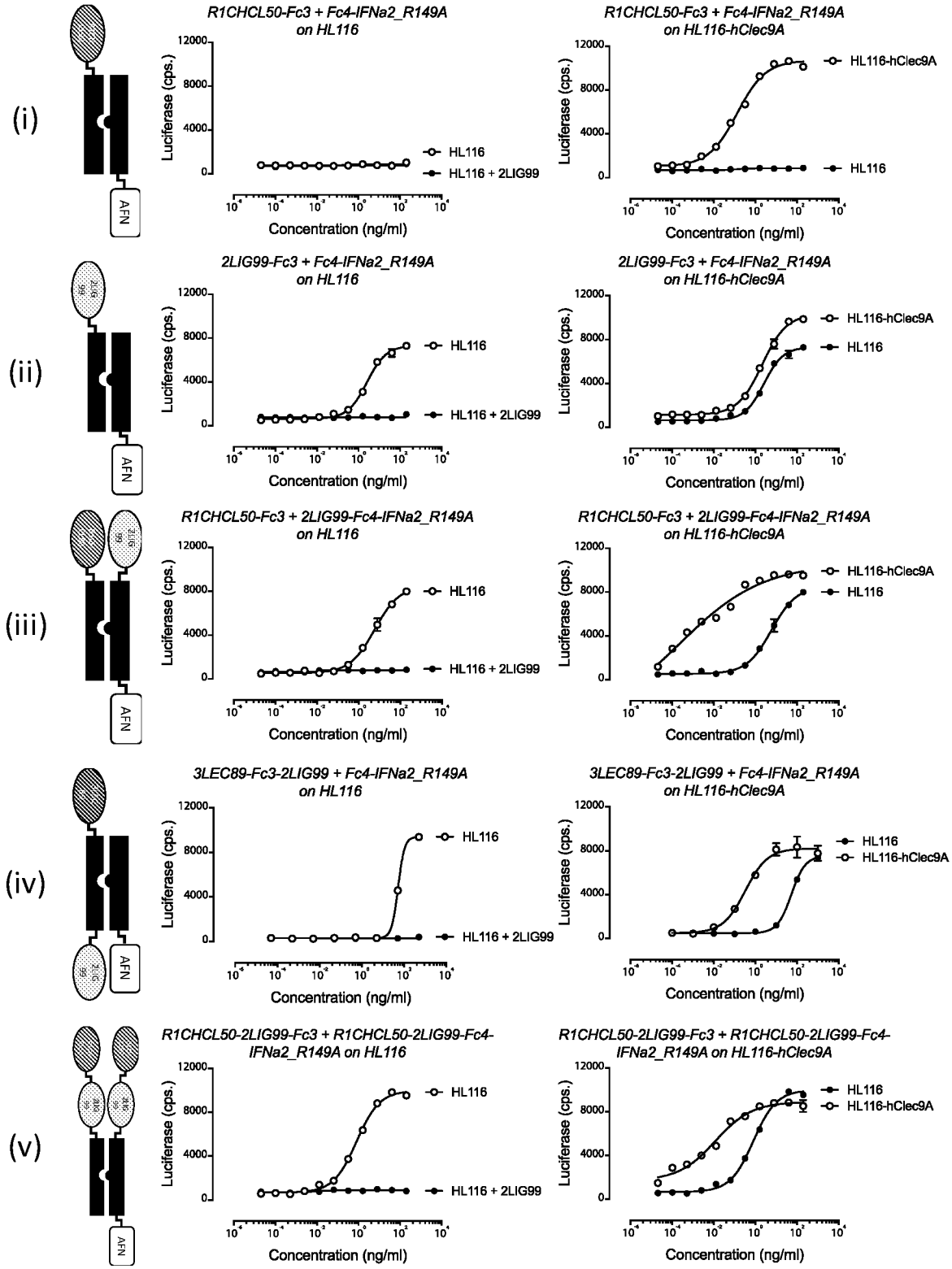

(i)
R1CHCL50-Fc3 + Fc4-IFNa2_R149A on HL116
R1CHCL50-Fc3 + Fc4-IFNa2_R149A on HL116-hClec9A
(ii)
2LIG99-Fc3 + Fc4-IFNa2_R149A on HL116
2LIG99-Fc3 + Fc4-IFNa2_R149A on HL116-hClec9A
(iii)
R1CHCL50-Fc3 + 2LIG99-Fc4-IFNa2_R149A on HL116
R1CHCL50-Fc3 + 2LIG99-Fc4-IFNa2_R149A on HL116-hClec9A
(iv)
3LEC89-Fc3-2LIG99 + Fc4-IFNa2_R149A on HL116
3LEC89-Fc3-2LIG99 + Fc4-IFNa2_R149A on HL116-hClec9A
(v)
R1CHCL50-2LIG99-Fc3 + R1CHCL50-2LIG99-Fc4-IFNa2_R149A on HL116
R1CHCL50-2LIG99-Fc3 + R1CHCL50-2LIG99-Fc4-IFNa2_R149A on HL116-hClec9A
AFN
Luciferase (cps.)
Concentration (ng/ml)
HL116
HL116 + 2LIG99
HL116-hClec9A

FIG. 48

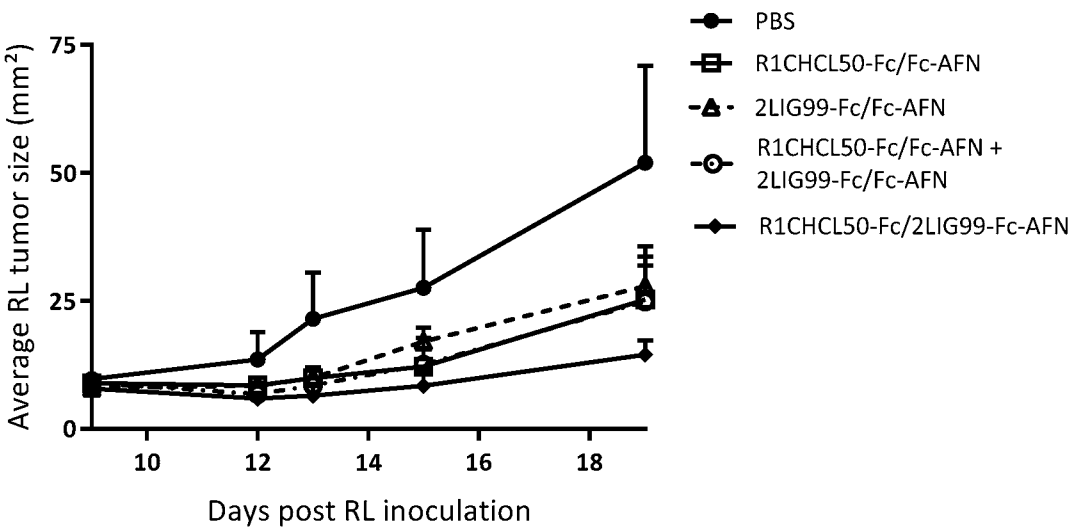

Average RL tumor size (mm²)
75
50
25
0
10
12
14
16
18
Days post RL inoculation
PBS
R1CHCL50-Fc/Fc-AFN
2LIG99-Fc/Fc-AFN
R1CHCL50-Fc/Fc-AFN +
2LIG99-Fc/Fc-AFN
R1CHCL50-Fc/2LIG99-Fc-AFN

FIG. 49

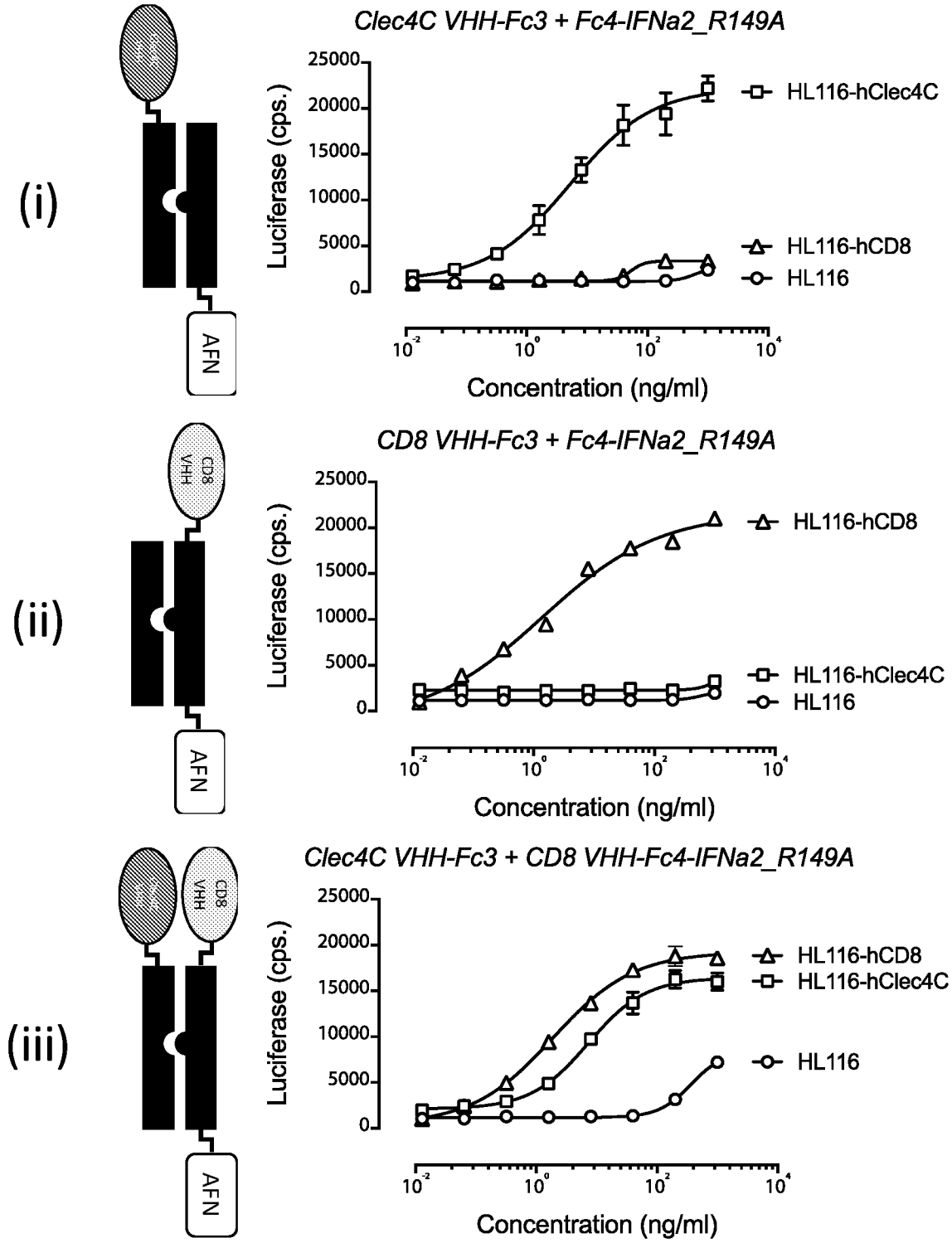

(i)
Clec4C VHH
AFN
Clec4C VHH-Fc3 + Fc4-IFNa2_R149A
Luciferase (cps.)
25000
20000
15000
10000
5000
0
HL116-hClec4C
HL116-hCD8
HL116
10-2
100
102
104
Concentration (ng/ml)
(ii)
CD8 VHH
AFN
CD8 VHH-Fc3 + Fc4-IFNa2_R149A
Luciferase (cps.)
HL116-hCD8
HL116-hClec4C
HL116
Concentration (ng/ml)
(iii)
Clec4C VHH
CD8 VHH
AFN
Clec4C VHH-Fc3 + CD8 VHH-Fc4-IFNa2_R149A
Luciferase (cps.)
HL116-hCD8
HL116-hClec4C
HL116
Concentration (ng/ml)

FIG. 50

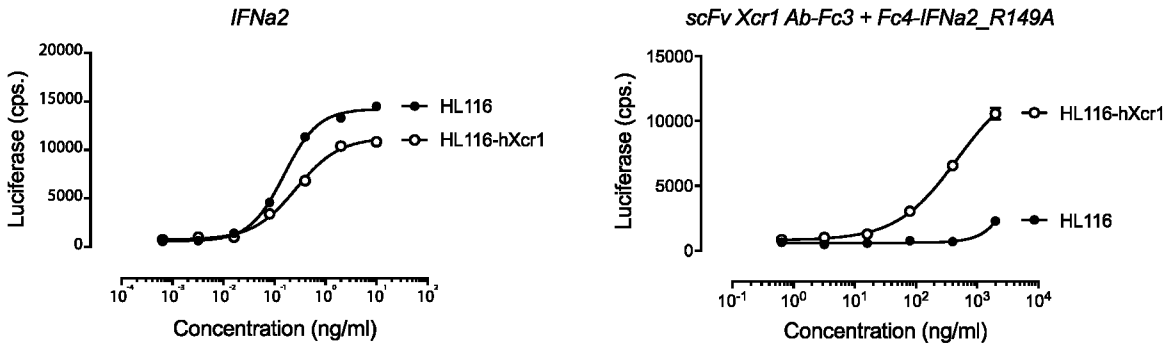

IFNa2
Luciferase (cps.)
20000
15000
10000
5000
0
HL116
HL116-hXcr1
Concentration (ng/ml)
scFv Xcr1 Ab-Fc3 + Fc4-IFNa2_R149A
15000
10000
5000
0
HL116-hXcr1
HL116
Concentration (ng/ml)

FIG. 51

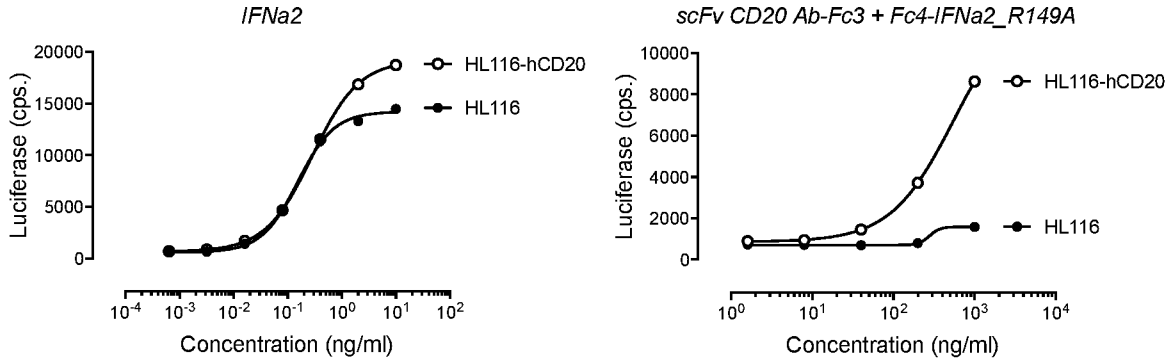

IFNa2
Luciferase (cps.)
20000
15000
10000
5000
0
HL116-hCD20
HL116
Concentration (ng/ml)
scFv CD20 Ab-Fc3 + Fc4-IFNa2_R149A
10000
8000
6000
4000
2000
0
HL116-hCD20
HL116
Concentration (ng/ml)

FIG. 52

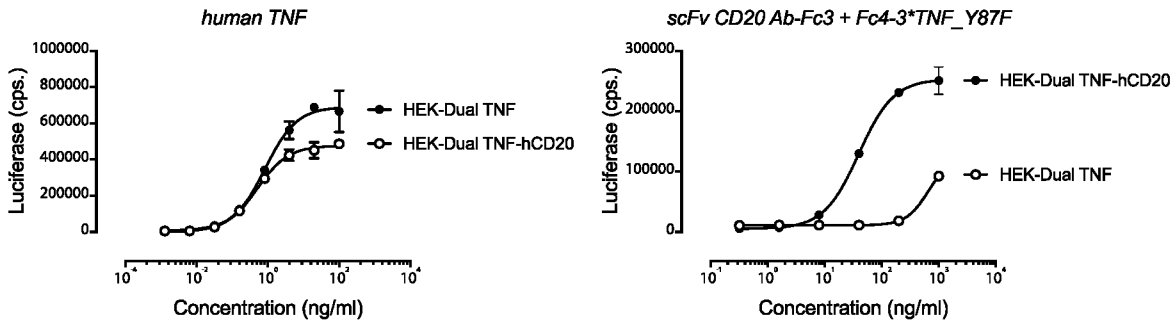

human TNF
Luciferase (cps.)
1000000
800000
600000
400000
200000
0
HEK-Dual TNF
HEK-Dual TNF-hCD20
Concentration (ng/ml)
scFv CD20 Ab-Fc3 + Fc4-3*TNF_Y87F
300000
200000
100000
HEK-Dual TNF-hCD20
HEK-Dual TNF

FIG. 53

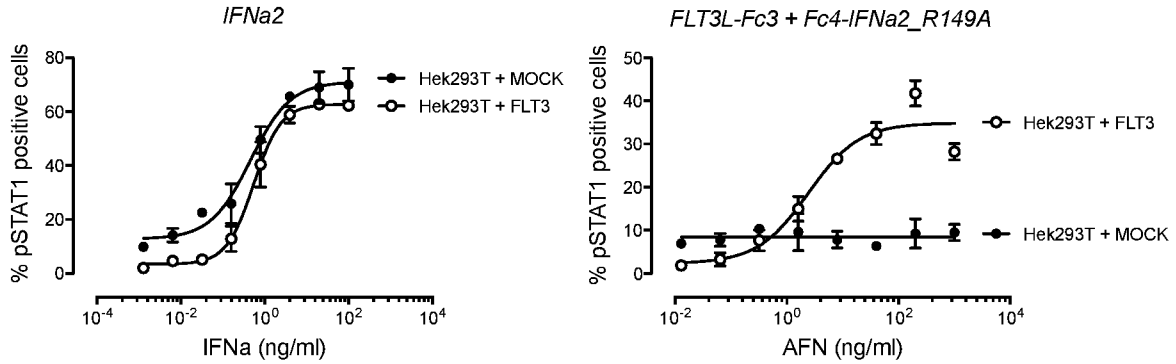

IFNa2
% pSTAT1 positive cells
80
60
40
20
Hek293T + MOCK
Hek293T + FLT3
IFNa (ng/ml)
FLT3L-Fc3 + Fc4-IFNa2_R149A
50
30
10
AFN (ng/ml)

FIG. 54

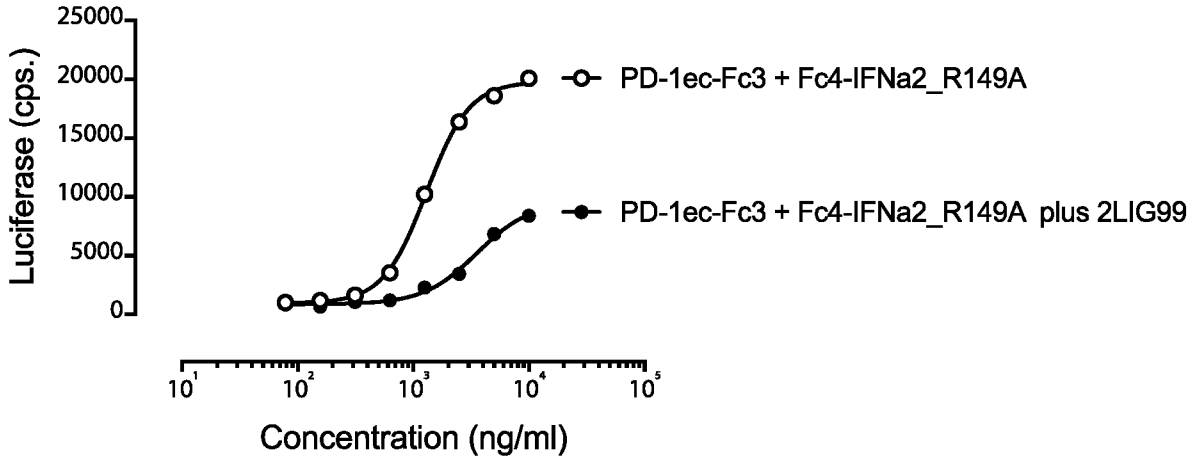

Luciferase (cps.)
25000
20000
15000
10000
5000
0
PD-1ec-Fc3 + Fc4-IFNa2_R149A
PD-1ec-Fc3 + Fc4-IFNa2_R149A plus 2LIG99
10^1
10^2
10^3
10^4
10^5
Concentration (ng/ml)

FIG. 55

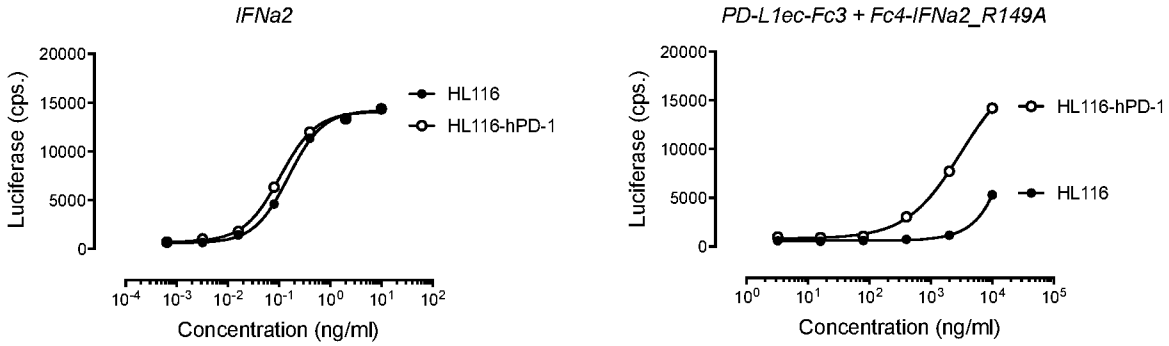

IFNa2
Luciferase (cps.)
20000
15000
10000
5000
0
HL116
HL116-hPD-1
10^-4
10^-3
10^-2
10^-1
10^0
10^1
10^2
Concentration (ng/ml)
PD-L1ec-Fc3 + Fc4-IFNa2_R149A
Luciferase (cps.)
20000
15000
10000
5000
0
HL116-hPD-1
HL116
10^0
10^1
10^2
10^3
10^4
10^5
Concentration (ng/ml)

FIG. 56

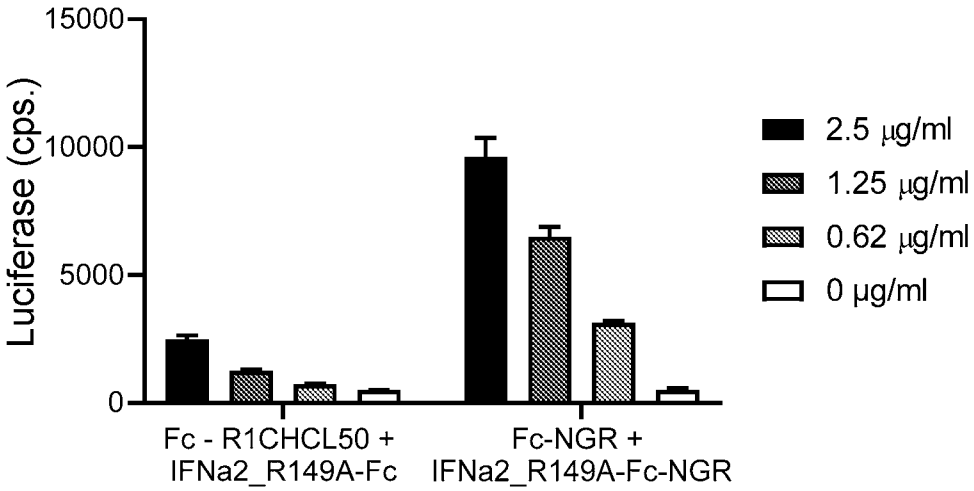

15000
10000
5000
0
Luciferase (cps.)
2.5 µg/ml
1.25 µg/ml
0.62 µg/ml
0 µg/ml
Fc - R1CHCL50 + IFNa2_R149A-Fc
Fc-NGR + IFNa2_R149A-Fc-NGR

FIG. 57

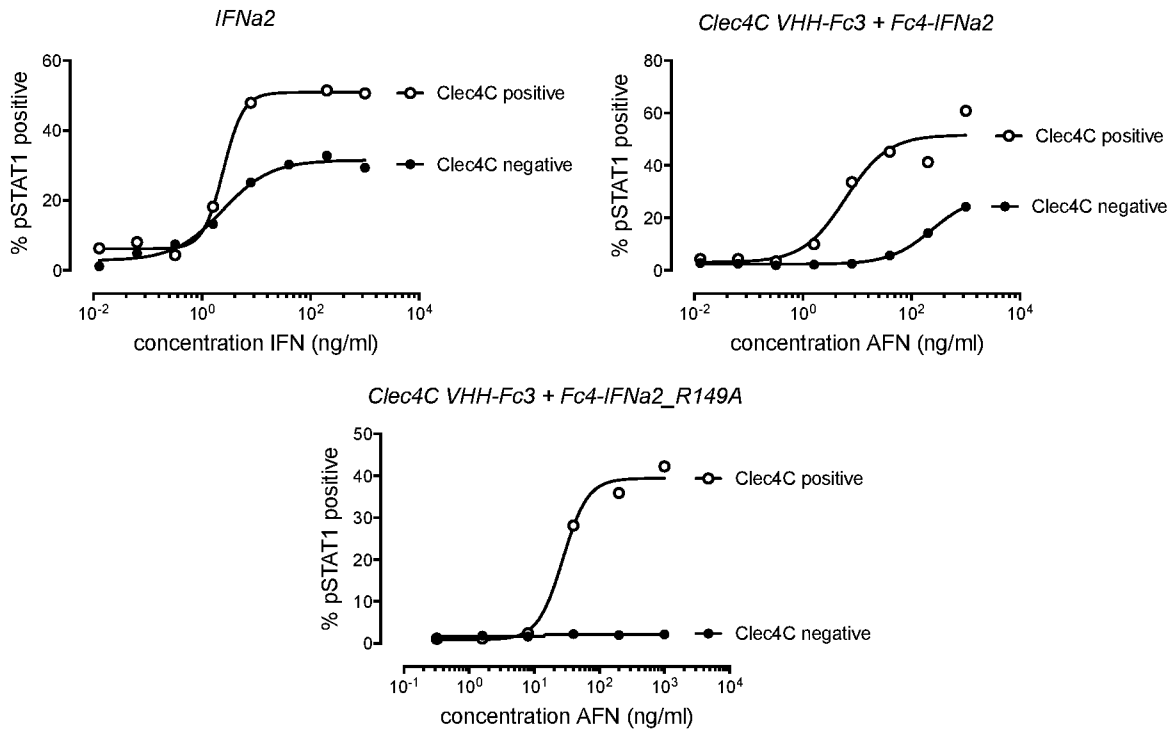

IFNa2
% pSTAT1 positive
Clec4C positive
Clec4C negative
concentration IFN (ng/ml)
Clec4C VHH-Fc3 + Fc4-IFNa2
concentration AFN (ng/ml)
Clec4C VHH-Fc3 + Fc4-IFNa2_R149A
concentration AFN (ng/ml)

FIG. 58

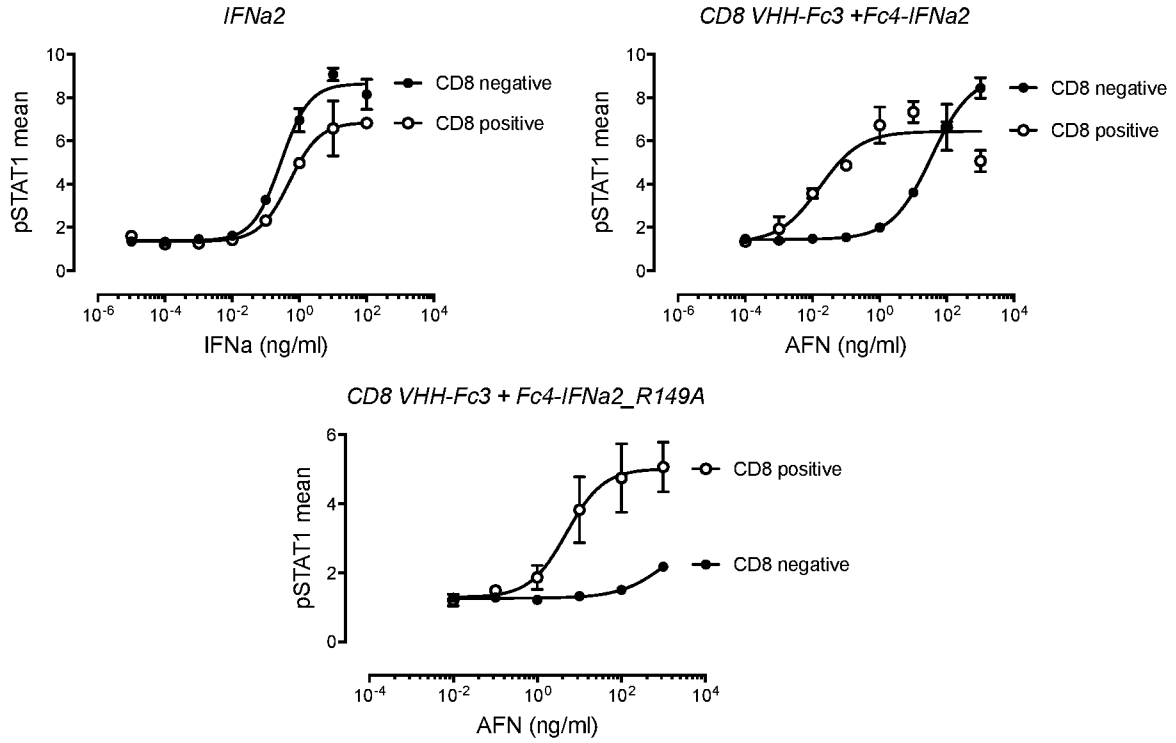

IFNa2
pSTAT1 mean
IFNa (ng/ml)
CD8 negative
CD8 positive
CD8 VHH-Fc3 +Fc4-IFNa2
AFN (ng/ml)
CD8 VHH-Fc3 + Fc4-IFNa2_R149A

FIG. 59

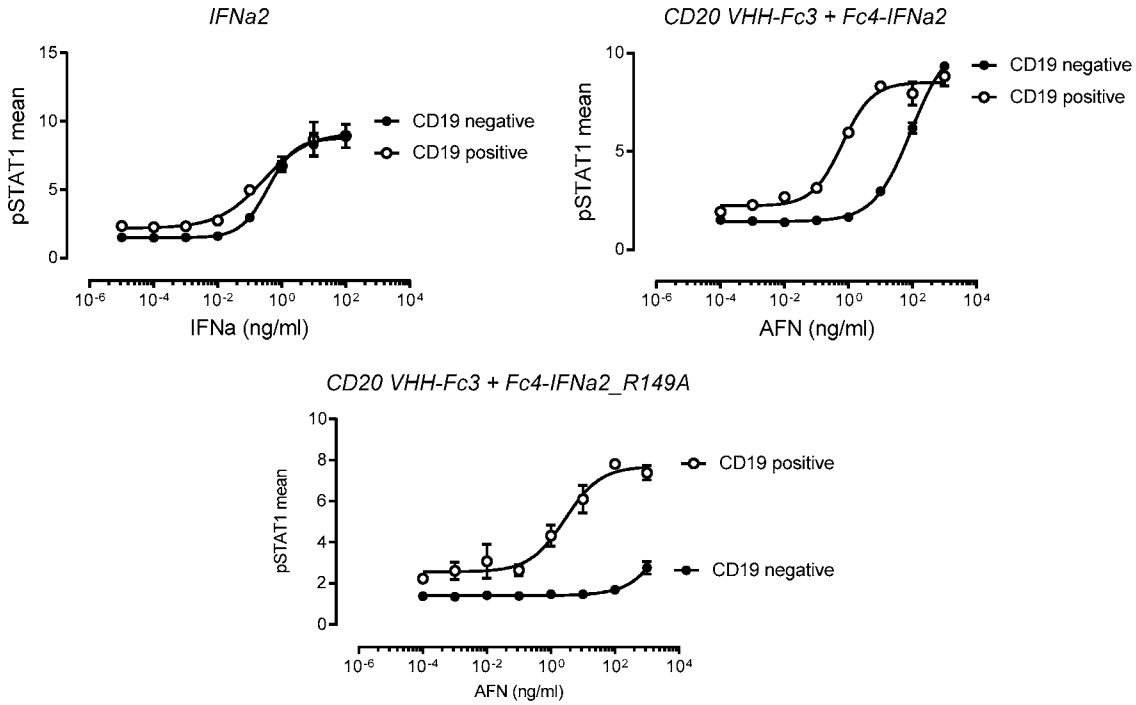

IFNa2
pSTAT1 mean
IFNa (ng/ml)
CD19 negative
CD19 positive
CD20 VHH-Fc3 + Fc4-IFNa2
AFN (ng/ml)
CD20 VHH-Fc3 + Fc4-IFNa2_R149A

FIG. 60

```
30-LKDRHDFGFP-//-VVRAEIMRSFSLSTNLQESLRSKE-165: wild type IFNa2
30-...A......-//-.......................-165: P-1838: Fc4-hIFNa2_R33A
30-..........-//-..A....................-165: P-1839: Fc4-hIFNa2_R144A
30-..........-//-..I....................-165: P-1840: Fc4-hIFNa2_R144I
30-..........-//-..L....................-165: P-1841: Fc4-hIFNa2_R144L
30-..........-//-..S....................-165: P-1842: Fc4-hIFNa2_R144S
30-..........-//-..T....................-165: P-1843: Fc4-hIFNa2_R144T
30-..........-//-..Y....................-165: P-1844: Fc4-hIFNa2_R144Y
30-..........-//-...D...................-165: P-1845: Fc4-hIFNa2_A145D
30-..........-//-...G...................-165: P-1846: Fc4-hIFNa2_A145G
30-..........-//-...H...................-165: P-1847: Fc4-hIFNa2_A145H
30-..........-//-...K...................-165: P-1848: Fc4-hIFNa2_A145K
30-..........-//-...Y...................-165: P-1849: Fc4-hIFNa2_A145Y
30-..........-//-......A................-165: P-1850: Fc4-hIFNa2_M148A
30-..........-//-.......A...............-165: P-1414: Fc4-hIFNa2_R149A
30-..........-//-...........A...........-165: P-1851: Fc4-hIFNa2_L153A
```

FIG. 61

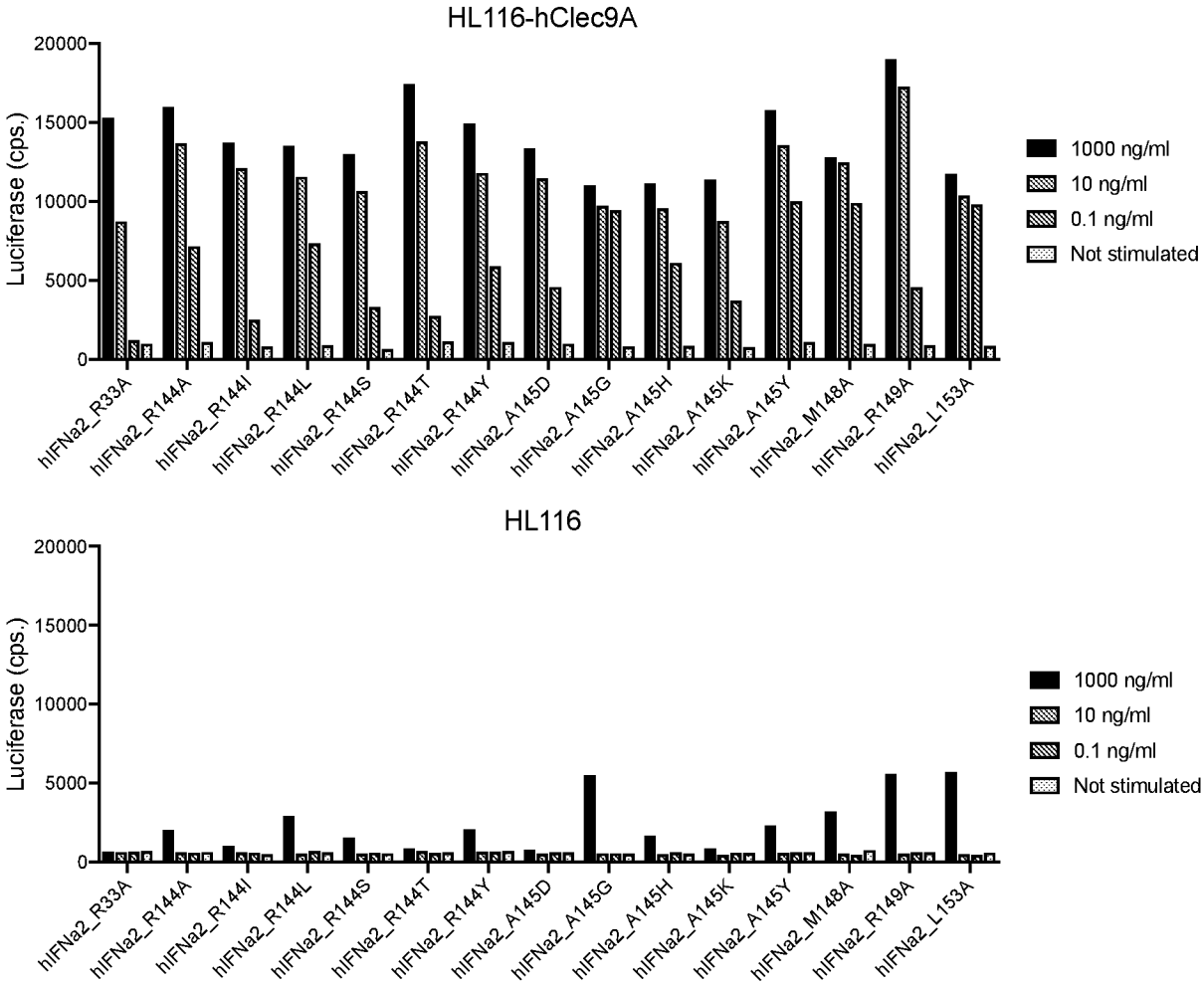

HL116-hClec9A
Luciferase (cps.)
20000
15000
10000
5000
0
1000 ng/ml
10 ng/ml
0.1 ng/ml
Not stimulated
hIFNa2_R33A
hIFNa2_R144A
hIFNa2_R144I
hIFNa2_R144L
hIFNa2_R144S
hIFNa2_R144T
hIFNa2_R144Y
hIFNa2_A145D
hIFNa2_A145G
hIFNa2_A145H
hIFNa2_A145K
hIFNa2_A145Y
hIFNa2_M148A
hIFNa2_R149A
hIFNa2_L153A
HL116
Luciferase (cps.)
20000
15000
10000
5000
0
1000 ng/ml
10 ng/ml
0.1 ng/ml
Not stimulated
hIFNa2_R33A
hIFNa2_R144A
hIFNa2_R144I
hIFNa2_R144L
hIFNa2_R144S
hIFNa2_R144T
hIFNa2_R144Y
hIFNa2_A145D
hIFNa2_A145G
hIFNa2_A145H
hIFNa2_A145K
hIFNa2_A145Y
hIFNa2_M148A
hIFNa2_R149A
hIFNa2_L153A

FIG. 62

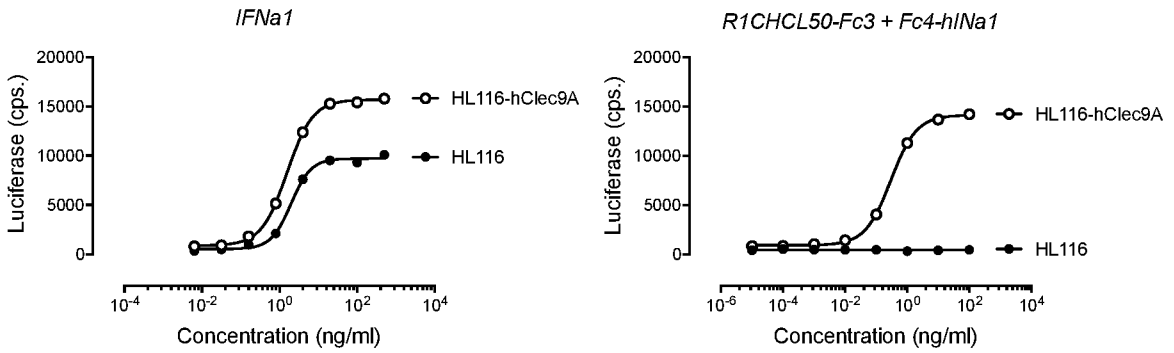


FIG. 63

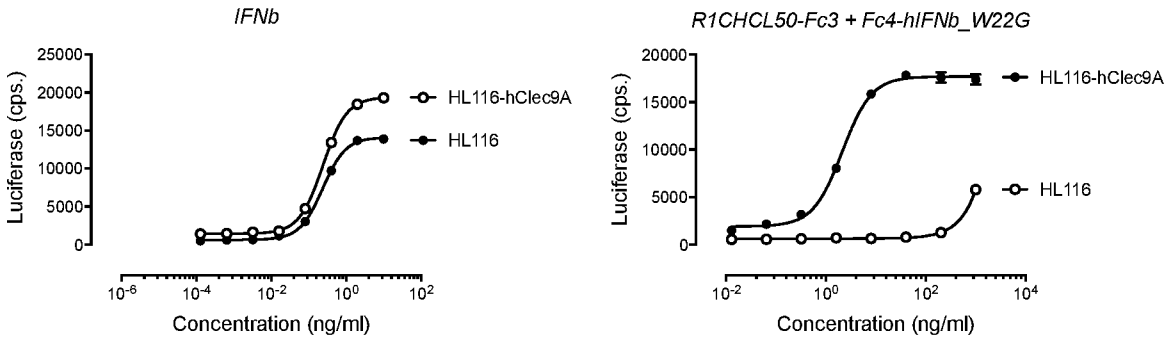


FIG. 64

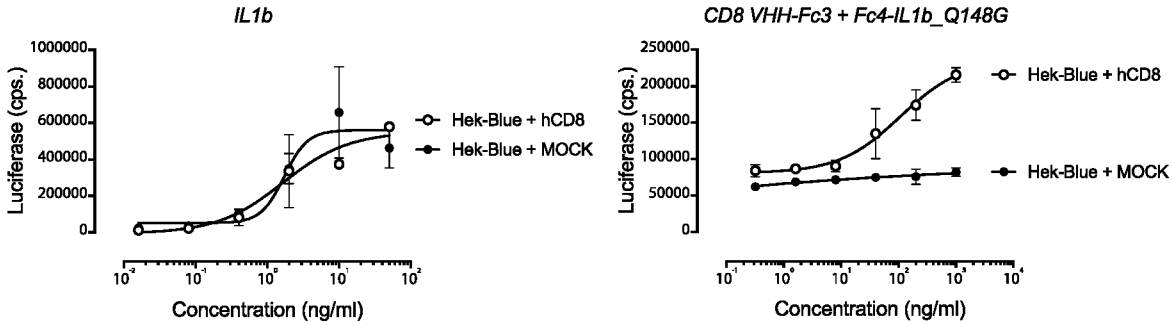


FIG. 65

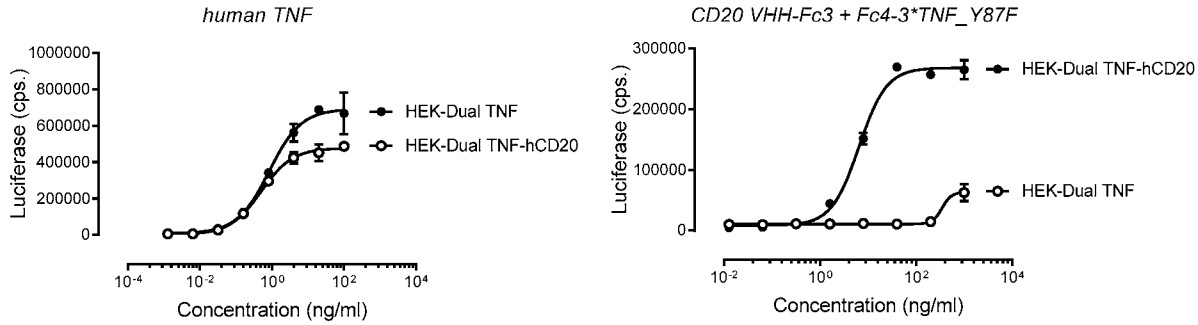


FIG. 66

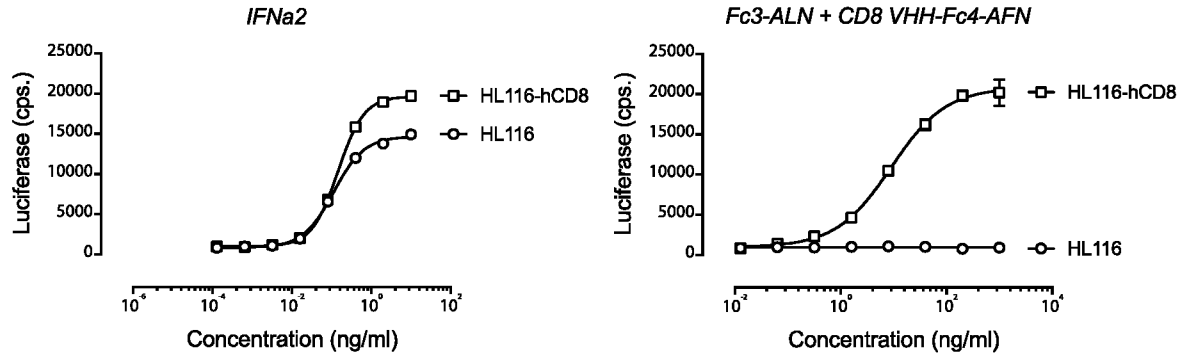


FIG. 67

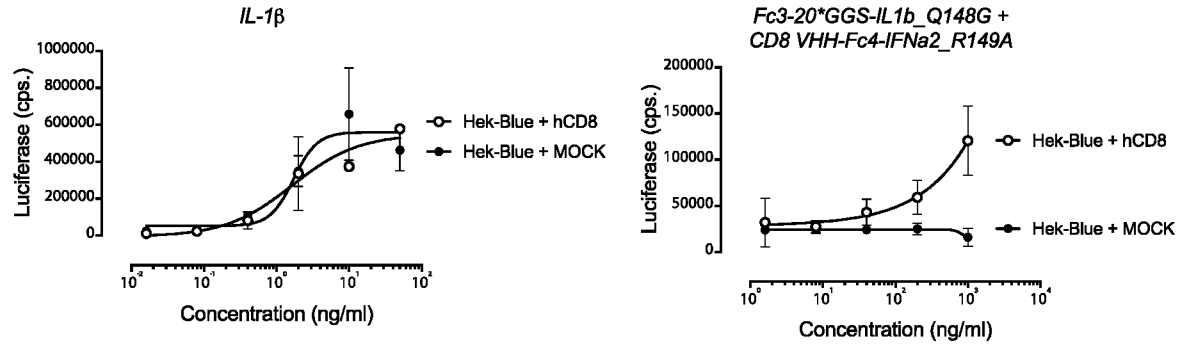


FIG. 68

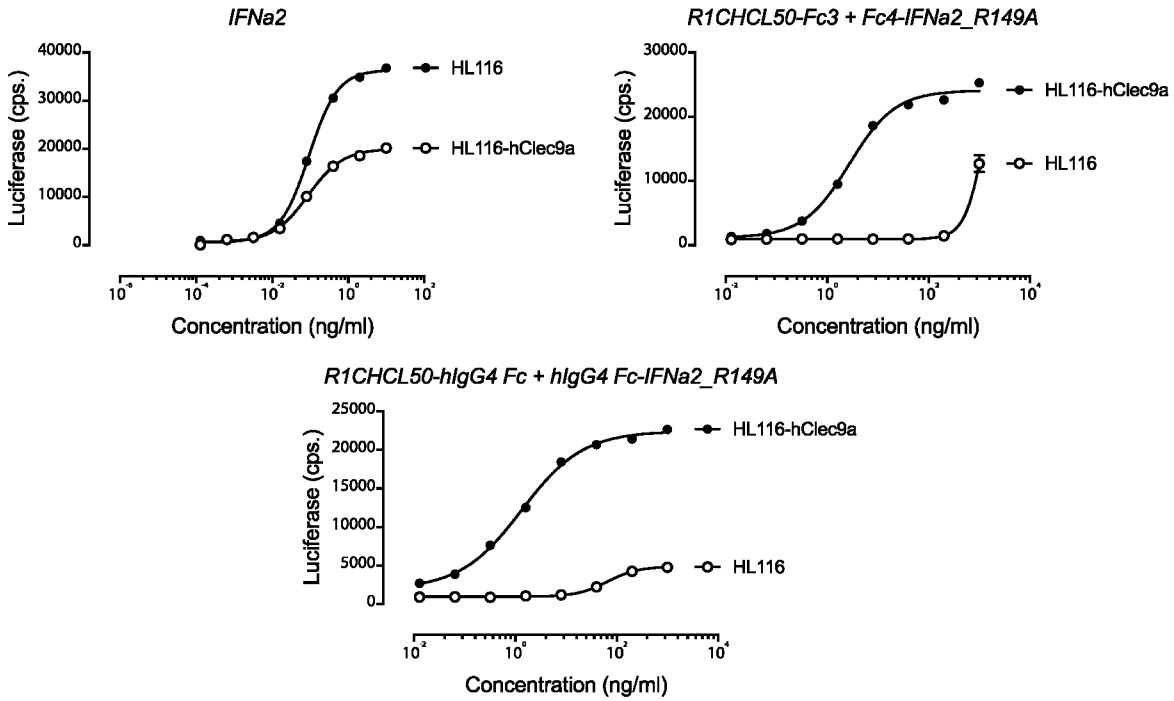
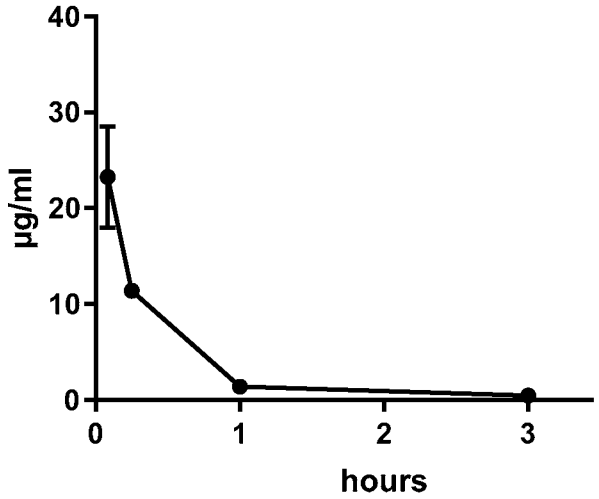

IFNa2
Luciferase (cps.)
40000
30000
20000
10000
0
HL116
HL116-hClec9a
Concentration (ng/ml)
R1CHCL50-Fc3 + Fc4-IFNa2_R149A
Luciferase (cps.)
30000
20000
10000
0
HL116-hClec9a
HL116
Concentration (ng/ml)
R1CHCL50-hIgG4 Fc + hIgG4 Fc-IFNa2_R149A
Luciferase (cps.)
25000
20000
15000
10000
5000
0
HL116-hClec9a
HL116
Concentration (ng/ml)

FIG. 69:


40
30
20
10
0
µg/ml
0
1
2
3
hours

SEQUENCE LISTING

<110> Orionis Biosciences LLC

<120> BI-FUNCTIONAL PROTEINS AND CONSTRUCTION THEREOF

<130> 114384-5042

<150> 62/649,238
<151> 2018-03-28

<160> 1570

<170> PatentIn version 3.5

<210> 1
<211> 165
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (IFN-alpha2a)

<400> 1

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                  10                  15


Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30


Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45


Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60


Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80


Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95
```

```
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110


Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125


Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140


Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160


Leu Arg Ser Lys Glu
                165


<210>  2
<211>  165
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (IFN-alpha2b)

<400>  2

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                   10                  15


Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30


Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45


Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60


Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
```

65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 3
<211> 166
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> human IFN-beta

<400> 3

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1 5 10 15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
20 25 30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln

```
        35                  40                  45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
    50                  55                  60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65                  70                  75                  80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
                85                  90                  95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
            100                 105                 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
        115                 120                 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
    130                 135                 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145                 150                 155                 160

Thr Gly Tyr Leu Arg Asn
                165
```

<210> 4
<211> 167
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (consensus interferon)

<400> 4

```
Met Cys Asp Leu Pro Gln Thr His Ser Leu Gly Asn Arg Arg Ala Leu
1               5                   10                  15
```

```
Ile Leu Leu Ala Gln Met Arg Arg Ile Ser Pro Phe Ser Cys Leu Lys
            20                  25                  30

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln
        35                  40                  45

Phe Gln Lys Ala Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln
    50                  55                  60

Thr Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
65                  70                  75                  80

Ser Leu Leu Glu Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
                85                  90                  95

Leu Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu
            100                 105                 110

Met Asn Val Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Gln Arg Ile
        115                 120                 125

Thr Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
    130                 135                 140

Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln
145                 150                 155                 160

Glu Arg Leu Arg Arg Lys Glu
                165
```

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

<220>
<223> Synthetic Sequence (consensus interferon)

<400> 5

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Asn Arg Arg Ala Leu Ile
1               5                  10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Pro Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln Phe
        35                  40                  45

Gln Lys Ala Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln Thr
    50                  55                  60

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Ser
65                  70                  75                  80

Leu Leu Glu Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
                85                  90                  95

Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met
            100                 105                 110

Asn Val Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Gln Arg Ile Thr
        115                 120                 125

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
145                 150                 155                 160

Arg Leu Arg Arg Lys Glu
                165
```

<210> 6

<211> 166
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (IFN-CON2)

<400> 6

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Asn Arg Arg Thr Leu Met
1               5                  10                  15


Leu Leu Ala Gln Met Arg Arg Ile Ser Pro Phe Ser Cys Leu Lys Asp
            20                  25                  30


Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln Phe
        35                  40                  45


Gln Lys Ala Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln Thr
    50                  55                  60


Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Ser
65                  70                  75                  80


Leu Leu Glu Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
                85                  90                  95


Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met
            100                 105                 110


Asn Val Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Gln Arg Ile Thr
        115                 120                 125


Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
    130                 135                 140


Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
145                 150                 155                 160
```

Arg Leu Arg Arg Lys Glu
165

<210> 7
<211> 166
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (IFN-CON3)

<400> 7

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Asn Arg Arg Ala Leu Ile
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Pro Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln Phe
35 40 45

Gln Lys Ala Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln Thr
50 55 60

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Ser
65 70 75 80

Leu Leu Glu Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
85 90 95

Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met
100 105 110

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

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val

```
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
145                 150                 155                 160

Arg Leu Arg Arg Lys Glu
                165

<210>  8
<211>  167
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (consensus variant)

<400>  8

Met Cys Asp Leu Pro Gln Thr His Ser Leu Gly Asn Arg Arg Ala Leu
1               5                   10                  15

Ile Leu Leu Ala Gln Met Arg Arg Ile Ser Pro Phe Ser Cys Leu Lys
            20                  25                  30

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln
        35                  40                  45

Phe Gln Lys Ala Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln
    50                  55                  60

Thr Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
65                  70                  75                  80

Ser Leu Leu Glu Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
                85                  90                  95

Leu Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu
            100                 105                 110
```

```
Met Asn Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
        115                 120                 125


Thr Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
    130                 135                 140


Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln
145                 150                 155                 160


Glu Arg Leu Arg Arg Lys Glu
                165


<210>  9
<211>  167
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (consensus interferon variant)

<400>  9

Met Cys Asp Leu Pro Gln Thr His Ser Leu Gly Asn Arg Arg Ala Leu
1               5                   10                  15


Ile Leu Leu Ala Gln Met Arg Arg Ile Ser Pro Phe Ser Cys Leu Lys
            20                  25                  30


Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln
        35                  40                  45


Phe Gln Lys Ala Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln
    50                  55                  60


Thr Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
65                  70                  75                  80


Ser Leu Leu Glu Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
```

85 90 95

Leu Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu
100 105 110

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

Thr Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
130 135 140

Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Cys Thr Asn Leu Gln
145 150 155 160

Glu Arg Leu Arg Arg Lys Glu
165

<210> 10
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (consensus interferon variant)

<400> 10

Glu Glu Phe Gly Asn Gln
1 5

<210> 11
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (consensus interferon variant)

<400> 11

Glu Glu Phe Asp Gly Asn Gln

1 5

<210> 12
<211> 165
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (wild type amino acid sequence of VEGF165)

<400> 12

Ala Pro Met Ala Glu Gly Gly Gly Gln Asn His His Glu Val Val Lys
1 5 10 15

Phe Met Asp Val Tyr Gln Arg Ser Tyr Cys His Pro Ile Glu Thr Leu
20 25 30

Val Asp Ile Phe Gln Glu Tyr Pro Asp Glu Ile Glu Tyr Ile Phe Lys
35 40 45

Pro Ser Cys Val Pro Leu Met Arg Cys Gly Gly Cys Cys Asn Asp Glu
50 55 60

Gly Leu Glu Cys Val Pro Thr Glu Glu Ser Asn Ile Thr Met Gln Ile
65 70 75 80

Met Arg Ile Lys Pro His Gln Gly Gln His Ile Gly Glu Met Ser Phe
85 90 95

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

Gln Glu Asn Pro Cys Gly Pro Cys Ser Glu Arg Arg Lys His Leu Phe
115 120 125

Val Gln Asp Pro Gln Thr Cys Lys Cys Ser Cys Lys Asn Thr Asp Ser
130 135 140

```
Arg Cys Lys Ala Arg Gln Leu Glu Leu Asn Glu Arg Thr Cys Arg Cys
145                 150                 155                 160


Asp Lys Pro Arg Arg
                165


<210>  13
<211>  165
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (wild type amino acid sequence of VEGF165b )

<400>  13

Ala Pro Met Ala Glu Gly Gly Gly Gln Asn His His Glu Val Val Lys
1               5                   10                  15


Phe Met Asp Val Tyr Gln Arg Ser Tyr Cys His Pro Ile Glu Thr Leu
            20                  25                  30


Val Asp Ile Phe Gln Glu Tyr Pro Asp Glu Ile Glu Tyr Ile Phe Lys
        35                  40                  45


Pro Ser Cys Val Pro Leu Met Arg Cys Gly Gly Cys Cys Asn Asp Glu
    50                  55                  60


Gly Leu Glu Cys Val Pro Thr Glu Glu Ser Asn Ile Thr Met Gln Ile
65                  70                  75                  80


Met Arg Ile Lys Pro His Gln Gly Gln His Ile Gly Glu Met Ser Phe
                85                  90                  95


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


Gln Glu Asn Pro Cys Gly Pro Cys Ser Glu Arg Arg Lys His Leu Phe
```

115 120 125

Val Gln Asp Pro Gln Thr Cys Lys Cys Ser Cys Lys Asn Thr Asp Ser
130 135 140

Arg Cys Lys Ala Arg Gln Leu Glu Leu Asn Glu Arg Thr Cys Arg Ser
145 150 155 160

Leu Thr Arg Lys Asp
165

<210> 14
<211> 157
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (wild type TNF-alpha)

<400> 14

Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Lys Pro Val Ala His Val
1 5 10 15

Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30

Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45

Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60

Lys Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80

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

```
Ile Lys Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys
            100                 105                 110


Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys
        115                 120                 125


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


Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155


<210>  15
<211>  171
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (wild type TNF-beta)

<400>  15

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


His Pro Lys Met His Leu Ala His Ser Asn Leu Lys Pro Ala Ala His
            20                  25                  30


Leu Ile Gly Asp Pro Ser Lys Gln Asn Ser Leu Leu Trp Arg Ala Asn
        35                  40                  45


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


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


Phe Ser Gly Lys Ala Tyr Ser Pro Lys Ala Thr Ser Ser Pro Leu Tyr
```

85 90 95

Leu Ala His Glu Val Gln Leu Phe Ser Ser Gln Tyr Pro Phe His Val
100 105 110

Pro Leu Leu Ser Ser Gln Lys Met Val Tyr Pro Gly Leu Gln Glu Pro
115 120 125

Trp Leu His Ser Met Tyr His Gly Ala Ala Phe Gln Leu Thr Gln Gly
130 135 140

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

Pro Ser Thr Val Phe Phe Gly Ala Phe Ala Leu
165 170

<210> 16
<211> 281
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (wild type TRAIL)

<400> 16

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

Val Leu Ile Val Ile Phe Thr Val Leu Leu Gln Ser Leu Cys Val Ala
20 25 30

Val Thr Tyr Val Tyr Phe Thr Asn Glu Leu Lys Gln Met Gln Asp Lys
35 40 45

Tyr Ser Lys Ser Gly Ile Ala Cys Phe Leu Lys Glu Asp Asp Ser Tyr
50 55 60

```
Trp Asp Pro Asn Asp Glu Glu Ser Met Asn Ser Pro Cys Trp Gln Val
65                  70                  75                  80

Lys Trp Gln Leu Arg Gln Leu Val Arg Lys Met Ile Leu Arg Thr Ser
                85                  90                  95

Glu Glu Thr Ile Ser Thr Val Gln Glu Lys Gln Gln Asn Ile Ser Pro
            100                 105                 110

Leu Val Arg Glu Arg Gly Pro Gln Arg Val Ala Ala His Ile Thr Gly
        115                 120                 125

Thr Arg Gly Arg Ser Asn Thr Leu Ser Ser Pro Asn Ser Lys Asn Glu
    130                 135                 140

Lys Ala Leu Gly Arg Lys Ile Asn Ser Trp Glu Ser Ser Arg Ser Gly
145                 150                 155                 160

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

His Glu Lys Gly Phe Tyr Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg Phe
            180                 185                 190

Gln Glu Glu Ile Lys Glu Asn Thr Lys Asn Asp Lys Gln Met Val Gln
        195                 200                 205

Tyr Ile Tyr Lys Tyr Thr Ser Tyr Pro Asp Pro Ile Leu Leu Met Lys
    210                 215                 220

Ser Ala Arg Asn Ser Cys Trp Ser Lys Asp Ala Glu Tyr Gly Leu Tyr
225                 230                 235                 240

Ser Ile Tyr Gln Gly Gly Ile Phe Glu Leu Lys Glu Asn Asp Arg Ile
                245                 250                 255
```

```
Phe Val Ser Val Thr Asn Glu His Leu Ile Asp Met Asp His Glu Ala
            260                 265                 270


Ser Phe Phe Gly Ala Phe Leu Val Gly
        275                 280


<210>  17
<211>  153
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (wild type IL-1beta)

<400>  17

Ala Pro Val Arg Ser Leu Asn Cys Thr Leu Arg Asp Ser Gln Gln Lys
1               5                   10                  15


Ser Leu Val Met Ser Gly Pro Tyr Glu Leu Lys Ala Leu His Leu Gln
            20                  25                  30


Gly Gln Asp Met Glu Gln Gln Val Val Phe Ser Met Ser Phe Val Gln
        35                  40                  45


Gly Glu Glu Ser Asn Asp Lys Ile Pro Val Ala Leu Gly Leu Lys Glu
    50                  55                  60


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


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


Lys Arg Phe Val Phe Asn Lys Ile Glu Ile Asn Asn Lys Leu Glu Phe
            100                 105                 110


Glu Ser Ala Gln Phe Pro Asn Trp Tyr Ile Ser Thr Ser Gln Ala Glu
```

115 120 125

Asn Met Pro Val Phe Leu Gly Gly Thr Lys Gly Gly Gln Asp Ile Thr
130 135 140

Asp Phe Thr Met Gln Phe Val Ser Ser
145 150

<210> 18
<211> 133
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (wild type IL-2)

<400> 18

Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His
1 5 10 15

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

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

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

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

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

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

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


Ile Ser Thr Leu Thr
    130


<210>  19
<211>  129
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (wild type IL-4)

<400>  19

His Lys Cys Asp Ile Thr Leu Gln Glu Ile Ile Lys Thr Leu Asn Ser
1               5                   10                  15


Leu Thr Glu Gln Lys Thr Leu Cys Thr Glu Leu Thr Val Thr Asp Ile
            20                  25                  30


Phe Ala Ala Ser Lys Asn Thr Thr Glu Lys Glu Thr Phe Cys Arg Ala
        35                  40                  45


Ala Thr Val Leu Arg Gln Phe Tyr Ser His His Glu Lys Asp Thr Arg
    50                  55                  60


Cys Leu Gly Ala Thr Ala Gln Gln Phe His Arg His Lys Gln Leu Ile
65                  70                  75                  80


Arg Phe Leu Lys Arg Leu Asp Arg Asn Leu Trp Gly Leu Ala Gly Leu
                85                  90                  95


Asn Ser Cys Pro Val Lys Glu Ala Asn Gln Ser Thr Leu Glu Asn Phe
            100                 105                 110


Leu Glu Arg Leu Lys Thr Ile Met Arg Glu Lys Tyr Ser Lys Cys Ser
```

115 120 125

Ser

<210> 20
<211> 185
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (wild type IL-6)

<400> 20

Ala Pro Val Pro Pro Gly Glu Asp Ser Lys Asp Val Ala Ala Pro His
1 5 10 15

Arg Gln Pro Leu Thr Ser Ser Glu Arg Ile Asp Lys Gln Ile Arg Tyr
20 25 30

Ile Leu Asp Gly Ile Ser Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser
35 40 45

Asn Met Cys Glu Ser Ser Lys Glu Ala Leu Ala Glu Asn Asn Leu Asn
50 55 60

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

Glu Glu Thr Cys Leu Val Lys Ile Ile Thr Gly Leu Leu Glu Phe Glu
85 90 95

Val Tyr Leu Glu Tyr Leu Gln Asn Arg Phe Glu Ser Ser Glu Glu Gln
100 105 110

Ala Arg Ala Val Gln Met Ser Thr Lys Val Leu Ile Gln Phe Leu Gln
115 120 125

```
Lys Lys Ala Lys Asn Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr Thr
    130                 135                 140


Asn Ala Ser Leu Thr Thr Lys Leu Gln Ala Gln Asn Gln Trp Leu Gln
145                 150                 155                 160


Asp Met Thr Thr His Leu Ile Leu Arg Ser Phe Lys Glu Phe Leu Gln
                165                 170                 175


Ser Ser Leu Arg Ala Leu Arg Gln Met
            180                 185


<210>  21
<211>  114
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (wild type IL-13)

<400>  21

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


Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly
            20                  25                  30


Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala
        35                  40                  45


Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr
    50                  55                  60


Gln Arg Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln
65                  70                  75                  80


Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe
```

85 90 95

Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg
100 105 110

Phe Asn

<210> 22
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (wild type IL-18)

<400> 22

Met Ala Ala Glu Pro Val Glu Asp Asn Cys Ile Asn Phe Val Ala Met
1 5 10 15

Lys Phe Ile Asp Asn Thr Leu Tyr Phe Ile Ala Glu Asp Asp Glu Asn
20 25 30

Leu Glu Ser Asp Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile
35 40 45

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

Leu Phe Glu Asp Met Thr Asp Ser Asp Cys Arg Asp Asn Ala Pro Arg
65 70 75 80

Thr Ile Phe Ile Ile Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met
85 90 95

Ala Val Thr Ile Ser Val Lys Cys Glu Lys Ile Ser Thr Leu Ser Cys
100 105 110

```
Glu Asn Lys Ile Ile Ser Phe Lys Glu Met Asn Pro Pro Asp Asn Ile
        115                 120                 125


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


His Asp Asn Lys Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe
145                 150                 155                 160


Leu Ala Cys Glu Lys Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys
                165                 170                 175


Glu Asp Glu Leu Gly Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu
            180                 185                 190


Asp Leu
```

<210> 23
<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (wild type IL-33)

<400> 23

```
Met Lys Pro Lys Met Lys Tyr Ser Thr Asn Lys Ile Ser Thr Ala Lys
1               5                   10                  15


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


Gln Gln Lys Ala Lys Glu Val Cys Pro Met Tyr Phe Met Lys Leu Arg
        35                  40                  45


Ser Gly Leu Met Ile Lys Lys Glu Ala Cys Tyr Phe Arg Arg Glu Thr
```

```
    50                  55                  60

Thr Lys Arg Pro Ser Leu Lys Thr Gly Arg Lys His Lys Arg His Leu
65                  70                  75                  80

Val Leu Ala Ala Cys Gln Gln Gln Ser Thr Val Glu Cys Phe Ala Phe
                85                  90                  95

Gly Ile Ser Gly Val Gln Lys Tyr Thr Arg Ala Leu His Asp Ser Ser
            100                 105                 110

Ile Thr Gly Ile Ser Pro Ile Thr Glu Tyr Leu Ala Ser Leu Ser Thr
        115                 120                 125

Tyr Asn Asp Gln Ser Ile Thr Phe Ala Leu Glu Asp Glu Ser Tyr Glu
    130                 135                 140

Ile Tyr Val Glu Asp Leu Lys Lys Asp Glu Lys Lys Asp Lys Val Leu
145                 150                 155                 160

Leu Ser Tyr Tyr Glu Ser Gln His Pro Ser Asn Glu Ser Gly Asp Gly
                165                 170                 175

Val Asp Gly Lys Met Leu Met Val Thr Leu Ser Pro Thr Lys Asp Phe
            180                 185                 190

Trp Leu His Ala Asn Asn Lys Glu His Ser Val Glu Leu His Lys Cys
        195                 200                 205

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

Ser Asn Cys Val Ser Phe Glu Cys Lys Thr Asp Pro Gly Val Phe Ile
225                 230                 235                 240

Gly Val Lys Asp Asn His Leu Ala Leu Ile Lys Val Asp Ser Ser Glu
```

245 250 255

Asn Leu Cys Thr Glu Asn Ile Leu Phe Lys Leu Ser Glu Thr
260 265 270

<210> 24
<211> 193
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> human EPO (the first 27 amino acids are the signal peptide)

<400> 24

Met Gly Val His Glu Cys Pro Ala Trp Leu Trp Leu Leu Leu Ser Leu
1 5 10 15

Leu Ser Leu Pro Leu Gly Leu Pro Val Leu Gly Ala Pro Pro Arg Leu
20 25 30

Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu
35 40 45

Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu
50 55 60

Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
65 70 75 80

Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
85 90 95

Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser
100 105 110

Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly

115 120 125

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

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

Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu
165 170 175

Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp
180 185 190

Arg

<210> 25
<211> 166
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> mature form of human EPO

<400> 25

Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu
1 5 10 15

Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His
20 25 30

Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe
35 40 45

Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp

50 55 60

Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu
65 70 75 80

Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp
85 90 95

Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu
100 105 110

Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala
115 120 125

Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val
130 135 140

Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala
145 150 155 160

Cys Arg Thr Gly Asp Arg
165

<210> 26
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> human Clec9A

<400> 26

Met His Glu Glu Glu Ile Tyr Thr Ser Leu Gln Trp Asp Ser Pro Ala
1 5 10 15

Pro Asp Thr Tyr Gln Lys Cys Leu Ser Ser Asn Lys Cys Ser Gly Ala

```
            20                  25                  30

Cys Cys Leu Val Met Val Ile Ser Cys Val Phe Cys Met Gly Leu Leu
        35                  40                  45

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

Ala Met Gln Gln Gln Glu Lys Leu Ile Gln Gln Glu Arg Ala Leu Leu
65                  70                  75                  80

Asn Phe Thr Glu Trp Lys Arg Ser Cys Ala Leu Gln Met Lys Tyr Cys
                85                  90                  95

Gln Ala Phe Met Gln Asn Ser Leu Ser Ser Ala His Asn Ser Ser Pro
            100                 105                 110

Cys Pro Asn Asn Trp Ile Gln Asn Arg Glu Ser Cys Tyr Tyr Val Ser
        115                 120                 125

Glu Ile Trp Ser Ile Trp His Thr Ser Gln Glu Asn Cys Leu Lys Glu
    130                 135                 140

Gly Ser Thr Leu Leu Gln Ile Glu Ser Lys Glu Glu Met Asp Phe Ile
145                 150                 155                 160

Thr Gly Ser Leu Arg Lys Ile Lys Gly Ser Tyr Asp Tyr Trp Val Gly
                165                 170                 175

Leu Ser Gln Asp Gly His Ser Gly Arg Trp Leu Trp Gln Asp Gly Ser
            180                 185                 190

Ser Pro Ser Pro Gly Leu Leu Pro Ala Glu Arg Ser Gln Ser Ala Asn
        195                 200                 205

Gln Val Cys Gly Tyr Val Lys Ser Asn Ser Leu Leu Ser Ser Asn Cys
```

210 215 220

Ser Thr Trp Lys Tyr Phe Ile Cys Glu Lys Tyr Ala Leu Arg Ser Ser
225 230 235 240

Val

<210> 27
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 27

Gly Ser Ile Ser Ser Ile Asn Val Met Gly
1 5 10

<210> 28
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 28

Gly Ser Phe Ser Ser Ile Asn Val Met Gly
1 5 10

<210> 29
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 29

Gly Ser Ile Ser Ser Ile Asn Ile Met Gly
1   5   10

<210> 30
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 30

Gly Ser Ile Ser Ser Ile Asn Ile Met Gly
1   5   10

<210> 31
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 31

Val Ser Ile Phe Ser Ile Asn Ala Met Gly
1   5   10

<210> 32
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 32

Gly Ser Ile Phe Ser Leu Asn Ala Met Gly
1   5   10

<210> 33

<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 33

Gly Arg Thr Ile Ser Asn Tyr Asp Met Ala
1 5 10

<210> 34
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 34

Gly Arg Thr Phe Thr Thr Ser Leu Met Gln
1 5 10

<210> 35
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 35

Glu Arg Asn Leu Arg Ile Tyr Asp Met Ala
1 5 10

<210> 36
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 36

Glu Arg Asn Leu Arg Ser Tyr Asp Met Ala
1 5 10

<210> 37
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 37

Gly Leu Thr Phe Ser Asn Tyr His Met Gly
1 5 10

<210> 38
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 38

Gly Leu Thr Phe Ser Ser Tyr His Met Gly
1 5 10

<210> 39
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 39

Gly Leu Thr Phe Ser Arg Tyr His Met Gly
1 5 10

<210> 40
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 40

Gly Leu Thr Leu Ser Ser Tyr Tyr Ile Ala
1 5 10

<210> 41
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 41

Gly Leu Thr Phe Ser Ser Tyr Tyr Thr Gly
1 5 10

<210> 42
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 42

Gly Leu Thr Leu Ser Ser Tyr His Met Gly
1 5 10

<210> 43
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 43

Gly Arg Thr Ser Ser Pro Tyr Val Thr Gly
1   5   10

<210> 44
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 44

Gly Phe Thr Phe Ser Gly Tyr Val Met Ser
1   5   10

<210> 45
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 45

Gly Phe Thr Phe Ser Gly Tyr Val Met Thr
1   5   10

<210> 46
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 46

Gly Phe Thr Phe Ser Gly Tyr Leu Met Ser

1 5 10

<210> 47
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 47

Gly Arg Ile Ser Ser Ile Asn Ser Met Gly
1 5 10

<210> 48
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 48

Gly Ser Ile Thr Ser Ile Asn Ala Met Gly
1 5 10

<210> 49
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 49

Gly Arg Phe Phe Arg Val Asn Ala Met Gly
1 5 10

<210> 50
<211> 10
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 50

Gly Ser Ser Asp Ser Ile Asn Ala Met Gly
1   5   10

<210> 51
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 51

Gly Ser Val Phe Ser Ile Asn Ala Trp Gly
1   5   10

<210> 52
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 52

Gly Ser Ile Leu Ser Ile Asn Ser Met Gly
1   5   10

<210> 53
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 53

Val Ser Ile Ser Ser Ile Asn Ser Met Gly
1   5   10

<210> 54
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 54

Gly Arg Val Phe Ser Ile Asn Ala Met Gly
1   5   10

<210> 55
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 55

Val Asn Ile Asp Thr Leu Asn Ser Met Ala
1   5   10

<210> 56
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 56

Gly Gly Ile Ser Ser Ile Asn Ser Met Gly
1   5   10

<210> 57

<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 57

Gly Ser Met His Ser Val Asn Ser Met Ala
1   5   10

<210> 58
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 58

Gly Asp Ile Ser Ser Ile Asn Ala Met Gly
1   5   10

<210> 59
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 59

Gly Ser Ile Phe Ser Ile Asp Ala Met Gly
1   5   10

<210> 60
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 60

Gly Ser Ile Phe Ser Ile Asn Ala Met Gly
1 5 10

<210> 61
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 61

Gly Ser Ile Phe Ser Ile Ala Ala Met Gly
1 5 10

<210> 62
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 62

Gly Asn Ile Ala Ser Ile Thr Ala Met Gly
1 5 10

<210> 63
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 63

Gly Phe Thr Phe Asp Asp Tyr Ala Ile Gly
1 5 10

<210> 64
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 64

Gly Ser Ile Ser Ser Ile Asn Ala Met Gly
1 5 10

<210> 65
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 65

Val Ser Ile Phe Arg Ser Tyr Phe Met Gly
1 5 10

<210> 66
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 66

Gly Ser Ile Val Ser Ile Asn Ala Ile Gly
1 5 10

<210> 67
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 67

Gly Ser Ile Phe Ser Ile Asn Ala Met Gly
1   5   10

<210> 68
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 68

Arg Ser Phe Ser Ser Phe Asn Ala Met Gly
1   5   10

<210> 69
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 69

Gly Ser Phe Ser Ser Ile Asn Ala Met Gly
1   5   10

<210> 70
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 70

Gly Thr Ser Phe Ser Ile Asn Gly Met Ala

1 5 10

<210> 71
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 71

Gly Arg Thr Phe Ser Thr Tyr Ala Met Gly
1 5 10

<210> 72
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 72

Gly Ser Ile Phe Ser Ile Asn Ala Met Gly
1 5 10

<210> 73
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 73

Gly Arg Ile Phe Asp Ile Asn Ala Met Gly
1 5 10

<210> 74
<211> 10
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 74

Gly Thr Leu Phe Ser Ile Asn Gly Met Ala
1 5 10

<210> 75
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 75

Gly Ser Ile Asp Ser Ile Asn Ala Met Gly
1 5 10

<210> 76
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 76

Gly Arg Ala Phe Ser Thr Asn Ser Met Gly
1 5 10

<210> 77
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 77

Gly Ser Ile Ile Ser Ile Asn Ser Met Gly
1 5 10

<210> 78
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 78

Arg Asn Phe Phe Ser Ile Asn Ala Met Gly
1 5 10

<210> 79
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 79

Gly Arg Phe Phe Arg Val Asn Ala Met Gly
1 5 10

<210> 80
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 80

Gly Ser Ile Val Ser Ile Asn Ser Met Gly
1 5 10

<210> 81

<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 81

Gly Ser Ile Phe Ser Ile Asn Ala Met Gly
1   5   10

<210> 82
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 82

Gly Ser Ile Ile Gly Ile Asn Ser Met Gly
1   5   10

<210> 83
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 83

Gly Arg Thr Phe Pro Gly Tyr Val Met Ala
1   5   10

<210> 84
<211> 10
<212> PRT
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<220>
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<400> 84

Gly Ser Ile Phe Ser Ile Asn Ala Met Gly
1 5 10

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<220>
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<400> 85

Gly Arg Thr Phe Ser Ile Asn Ala Met Gly
1 5 10

<210> 86
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<220>
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<400> 86

Gly Arg Thr Leu Ser Ser Tyr Thr Ile Gly
1 5 10

<210> 87
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<220>
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<400> 87

Gly Ser Phe Phe Ser Ile Asn Ala Met Gly
1 5 10

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<220>
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<400> 88

Gly Ser Ile Phe Ser Ile Asn Ser Met Gly
1 5 10

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<400> 89

Gly Ser Ile Phe Ser Phe Asn Ala Met Gly
1 5 10

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<400> 90

Gly Ser Ile Phe Ser Ile Asn Ala Met Gly
1 5 10

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<400> 91

Gly Arg Thr Phe Ser Thr Tyr Ala Met Ala
1   5   10

<210> 92
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<400> 92

Gly Ser Phe Phe Ser Ile Asn Ala Met Gly
1   5   10

<210> 93
<211> 10
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<400> 93

Val Asn Ile Gly Ser Leu Asn Ser Met Val
1   5   10

<210> 94
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<220>
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<400> 94

Gly Arg Thr Leu Ser Asn Tyr Ala Val Gly

1 5 10

<210> 95
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<220>
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<400> 95

Gly Ser Ile Ser Ser Ile Asn Ala Met Gly
1 5 10

<210> 96
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<400> 96

Gly Arg Phe Phe Arg Val Asn Ala Met Gly
1 5 10

<210> 97
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<220>
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<400> 97

Gly Ser Val Phe Ser Ile Asn Ala Met Gly
1 5 10

<210> 98
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<220>
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<400> 98

Gly Ser Ile Phe Glu Ile Asn Ser Ile Gly
1   5   10

<210> 99
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<400> 99

Gly Ser Ile Phe Asn Ile Asn Ser Met Gly
1   5   10

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<400> 100

Val Asn Ile Gly Thr Leu Asn Ser Met Ala
1   5   10

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<400> 101

Gly Ser Ile Phe Ser Ile Asn Ser Met Gly
1   5   10

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<400> 102

Gly Arg Ile Gly Ser Ile Asn Ser Met Gly
1   5   10

<210> 103
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<220>
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<400> 103

Gly Ser Ile Phe Ser Phe Asn Ala Met Gly
1   5   10

<210> 104
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<400> 104

Gly Arg Ile Ser Ser Ile Asn Ser Met Gly
1   5   10

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<400> 105

Gly Arg Thr Leu Ser Asn Tyr Ala Val Ala
1 5 10

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<400> 106

Gly Arg Ile Gly Ser Ile Asn Ser Met Gly
1 5 10

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<400> 107

Arg Ser Phe Phe Ser Phe Asn Ala Met Gly
1 5 10

<210> 108
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<220>
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<400> 108

Gly Arg Phe Phe Arg Val Asn Ala Met Gly
1 5 10

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<400> 109

Gly Ile Ile Phe Ser Ile Asn Ala Met Gly
1 5 10

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<400> 110

Gly Arg Thr Leu Ser Asn Tyr Ala Val Ala
1 5 10

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<400> 111

Gly Arg Ile Phe Ser Val Asn Ala Met Gly
1 5 10

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<400> 112

Gly Arg Thr Phe Ser Ser Tyr Ala Met Ala
1 5 10

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<220>
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<400> 113

Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Trp Leu Lys Asp
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<400> 114

Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr Gly
1 5 10 15

<210> 115
<211> 16
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<400> 115

Arg Ile Thr Asn Ile Gly Leu Pro Asn Tyr Ala Asp Ser Val Lys Gly
1   5   10   15

<210> 116
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<400> 116

Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Glu Gly
1   5   10   15

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<400> 117

Ala Ile Thr Ser Gly Gly Arg Val Val Tyr Ser Asp Ser Val Lys Gly
1   5   10   15

<210> 118
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<400> 118

Ala Ile Thr Ser Gly Gly Arg Thr Ala Tyr Ala Asp Ser Val Lys Gly

1 5 10 15

<210> 119
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<400> 119

His Ile Thr Ser Asp Gly Arg Ile Val Tyr Ala Asp Pro Val Lys Gly
1 5 10 15

<210> 120
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<400> 120

Arg Ile Ser Gly Ser Gly Asp Arg Thr Asp Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

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<400> 121

Ser Ile Thr Trp Ser Thr Gly Asn Thr His Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 122
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<220>
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<400> 122

Val Ile Ser Ser Ser Gly Asp Ser Thr His Tyr Ser Asp Phe Val Lys
1 5 10 15

Gly

<210> 123
<211> 17
<212> PRT
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<220>
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<400> 123

Val Ile Thr Ser Ser Gly Asp Ser Thr His Tyr Ser Asp Phe Val Lys
1 5 10 15

Gly

<210> 124
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<220>
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<400> 124

Gln Ile Thr Trp Ser Asp Ala Ser Ile Tyr Tyr Ala Gly Ser Val Lys
1 5 10 15

Gly

<210> 125
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<400> 125

Gln Ile Thr Trp Ser Asp Thr Ser Ile Tyr Tyr Ala Gly Ser Val Lys
1 5 10 15

Gly

<210> 126
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<400> 126

Gln Ile Thr Trp Ser Asp Gly Thr Thr Tyr Tyr Pro Gly Ser Val Lys
1 5 10 15

Gly

<210> 127

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<400> 127

Gln Ile Arg Trp Ser Asp Asp Ser Thr Tyr Tyr Pro Gly Ser Val Lys
1 5 10 15

Gly

<210> 128
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<400> 128

Gln Ile Ser Trp Ser Asp Asp Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 129
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<400> 129

Thr Val Ser Trp Gly Gly Val Thr Tyr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

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<400> 130

Ser Ile Gly Ser Gly Gly Gly Tyr Pro Ser Tyr Thr Asp Ser Val Glu
1 5 10 15

Gly

<210> 131
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<400> 131

Ser Ile Gly Ser Gly Gly Gly Tyr Pro Ser Tyr Thr Gly Ser Val Glu
1 5 10 15

Gly

<210> 132
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<400> 132

His Ile Gly Ser Gly Gly Gly Tyr Pro Ser Tyr Thr Asp Ser Val Gln

1 5 10 15

Gly

<210> 133
<211> 17
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<400> 133

His Ile Gly Ser Gly Gly Gly His Ala Thr Tyr Thr Asp Ser Val Glu
1 5 10 15

Gly

<210> 134
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<400> 134

Thr Ile Gly Ser Gly Gly Gly Ile Thr Ser Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 135
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<400> 135

Ala Ile Thr Asn Gly Gly Ala Lys Thr Tyr Ala Asp Ser Val Lys Gly
1   5   10   15

<210> 136
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<400> 136

Ala Ile Thr Ser Gly Gly Arg Leu Ser Tyr Ala Asp Ser Val Lys Gly
1   5   10   15

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<400> 137

Ala Ile Thr Asn Gly Gly Gln Thr Ala Tyr Ala Asp Ser Val Lys Gly
1   5   10   15

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<400> 138

Ala Ile Thr Ser Gly Gly Arg Ser Thr Tyr Ile Asp Ser Ala Lys Gly

1 5 10 15

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<400> 139

Ala Ile Thr Asn Gln Gly Arg Ile Ala Tyr Ala Pro Ser Val Asn Gly
1 5 10 15

<210> 140
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<400> 140

Ala Ile Thr Asn Asp Gly Arg Thr Thr Tyr Val Asp Ser Val Lys Gly
1 5 10 15

<210> 141
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Ala Val Thr Val Gly Gly Arg Tyr Ala Tyr Ala Asp Ser Ala Lys Asn
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<400> 142

Ala Ile Thr Asn Gln Gly Ala Thr Thr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

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<400> 143

Gly Ile Thr Gly Ser Gly Gln Ile Thr Tyr Ala Asn Ser Val Arg Gly
1 5 10 15

<210> 144
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<400> 144

Ala Ile Thr Asn Gly Gly Arg Thr Val Tyr Gly Asp Ser Val Lys Gly
1 5 10 15

<210> 145
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<400> 145

Ala Ile Thr Ser Gly Gly Arg Leu Ala Tyr Ala Pro Ser Val Asn Gly
1 5 10 15

<210> 146
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<400> 146

Ala Ile Thr Asn Gly Gly Arg Thr Thr Tyr Val Asp Ser Val Lys Gly
1 5 10 15

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<400> 147

Ala Ile Thr Thr Gly Gly Arg Thr Thr Tyr Val Asp Ser Val Lys Gly
1 5 10 15

<210> 148
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<400> 148

Ala Ile Thr Asn Gln Gly Arg Leu Thr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> 149

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<400> 149

Ala Ile Thr Ser Gly Gly Arg Arg Ala Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> 150
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<400> 150

Ala Ile Thr Ser Ala Ser Ala Ser Arg Thr Thr Tyr Ala Asp Ser Val
1 5 10 15

Lys Gly

<210> 151
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<400> 151

Cys Ile Ser Arg Ser Asp Gly Ser Thr Tyr Tyr Asp Asp Ser Val Lys
1 5 10 15

Gly

<210> 152
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<400> 152

Ala Ile Thr Asn Gln Gly Arg Val Thr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> 153
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<213> Artificial Sequence

<220>
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<400> 153

Ala Ile Thr Asp Gly Gly Arg Leu Ala Tyr Ala Asp Ser Ala Lys Gly
1 5 10 15

<210> 154
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<220>
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<400> 154

Ser Ile Thr Asn Gln Gly Ile Arg Asn Tyr Ser Thr Ser Val Met Gly
1 5 10 15

<210> 155
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<400> 155

Ala Ile Thr Asn Gln Gly Arg Thr Thr Tyr Ala Asp Ser Val Lys Gly
1   5   10   15

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<220>
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<400> 156

Ala Ile Thr Asn Gly Gly Arg Ile Ala Tyr Gly Ile Ala Val Asn Gly
1   5   10   15

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<400> 157

Ala Ile Thr Asn Gly Gly Arg Ile Ala Tyr Ser Asp Ser Ala Lys Gly
1   5   10   15

<210> 158
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<220>
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<400> 158

Gly Ile Thr Ser Asp Gly Ser Thr Gly Tyr Ala Asp Ser Val Lys Gly

1 5 10 15

<210> 159
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<400> 159

Ala Ile Ser Trp Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

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<400> 160

Ala Ile Thr Asp Gln Gly Arg Leu Ala Tyr Ala Asp Ser Ala Lys Gly
1 5 10 15

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<400> 161

Ala Ile Thr Asn Gly Gly Gln Thr Thr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

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<400> 162

Gly Ile Thr Ser Asp Gly Ser Thr Gly Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

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<400> 163

Ala Ile Thr Thr Gly Gly Arg Thr Ala Tyr Val Asp Ser Val Lys Gly
1 5 10 15

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Ala Ile Thr Ser Gln Gly Arg Ile Thr Leu Ala Asp Ser Val Lys Gly
1 5 10 15

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<400> 165

Ala Ile Thr Val Asp Gly Arg Leu Ala Tyr Ala Asp Ser Ala Lys His
1   5   10   15

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<400> 166

Ala Ile Thr Asn Gly Gly Arg Ile Ala Tyr Gly Thr Ser Val Met Gly
1   5   10   15

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<400> 167

Ala Ile Thr Asn Gly Gly Gln Ile Ala Tyr Ala Asp Ser Val Lys Gly
1   5   10   15

<210> 168
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<400> 168

Ala Ile Thr Asp Gln Gly Arg Thr Thr Tyr Ala Asp Ser Val Lys Gly

1 5 10 15

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Gly Ile Thr Thr Gln Gly Arg Ile Thr Tyr Gly Asn Ser Val Arg Gly
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Ala Ile Thr Ser Gly Gly Arg Thr Thr Tyr Val Asp Ser Val Lys Gly
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Ala Ile Asn Trp Arg Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val Lys
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Gly

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Ala Ile Thr Asp Gly Gly Ala Lys Thr Tyr Ala Asp Ser Val Lys Gly
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Ala Ile Thr Asn Gln Gly Arg Leu Ser Tyr Val Asp Ser Val Lys Gly
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Ala Ile Thr Asn Gln Gly Arg Arg Thr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

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<400> 175

Ala Ile Thr Asn Gly Gly Arg Ile Ala Tyr Thr Asp Ser Val Lys Gly
1   5   10   15

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Ala Ile Thr Asn Gly Gly Arg Thr Thr Tyr Ala Asp Ser Val Lys Gly
1   5   10   15

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Ala Ile Thr Asp Gly Gly Arg Leu Thr Tyr Ala Asp Ser Ala Lys Gly
1   5   10   15

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Ala Ile Thr Thr Gly Gly Arg Thr Thr Tyr Val Asp Ser Val Lys Gly

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Ala Ile Thr Asn Gln Gly Arg Ile Ala Tyr Ala Asp Ser Val Lys Gly
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Ala Ile Asn Trp Ser Ser Gly Gly Ile Ser Tyr Ser Asn Ser Ala Lys
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Gly

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Ala Ile Thr Gly Gln Gly Arg Thr Thr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

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Ala Ile Thr Asn Gly Gly Gln Ile Val Tyr Ala Asp Ser Val Lys Gly
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1 5 10 15

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Ala Ile Thr Ser Gly Gly Ile Thr Asn Tyr Ala Asn Ser Val Gln Gly
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<400> 187

Ala Ile Thr Val Gly Gly Arg Leu Ala Tyr Ala Asp Ser Ala Lys Gly
1 5 10 15

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Gly Ile Thr Gly Gly Gly Gln Ile Thr Tyr Ala Asn Ser Val Arg Gly
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Ala Ile Thr Ser Gln Gly Arg Ser Thr Tyr Ala Asp Ser Ala Lys Gly
1   5   10   15

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Ala Ile Thr Asn Gly Gly Ala Thr Val Tyr Ala Asp Ser Val Lys Gly
1   5   10   15

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Ala Ile Thr Asp Gly Gly Arg Leu Thr Tyr Ala Asp Ser Ala Lys Asn
1   5   10   15

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Ala Ile Thr Asn Gly Gly Ala Lys Thr Tyr Ala Asp Ser Val Lys Gly
1   5   10   15

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Ala Ile Asn Trp Ser Ser Gly Gly Ile Ser Tyr Ser Asn Ala Ala Lys
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Gly

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Ala Ile Thr Asn Gly Gly Ala Thr Val Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

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Ala Ile Thr Asn Gly Gly Arg Ile Ala Tyr Gly Thr Ser Val Met Gly
1 5 10 15

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Ala Ile Thr Asn Gly Gly Gln Thr Ala Tyr Ala Asp Ser Val Lys Gly
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<400> 197

Ala Ile Thr Asn Xaa Gly Arg Thr Thr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> 198
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<220>
<223> Synthetic Sequence

<400> 198

Ala Ile Trp Trp Ala Ser Gly Gly Ile Ser Tyr Ala Asn Ser Ala Lys
1 5 10 15

Gly

<210> 199
<211> 16
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<220>
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<400> 199

Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

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<220>
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<400> 200

Ala Ile Ser Trp Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 201
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<400> 201

Val Ala Leu Ser Ala Glu Tyr
1 5

<210> 202
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<400> 202

Val Ala Leu Lys Ala Glu Tyr
1 5

<210> 203
<211> 7
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<220>
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<400> 203

Val Gly Leu Lys Ala Glu Tyr
1 5

<210> 204
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<220>
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<400> 204

Lys Thr Lys Ser Ala Val Leu Phe Gly Gly Met Asp Tyr
1 5 10

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<400> 205

Tyr Ile Arg Gly Glu Asp Tyr
1   5

<210> 206
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<220>
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<400> 206

Lys His Tyr Ala Ser Asn Tyr
1   5

<210> 207
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<220>
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<400> 207

Gln Asp Phe Gly Ser Pro Ser Phe
1   5

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<220>
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<400> 208

Gln Asp Phe Arg Ser Pro Asp Phe
1   5

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<400> 209

Gln Ile Phe Gly Ser Pro Asn Phe
1   5

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<400> 210

Leu Ala Ile His Gly Asp Tyr
1   5

<210> 211
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<220>
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<400> 211

Asn Gln Ile Arg Gln Trp Pro
1   5

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<220>
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<400> 212

Asn Ser Ile Arg Gln Trp Pro
1 5

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<220>
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<400> 213

Asn Ala Ile Arg Gln Trp Pro
1 5

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<400> 214

Arg Lys Val Gly Gly Pro Asp Tyr
1 5

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<400> 215

Asn Thr Phe Gly Asn Val Tyr
1 5

<210> 216
<211> 7
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<220>
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<400> 216

Phe Thr Arg Arg Asp Asp Tyr
1 5

<210> 217
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<220>
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<400> 217

Phe Gln Ser Ser Gly Ile Asp
1 5

<210> 218
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<220>
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<400> 218

Trp Ala Ala Asp Tyr Gln Gln Tyr
1 5

<210> 219
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<220>
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<400> 219

Trp Asn Arg Asp Arg Gln Gln Tyr
1 5

<210> 220
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<220>
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<400> 220

Lys Pro Thr Pro Val Tyr Gly Ser Thr Val Gly Asp Tyr
1 5 10

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<220>
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<400> 221

Phe Thr Arg Asp Lys Asp Tyr
1 5

<210> 222
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<220>

<223> Synthetic Sequence

<400> 222

Trp Asp Arg Asp Arg Gln Gln Tyr
1   5

<210> 223
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<400> 223

Phe Thr Arg Thr Asp Asp Tyr
1   5

<210> 224
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<220>
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<400> 224

Tyr Asp Arg Ser Ser Thr Pro Tyr
1   5

<210> 225
<211> 7
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<220>
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<400> 225

Phe Thr Arg Gly Asp Asp Tyr
1   5

<210> 226
<211> 7
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<220>
<223> Synthetic Sequence

<400> 226

Leu Asn Ser Ala Thr Thr Tyr
1 5

<210> 227
<211> 7
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<220>
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<400> 227

Tyr Thr Arg Asp Glu Asp Tyr
1 5

<210> 228
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<220>
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<400> 228

Phe Thr Arg Asp Glu Asp Tyr
1 5

<210> 229
<211> 13
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<220>
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<400> 229

Lys Trp Tyr Asp Pro Leu Val Ile Glu Tyr Tyr Asp Asn
1   5   10

<210> 230
<211> 7
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<220>
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<400> 230

Lys Ala Asp His Asn Asp Tyr
1   5

<210> 231
<211> 8
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<220>
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<400> 231

Phe Arg Ser Gly Ala Asp Asp Tyr
1   5

<210> 232
<211> 15
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<220>
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<400> 232

Glu Val Pro Ser Thr Tyr Ser Cys Ser Gly Phe Arg Glu Asp Tyr
1   5   10   15

<210> 233
<211> 8
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<220>
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<400> 233

Phe Ala Ala Ser Gly Met Glu Tyr
1   5

<210> 234
<211> 8
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<213> Artificial Sequence

<220>
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<400> 234

Trp Thr Thr Asp Arg Gln Gln Tyr
1   5

<210> 235
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<220>
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<400> 235

Phe Ala Gly Trp Gly Lys Glu Asp Tyr
1   5

<210> 236
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<220>
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<400> 236

Phe Ser Pro Thr Gly Asp Tyr
1   5

<210> 237
<211> 13
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<220>
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<400> 237

Lys Pro Thr Pro Val Tyr Gly Ser Thr Val Gly Asp Tyr
1   5   10

<210> 238
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<220>
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<400> 238

Lys Ala Ser Pro Val Tyr Gly Ser Thr Val Glu Asp Tyr
1   5   10

<210> 239
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<220>
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<400> 239

Ser Thr Pro Arg Gly Asp Ser Tyr
1 5

<210> 240
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<220>
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<400> 240

Glu Ala Glu Gly Ser Gly Arg Glu Gly Asn Phe Tyr Glu Arg Ser
1 5 10 15

<210> 241
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<220>
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<400> 241

Trp Asp Arg Asp Arg Gln Gln Tyr
1 5

<210> 242
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<220>
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<400> 242

Phe Thr Arg Ser Asp Asp Tyr
1 5

<210> 243
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<400> 243

Ser Thr Pro Arg Gly Asp Ser Tyr
1 5

<210> 244
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<220>
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<400> 244

Phe Thr Arg Asp Thr Asp Tyr
1 5

<210> 245
<211> 7
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<220>
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<400> 245

Trp Thr Thr Leu Gly Thr Phe
1 5

<210> 246
<211> 8
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<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 246

Trp Val Arg Asp Gly Gln Gln Tyr
1   5

<210> 247
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<400> 247

Lys Ala Ile Pro Val Tyr Gly Ser Thr Val Glu Asp Tyr
1   5   10

<210> 248
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<212> PRT
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<220>
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<400> 248

Lys Ala Ala Ala Thr His Leu Ser Thr Val Ala Asp Tyr
1   5   10

<210> 249
<211> 7
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<220>
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<400> 249

Phe Gly Arg Phe Asp Asp Tyr
1   5

<210> 250
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<220>
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<400> 250

Trp Gly Val Lys Thr Gly Pro Glu Ser Gly Ser Gly Thr Leu
1 5 10

<210> 251
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<220>
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<400> 251

Phe Thr Arg Asp Glu Asp Tyr
1 5

<210> 252
<211> 10
<212> PRT
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<220>
<223> Synthetic Sequence

<400> 252

Arg Leu Thr Thr Glu Tyr Asp Tyr Ala Tyr
1 5 10

<210> 253
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 253

Phe Thr Arg Gly Asn Asp Tyr
1   5

<210> 254
<211> 7
<212> PRT
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<220>
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<400> 254

Phe Gln Ser Ser Gly Ile Asp
1   5

<210> 255
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<400> 255

Phe Ser Pro Thr Asp Asp Phe
1   5

<210> 256
<211> 13
<212> PRT
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<220>
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<400> 256

Lys Ala Ile Pro Ile Tyr Gly Ser Thr Ala Glu Asp Tyr
1   5   10

<210> 257
<211> 7
<212> PRT
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<220>
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<400> 257

Phe Ser Leu Thr Asp Asp Tyr
1   5

<210> 258
<211> 8
<212> PRT
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<220>
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<400> 258

Trp Thr Arg Asp Arg Gln Gln Tyr
1   5

<210> 259
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<400> 259

Phe Thr Arg Asp Glu Asp Phe
1   5

<210> 260
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<212> PRT
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<400> 260

Glu Val Glu Gly Ser Gly Arg Glu Gly Asn Phe Tyr Gly Ala
1 5 10

<210> 261

<400> 261
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<210> 262

<400> 262
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<210> 263

<400> 263
000

<210> 264

<400> 264
000

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000

<210> 266

<400> 266
000

<210> 267
<211> 5
<212> PRT
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<220>

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<400> 267

Pro Gly Trp Asp Tyr
1   5

<210> 268
<211> 8
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<220>
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<400> 268

Tyr Asp Arg Ser Ala Thr Ala Tyr
1   5

<210> 269
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<220>
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<400> 269

Ala Ser Ser Val Leu Ser Gly Thr Val Asp Tyr
1   5   10

<210> 270
<211> 8
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<220>
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<400> 270

Phe Ala Ala Asp Gly Met Glu Tyr
1   5

<210> 271
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<400> 271

Lys Ala Ala Ala Ser Tyr Val Ser Thr Val Ala Asp Tyr
1 5 10

<210> 272
<211> 6
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<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 272

Thr Ala Lys Asp Asp Tyr
1 5

<210> 273
<211> 9
<212> PRT
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<220>
<223> Synthetic Sequence

<400> 273

Phe Thr Gly Trp Gly Lys Glu Asp Tyr
1 5

<210> 274
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 274

Trp Ala Ala Asp Tyr Gln Gln Tyr
1   5

<210> 275
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 275

Tyr Asp Arg Ser Ala Thr Pro Tyr
1   5

<210> 276
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 276

Trp Ala Arg Asp Arg Gln Gln Tyr
1   5

<210> 277
<211> 7
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<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 277

Phe Thr Arg Gly Asp Asp Tyr
1   5

<210> 278
<211> 8
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<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 278

Trp Thr Lys Asp Arg Gln Gln Tyr
1   5

<210> 279
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 279

Phe Thr Arg Thr Tyr Asp Tyr
1   5

<210> 280
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 280

Ala Ser Ser Ile Leu Ser Gly Thr Val Asp Tyr
1   5   10

<210> 281
<211> 8

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 281

Trp Ala Ala Asp Tyr Gln Gln Tyr
1   5

<210> 282
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 282

Lys Pro Ala Pro Val Tyr Gly Ser Thr Val Gly Asp Tyr
1   5   10

<210> 283
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 283

Phe Ala Ala Asp Gly Met Glu Tyr
1   5

<210> 284
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 284

Phe Gly Ser Gly Gly Gly
1 5

<210> 285
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 285

Ala Ser Ser Val Leu Ser Gly Thr Ala Asp Tyr
1 5 10

<210> 286
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 286

Phe Thr Arg Gly Asp Asp Tyr
1 5

<210> 287
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 287

Glu Ala Glu Gly Ser Gly Arg Glu Gly Asn Phe Tyr Glu Arg Ser
1 5 10 15

<210> 288
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R2CHCL8)

<400> 288

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


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


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


Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Trp Leu Lys
    50                  55                  60


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


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


Leu Val Ala Leu Ser Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser
        115
```

<210> 289
<211> 115
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence (R1CHCL50)

<400> 289

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

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

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

Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr
    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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85   90   95

Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100   105   110

Val Ser Ser
        115

<210> 290
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R1CHCL21)

<400> 290

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

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Ser Ser Ile Asn
            20                  25                  30


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


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


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


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


Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  291
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (R2CHCL87)

<400>  291

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Ser Ser Ile Asn
            20                  25                  30
```

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

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

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

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

Leu Val Gly Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser
        115
```

<210> 292
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R2CHCL24)

<400> 292

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ser Asp Ser Ile Asn
            20                  25                  30

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

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

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


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


Val Lys Thr Lys Ser Ala Val Leu Phe Gly Gly Met Asp Tyr Trp Gly
            100                 105                 110


Lys Gly Thr Gln Val Thr Val Ser Ser
        115                 120


<210>  293
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (R2CHCL38)

<400>  293

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Val Ser Ile Phe Ser Ile Asn
            20                  25                  30


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


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


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

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

Ala Tyr Ile Arg Gly Glu Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
100 105 110

Val Ser Ser
115

<210> 294
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R1CHCL16)

<400> 294

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

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

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

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

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

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

Ala Lys His Tyr Ala Ser Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser
        115

<210> 295
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R2CHCL10)

<400> 295

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Ile Ser Asn Tyr
            20   25   30

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

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

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

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

Gln Ile Gln Asp Phe Gly Ser Pro Ser Phe Ser Gly Gln Gly Thr Gln
            100   105   110

Val Thr Val Ser Ser
        115

<210> 296
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R1CHCL34)

<400> 296

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Ile Ser Asn Tyr
            20                  25                  30


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


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


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


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


Gln Ile Gln Asp Phe Arg Ser Pro Asp Phe Trp Ser Gln Gly Thr Gln
            100                 105                 110


Val Thr Val Ser Ser
        115
```

<210> 297
<211> 117
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence (R1CHCL82)

<400> 297

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Ile Ser Asn Tyr
            20                  25                  30


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


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


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


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


Gln Thr Gln Ile Phe Gly Ser Pro Asn Phe Ser Gly Gln Gly Thr Gln
            100                 105                 110


Val Thr Val Ser Ser
        115
```

<210> 298
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R2CHCL3)

<400> 298

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

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


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


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


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


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


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


Thr Val Ser Ser
        115


<210>  299
<211>  116
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (R2CHCL69)

<400>  299

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Arg Asn Leu Arg Ile Tyr
            20                  25                  30
```

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

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

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

Leu Gln Met Asp Ser Leu Lys Pro Glu Asp Thr Ala Phe Tyr Tyr Cys
                85   90   95

Asn Val Asn Gln Ile Arg Gln Trp Pro Trp Gly Gln Gly Thr Gln Val
            100   105   110

Thr Val Ser Ser
        115

<210> 300
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R1CHCL56)

<400> 300

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Arg Asn Leu Arg Ile Tyr
            20   25   30

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

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

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


Leu Gln Met Asp Ser Leu Lys Pro Glu Asp Thr Ala Phe Tyr Tyr Cys
                85                  90                  95


Asn Val Asn Ser Ile Arg Gln Trp Pro Trp Gly Gln Gly Thr Gln Val
            100                 105                 110


Thr Val Ser Ser
        115


<210>  301
<211>  116
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (R2CHCL32)

<400>  301

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


Ser Leu Arg Leu Ser Cys Thr Ala Ser Glu Arg Asn Leu Arg Ser Tyr
            20                  25                  30


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


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


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

```
Leu Gln Met Asp Ser Leu Lys Pro Glu Asp Thr Ala Ser Tyr Tyr Cys
                85                  90                  95


Asn Val Asn Ala Ile Arg Gln Trp Pro Trp Gly Gln Gly Thr Gln Val
            100                 105                 110


Thr Val Ser Ser
        115


<210>  302
<211>  117
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (R2CHCL49)

<400>  302

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


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


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


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


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


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


Asp Ala Arg Lys Val Gly Gly Pro Asp Tyr Trp Gly Gln Gly Thr Gln
            100                 105                 110
```

```
Val Thr Val Ser Ser
        115


<210>  303
<211>  117
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (R2CHCL53)

<400>  303

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


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


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


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


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


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


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


Val Thr Val Ser Ser
        115
```

<210> 304
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R2CHCL22)

<400> 304

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


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


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


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


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


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


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


Val Thr Val Ser Ser
        115
```

<210> 305
<211> 117
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence (R2CHCL25)

<400> 305

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

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

Tyr Ile Ala Trp Tyr Arg Gln Ala Pro Gly Arg Glu Arg Glu Phe Val
        35   40   45

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

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

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

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

Val Thr Val Ser Ser
        115

<210> 306
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R2CHCL18)

<400> 306

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

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


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


Ala Gln Ile Ser Trp Ser Asp Asp Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


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


Leu Gln Met Asn Asn Leu Lys Pro Gly Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95


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


Val Thr Val Ser Ser
        115


<210>  307
<211>  117
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (R1CHCL23)

<400>  307

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


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

```
His Met Gly Trp Tyr Arg Gln Ala Pro Gly Arg Glu Arg Glu Phe Val
        35                  40                  45


Ala Gln Ile Ser Trp Ser Asp Asp Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


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


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


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


Val Thr Val Ser Ser
        115


<210>  308
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (R1CHCL27)

<400>  308

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


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


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


Ala Thr Val Ser Trp Gly Gly Val Thr Tyr 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 Ala Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Asn
                85                  90                  95


Val Asn Thr Phe Gly Asn Val Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  309
<211>  112
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (R2CHCL13)

<400>  309

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


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


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


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


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

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

Glu Met Leu Gly Arg Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
100 105 110

<210> 310
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R2CHCL14)

<400> 310

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

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

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

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

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

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

Glu Met Leu Gly Arg Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
100 105 110

<210> 311
<211> 112

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R2CHCL42)

<400> 311

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

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

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

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

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

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

Glu Met Leu Gly Arg Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
            100   105   110

<210> 312
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R2CHCL41)

<400> 312

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

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


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


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


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


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


Glu Met Leu Gly Arg Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
            100                 105                 110


<210>  313
<211>  112
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (R2CHCL94)

<400>  313

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


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


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

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

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

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

Glu Phe Leu Gly Arg Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
            100   105   110

<210> 314
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (R2CHCL27)

<400> 314

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

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

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

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

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

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

```
Glu Thr Val Ile Lys Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
            100                 105                 110


<210>  315
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (1LEC 7)

<400>  315

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


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


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


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


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


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


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


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125
```

His His His His His His
    130

<210> 316
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 9)

<400> 316

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

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

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

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

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

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

Ala Phe Gln Ser Ser Gly Ile Asp Trp Gly Gln Gly Thr Gln Val Thr
            100   105   110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115   120   125

His His His His His His
    130

<210> 317
<211> 135
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 26)

<400> 317

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


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


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


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


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


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


Ile Trp Ala Ala Asp Tyr Gln Gln Tyr Trp Gly Gln Gly Thr Gln Val
            100                 105                 110


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


Ser His His His His His His
    130                 135
```

<210> 318
<211> 135
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 27)

<400> 318

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ser Asp Ser Ile Asn
            20                  25                  30


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


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


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


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


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


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


Ser His His His His His His
    130                 135
```

<210> 319
<211> 140

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 28)

<400> 319

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


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


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


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


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


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


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


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 320
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 30)

<400> 320

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


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


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


Ala Ala Ile Thr Asn Asp Gly Arg Thr Thr Tyr Val 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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Trp Cys Lys
                85                  90                  95


Ala Phe Thr Arg Asp Lys Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130
```

<210> 321

<400> 321
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<210> 322

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<210> 332

<400> 332
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<210> 333
<211> 135
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 38)

<220>
<221> misc_feature
<222> (108)..(108)
<223> Xaa can be any naturally occurring amino acid

<400> 333

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Val Ser Ile Ser Ser Ile Asn
            20   25   30

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

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

Asn Arg Phe Thr Ile Ser Arg Asp Asp Ala Gln Asn Thr Val His Leu
65   70   75   80

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

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

```
Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly
        115                 120                 125


Ser His His His His His His
    130                 135


<210>  334
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (1LEC 42)

<400>  334

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


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


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


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


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


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


Ala Phe Thr Arg Thr Asp Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110
```

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115   120   125

His His His His His His
    130

<210> 335
<211> 135
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 51)

<400> 335

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

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

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

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

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

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

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

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

```
Ser His His His His His His
    130                 135


<210>  336
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (1LEC 61)

<400>  336

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


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


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


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


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


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


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


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125
```

His His His His His His
    130

<210> 337
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 62)

<400> 337

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

Phe Leu Ser Leu Ser Cys Ala Ala Ser Gly Ser Met His Ser Val Asn
            20   25   30

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

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

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

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

Ala Leu Asn Ser Ala Thr Thr Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100   105   110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115   120   125

His His His His His His
    130

<210> 338
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 63)

<400> 338

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


Ser Leu Arg Leu Ser Cys Ala Ala Thr Gly Asp Ile Ser Ser Ile Asn
            20                  25                  30


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


Ala Ala Ile Thr Asn Gly Gly Arg Thr Thr Tyr Val 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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Phe Cys Lys
                85                  90                  95


Ala Tyr Thr Arg Asp Glu Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130
```

<210> 339
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 64)

<400> 339

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Ile Asp
            20                  25                  30


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


Ala Ala Ile Thr Thr Gly Gly Arg Thr Thr Tyr Val 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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Phe Cys Lys
                85                  90                  95


Ala Phe Thr Arg Asp Glu Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130
```

<210> 340
<211> 140

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 70)

<400> 340

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

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

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

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

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

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

Ala Lys Trp Tyr Asp Pro Leu Val Ile Glu Tyr Tyr Asp Asn Trp Gly
100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
115 120 125

Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 341
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 84)

<400> 341

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


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


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


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


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


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


Ala Lys Ala Asp His Asn Asp Tyr Trp Gly Gln Gly Thr Gln Ile Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130
```

<210> 342
<211> 137
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence (1LEC 88)

<400> 342

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


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


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


Ala Ala Ile Thr Ser Ala Ser Ala Ser Arg Thr Thr Tyr Ala Asp Ser
    50                  55                  60


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


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


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


Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp
        115                 120                 125


Tyr Gly Ser His His His His His His
    130                 135
```

<210> 343
<211> 143
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 91)

<400> 343

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


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


Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu His Glu Gly Val
        35                  40                  45


Ser Cys Ile Ser Arg Ser Asp Gly Ser Thr Tyr Tyr Asp Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys 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


Ala Ala Glu Val Pro Ser Thr Tyr Ser Cys Ser Gly Phe Arg Glu Asp
            100                 105                 110


Tyr Lys Gly Lys Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr
        115                 120                 125


Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 344
<211> 135
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (1LEC 92)

<400> 344

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


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


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


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


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


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


Val Phe Ala Ala Ser Gly Met Glu Tyr Trp Gly Lys Gly Thr Gln Val
            100                 105                 110


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


Ser His His His His His His
    130                 135


<210>  345
<211>  135
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (1LEC 94)

<400>  345

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

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Val Ser Ile Phe Arg Ser Tyr
            20                  25                  30


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


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


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


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


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


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


Ser His His His His His His
    130                 135


<210>  346
<211>  136
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 6)

<400>  346

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

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


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


Ala Ser Ile Thr Asn Gln Gly Ile Arg Asn Tyr Ser Thr Ser Val Met
    50                  55                  60


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


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


Gly Phe Ala Gly Trp Gly Lys Glu Asp Tyr Trp Gly Gln Gly Thr Gln
            100                 105                 110


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
        115                 120                 125


Gly Ser His His His His His His
    130                 135


<210>  347
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 13)

<400>  347

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


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

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


Ala Ala Ile Thr Asn Gln Gly Arg Thr Thr 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 Asp Ser Leu Glu Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Lys
                85                  90                  95


Gly Phe Ser Pro Thr Gly Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130


<210>  348
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 16)

<400>  348

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


Ser Leu Arg Leu Ser Cys Leu Ala Ser Arg Ser Phe Ser Ser Phe Asn
            20                  25                  30
```

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

Ala Ala Ile Thr Asn Gly Gly Arg Ile Ala Tyr Gly Ile Ala Val Asn
    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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

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

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125

Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  349
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 20)

<400>  349

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

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

Ala Met Gly Tyr Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45
```

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

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

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

Ala Lys Ala Ser Pro Val Tyr Gly Ser Thr Val Glu Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125

Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  350
<211>  135
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 23)

<400>  350

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

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

Gly Met Ala Trp Tyr Arg Gln Ala Pro Gly Gly Gln Arg Glu Leu Val
        35                  40                  45
```

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

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

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

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

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

Ser His His His His His His
    130                 135


<210>  351
<211>  145
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 24)

<400>  351

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

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

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

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

```
Lys Gly Arg Phe Thr Ile Phe Arg Asp Asn Ala Glu 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


Ala Ala Glu Ala Glu Gly Ser Gly Arg Glu Gly Asn Phe Tyr Glu Arg
            100                 105                 110


Ser Trp Tyr Gln Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala
        115                 120                 125


Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His
    130                 135                 140


His
145


<210>  352
<211>  135
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 26)

<400>  352

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


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


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

```
Ala Ala Ile Thr Asp Gln Gly Arg Leu Ala Tyr Ala Asp Ser Ala Lys
    50                  55                  60


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


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


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


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


Ser His His His His His His
    130                 135


<210>  353
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 38)

<400>  353

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


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


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


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

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


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


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


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130


<210>  354
<211>  135
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 48)

<400>  354

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


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


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


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

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


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


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


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


Ser His His His His His His
    130                 135


<210>  355
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 53)

<400>  355

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Asp Ser Ile Asn
            20                  25                  30


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


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


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

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


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


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130


<210>  356
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 54)

<400>  356

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


Ser Leu Gln Leu Ser Cys Ala Ala Ser Gly Arg Ala Phe Ser Thr Asn
            20                  25                  30


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


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


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

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


Ala Trp Thr Thr Leu Gly Thr Phe Gly Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130


<210>  357
<211>  136
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 55)

<400>  357

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


Ser Leu Ser Leu Ser Cys Ala Val Ala Ser Gly Ser Ile Ile Ser Ile
            20                  25                  30


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


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


Lys His Arg Phe Thr Ile Ser Lys Glu Ser Ala Arg Asn Thr Val His
65                  70                  75                  80


Leu His Met Ser Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

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


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
        115                 120                 125


Gly Ser His His His His His His
    130                 135


<210>  358
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 59)

<400>  358

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


Ser Leu Arg Leu Ser Cys Ala Val Ser Arg Asn Phe Phe Ser Ile Asn
            20                  25                  30


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


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


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


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

Ala Lys Ala Ile Pro Val Tyr Gly Ser Thr Val Glu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
115 120 125

Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 359
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (2LEC 60)

<400> 359

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

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

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

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

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

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

Ala Lys Ala Ala Ala Thr His Leu Ser Thr Val Ala Asp Tyr Trp Gly
100 105 110

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


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  360
<211>  136
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 61)

<400>  360

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


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


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


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


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


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


Cys Lys Ala Phe Gly Arg Phe Asp Asp Tyr Trp Gly Gln Gly Thr Gln
            100                 105                 110
```

Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
        115   120   125

Gly Ser His His His His His His
    130   135

<210> 361
<211> 141
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (2LEC 62)

<400> 361

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

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

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

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

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

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

Ala Trp Gly Val Lys Thr Gly Pro Glu Ser Gly Ser Gly Thr Leu Glu
            100   105   110

Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr
        115   120   125

```
Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  362
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 63)

<400>  362

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


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


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


Ala Ala Ile Thr Ser Gly Gly Arg Thr Thr Tyr Val 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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Phe Cys Lys
                85                  90                  95


Ala Phe Thr Arg Asp Glu Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125
```

His His His His His His
    130

<210> 363
<211> 138
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (2LEC 67)

<400> 363

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

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

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

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

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

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

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

Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro
        115   120   125

Asp Tyr Gly Ser His His His His His His
    130   135

<210> 364
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (2LEC 68)

<400> 364

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


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


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


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


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


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


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


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130
```

<210> 365
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (2LEC 76)

<400> 365

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


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


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


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


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


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


Ala Phe Gln Ser Ser Gly Ile Asp Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130
```

<210> 366
<211> 134

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (2LEC 83)

<400> 366

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

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

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

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

Gly Phe Ser Pro Thr Asp Asp Phe Trp Gly Gln Gly Thr Gln Val Thr
            100   105   110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115   120   125

His His His His His His
    130

<210> 367
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (2LEC 88)

<400> 367

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


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


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


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


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


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


Ala Lys Ala Ile Pro Ile Tyr Gly Ser Thr Ala Glu Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 368
<211> 134
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence (2LEC 89)

<400> 368

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

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

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

Ala Ala Ile Thr Asn Gly Gly Arg Thr Thr 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 Asp Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
85 90 95

Gly Phe Ser Leu Thr Asp Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
115 120 125

His His His His His His
130

<210> 369
<211> 135
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (2LEC 90)

<400> 369

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


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


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


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


Gly Arg Phe Thr Ile Ser Arg Glu Asn Thr Arg Asn Thr Val His Leu
65                  70                  75                  80


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


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


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


Ser His His His His His His
    130                 135
```

<210> 370
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (2LEC 93)

<400> 370

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


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


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


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


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


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


Ala Phe Thr Arg Asp Glu Asp Phe Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130


<210>  371
<211>  145
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (2LEC 95)

<400>  371

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

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

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

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

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

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

Ala Ala Glu Val Glu Gly Ser Gly Arg Glu Gly Asn Phe Tyr Gly Ala
            100                 105                 110

Ser Trp Tyr Pro Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala
        115                 120                 125

Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His
    130                 135                 140

His
145
```

<210> 372
<211> 132
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (3LEC 4)

<400> 372

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

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

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

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

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

Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His
115 120 125

His His His His
130

<210> 373
<211> 135
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (3LEC 6)

<400> 373

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

```
Ser Leu Arg Leu Ser Cys Val Ala Ser Val Asn Ile Gly Ser Leu Asn
            20                  25                  30


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


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


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


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


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


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


Ser His His His His His His
    130                 135


<210>  374
<211>  139
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (3LEC 9)

<400>  374

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

```
Ser Leu Arg Val Ser Cys Ala Ala Ser Gly Arg Thr Leu Ser Asn Tyr
            20                  25                  30


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


Ala Ala Ile Asn Trp Ser Ser Gly Gly Ile Ser Tyr Ser Asn Ser Ala
    50                  55                  60


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


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


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


Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val
        115                 120                 125


Pro Asp Tyr Gly Ser His His His His His His
    130                 135


<210>  375
<211>  135
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (3LEC 11)

<400>  375

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Ser Ser Ile Asn
            20                  25                  30
```

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


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


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


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


Val Phe Ala Ala Asp Gly Met Glu Tyr Trp Gly Lys Gly Thr Gln Val
            100                 105                 110


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


Ser His His His His His His
    130                 135


<210>  376
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (3LEC 13)

<400>  376

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Phe Phe Arg Val Asn
            20                  25                  30
```

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


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


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


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


Ala Lys Ala Ala Ala Ser Tyr Val Ser Thr Val Ala Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  377
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (3LEC 15)

<400>  377

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


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


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

```
Ala Ala Ile Thr Thr Gln Gly Arg Thr Thr Tyr Glu Asp Ser Val Lys
    50                  55                  60

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

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

Ala Trp Thr Ala Lys Asp Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125

His His His His His His
    130
```

<210> 378
<211> 136
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (3LEC 22)

<400> 378

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

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

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

```
Ala Ala Ile Thr Ser Gly Gly Ile Thr Asn Tyr Ala Asn Ser Val Gln
    50                  55                  60

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

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

Gly Phe Thr Gly Trp Gly Lys Glu Asp Tyr Trp Gly Gln Gly Thr Gln
            100                 105                 110

Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
        115                 120                 125

Gly Ser His His His His His His
    130                 135
```

<210> 379
<211> 135
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (3LEC 23)

<400> 379

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

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

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

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

```
Gly Arg Phe Thr Ile Ser Lys Glu Ser Ala Arg Asn Thr Val His Leu
65                  70                  75                  80


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


Ile Trp Ala Ala Asp Tyr Gln Gln Tyr Trp Gly Gln Gly Thr Gln Val
            100                 105                 110


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


Ser His His His His His His
    130                 135


<210>  380
<211>  135
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (3LEC 27)

<400>  380

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


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


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


Ala Gly Ile Thr Gly Gly Gly Gln Ile Thr Tyr Ala Asn Ser Val Arg
    50                  55                  60
```

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


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


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


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


Ser His His His His His His
    130                 135


<210>  381
<211>  135
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (3LEC 30)

<400>  381

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


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


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


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


Gly Arg Phe Thr Ile Ser Leu Gly Asn Ala Arg Asn Thr Val Asn Leu
65                  70                  75                  80
```

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


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


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


Ser His His His His His His
    130                 135


<210>  382
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (3LEC 36)

<400>  382

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


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


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


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


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

His Met Asn Ser Leu Arg Pro Glu Asp Ser Ala Val Tyr Tyr Cys Lys
85 90 95

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

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
115 120 125

His His His His His His
130

<210> 383
<211> 135
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (3LEC 55)

<400> 383

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Phe Asn
20 25 30

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

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

Asn Arg Phe Thr Ile Ser Arg Glu Asn Thr Arg Asn Thr Val His Leu
65 70 75 80

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

```
Ile Trp Thr Lys Asp Arg Gln Gln Tyr Trp Gly Gln Gly Thr Gln Val
            100                 105                 110


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


Ser His His His His His His
    130                 135


<210>  384
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (3LEC 57)

<400>  384

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


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


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


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


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


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

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

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
115 120 125

His His His His His His
130

<210> 385
<211> 139
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (3LEC 61)

<400> 385

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

Ser Leu Arg Val Ser Cys Ala Ala Ser Gly Arg Thr Leu Ser Asn Tyr
20 25 30

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

Ala Ala Ile Asn Trp Ser Ser Gly Gly Ile Ser Tyr Ser Asn Ala Ala
50 55 60

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

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

Ala Ala Ala Ser Ser Ile Leu Ser Gly Thr Val Asp Tyr Trp Gly Gln
100 105 110

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


Pro Asp Tyr Gly Ser His His His His His His
    130                 135


<210>  386
<211>  135
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (3LEC 62)

<400>  386

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


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


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


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


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


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


Ile Trp Ala Ala Asp Tyr Gln Gln Tyr Trp Gly Gln Gly Thr Gln Val
            100                 105                 110
```

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

Ser His His His His His His
    130   135

<210> 387
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (3LEC 66)

<400> 387

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

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

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

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

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

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115   120   125

```
Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  388
<211>  135
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (3LEC 69)

<400>  388

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


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


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


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


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


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


Val Phe Ala Ala Asp Gly Met Glu Tyr Trp Gly Lys Gly Thr Gln Val
            100                 105                 110


Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly
        115                 120                 125
```

Ser His His His His His His
130 135

<210> 389
<211> 133
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (3LEC 76)

<220>
<221> misc_feature
<222> (54)..(54)
<223> Xaa can be any naturally occurring amino acid

<400> 389

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

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

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

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

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

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

Ala Phe Gly Ser Gly Gly Gly Val Gly Gln Gly Thr Gln Val Thr Val
100 105 110

Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His
        115   120   125

His His His His His
    130

<210> 390
<211> 139
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (3LEC 82)

<400> 390

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

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

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

Ala Ala Ile Trp Trp Ala Ser Gly Gly Ile Ser Tyr Ala Asn Ser Ala
    50   55   60

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

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

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

Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val
        115   120   125

```
Pro Asp Tyr Gly Ser His His His His His His
    130                 135


<210>  391
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (3LEC 89)

<400>  391

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


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


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


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


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


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


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


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125
```

His His His His His His
    130

<210> 392
<211> 145
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (3LEC 94)

<400> 392

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

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

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

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu 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

Ala Ala Glu Ala Glu Gly Ser Gly Arg Glu Gly Asn Phe Tyr Glu Arg
            100   105   110

Ser Trp Tyr Gln Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala
        115   120   125

Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His
    130   135   140

His
145

<210> 393
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 393

His His His His His His
1 5

<210> 394
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 394

Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
1 5 10

<210> 395
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 395

Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His
1 5 10 15

His His His

<210> 396
<211> 235
<212> PRT
<213> Homo sapiens

<400> 396

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

His Ala Ala Arg Pro Ser Gln Phe Arg Val Ser Pro Leu Asp Arg Thr
            20                  25                  30

Trp Asn Leu Gly Glu Thr Val Glu Leu Lys Cys Gln Val Leu Leu Ser
        35                  40                  45

Asn Pro Thr Ser Gly Cys Ser Trp Leu Phe Gln Pro Arg Gly Ala Ala
    50                  55                  60

Ala Ser Pro Thr Phe Leu Leu Tyr Leu Ser Gln Asn Lys Pro Lys Ala
65                  70                  75                  80

Ala Glu Gly Leu Asp Thr Gln Arg Phe Ser Gly Lys Arg Leu Gly Asp
                85                  90                  95

Thr Phe Val Leu Thr Leu Ser Asp Phe Arg Arg Glu Asn Glu Gly Tyr
            100                 105                 110

Tyr Phe Cys Ser Ala Leu Ser Asn Ser Ile Met Tyr Phe Ser His Phe
        115                 120                 125

Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg
    130                 135                 140

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
```

```
145                 150                 155                 160

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
                165                 170                 175

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
            180                 185                 190

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His
        195                 200                 205

Arg Asn Arg Arg Arg Val Cys Lys Cys Pro Arg Pro Val Val Lys Ser
    210                 215                 220

Gly Asp Lys Pro Ser Leu Ser Ala Arg Tyr Val
225                 230                 235


<210>  397
<211>  198
<212>  PRT
<213>  Homo sapiens

<400>  397

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

His Ala Ala Arg Pro Ser Gln Phe Arg Val Ser Pro Leu Asp Arg Thr
            20                  25                  30

Trp Asn Leu Gly Glu Thr Val Glu Leu Lys Cys Gln Val Leu Leu Ser
        35                  40                  45

Asn Pro Thr Ser Gly Cys Ser Trp Leu Phe Gln Pro Arg Gly Ala Ala
    50                  55                  60

Ala Ser Pro Thr Phe Leu Leu Tyr Leu Ser Gln Asn Lys Pro Lys Ala
65                  70                  75                  80
```

```
Ala Glu Gly Leu Asp Thr Gln Arg Phe Ser Gly Lys Arg Leu Gly Asp
                85                  90                  95

Thr Phe Val Leu Thr Leu Ser Asp Phe Arg Arg Glu Asn Glu Gly Tyr
            100                 105                 110

Tyr Phe Cys Ser Ala Leu Ser Asn Ser Ile Met Tyr Phe Ser His Phe
        115                 120                 125

Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg
    130                 135                 140

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

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Gly Asn Arg Arg Arg
                165                 170                 175

Val Cys Lys Cys Pro Arg Pro Val Val Lys Ser Gly Asp Lys Pro Ser
            180                 185                 190

Leu Ser Ala Arg Tyr Val
        195


<210>  398
<211>  276
<212>  PRT
<213>  Homo sapiens

<400>  398

Met Arg Asn Gln Ala Pro Gly Arg Pro Lys Gly Ala Thr Phe Pro Pro
1               5                   10                  15

Arg Arg Pro Thr Gly Ser Arg Ala Pro Pro Leu Ala Pro Glu Leu Arg
            20                  25                  30
```

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

Leu Leu Leu Pro Leu Ala Leu Leu Leu His Ala Ala Arg Pro Ser Gln
    50                  55                  60

Phe Arg Val Ser Pro Leu Asp Arg Thr Trp Asn Leu Gly Glu Thr Val
65                  70                  75                  80

Glu Leu Lys Cys Gln Val Leu Leu Ser Asn Pro Thr Ser Gly Cys Ser
                85                  90                  95

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

Tyr Leu Ser Gln Asn Lys Pro Lys Ala Ala Glu Gly Leu Asp Thr Gln
        115                 120                 125

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

Asp Phe Arg Arg Glu Asn Glu Gly Tyr Tyr Phe Cys Ser Ala Leu Ser
145                 150                 155                 160

Asn Ser Ile Met Tyr Phe Ser His Phe Val Pro Val Phe Leu Pro Ala
                165                 170                 175

Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
            180                 185                 190

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
        195                 200                 205

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
    210                 215                 220
```

```
Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
225                 230                 235                 240


Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Arg Arg Val Cys
                245                 250                 255


Lys Cys Pro Arg Pro Val Val Lys Ser Gly Asp Lys Pro Ser Leu Ser
            260                 265                 270


Ala Arg Tyr Val
        275


<210>  399
<211>  210
<212>  PRT
<213>  Homo sapiens

<400>  399

Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1               5                   10                  15


His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
            20                  25                  30


Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
        35                  40                  45


Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
    50                  55                  60


Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65                  70                  75                  80


His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
                85                  90                  95
```

```
Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
            100                 105                 110


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


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


Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145                 150                 155                 160


Glu Thr Gln Lys Gly Pro Leu Cys Ser Pro Ile Thr Leu Gly Leu Leu
                165                 170                 175


Val Ala Gly Val Leu Val Leu Leu Val Ser Leu Gly Val Ala Ile His
            180                 185                 190


Leu Cys Cys Arg Arg Arg Arg Ala Arg Leu Arg Phe Met Lys Gln Phe
        195                 200                 205


Tyr Lys
    210


<210>  400
<211>  221
<212>  PRT
<213>  Homo sapiens

<400>  400

Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1               5                   10                  15


His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
            20                  25                  30


Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
```

```
        35                  40                  45

Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
    50                  55                  60

Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65                  70                  75                  80

His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
                85                  90                  95

Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
            100                 105                 110

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

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

Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145                 150                 155                 160

Glu Thr Gln Lys Gly Pro Leu Cys Ser Pro Ile Thr Leu Gly Leu Leu
                165                 170                 175

Val Ala Gly Val Leu Val Leu Leu Val Ser Leu Gly Val Ala Ile His
            180                 185                 190

Leu Cys Cys Arg Arg Arg Arg Ala Arg Leu Arg Phe Met Lys Gln Leu
        195                 200                 205

Arg Leu His Pro Leu Glu Lys Cys Ser Arg Met Asp Tyr
    210                 215                 220
```

<210> 401

<211> 213
<212> PRT
<213> Homo sapiens

<400> 401

```
Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1               5                  10                  15

His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
            20                  25                  30

Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
        35                  40                  45

Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
    50                  55                  60

Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65                  70                  75                  80

His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
                85                  90                  95

Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
            100                 105                 110

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

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

Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145                 150                 155                 160

Glu Thr Gln Lys Gly Arg Arg Arg Arg Ala Arg Leu Arg Phe Met Lys
                165                 170                 175
```

```
Gln Pro Gln Gly Glu Gly Ile Ser Gly Thr Phe Val Pro Gln Cys Leu
            180                 185                 190


His Gly Tyr Tyr Ser Asn Thr Thr Thr Ser Gln Lys Leu Leu Asn Pro
        195                 200                 205


Trp Ile Leu Lys Thr
    210


<210>  402
<211>  246
<212>  PRT
<213>  Homo sapiens

<400>  402

Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1               5                   10                  15


His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
            20                  25                  30


Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
        35                  40                  45


Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
    50                  55                  60


Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65                  70                  75                  80


His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
                85                  90                  95


Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
            100                 105                 110
```

```
Ile Tyr Phe Cys Met Ile Val Gly Ser Pro Glu Leu Thr Phe Gly Lys
        115                 120                 125


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


Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145                 150                 155                 160


Glu Thr Gln Lys Gly Pro Leu Cys Ser Pro Ile Thr Leu Gly Leu Leu
                165                 170                 175


Val Ala Gly Val Leu Val Leu Leu Val Ser Leu Gly Val Ala Ile His
            180                 185                 190


Leu Cys Cys Arg Arg Arg Arg Ala Arg Leu Arg Phe Met Lys Gln Lys
        195                 200                 205


Phe Asn Ile Val Cys Leu Lys Ile Ser Gly Phe Thr Thr Cys Cys Cys
    210                 215                 220


Phe Gln Ile Leu Gln Ile Ser Arg Glu Tyr Gly Phe Gly Val Leu Leu
225                 230                 235                 240


Gln Lys Asp Ile Gly Gln
                245


<210>  403
<211>  243
<212>  PRT
<213>  Homo sapiens

<400>  403

Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1               5                   10                  15
```

```
His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
            20                  25                  30

Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
        35                  40                  45

Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
    50                  55                  60

Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65                  70                  75                  80

His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
                85                  90                  95

Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
            100                 105                 110

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

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

Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145                 150                 155                 160

Glu Thr Gln Lys Gly Pro Leu Cys Ser Pro Ile Thr Leu Gly Leu Leu
                165                 170                 175

Val Ala Gly Val Leu Val Leu Leu Val Ser Leu Gly Val Ala Ile His
            180                 185                 190

Leu Cys Cys Arg Arg Arg Arg Ala Arg Leu Arg Phe Met Lys Gln Pro
        195                 200                 205
```

```
Gln Gly Glu Gly Ile Ser Gly Thr Phe Val Pro Gln Cys Leu His Gly
    210                 215                 220

Tyr Tyr Ser Asn Thr Thr Thr Ser Gln Lys Leu Leu Asn Pro Trp Ile
225                 230                 235                 240

Leu Lys Thr
```

<210> 404
<211> 180
<212> PRT
<213> Homo sapiens

<400> 404

```
Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1               5                   10                  15

His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
            20                  25                  30

Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
        35                  40                  45

Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
    50                  55                  60

Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65                  70                  75                  80

His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
                85                  90                  95

Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
            100                 105                 110

Ile Tyr Phe Cys Met Ile Val Gly Ser Pro Glu Leu Thr Phe Gly Lys
```

115 120 125

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

Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145 150 155 160

Glu Thr Gln Lys Gly Arg Arg Arg Arg Ala Arg Leu Arg Phe Met Lys
165 170 175

Gln Phe Tyr Lys
180

<210> 405
<211> 206
<212> PRT
<213> Homo sapiens

<400> 405

Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1 5 10 15

His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
20 25 30

Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
35 40 45

Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
50 55 60

Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65 70 75 80

His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
85 90 95

```
Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
            100                 105                 110


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


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


Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145                 150                 155                 160


Glu Thr Gln Lys Asp Phe Thr Asn Lys Gln Arg Ile Gly Phe Trp Cys
                165                 170                 175


Pro Ala Thr Lys Arg His Arg Ser Val Met Ser Thr Met Trp Lys Asn
            180                 185                 190


Glu Arg Arg Asp Thr Phe Asn Pro Gly Glu Phe Asn Gly Cys
        195                 200                 205


<210>  406
<211>  198
<212>  PRT
<213>  Homo sapiens

<400>  406

Met Arg Pro Arg Leu Trp Leu Leu Leu Ala Ala Gln Leu Thr Val Leu
1               5                   10                  15


His Gly Asn Ser Val Leu Gln Gln Thr Pro Ala Tyr Ile Lys Val Gln
            20                  25                  30


Thr Asn Lys Met Val Met Leu Ser Cys Glu Ala Lys Ile Ser Leu Ser
        35                  40                  45
```

```
Asn Met Arg Ile Tyr Trp Leu Arg Gln Arg Gln Ala Pro Ser Ser Asp
    50                  55                  60

Ser His His Glu Phe Leu Ala Leu Trp Asp Ser Ala Lys Gly Thr Ile
65                  70                  75                  80

His Gly Glu Glu Val Glu Gln Glu Lys Ile Ala Val Phe Arg Asp Ala
                85                  90                  95

Ser Arg Phe Ile Leu Asn Leu Thr Ser Val Lys Pro Glu Asp Ser Gly
            100                 105                 110

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

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

Thr Lys Lys Ser Thr Leu Lys Lys Arg Val Cys Arg Leu Pro Arg Pro
145                 150                 155                 160

Glu Thr Gln Lys Gly Leu Lys Gly Lys Val Tyr Gln Glu Pro Leu Ser
                165                 170                 175

Pro Asn Ala Cys Met Asp Thr Thr Ala Ile Leu Gln Pro His Arg Ser
            180                 185                 190

Cys Leu Thr His Gly Ser
        195


<210>  407
<211>  10
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence
```

<400> 407

Gly Phe Thr Phe Asp Asp Tyr Ala Met Ser
1   5   10

<210> 408
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 408

Gly Phe Thr Phe Asp Asp Tyr Ala Ile Gly
1   5   10

<210> 409
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 409

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

<210> 410
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 410

Gly Arg Thr Phe Ser Ser Tyr Thr Met Gly
1   5   10

<210> 411
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 411

Gly Arg Thr Phe Ser Ser Tyr Ile Met Gly
1 5 10

<210> 412
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 412

Gly Arg Thr Phe Ser Ser Tyr Thr Met Gly
1 5 10

<210> 413
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 413

Gly Arg Thr Ser Gly Arg Thr Phe Ser Ser Tyr Thr Met Gly
1 5 10

<210> 414
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 414

Gly Arg Thr Phe Ser Ser Tyr Ala Met Gly
1   5   10

<210> 415
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 415

Gly Leu Thr Phe Ser Asn Tyr Ile Met Gly
1   5   10

<210> 416
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 416

Gly Arg Thr Phe Ser Ser Tyr Thr Met Gly
1   5   10

<210> 417
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 417

Gly Arg Thr Phe Ser Ser Asp Thr Met Gly

1 5 10

<210> 418
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 418

Gly Leu Thr Phe Ser Asn Tyr Ile Met Gly
1 5 10

<210> 419
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 419

Gly Phe Thr Leu Asp Tyr Tyr Gly Ile Gly
1 5 10

<210> 420
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 420

Gly His Thr Phe Ser Ser Tyr Thr Met Gly
1 5 10

<210> 421
<211> 10
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 421

Gly Arg Thr Phe Ser Ser Tyr Val Ile Gly
1   5   10

<210> 422
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 422

Gly Phe Ala Phe Asp Gly Tyr Ala Ile Gly
1   5   10

<210> 423
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 423

Gly Phe Ala Phe Gly Phe Phe Asp Met Thr
1   5   10

<210> 424
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 424

Gly Arg Thr Phe Ser Asn Tyr Val Ile Gly
1   5   10

<210> 425
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 425

Gly Ser Ile Phe Ser Ile Asn Val Met Gly
1   5   10

<210> 426
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 426

Gly Arg Thr Phe Ser Asn Tyr Asn Val Gly
1   5   10

<210> 427
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 427

Gly His Thr Phe Ser Ser Tyr Thr Met Gly
1   5   10

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Gly Val Ser Ile Gly Asp Tyr Asn Ile Gly
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Gly Phe Thr Phe Asp Asp Tyr Thr Ile Ala
1   5   10

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Gly Phe Thr Phe Asp Asp Tyr Thr Ile Ala
1   5   10

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Gly

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Cys Ile Arg Val Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Pro Val Lys
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Gly

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Ala Ser Ile Thr Trp Gly Gly Gly Asn Thr Tyr
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Ala Ala Thr Val Trp Thr Gly Ala Gly Thr Val
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Ala Ala Ile Gly Trp Ser Ala Asp Ile Thr Val
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Ala Phe Ile Asp Trp Ser Gly Gly Gly Thr Tyr
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Ala Thr Ile Thr Trp Gly Gly Gly Ser Thr Tyr
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Ala Ala Ile Ser Trp Ser Gly Gly Pro Thr Val

1 5 10

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Ala Ala Ile Thr Trp Gly Gly Gly Ser Thr Val
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Ala Ala Ile Thr Trp Ser Gly Val Ser Thr Val
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Ala Ala Ile Thr Trp Gly Gly Gly Ser Thr Val
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Ala Val Ile Thr Trp Ser Gly Asp Ser Thr Tyr
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Ala Cys Ile Ser Ser Lys Asp Gly Ser Thr Tyr
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Ala Val Val Thr Trp Ser Gly Asp Ser Thr Tyr
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Ala Phe Ile Asp Trp Ser Gly Gly Gly Thr Tyr
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Ala Val Ile Leu Trp Ser Gly Val Ser Thr Tyr
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Ala Ala Val Leu Trp Ser Gly Val Ser Thr Ala
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Val Ala Ile Thr Trp Asp Gly Ser Ala Thr Thr
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Ala Ala Ile Gly Trp Asn Gly Gly Ile Thr Tyr
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Gly Phe Ile Thr Trp Ser Gly Ala Ser Thr Tyr
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Ser Cys Ile Glu Arg Ser Asp Gly Ser Thr Tyr
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Ala Gln Ile Ser Trp Ser Ala Gly Ser Ile Tyr
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Ala Gly Met Ser Trp Asn Pro Gly Pro Ala Val
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<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 550

Lys Asp Ala Asp Leu Val Trp Tyr Asn Leu Arg
1 5 10

<210> 551
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 551

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

Arg Pro Tyr Tyr Asp Met Asp Tyr
20

<210> 552
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 552

Ala Lys Gly Leu Arg Asn Ser Asp Trp Asp Leu Arg Arg Gly Tyr Glu
1 5 10 15

Tyr Asp Tyr

<210> 553
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 553

Ala Asp Gln Ala Ser Val Pro Pro Pro Tyr Gly Ser Glu Arg Tyr Asp

1 5 10 15

Ile Ala Ser Pro Ser Glu Tyr Asp Tyr
20 25

<210> 554
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 554

Ala Asn Ser Arg Ala Tyr Tyr Ser Ser Ser Tyr Asp Leu Gly Arg Leu
1 5 10 15

Ala Ser Tyr Asp Tyr
20

<210> 555
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 555

Ala Ala Gln Arg Leu Gly Ser Val Thr Asp Tyr Thr Lys Tyr Asp Tyr
1 5 10 15

<210> 556
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 556

Ala Ser Val Lys Val Val Ala Gly Ser Gly Ile Asp Ile Ser Gly Ser
1   5   10   15

Arg Asn Tyr Asp Tyr
            20

<210> 557
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 557

Ala Lys Arg Leu Asp Tyr Ser Ala Thr Asp Lys Gly Val Asp Leu Ser
1   5   10   15

Asp Glu Tyr Asp Tyr
            20

<210> 558
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 558

Ala Ala Gly Gly Ser Gly Arg Leu Arg Asp Leu Lys Val Gly Gln Asn
1   5   10   15

Tyr Asp Tyr

<210> 559
<211> 23
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 559

Ala Asp Ser Pro Pro Arg Thr Tyr Ser Ser Gly Ser Val Asn Leu Glu
1   5   10   15

Asp Gly Ser Glu Tyr Asp Tyr
            20

<210> 560
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 560

Val Ile Pro Gly Arg Gly Ser Ala Leu Pro Ile Asp Val Gly Lys Ser
1   5   10   15

Asp Glu Tyr Glu Tyr
            20

<210> 561
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 561

Ala Ala Gly Ala Ser Gly Arg Leu Arg Asp Leu Lys Val Gly Gln Asn
1   5   10   15

Tyr Asp Tyr

<210> 562
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 562

Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly Pro
1 5 10 15

Pro Pro Gly Gly Met Asp Tyr
20

<210> 563
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 563

Ala Ala Gln Arg Leu Gly Ser Val Thr Asp Tyr Thr Lys Tyr Asp Tyr
1 5 10 15

<210> 564
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 564

Ala Ile Pro Pro Arg Ala Tyr Ser Gly Gly Ser Tyr Ser Leu Lys Asp
1 5 10 15

Gln Ser Lys Tyr Glu Tyr
            20

<210> 565
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 565

Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Ser Ser Ala Gly Pro
1   5   10   15

Pro Pro Gly Gly Met Asp Tyr
            20

<210> 566
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 566

Lys Ser Arg Ser Ser Tyr Ser Asn Asn
1   5

<210> 567
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 567

Ala Met Pro Pro Arg Ala Tyr Thr Gly Arg Ser Val Ser Leu Lys Asp

1 5 10 15

Gln Ser Lys Tyr Glu Tyr
20

<210> 568
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 568

Leu Asp Thr Thr Gly Trp Gly Pro Pro Pro Tyr Gln Tyr
1 5 10

<210> 569
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 569

Ala His Pro Pro Asp Pro Ser Arg Gly Gly Glu Trp Arg Leu Gln Thr
1 5 10 15

Pro Ser Glu Tyr Asp Tyr
20

<210> 570
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 570

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Ala Ala Gln Arg Leu Gly Ser Val Thr Asp Tyr Thr Lys Tyr Asp Tyr
1               5                   10                  15


<210>  571
<211>  24
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  571

Val Pro Arg Ser His Phe Thr Thr Ala Gln Asp Met Gly Gln Asp Met
1               5                   10                  15


Gly Ala Pro Ser Trp Tyr Glu Tyr
            20


<210>  572
<211>  22
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  572

Ala Val Leu Ile Arg Tyr Tyr Ser Gly Gly Tyr Gln Gly Leu Ser Asp
1               5                   10                  15


Ala Asn Glu Tyr Asp Tyr
            20


<210>  573
<211>  17
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence
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<400> 573

Val Val Lys Tyr Leu Ser Gly Ser Tyr Ser Tyr Ala Gly Gln Tyr Asn
1 5 10 15

Phe

<210> 574
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 574

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Val Gly Pro
1 5 10 15

Pro Pro Gly Gly Met Asp Tyr
20

<210> 575
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 575

Ala His Glu Ser Thr Tyr Tyr Ser Gly Thr Tyr Tyr Leu Thr Asp Pro
1 5 10 15

Arg Arg Tyr Val Tyr
20

<210> 576

<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 576

Ala Val Pro Ala Arg Gly Leu Thr Met Asp Leu Glu Asn Ser Asp Ile
1 5 10 15

Tyr Asp His

<210> 577
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 577

Ala Ala Thr Leu Gln Val Thr Gly Ser Tyr Tyr Leu Asp Leu Ser Thr
1 5 10 15

Val Asp Ile Tyr Asp Asn
20

<210> 578
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 578

Ala Thr Leu Phe Arg Ser Asn Gly Pro Lys Asp Leu Ser Ser Gly Tyr
1 5 10 15

Glu Tyr Asp Tyr
            20

<210> 579
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 579

Ala Gly Glu Ser Gly Val Trp Val Gly Gly Leu Asp Tyr
1   5   10

<210> 580
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 580

Val Gly Ser Ala Asn Ser Gly Glu Phe Arg Phe Gly Trp Val Leu Lys
1   5   10   15

Pro Asp Leu Tyr Asn Tyr
            20

<210> 581
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 581

Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly Pro

1 5 10 15

Pro Pro Gly Gly Met Asp Tyr
20

<210> 582
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 582

Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly Pro
1 5 10 15

Pro Pro Gly Gly Met Asp Tyr
20

<210> 583
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 583

Glu Arg Gly Tyr Ala Tyr Cys Ser Asp Asp Gly Cys Gln Arg Thr Gln
1 5 10 15

Asp Tyr Asp Tyr
20

<210> 584
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 584

Gly Ala Ala Arg Ala Trp Trp Ser Gly Ser Tyr Asp Tyr Thr Arg Met
1   5   10   15

Asn Asn Tyr Asp Tyr
            20

<210> 585
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 585

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

Lys Pro Ser Leu Tyr Asp Tyr
            20

<210> 586
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 586

Ala Ala Gly Ser Ala Tyr Ser Gly Ser Tyr Trp Asn Ile Thr Met Ala
1   5   10   15

Ala Asn Tyr Asp Tyr
            20

<210> 587
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 587

Ala Gln Arg Ile Phe Gly Ala Gln Pro Met Asp Leu Ser Gly Asp Tyr
1 5 10 15

Glu Tyr

<210> 588
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 588

Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly Pro
1 5 10 15

Pro Pro Gly Gly Met Asp Tyr
20

<210> 589
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 589

Ala Arg Asp Tyr Arg Gly Ile Lys Asp Leu Asp Leu Lys Gly Asp Tyr

1 5 10 15

Asp Tyr

<210> 590
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 590

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ile Trp Tyr
1 5 10 15

Gly Pro Pro Pro Arg Gly Met Asp Tyr
20 25

<210> 591
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 591

Ala Asp Ser Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Arg Trp Tyr
1 5 10 15

Gly Pro Pro Pro Gly Gly Met Ala Tyr
20 25

<210> 592
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 592

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Asn Trp Tyr
1   5   10   15

Gly Pro Pro Pro Gly Gly Met Asp Tyr
            20   25

<210> 593
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 593

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ile Trp Tyr
1   5   10   15

Gly Pro Pro Pro Gly Gly Met Asp Tyr
            20   25

<210> 594
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 594

Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly Pro
1   5   10   15

Pro Pro Gly Gly Met Asp Tyr
            20

<210> 595
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 595

Ala Arg Ile Ile Thr Val Ala Thr Met Arg Leu Asp Ser Asp Tyr Asp
1 5 10 15

Tyr

<210> 596
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 596

Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly Pro
1 5 10 15

Pro Pro Gly Gly Met Asp Tyr
20

<210> 597
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 597

Ala Asp Ser Asn Val Trp Ser Pro Pro Ile Cys Gly Arg Thr Trp Tyr

1 5 10 15

Gly Pro Pro Pro Gly Gly Met Asp Tyr
20 25

<210> 598
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 598

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ile Trp Tyr
1 5 10 15

Gly Pro Pro Pro Gly Gly Met Ala Tyr
20 25

<210> 599
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 599

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Asn Trp Tyr
1 5 10 15

Gly Pro Pro Pro Gly Gly Met Asp Tyr
20 25

<210> 600
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 600

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ser Trp Tyr
1   5   10   15

Gly Pro Pro Pro Gly Gly Met Asp Tyr
            20   25

<210> 601
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 601

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Arg Trp Tyr
1   5   10   15

Gly Pro Pro Pro Gly Gly Met Glu Tyr
            20   25

<210> 602
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 602

Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly Pro
1   5   10   15

Pro Pro Gly Gly Met Asp Tyr
            20

<210> 603
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 603

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Arg Trp Tyr
1 5 10 15

Gly Pro Pro Pro Gly Gly Met Ala Tyr
20 25

<210> 604
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 604

Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly Pro
1 5 10 15

Pro Pro Gly Gly Met Asp Tyr
20

<210> 605
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 605

Ala Asp Ser Asn Val Trp Ser Pro Pro Ile Cys Gly Lys Thr Trp Tyr

1 5 10 15

Gly Pro Pro Pro Gly Gly Met Asp Tyr
20 25

<210> 606
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 606

Ala Gly Glu Ser Gly Val Trp Val Gly Gly Leu Asp Tyr
1 5 10

<210> 607
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 607

Ala Asp Ser Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Thr Trp Tyr
1 5 10 15

Gly Pro Pro Pro Gly Gly Met Ala Tyr
20 25

<210> 608
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 608

Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly Pro
1   5   10   15

Pro Pro Gly Gly Met Asp Tyr
            20

<210> 609
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 609

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Arg Trp Tyr
1   5   10   15

Gly Pro Pro Pro Gly Gly Met Asp Tyr
            20   25

<210> 610
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 610

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Arg Trp Tyr
1   5   10   15

Gly Pro Pro Pro Gly Gly Met Asp Tyr
            20   25

<210> 611
<211> 25
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 611

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Arg Trp Tyr
1   5   10   15

Gly Pro Pro Pro Gly Gly Met Asp Tyr
            20   25

<210> 612
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 612

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ile Trp Tyr
1   5   10   15

Gly Pro Pro Pro Gly Gly Met Asp Tyr
            20   25

<210> 613
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 613

Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly Pro
1   5   10   15

Pro Pro Gly Gly Met Asp Tyr

20

<210> 614
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 614

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Val Gly Pro
1 5 10 15

Pro Pro Gly Gly Met Asp Tyr
20

<210> 615
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 615

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ser Trp Tyr
1 5 10 15

Gly Pro Pro Pro Gly Gly Met Ala Tyr
20 25

<210> 616
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 616

```
Ala Gly Glu Ser Gly Val Trp Val Gly Gly Leu Asp Tyr
1               5                   10


<210>  617
<211>  25
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  617

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ser Trp Tyr
1               5                   10                  15


Gly Pro Pro Pro Gly Gly Met Glu Tyr
            20                  25


<210>  618
<211>  23
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  618

Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly Pro
1               5                   10                  15


Pro Pro Gly Gly Met Asp Tyr
            20


<210>  619
<211>  25
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence
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<400> 619

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Ser Ser Asn Trp Tyr
1 5 10 15

Gly Pro Pro Pro Arg Gly Met Asp Tyr
20 25

<210> 620
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 620

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ile Trp Tyr
1 5 10 15

Gly Pro Pro Pro Arg Gly Met Asp Tyr
20 25

<210> 621
<211> 132
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 621

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

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

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

        35   40   45

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

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

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

Ala Lys Asp Ala Asp Leu Val Trp Tyr Asn Leu Ser Thr Gly Gln Gly
            100   105   110

Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro
        115   120   125

Asp Tyr Gly Ser
    130

<210> 622
<211> 132
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 622

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

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

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

```
Ser Thr Ile Asn Trp Asn Gly Gly Ser Ala Glu Tyr Ala Glu Pro Val
    50                  55                  60


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


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


Ala Lys Asp Ala Asp Leu Val Trp Tyr Asn Leu Arg Thr Gly Gln Gly
            100                 105                 110


Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro
        115                 120                 125


Asp Tyr Gly Ser
    130


<210>  623
<211>  145
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  623

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


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


Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35                  40                  45


Ser Cys Ile Arg Val Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Pro Val
```

50 55 60

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

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

Ala Ala Gly Ser Leu Tyr Thr Cys Val Gln Ser Ile Val Val Val Pro
100 105 110

Ala Arg Pro Tyr Tyr Asp Met Asp Tyr Trp Gly Lys Gly Thr Gln Val
115 120 125

Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly
130 135 140

Ser
145

<210> 624
<211> 146
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 624

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

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

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

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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ala Lys 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


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


Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala
        115                 120                 125


Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His
    130                 135                 140


His His
145


<210>  625
<211>  152
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  625

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


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


Thr Met Gly Trp Phe Arg Gln Gly Pro Gly Lys Glu Arg Glu Phe Val
```

```
        35                  40                  45

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

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

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

Ala Ala Asp Gln Ala Ser Val Pro Pro Pro Tyr Gly Ser Glu Arg Tyr
            100                 105                 110

Asp Ile Ala Ser Pro Ser Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Gln
        115                 120                 125

Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140

Gly Ser His His His His His His
145                 150


<210>  626
<211>  148
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  626

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

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

```
Ile Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


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


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


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


Ala Ala Asn Ser Arg Ala Tyr Tyr Ser Ser Ser Tyr Asp Leu Gly Arg
            100                 105                 110


Leu Ala Ser Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser
        115                 120                 125


Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His
    130                 135                 140


His His His His
145


<210>  627
<211>  143
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  627

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Tyr
```

```
            20                  25                  30

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

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

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

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

Ala Ala Ala Gln Arg Leu Gly Ser Val Thr Asp Tyr Thr Lys Tyr Asp
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr
        115                 120                 125

Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  628
<211>  152
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  628

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Ser Gly Arg Thr
            20                  25                  30
```

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


Arg Glu Phe Val Ala Thr Ile Thr Trp Gly Gly Gly Ser Thr Tyr Tyr
    50                  55                  60


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


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


Val Tyr Tyr Cys Ala Ala Ser Val Lys Val Val Ala Gly Ser Gly Ile
            100                 105                 110


Asp Ile Ser Gly Ser Arg Asn Tyr Asp Tyr Trp Gly Gln Gly Thr Gln
        115                 120                 125


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140


Gly Ser His His His His His His
145                 150


<210>  629
<211>  148
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  629

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


Ser Leu Arg Leu Ser Cys Leu Ala Ser Gly Arg Thr Phe Ser Ser Tyr
```

            20   25   30

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

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

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

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

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

Ser Asp Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser
        115   120   125

Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His
    130   135   140

His His His His
145

<210> 630
<211> 146
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 630

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

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


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


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


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


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


Ala Ala Ala Gly Gly Ser Gly Arg Leu Arg Asp Leu Lys Val Gly Gln
            100                 105                 110


Asn Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala
        115                 120                 125


Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His
    130                 135                 140


His His
145


<210>  631
<211>  150
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  631

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
```

1 5 10 15

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

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

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

Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Lys 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

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

Glu Asp Gly Ser Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
115 120 125

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
130 135 140

His His His His His His
145 150

<210> 632
<211> 148
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 632

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


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


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


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


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


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


Ala Val Ile Pro Gly Arg Gly Ser Ala Leu Pro Ile Asp Val Gly Lys
            100                 105                 110


Ser Asp Glu Tyr Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser
        115                 120                 125


Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His
    130                 135                 140


His His His His
145


<210>  633
<211>  146
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence
```

<400> 633

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

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

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

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

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

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

Ala Ala Ala Gly Ala Ser Gly Arg Leu Arg Asp Leu Lys Val Gly Gln
100 105 110

Asn Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala
115 120 125

Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His
130 135 140

His His
145

<210> 634
<211> 150
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 634

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


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


Gly Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35                  40                  45


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


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


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


Ala Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly
            100                 105                 110


Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
        115                 120                 125


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
    130                 135                 140


His His His His His His
145                 150
```

<210> 635
<211> 143
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 635

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


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


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


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


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


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


Ala Ala Ala Gln Arg Leu Gly Ser Val Thr Asp Tyr Thr Lys Tyr Asp
            100                 105                 110


Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr
        115                 120                 125


Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 636
<211> 149
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 636

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


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


Val Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


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


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


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


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


Asp Gln Ser Lys Tyr Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
        115                 120                 125


Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His
    130                 135                 140


His His His His His
145
```

<210> 637
<211> 149
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 637

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


Ser Leu Lys Leu Ser Cys Ile Ser Gly Phe Ala Phe Asp Gly Tyr Ala
            20                  25                  30


Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val Ala
        35                  40                  45


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


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


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


Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Ser Ser Ala Gly Pro
            100                 105                 110


Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr Val
        115                 120                 125


Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His
    130                 135                 140


His His His His His
145
```

<210> 638

<211> 139
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 638

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

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

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

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

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

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

Ala Lys Ser Arg Ser Ser Tyr Ser Asn Asn Trp Arg Pro Pro Gly Gln
100 105 110

Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val
115 120 125

Pro Asp Tyr Gly Ser His His His His His His
130 135

<210> 639
<211> 149
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 639

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


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


Val Ile Gly Trp Phe Arg Gln Ala Pro Gly Glu Glu Arg Glu Phe Val
        35                  40                  45


Ala Val Val Thr Trp Ser Gly Asp Ser Thr Tyr Ser Ser Asp Ser Leu
    50                  55                  60


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


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


Ala Ala Met Pro Pro Arg Ala Tyr Thr Gly Arg Ser Val Ser Leu Lys
            100                 105                 110


Asp Gln Ser Lys Tyr Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
        115                 120                 125


Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His
    130                 135                 140


His His His His His
145
```

<210> 640

<211> 139
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 640

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

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

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

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

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

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

Leu Asp Thr Thr Gly Trp Gly Pro Pro Pro Tyr Gln Tyr Trp Gly Gln
100 105 110

Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val
115 120 125

Pro Asp Tyr Gly Ser His His His His His His
130 135

<210> 641
<211> 149
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 641

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


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


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


Ser Phe Ile Ser Trp Ile Ser Asp Ile Thr Tyr Tyr Ser Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Met 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


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


Thr Pro Ser Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
        115                 120                 125


Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His
    130                 135                 140


His His His His His
145
```

<210> 642

<211> 143
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 642

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

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

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

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

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

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

Ala Ala Ala Gln Arg Leu Gly Ser Val Thr Asp Tyr Thr Lys Tyr Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr
115 120 125

Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 643
<211> 151
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 643

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


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


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


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


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


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


Ala Val Pro Arg Ser His Phe Thr Thr Ala Gln Asp Met Gly Gln Asp
            100                 105                 110


Met Gly Ala Pro Ser Trp Tyr Glu Tyr Trp Gly Gln Gly Thr Gln Val
        115                 120                 125


Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly
    130                 135                 140


Ser His His His His His His
145                 150
```

<210> 644

<211> 149
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 644

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


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


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


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Val Leu Ile Arg Tyr Tyr Ser Gly Gly Tyr Gln Gly Leu Ser
            100                 105                 110


Asp Ala Asn Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
        115                 120                 125


Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His
    130                 135                 140


His His His His His
145
```

<210> 645
<211> 144
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 645

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


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


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


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


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


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


Ala Val Val Lys Tyr Leu Ser Gly Ser Tyr Ser Tyr Ala Gly Gln Tyr
            100                 105                 110


Asn Phe Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala
        115                 120                 125


Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 646

<211> 150
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 646

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


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


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


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


Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys 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


Ala Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Val Gly
            100                 105                 110


Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
        115                 120                 125


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
    130                 135                 140


His His His His His His
145                 150
```

<210> 647
<211> 148
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 647

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


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


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


Ala Ala Val Leu Trp Ser Gly Val Ser Thr Ala Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Ala Ala His Glu Ser Thr Tyr Tyr Ser Gly Thr Tyr Tyr Leu Thr Asp
            100                 105                 110


Pro Arg Arg Tyr Val Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser
        115                 120                 125


Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His
    130                 135                 140


His His His His
```

145

<210> 648
<211> 146
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 648

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


Ser Leu Arg Leu Ser Cys Val Gly Asp Gly Arg Thr Phe Ser Ser Tyr
            20                  25                  30


Ile Ile Gly Trp Phe Arg Gln Ala Pro Gly Asn Glu Arg Glu Phe Val
        35                  40                  45


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


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


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


Ala Ala Val Pro Ala Arg Gly Leu Thr Met Asp Leu Glu Asn Ser Asp
            100                 105                 110


Ile Tyr Asp His Trp Gly Arg Gly Thr Gln Val Thr Val Ser Ser Ala
        115                 120                 125


Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His
    130                 135                 140
```

His His
145

<210> 649
<211> 149
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 649

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

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

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

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

Lys Gly Arg Phe Ala Ile Ser Arg Asp Asn Ala Lys 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

Ala Ala Ala Thr Leu Gln Val Thr Gly Ser Tyr Tyr Leu Asp Leu Ser
100 105 110

Thr Val Asp Ile Tyr Asp Asn Trp Gly Gln Gly Thr Gln Val Thr Val
115 120 125

Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His

130 135 140

His His His His His
145

<210> 650
<211> 147
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 650

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

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

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

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu 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

Ala Ala Thr Leu Phe Arg Ser Asn Gly Pro Lys Asp Leu Ser Ser Gly
100 105 110

Tyr Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120 125

Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His
130 135 140

His His His
145

<210> 651
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<220>
<221> misc_feature
<222> (112)..(112)
<223> Xaa can be any naturally occurring amino acid

<400> 651

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

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

Gly Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

Ala Ala Gly Glu Ser Gly Val Trp Val Gly Gly Leu Asp Tyr Trp Xaa
100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
115 120 125

Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 652
<211> 149
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 652

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

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

Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys 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

Ala Val Gly Ser Ala Asn Ser Gly Glu Phe Arg Phe Gly Trp Val Leu

100 105 110

Lys Pro Asp Leu Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
115 120 125

Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His
130 135 140

His His His His His
145

<210> 653
<211> 150
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 653

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

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

Thr Val Ala Trp Phe Arg Gln Ser Pro Gly Lys Glu Arg Glu Gly Ile
35 40 45

Ser Cys Ile Ser Asn Thr Asp Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

```
Ala Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly
            100                 105                 110


Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
        115                 120                 125


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
    130                 135                 140


His His His His His His
145                 150


<210>  654
<211>  150
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  654

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


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


Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35                  40                  45


Ser Cys Ile Ser Asn Thr Asp Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


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


Leu Gln Met Ser Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
```

85 90 95

Ala Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly
100 105 110

Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
115 120 125

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
130 135 140

His His His His His His
145 150

<210> 655
<211> 147
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 655

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

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

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

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

Lys Gly Arg Phe Thr Ile Ser Asn Asp Asn Ala Lys Arg 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


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


Gln Asp Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120                 125


Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His
    130                 135                 140


His His His
145


<210>  656
<211>  148
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  656

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Leu Ser Ser Asn
            20                  25                  30


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


Ala Gly Met Ser Trp Asn Pro Gly Pro Ala Val Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Glu 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

Ala Gly Ala Ala Arg Ala Trp Trp Ser Gly Ser Tyr Asp Tyr Thr Arg
100 105 110

Met Asn Asn Tyr Asp Tyr Trp Gly Pro Gly Thr Gln Val Thr Val Ser
115 120 125

Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His
130 135 140

His His His His
145

<210> 657
<211> 150
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 657

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

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

```
Arg Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys 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


Ala Ala Glu Thr Ser Ala Asp Ser Gly Glu Phe Arg Phe Gly Trp Val
            100                 105                 110


Leu Lys Pro Ser Leu Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
        115                 120                 125


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
    130                 135                 140


His His His His His His
145                 150


<210>  658
<211>  148
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  658

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


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


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


Ala Asn Ile Gly Trp Thr Gly Asp Met Thr Tyr Tyr Ala Asp Ser Val
```

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

Ala Ala Ala Gly Ser Ala Tyr Ser Gly Ser Tyr Trp Asn Ile Thr Met
100 105 110

Ala Ala Asn Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser
115 120 125

Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His
130 135 140

His His His His
145

<210> 659
<211> 145
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 659

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

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

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

```
Ala Ala Ile Ile Trp Ser Gly Ser Met Thr Tyr Tyr Ala Asp Ser Met
    50                  55                  60


Lys Gly Arg Phe Thr Val Ser Ile Asp Asn Ala Lys 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


Ala Ala Gln Arg Ile Phe Gly Ala Gln Pro Met Asp Leu Ser Gly Asp
            100                 105                 110


Tyr Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala
        115                 120                 125


Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His
    130                 135                 140


His
145


<210>  660
<211>  150
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  660

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


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


Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
```

```
        35                  40                  45

Ser Cys Ile Ser Asn Thr Asp Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

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

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

Ala Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly
            100                 105                 110

Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
        115                 120                 125

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
    130                 135                 140

His His His His His His
145                 150
```

<210> 661
<211> 145
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 661

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

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

```
Ile Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


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


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


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


Ala Ala Arg Asp Tyr Arg Gly Ile Lys Asp Leu Asp Leu Lys Gly Asp
            100                 105                 110


Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala
        115                 120                 125


Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His
    130                 135                 140


His
145


<210>  662
<211>  151
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  662

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


Ser Leu Lys Leu Ser Cys Ala Thr Ser Gly Arg Ser Phe Ser Ser Tyr
```

20 25 30

Thr Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
35 40 45

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

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

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

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ile Trp Tyr
100 105 110

Gly Pro Pro Pro Arg Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val
115 120 125

Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly
130 135 140

Ser His His His His His His
145 150

<210> 663
<211> 152
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 663

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

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


Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
        35                  40                  45


Ser Cys Tyr Ser Ser Ser Asp Gly Ser Thr Gly Phe Ala Asp Ser Val
    50                  55                  60


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


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


Ala Ala Asp Ser Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Arg Trp
            100                 105                 110


Tyr Gly Pro Pro Pro Gly Gly Met Ala Tyr Trp Gly Lys Gly Thr Gln
        115                 120                 125


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140


Gly Ser His His His His His His
145                 150


<210>  664
<211>  151
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  664

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Ala Gln Val Gly Gly
```

```
1               5                   10                  15

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

Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
        35                  40                  45

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

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

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

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Asn Trp Tyr
            100                 105                 110

Gly Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val
        115                 120                 125

Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly
    130                 135                 140

Ser His His His His His His
145                 150
```

<210> 665
<211> 152
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 665

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


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


Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
        35                  40                  45


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


Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys 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


Ala Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ile Trp
            100                 105                 110


Tyr Gly Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln
        115                 120                 125


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140


Gly Ser His His His His His His
145                 150
```

<210> 666
<211> 150
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 666

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


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


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


Ser Cys Ile Ser Asn Thr Asp Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


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


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


Ala Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly
            100                 105                 110


Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
        115                 120                 125


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
    130                 135                 140


His His His His His His
145                 150
```

<210> 667
<211> 144
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 667

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


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


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


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


Lys Gly Arg Phe Ala Ile Ser Arg Asp Asn Ala Glu 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


Ala Ala Arg Ile Ile Thr Val Ala Thr Met Arg Leu Asp Ser Asp Tyr
            100                 105                 110


Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala
        115                 120                 125


Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 668
<211> 150
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 668

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

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

Ala Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly
100 105 110

Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
115 120 125

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
130 135 140

His His His His His His
145 150

<210> 669
<211> 152
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 669

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


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


Thr Ile Ala Trp Phe Arg Arg Ala Pro Gly Lys Glu Arg Glu Gly Ile
        35                  40                  45


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


Lys Gly Arg Phe Thr Ile Thr Ser Asp Ser Ala Lys 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


Ala Ala Asp Ser Asn Val Trp Ser Pro Pro Ile Cys Gly Arg Thr Trp
            100                 105                 110


Tyr Gly Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln
        115                 120                 125


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140


Gly Ser His His His His His His
145                 150
```

<210> 670
<211> 152
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 670

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


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


Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
        35                  40                  45


Ser Cys Tyr Ser Ser Arg Asp Gly Thr Thr Gly Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys 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


Ala Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ile Trp
            100                 105                 110


Tyr Gly Pro Pro Pro Gly Gly Met Ala Tyr Trp Gly Gln Gly Thr Gln
        115                 120                 125


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140


Gly Ser His His His His His His
145                 150
```

<210> 671

<211> 151
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 671

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


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


Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
        35                  40                  45


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


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


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


Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Asn Trp Tyr
            100                 105                 110


Gly Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val
        115                 120                 125


Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly
    130                 135                 140


Ser His His His His His His
145                 150
```

<210> 672
<211> 152
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 672

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


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


Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
        35                  40                  45


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


Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys 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


Ala Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ser Trp
            100                 105                 110


Tyr Gly Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln
        115                 120                 125


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140


Gly Ser His His His His His His
```

145 150

<210> 673
<211> 152
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 673

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Ser Asp Asp Tyr
20 25 30

Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
35 40 45

Ser Cys Phe Ser Ser Ser Asp Gly Ser Thr Gly Phe Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Thr Asn Thr Val Tyr
65 70 75 80

Leu Glu Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Arg Trp
100 105 110

Tyr Gly Pro Pro Pro Gly Gly Met Glu Tyr Trp Gly Lys Gly Thr Gln
115 120 125

Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
130 135 140

```
Gly Ser His His His His His His
145                 150


<210>  674
<211>  150
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  674

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Thr Phe Gly Phe Ser Phe Asp Asp Tyr
            20                  25                  30


Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
        35                  40                  45


Ser Cys Ile Ser Asn Thr Asp Ser Ser Thr Phe Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Thr Val His
65                  70                  75                  80


Leu Gln Met Ser Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly
            100                 105                 110


Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
        115                 120                 125


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
```

130 135 140

His His His His His His
145 150

<210> 675
<211> 152
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 675

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Ser Asp Asp Tyr
20 25 30

Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
35 40 45

Ser Cys Tyr Ser Ser Ser Asp Gly Ser Thr Gly Phe Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Arg Trp
100 105 110

Tyr Gly Pro Pro Pro Gly Gly Met Ala Tyr Trp Gly Lys Gly Thr Gln
115 120 125

```
Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140


Gly Ser His His His His His His
145                 150


<210>  676
<211>  151
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  676

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Val Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Thr Ile Ser Gly Phe Thr Gly Asn Asp Leu
            20                  25                  30


Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Asp Gln Arg Glu Gly
        35                  40                  45


Ile Ser Cys Ile Ser Asn Thr Asp Ser Ser Thr Tyr Tyr Ala Asp Ser
    50                  55                  60


Val Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Thr Val
65                  70                  75                  80


His Leu Gln Met Ser Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr
                85                  90                  95


Cys Ala Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala
            100                 105                 110


Gly Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val
```

115 120 125

Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly
130 135 140

Ser His His His His His His
145 150

<210> 677
<211> 152
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 677

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Ser Asp Asp Tyr
20 25 30

Thr Ile Ala Trp Phe Arg Arg Ala Pro Gly Lys Glu Arg Glu Gly Ile
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Asp Ser Asn Val Trp Ser Pro Pro Ile Cys Gly Lys Thr Trp
100 105 110

```
Tyr Gly Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln
        115                 120                 125


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140


Gly Ser His His His His His His
145                 150


<210>  678
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  678

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Gly Ser Glu Gly Thr Leu Ser Ser Tyr
            20                  25                  30


Gly Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Gly Gly Ile Asn Trp Ser Gly Asp Ser Thr Asp Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys 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


Ala Ala Gly Glu Ser Gly Val Trp Val Gly Gly Leu Asp Tyr Trp Gly
```

100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
115 120 125

Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 679
<211> 152
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 679

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Ser Asp Asp Tyr
20 25 30

Thr Ile Ala Trp Phe Arg Arg Ala Pro Gly Lys Glu Arg Glu Gly Ile
35 40 45

Ser Cys Phe Ser Ser Ser Asp Gly Ser Ala Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Val Ser Ser Asp Asn Ala Lys 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

Ala Ala Asp Ser Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Thr Trp
100 105 110

```
Tyr Gly Pro Pro Pro Gly Gly Met Ala Tyr Trp Gly Lys Gly Thr Gln
        115                 120                 125


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140


Gly Ser His His His His His His
145                 150


<210>  680
<211>  150
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  680

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30


Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35                  40                  45


Ser Cys Ile Ser Asn Thr Asp Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Thr Val Tyr
65                  70                  75                  80


Leu Gln Met Ser Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly
```

```
            100                 105                 110

Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
        115                 120                 125

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
    130                 135                 140

His His His His His His
145                 150

<210>  681
<211>  152
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  681

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Glu Val Ser Gly Leu Ser Ser Asp Asp Tyr
            20                  25                  30

Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Phe
        35                  40                  45

Ser Cys Phe Ser Thr Arg Asp Gly Asn Ala Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Thr Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Asn Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Arg Trp
            100                 105                 110


Tyr Gly Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln
        115                 120                 125


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140


Gly Ser His His His His His His
145                 150


<210>  682
<211>  152
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  682

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Glu Val Ser Gly Leu Ser Ser Asp Asp Tyr
            20                  25                  30


Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Lys Arg Glu Gly Phe
        35                  40                  45


Ser Cys Phe Ser Ser Arg Asp Gly Ser Thr Gly Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys 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

Ala Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Arg Trp
100 105 110

Tyr Gly Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln
115 120 125

Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
130 135 140

Gly Ser His His His His His His
145 150

<210> 683
<211> 152
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 683

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Ser Asp Asp Tyr
20 25 30

Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Phe
35 40 45

Ser Cys Phe Ser Ser Arg Asp Gly Ser Thr Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys 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


Ala Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Arg Trp
            100                 105                 110


Tyr Gly Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln
        115                 120                 125


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140


Gly Ser His His His His His His
145                 150


<210>  684
<211>  151
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  684

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Asp Asp Tyr
            20                  25                  30


Thr Ile Gly Trp Phe Arg Gln Val Pro Gly Lys Glu Arg Glu Gly Ile
        35                  40                  45


Ser Cys Ile Ser Ser Asp Gly Ser Thr Gly Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Thr Val Tyr Leu
```

65 70 75 80

Gln Ile Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ile Trp Tyr
100 105 110

Gly Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val
115 120 125

Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly
130 135 140

Ser His His His His His His
145 150

<210> 685
<211> 150
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 685

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Thr Phe Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
35 40 45

Ser Cys Ile Ser Asn Thr Asp Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

```
Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Thr Val His
65                  70                  75                  80


Leu Gln Met Ser Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly
            100                 105                 110


Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
        115                 120                 125


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
    130                 135                 140


His His His His His His
145                 150


<210>  686
<211>  150
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence


<220>
<221>  misc_feature
<222>  (19)..(19)
<223>  Xaa can be any naturally occurring amino acid

<400>  686

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Xaa Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
```

```
Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35                  40                  45


Ser Cys Ile Ser Ser Pro Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys 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


Ala Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Val Gly
            100                 105                 110


Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
        115                 120                 125


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
    130                 135                 140


His His His His His His
145                 150


<210>  687
<211>  152
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  687

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Ala
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Phe Thr Phe Gly Asp Tyr
```

```
            20                  25                  30

Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
        35                  40                  45

Ser Cys Tyr Ser Ser Ser Asp Gly Asn Thr Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Thr Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ser Trp
            100                 105                 110

Tyr Gly Pro Pro Pro Gly Gly Met Ala Tyr Trp Gly Lys Gly Thr Gln
        115                 120                 125

Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140

Gly Ser His His His His His His
145                 150


<210>  688
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  688

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Gly Ser Glu Gly Thr Phe Ser Ser Tyr
            20                  25                  30


Gly Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Gly Gly Ile Asn Trp Ser Gly Asp Ser Thr Asp Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Gly Glu Ser Gly Val Trp Val Gly Gly Leu Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  689
<211>  152
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  689

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Ser Asp Asp Tyr
```

```
            20                  25                  30

Thr Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
        35                  40                  45

Ser Cys Phe Ser Ser Ser Asp Gly Ser Thr Gly Phe Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Thr 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

Ala Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ser Trp
            100                 105                 110

Tyr Gly Pro Pro Pro Gly Gly Met Glu Tyr Trp Gly Lys Gly Thr Gln
        115                 120                 125

Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140

Gly Ser His His His His His His
145                 150


<210>  690
<211>  150
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  690

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Val Ser Ile Gly Asp Tyr
            20                  25                  30


Asn Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35                  40                  45


Ser Cys Ile Ser Ser Gly Asp Gly Thr Thr Tyr Tyr Thr Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Thr Asp Asn Ala Lys 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


Ala Ala Asp Gly Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ala Gly
            100                 105                 110


Pro Pro Pro Gly Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
        115                 120                 125


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
    130                 135                 140


His His His His His His
145                 150


<210>  691
<211>  152
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  691

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
```

```
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30

Thr Ile Ala Trp Phe Arg Gln Ala Pro Gly Gly Lys Glu Arg Glu Gly
        35                  40                  45

Ile Ser Cys Ile Ser Ser Asp Gly Ser Thr Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Met Val Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Ser Ser Asn Trp
            100                 105                 110

Tyr Gly Pro Pro Pro Arg Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln
        115                 120                 125

Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
    130                 135                 140

Gly Ser His His His His His His
145                 150
```

<210> 692
<211> 151
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 692

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30


Thr Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Ile
        35                  40                  45


Ser Cys Ile Ser Ser Asp Gly Ser Thr Gly Tyr Ala Asp Ser Val Arg
    50                  55                  60


Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Ala Asp Phe Asn Val Trp Ser Pro Pro Ile Cys Gly Ser Ile Trp Tyr
            100                 105                 110


Gly Pro Pro Pro Arg Gly Met Asp Tyr Trp Gly Lys Gly Thr Gln Val
        115                 120                 125


Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly
    130                 135                 140


Ser His His His His His His
145                 150
```

<210> 693
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 693

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Asp Pro Ala Asn Asp Asn Thr Leu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Ala Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Gly Arg Gly Tyr Gly Tyr Tyr Val Phe Asp His Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 694
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 694

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

```
Thr Val Lys Ile Ser Cys Lys Val Ser Gly Phe Asn Ile Lys Asp Thr
            20                  25                  30


Tyr Ile His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45


Gly Arg Ile Asp Pro Ala Asn Asp Asn Thr Leu Tyr Ala Ser Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Tyr Gly Tyr Tyr Val Phe Asp His Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser
        115


<210>  695
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  695

Asp Val Gln Ile Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Arg Ser Ile Ser Gln Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
```

```
        35                  40                  45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln His Asn Glu Asn Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105

<210>  696
<211>  288
<212>  PRT
<213>  Homo sapiens

<220>
<221>  MISC_FEATURE
<223>  human PD-1

<400>  696

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1               5                   10                  15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp
            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
```

```
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
```

260 265 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
275 280 285

<210> 697
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 697

Gly Phe Ser Met Asp Tyr Tyr Ala Ile Ala
1 5 10

<210> 698
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 698

Gly Phe Ser Met Asp Tyr Tyr Ala Ile Ala
1 5 10

<210> 699
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 699

Gly Phe Ser Val Asp Tyr Tyr Ala Ile Ala
1 5 10

<210> 700
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 700

Gly Phe Ser Met Asp Tyr Tyr Ala Ile Ala
1 5 10

<210> 701
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 701

Gly Gly Phe Asn Arg Val Ser Tyr Met Gly
1 5 10

<210> 702
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 702

Gly Gly Phe Asn Arg Val Ser Tyr Met Gly
1 5 10

<210> 703
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 703

Gly Ile Ile Lys Ser Ile Asn Phe Met Gly
1   5   10

<210> 704
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 704

Gly Phe Ile Leu Asp Tyr Tyr Gly Ile Gly
1   5   10

<210> 705
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 705

Gly Leu Ser Leu Asp Tyr Asp Gly Val Gly
1   5   10

<210> 706
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 706

Gly Phe Ile Leu Asp Tyr Tyr Gly Ile Gly

1 5 10

<210> 707
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 707

Gly Arg Thr Phe Ser Ser Leu Gly Met Gly
1 5 10

<210> 708
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 708

Gly Arg Thr Phe Ser Ser Leu Gly Met Gly
1 5 10

<210> 709
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 709

Gly Phe Ala Phe Gly Ser Tyr Asp Met Gly
1 5 10

<210> 710
<211> 10
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 710

Gly Phe Ser Phe Gly Asn Asn Asp Met Ser
1   5   10

<210> 711
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 711

Cys Ile Thr Gly Ser Asp Phe Met Val Asp Thr
1   5   10

<210> 712
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 712

Cys Ile Thr Gly Ser Asp Phe Met Val Asp Thr
1   5   10

<210> 713
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 713

Cys Ile Thr Gly Ser Asp Phe Met Val Asp Thr
1   5   10

<210> 714
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 714

Cys Ile Thr Gly Ser Asp Phe Met Val Asp Thr
1   5   10

<210> 715
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 715

Ser Val Thr Ser Gly Gly Glu Ile
1   5

<210> 716
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 716

Ser Val Thr Ser Gly Gly Glu Ile
1   5

<210> 717

<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 717

Ser Thr Thr Ser Asp Gly Arg Thr
1 5

<210> 718
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 718

Cys Ile Ser Ser Ser Asp Gly Ser Thr
1 5

<210> 719
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 719

Cys Ile Ser Ser Ser Asp Gly Ser Thr
1 5

<210> 720
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 720

Cys Ile Ser Ser Ser Asp Gly Ser Thr
1 5

<210> 721
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 721

Ala Ile Ala Trp Asn Gly Ala Ser Thr
1 5

<210> 722
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 722

Ala Ile Ala Trp Asn Gly Ala Ser Thr
1 5

<210> 723
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 723

Gly Ile Asn Ser Gly Gly Arg Ile Thr
1 5

<210> 724
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 724

Ala Ile Asn Ser Gly Gly Gly Ser Thr
1 5

<210> 725
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 725

Ala Val Arg Ser Thr Ala Asn Thr Leu Cys Pro Ser His Tyr Ser Val
1 5 10 15

Met Asp Tyr

<210> 726
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 726

Ala Val Arg Ser Thr Ala Asn Thr Leu Cys Pro Ser His Tyr Ser Val
1 5 10 15

Met Asp Tyr

<210> 727
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 727

Ala Val Arg Ser Thr Ala Asn Thr Leu Cys Pro Ser His Tyr Ser Ile
1 5 10 15

Met Asp Tyr

<210> 728
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 728

Ala Val Arg Ser Thr Ala Asn Thr Leu Cys Pro Ser His Tyr Ser Val
1 5 10 15

Met Asp Tyr

<210> 729
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 729

Asn Ala Asp Ile Trp Val Ser Asp Ala Arg Met Tyr Asn Tyr
1 5 10

<210> 730
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 730

Asn Ala Asp Ile Trp Val Ser Asp Ala Arg Met Tyr Asn Tyr
1 5 10

<210> 731
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 731

Asn Ala Asp Ile Trp Leu Pro Ser Asp Arg Met Tyr Asn Tyr
1 5 10

<210> 732
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 732

Ala Thr Ala Thr Leu Cys Asp Gly Gly Ile Trp Gly Tyr
1 5 10

<210> 733

<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 733

Ala Thr Ala Thr Leu Cys Asp Gly Gly Ile Trp Gly Tyr
1 5 10

<210> 734
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 734

Ala Thr Ala Thr Leu Cys Asp Gly Gly Ile Trp Gly Tyr
1 5 10

<210> 735
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 735

Ala Ala Ser Gly Leu Gly Ser Val Val Val Thr Ala Asn Glu Tyr Asp
1 5 10 15

Tyr

<210> 736
<211> 17
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 736

Ala Ala Ser Gly Leu Gly Ser Val Val Val Thr Ala Asn Glu Tyr Asp
1   5   10   15

Tyr

<210> 737
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 737

Ala Gln Gly Asp Arg Ser Ser Trp His Tyr Tyr Gly Met Asp Tyr
1   5   10   15

<210> 738
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 738

Ala Thr Lys Ser Asp Pro Met Thr Asn Glu Tyr Asp Leu
1   5   10

<210> 739
<211> 147
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 739

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Met Asp Tyr Tyr
            20                  25                  30


Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Ile
        35                  40                  45


Ser Cys Ile Thr Gly Ser Asp Phe Met Val Asp Thr Tyr Tyr Val Ala
    50                  55                  60


Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Thr
65                  70                  75                  80


Ala Tyr Leu Gln Met Asn Asn Leu Lys Pro Glu Asp Thr Gly Val Tyr
                85                  90                  95


Phe Cys Ala Val Arg Ser Thr Ala Asn Thr Leu Cys Pro Ser His Tyr
            100                 105                 110


Ser Val Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr Val Ser Ser
        115                 120                 125


Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His
    130                 135                 140


His His His
145
```

<210> 740
<211> 147
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 740

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Met Asp Tyr Tyr
            20                  25                  30


Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Ile
        35                  40                  45


Ser Cys Ile Thr Gly Ser Asp Phe Met Val Asp Thr Tyr Tyr Val Ala
    50                  55                  60


Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Thr
65                  70                  75                  80


Ala Tyr Leu Gln Met Asn Asn Leu Lys Pro Glu Asp Thr Gly Val Tyr
                85                  90                  95


Phe Cys Ala Val Arg Ser Thr Ala Asn Thr Leu Cys Pro Ser His Tyr
            100                 105                 110


Ser Val Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr Val Ser Ser
        115                 120                 125


Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His
    130                 135                 140


His His His
145
```

<210> 741

<211> 147
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 741

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Ser Val Asp Tyr Tyr
20 25 30

Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Ile
35 40 45

Ser Cys Ile Thr Gly Ser Asp Phe Met Val Asp Thr Tyr Tyr Val Ala
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr
65 70 75 80

Ala Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Gly Val Tyr
85 90 95

Phe Cys Ala Val Arg Ser Thr Ala Asn Thr Leu Cys Pro Ser His Tyr
100 105 110

Ser Ile Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr Val Ser Ser
115 120 125

Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His
130 135 140

His His His
145

<210> 742
<211> 147
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 742

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Ser Met Asp Tyr Tyr
            20                  25                  30


Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Ile
        35                  40                  45


Ser Cys Ile Thr Gly Ser Asp Phe Met Val Asp Thr Tyr Tyr Val Ala
    50                  55                  60


Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr
65                  70                  75                  80


Ala His Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Gly Val Tyr
                85                  90                  95


Phe Cys Ala Val Arg Ser Thr Ala Asn Thr Leu Cys Pro Ser His Tyr
            100                 105                 110


Ser Val Met Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr Val Ser Ser
        115                 120                 125


Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His
    130                 135                 140


His His His
```

145

<210> 743
<211> 139
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 743

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Gly Phe Asn Arg Val Ser
            20                  25                  30


Tyr Met Gly Trp Tyr Arg Gln Ala Pro Gly Thr Lys Arg Glu Leu Val
        35                  40                  45


Ala Ser Val Thr Ser Gly Gly Glu Ile Thr Ile Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Val Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80


Gln Met Asn Gly Leu Lys Pro Glu Asp Gly Ala Thr Tyr Trp Cys Asn
                85                  90                  95


Ala Asp Ile Trp Val Ser Asp Ala Arg Met Tyr Asn Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val
        115                 120                 125


Pro Asp Tyr Gly Ser His His His His His His
    130                 135
```

<210> 744
<211> 139
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 744

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Glu
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Gly Phe Asn Arg Val Ser
            20                  25                  30


Tyr Met Gly Trp Tyr Arg Gln Ala Pro Gly Ser Lys Arg Glu Leu Val
        35                  40                  45


Ala Ser Val Thr Ser Gly Gly Glu Ile Thr Val Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Val Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80


Gln Met Asn Gly Leu Lys Pro Glu Asp Gly Ala Thr Tyr Trp Cys Asn
                85                  90                  95


Ala Asp Ile Trp Val Ser Asp Ala Arg Met Tyr Asn Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val
        115                 120                 125


Pro Asp Tyr Gly Ser His His His His His His
    130                 135
```

<210> 745

<211> 139
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 745

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Glu
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Ile Lys Ser Ile Asn
20 25 30

Phe Met Gly Trp Tyr Arg Gln Pro Pro Gly Thr Lys Arg Glu Leu Val
35 40 45

Ala Ser Thr Thr Ser Asp Gly Arg Thr Thr Val Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Ile Tyr Leu
65 70 75 80

Glu Met Ser Ser Leu Lys Pro Glu Asp Thr Ala Thr Tyr Trp Cys Asn
85 90 95

Ala Asp Ile Trp Leu Pro Ser Asp Arg Met Tyr Asn Tyr Trp Gly Gln
100 105 110

Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val
115 120 125

Pro Asp Tyr Gly Ser His His His His His His
130 135

<210> 746
<211> 139
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 746

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ile Leu Asp Tyr Tyr
20 25 30

Gly Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ala Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Leu Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr His Cys
85 90 95

Ala Thr Ala Thr Leu Cys Asp Gly Gly Ile Trp Gly Tyr Trp Gly Gln
100 105 110

Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val
115 120 125

Pro Asp Tyr Gly Ser His His His His His His
130 135

<210> 747
<211> 139
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 747

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Ala Gln Ala Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Glu Gly Ser Gly Leu Ser Leu Asp Tyr Asp
            20                  25                  30


Gly Val Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ala Val
        35                  40                  45


Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Gly Asn Ala Leu Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Thr Ala Thr Leu Cys Asp Gly Gly Ile Trp Gly Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val
        115                 120                 125


Pro Asp Tyr Gly Ser His His His His His His
    130                 135
```

<210> 748
<211> 139
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 748

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ile Leu Asp Tyr Tyr
20 25 30

Gly Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ala Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Leu Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Ala Thr Leu Cys Asp Gly Gly Ile Trp Gly Tyr Trp Gly Gln
100 105 110

Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val
115 120 125

Pro Asp Tyr Gly Ser His His His His His His
130 135

<210> 749
<211> 143
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 749

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Asp
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Arg Thr Phe Ser Ser Leu
            20                  25                  30


Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ser Ala Ile Ala Trp Asn Gly Ala Ser Thr Tyr Tyr Thr Glu Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ala Lys Asn Thr Val Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Thr Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95


Ala Ala Ser Gly Leu Gly Ser Val Val Val Thr Ala Asn Glu Tyr Asp
            100                 105                 110


Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr
        115                 120                 125


Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  750
<211>  143
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  750

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Pro Gly Lys
```

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Leu
20 25 30

Gly Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ser Ala Ile Ala Trp Asn Gly Ala Ser Thr Tyr Tyr Thr Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Thr Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Ala Ser Gly Leu Gly Ser Val Val Val Thr Ala Asn Glu Tyr Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr
115 120 125

Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 751
<211> 141
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 751

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Thr Thr Ser Gly Phe Ala Phe Gly Ser Tyr
            20                  25                  30


Asp Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35                  40                  45


Ser Gly Ile Asn Ser Gly Gly Arg Ile Thr Asp Tyr Ala Asp Ser Val
    50                  55                  60


Thr Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Gln Gly Asp Arg Ser Ser Trp His Tyr Tyr Gly Met Asp Tyr Trp
            100                 105                 110


Gly Lys Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr
        115                 120                 125


Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  752
<211>  139
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence


<220>
<221>  misc_feature
<222>  (112)..(112)
<223>  Xaa can be any naturally occurring amino acid

<400>  752
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```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Gly Asn Asn
            20                  25                  30


Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35                  40                  45


Ser Ala Ile Asn Ser Gly Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Thr Lys Ser Asp Pro Met Thr Asn Glu Tyr Asp Leu Trp Gly Xaa
            100                 105                 110


Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val
        115                 120                 125


Pro Asp Tyr Gly Ser His His His His His His
    130                 135


<210>  753
<211>  447
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  753

Gln Val Gln Leu Val Gln Ser Gly Val Glu Val Lys Lys Pro Gly Ala
```

```
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30

Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Gly Ile Asn Pro Ser Asn Gly Gly Thr Asn Phe Asn Glu Lys Phe
    50                  55                  60

Lys Asn Arg Val Thr Leu Thr Thr Asp Ser Ser Thr Thr Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Lys Ser Leu Gln Phe Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Tyr Arg Phe Asp Met Gly Phe Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
```

```
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
    210                 215                 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
            260                 265                 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
```

385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 754
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 754

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Gly Val Ser Thr Ser
20 25 30

Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Arg
85 90 95

```
Asp Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
            100                 105                 110


Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
        115                 120                 125


Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140


Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160


Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175


Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
            180                 185                 190


His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
        195                 200                 205


Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  755
<211>  440
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  755

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
```

```
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100                 105                 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
        115                 120                 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
    130                 135                 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145                 150                 155                 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
                165                 170                 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
            180                 185                 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
        195                 200                 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
```

```
    210                 215                 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225                 230                 235                 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
                245                 250                 255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
            260                 265                 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
        275                 280                 285

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
    290                 295                 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305                 310                 315                 320

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
                325                 330                 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
            340                 345                 350

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
        355                 360                 365

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
    370                 375                 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385                 390                 395                 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
```

405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
420 425 430

Ser Leu Ser Leu Ser Leu Gly Lys
435 440

<210> 756
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 756

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ser Asn Trp Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

```
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190


Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205


Phe Asn Arg Gly Glu Cys
    210


<210>  757
<211>  106
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  757

Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
            20                  25                  30


His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
```

35 40 45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro Glu
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 758
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 758

Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr
35 40 45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Asn Ser Leu Gln Pro Glu
65 70 75 80

```
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
                85                  90                  95


Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  759
<211>  106
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  759

Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
            20                  25                  30


His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr
        35                  40                  45


Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60


Gly Ser Gly Thr Asp Tyr Cys Leu Thr Ile Asn Ser Leu Gln Pro Glu
65                  70                  75                  80


Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
                85                  90                  95


Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  760
```

<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 760

Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr
35 40 45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Cys Leu Thr Ile Asn Ser Leu Gln Pro Glu
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 761
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 761

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala

1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Ser Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
35 40 45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
85 90 95

Ala Lys Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 762
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 762

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

```
Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
        35                  40                  45


Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
    50                  55                  60


Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
                85                  90                  95


Ala Lys Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  763
<211>  117
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  763

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30


Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
        35                  40                  45


Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
```

50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
65 70 75 80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
85 90 95

Val Arg Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 764
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 764

Gln Ile Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
35 40 45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
65 70 75 80

```
Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
                85                  90                  95


Val Arg Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  765
<211>  117
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  765

Gln Ile Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30


Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
        35                  40                  45


Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
    50                  55                  60


Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
65                  70                  75                  80


Leu Gln Ile Thr Ser Leu Asn Ala Glu Asp Thr Gly Met Tyr Phe Cys
                85                  90                  95


Val Arg Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
```

100 105 110

Val Thr Val Ser Ser
115

<210> 766
<211> 254
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 766

Leu Phe Thr Val Thr Val Pro Lys Glu Leu Tyr Ile Ile Glu His Gly
1 5 10 15

Ser Asn Val Thr Leu Glu Cys Asn Phe Asp Thr Gly Ser His Val Asn
20 25 30

Leu Gly Ala Ile Thr Ala Ser Leu Gln Lys Val Glu Asn Asp Thr Ser
35 40 45

Pro His Arg Glu Arg Ala Thr Leu Leu Glu Glu Gln Leu Pro Leu Gly
50 55 60

Lys Ala Ser Phe His Ile Pro Gln Val Gln Val Arg Asp Glu Gly Gln
65 70 75 80

Tyr Gln Cys Ile Ile Ile Tyr Gly Val Ala Trp Asp Tyr Lys Tyr Leu
85 90 95

Thr Leu Lys Val Lys Ala Ser Tyr Arg Lys Ile Asn Thr His Ile Leu
100 105 110

Lys Val Pro Glu Thr Asp Glu Val Glu Leu Thr Cys Gln Ala Thr Gly
115 120 125

```
Tyr Pro Leu Ala Glu Val Ser Trp Pro Asn Val Ser Val Pro Ala Asn
    130                 135                 140


Thr Ser His Ser Arg Thr Pro Glu Gly Leu Tyr Gln Val Thr Ser Val
145                 150                 155                 160


Leu Arg Leu Lys Pro Pro Pro Gly Arg Asn Phe Ser Cys Val Phe Trp
                165                 170                 175


Asn Thr His Val Arg Glu Leu Thr Leu Ala Ser Ile Asp Leu Gln Ser
            180                 185                 190


Gln Met Glu Pro Arg Thr His Pro Thr Trp Leu Leu His Ile Phe Ile
        195                 200                 205


Pro Phe Cys Ile Ile Ala Phe Ile Phe Ile Ala Thr Val Ile Ala Leu
    210                 215                 220


Arg Lys Gln Leu Cys Gln Lys Leu Tyr Ser Ser Lys Asp Thr Thr Lys
225                 230                 235                 240


Arg Pro Val Thr Thr Thr Lys Arg Glu Val Asn Ser Ala Ile
                245                 250


<210>  767
<211>  453
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  767

Met Ile Phe Leu Leu Leu Met Leu Ser Leu Glu Leu Gln Leu His Gln
1               5                   10                  15


Ile Ala Ala Leu Phe Thr Val Thr Val Pro Lys Glu Leu Tyr Ile Ile
```

```
            20                  25                  30

Glu His Gly Ser Asn Val Thr Leu Glu Cys Asn Phe Asp Thr Gly Ser
        35                  40                  45

His Val Asn Leu Gly Ala Ile Thr Ala Ser Leu Gln Lys Val Glu Asn
    50                  55                  60

Asp Thr Ser Pro His Arg Glu Arg Ala Thr Leu Leu Glu Glu Gln Leu
65                  70                  75                  80

Pro Leu Gly Lys Ala Ser Phe His Ile Pro Gln Val Gln Val Arg Asp
                85                  90                  95

Glu Gly Gln Tyr Gln Cys Ile Ile Ile Tyr Gly Val Ala Trp Asp Tyr
            100                 105                 110

Lys Tyr Leu Thr Leu Lys Val Lys Ala Ser Tyr Arg Lys Ile Asn Thr
        115                 120                 125

His Ile Leu Lys Val Pro Glu Thr Asp Glu Val Glu Leu Thr Cys Gln
    130                 135                 140

Ala Thr Gly Tyr Pro Leu Ala Glu Val Ser Trp Pro Asn Val Ser Val
145                 150                 155                 160

Pro Ala Asn Thr Ser His Ser Arg Thr Pro Glu Gly Leu Tyr Gln Val
                165                 170                 175

Thr Ser Val Leu Arg Leu Lys Pro Pro Pro Gly Arg Asn Phe Ser Cys
            180                 185                 190

Val Phe Trp Asn Thr His Val Arg Glu Leu Thr Leu Ala Ser Ile Asp
        195                 200                 205

Leu Gln Ser Gln Met Glu Pro Arg Thr His Pro Thr Trp Glu Pro Lys
```

```
    210                 215                 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
        355                 360                 365

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
```

405 410 415

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
420 425 430

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
435 440 445

Leu Ser Pro Gly Lys
450

<210> 768
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 768

Glu Val Gln Leu Gln Gln Ser Gly Pro Val Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asn Ile Asn Pro Tyr Asn Gly Gly Thr Thr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Arg Thr Ala Tyr
65 70 75 80

Met Glu Ile Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

```
Ala Arg Gly Arg Ile Tyr Asp Gly Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Ala Leu Thr Val Ser Ser
        115


<210>  769
<211>  106
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  769

Asp Ile Gln Met Thr Gln Phe Pro Ser Ser Leu Cys Ala Ser Gln Gly
1               5                   10                  15


Gly Lys Val Thr Val Thr Cys Lys Ala Ser Gln Asp Ile Asn Asn Tyr
            20                  25                  30


Met Ala Trp Tyr Gln His Lys Pro Gly Lys Gly Pro Arg Leu Leu Ile
        35                  40                  45


His Tyr Thr Ser Thr Leu Leu Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser Asn Leu Glu Pro
65                  70                  75                  80


Glu Asp Ile Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Asn Leu Trp Thr
                85                  90                  95


Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  770
```

<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 770

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala
1 5 10 15

Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly His Ile Asn Pro Ser Ser Gly Phe Thr Thr Tyr Asn Gln Asn Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Asn Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Tyr Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Glu Asp Tyr Asp Val Asp Tyr Trp Gly Gln Gly Thr Thr Leu
100 105 110

Thr Val Ser Ser
115

<210> 771
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 771

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Ser Val Asp Thr Asn
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45

Phe Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 772
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 772

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

```
Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Thr Asp Thr Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe
65                  70                  75                  80


Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


Ala Arg Arg Gly Tyr Gly Ser Phe Tyr Glu Tyr Tyr Phe Asp Tyr Trp
            100                 105                 110


Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
        115                 120


<210>  773
<211>  106
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  773

Gln Ile Val Leu Thr Gln Ser Pro Ala Leu Met Ser Ala Ser Pro Gly
1               5                   10                  15


Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30


Tyr Trp Tyr Gln Gln Lys Pro Arg Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45


Leu Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
```

50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
85 90 95

Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 774
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 774

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Lys
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Ile His
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Ala Ile Thr Trp Ser Gly Gly Ile Thr Tyr Tyr Glu Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

```
Ala Ala Asp Arg Ala Glu Ser Ser Trp Tyr Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Gln Val Thr Val Ser Ser
        115


<210>  775
<211>  119
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  775

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Ala Ser Ile His
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Val Ile Thr Trp Ser Gly Gly Ile Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95


Ala Gly Asp Lys His Gln Ser Ser Trp Tyr Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Gln Val Thr Val Ser Ser
```

115

<210> 776
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 776

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Ser Ser Ile His
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Ala Ile Thr Trp Ser Gly Gly Ile Thr Tyr Tyr Ala Asp Ser Leu
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Gly Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Ala Asp Arg Ala Gln Ser Ser Trp Tyr Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Gln Val Thr Val Ser Ser
115

<210> 777
<211> 119
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 777

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Gly Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Ile Asn
            20                  25                  30


Ala Met Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Leu Ile Ser Trp Ser Gly Gly Ser Thr Tyr Tyr Glu Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95


Ala Ala Asp Arg Val Asp Ser Asn Trp Tyr Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Gln Val Thr Val Ser Ser
        115
```

<210> 778
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 778

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ala Phe Ser Ser Gly
            20                  25                  30


Thr Met Gly Trp Phe Arg Arg Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Ser Ile Pro Trp Ser Gly Gly Arg Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gln 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


Ala Val Lys Glu Arg Ser Thr Gly Trp Asp Phe Ala Ser Trp Gly Gln
            100                 105                 110


Cys Thr Gln Val Thr Val Ser Ser
        115                 120


<210>  779
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  779

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Leu Lys Gln Pro Gly Ala
1               5                   10                  15


Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Ser
```

20 25 30

Trp Ile His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Tyr Pro Ser Thr Gly Phe Thr Glu Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Arg Asp Ser Ser Gly Tyr His Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 780
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 780

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Gln Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Ser
20 25 30

Trp Ile His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

```
Gly Tyr Ile Tyr Pro Ser Thr Gly Phe Thr Glu Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Asp
                85                  90                  95


Cys Ala Arg Trp Arg Asp Ser Ser Gly Tyr His Ala Met Asp Tyr Trp
            100                 105                 110


Gly Gln Gly Thr Ser Val Thr Val Ser Ser
        115                 120


<210>  781
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  781

Gln Val Gln Leu Val Gln Ser Gly His Glu Val Lys Gln Pro Gly Ala
1               5                   10                  15


Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Ser
            20                  25                  30


Trp Ile His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Tyr Ile Tyr Pro Ser Thr Gly Phe Thr Glu Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
```

65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Arg Asp Ser Ser Gly Tyr His Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 782
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 782

Gln Val Gln Leu Val Gln Ser Gly His Glu Val Lys Gln Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Ser
20 25 30

Trp Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Tyr Pro Ser Thr Gly Phe Thr Glu Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Arg Asp Ser Ser Gly Tyr His Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 783
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 783

Gln Val Gln Leu Val Gln Ser Gly His Glu Val Lys Gln Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Ser
20 25 30

Trp Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Tyr Pro Ser Thr Gly Phe Thr Glu Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Ala Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Arg Asp Ser Ser Gly Tyr His Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser

115 120

<210> 784
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 784

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Thr Leu Ser Pro Gly
1 5 10 15

Gln Arg Leu Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro
35 40 45

Lys Leu Leu Ile Lys Phe Gly Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Glu Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Ser Trp
85 90 95

Glu Ile Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 785
<211> 111
<212> PRT
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<220>
<223> Synthetic Sequence

<400> 785

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Gln Arg Leu Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro
35 40 45

Lys Leu Leu Ile Lys Phe Gly Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Ser Trp
85 90 95

Glu Ile Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 786
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 786

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Gln Arg Leu Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

```
Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro
        35                  40                  45


Lys Leu Leu Ile Lys Phe Gly Ser Asn Leu Glu Ser Gly Ile Pro Ala
    50                  55                  60


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80


Ser Leu Glu Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Ser Trp
                85                  90                  95


Glu Ile Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210>  787
<211>  111
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  787

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Gln Arg Leu Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
            20                  25                  30


Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro
        35                  40                  45


Lys Leu Leu Ile Lys Phe Gly Ser Asn Leu Glu Ser Gly Ile Pro Ala
    50                  55                  60


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
```

65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Trp
85 90 95

Glu Ile Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 788
<211> 290
<212> PRT
<213> Homo sapiens

<400> 788

Met Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu Leu
1 5 10 15

Asn Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr
20 25 30

Gly Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu
35 40 45

Asp Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile
50 55 60

Ile Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser
65 70 75 80

Tyr Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn
85 90 95

Ala Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr
100 105 110

Arg Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val
115 120 125

```
Lys Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val
    130                 135                 140

Asp Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr
145                 150                 155                 160

Pro Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser
                165                 170                 175

Gly Lys Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn
            180                 185                 190

Val Thr Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr
        195                 200                 205

Cys Thr Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu
    210                 215                 220

Val Ile Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Thr His
225                 230                 235                 240

Leu Val Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu Thr
                245                 250                 255

Phe Ile Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys Cys
            260                 265                 270

Gly Ile Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu Glu
        275                 280                 285

Glu Thr
    290


<210>  789
<211>  176
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<212> PRT
<213> Homo sapiens

<400> 789

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Met Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu Leu
1               5                   10                  15


Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val Asp Pro
            20                  25                  30


Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr Pro Lys
        35                  40                  45


Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser Gly Lys
    50                  55                  60


Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn Val Thr
65                  70                  75                  80


Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr Cys Thr
                85                  90                  95


Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu Val Ile
            100                 105                 110


Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Thr His Leu Val
        115                 120                 125


Ile Leu Gly Ala Ile Leu Leu Cys Leu Gly Val Ala Leu Thr Phe Ile
    130                 135                 140


Phe Arg Leu Arg Lys Gly Arg Met Met Asp Val Lys Lys Cys Gly Ile
145                 150                 155                 160


Gln Asp Thr Asn Ser Lys Lys Gln Ser Asp Thr His Leu Glu Glu Thr
                165                 170                 175
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<210> 790
<211> 178
<212> PRT
<213> Homo sapiens

<400> 790

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Met Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu Leu
1               5                   10                  15


Asn Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr
            20                  25                  30


Gly Ser Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu
        35                  40                  45


Asp Leu Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile
    50                  55                  60


Ile Gln Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser
65                  70                  75                  80


Tyr Arg Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn
                85                  90                  95


Ala Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr
            100                 105                 110


Arg Cys Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val
        115                 120                 125


Lys Val Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val
    130                 135                 140


Asp Pro Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr
145                 150                 155                 160
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Pro Lys Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser
165 170 175

Gly Asp

<210> 791
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 791

Gly Phe Thr Leu Asp Tyr Tyr Ala Ile Gly
1 5 10

<210> 792
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 792

Gly Thr Ile Phe Ser Ile Asn His Met Asp
1 5 10

<210> 793
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 793

Gly Phe Thr Phe Asp Asp Tyr Gly Met Ser
1 5 10

<210> 794
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 794

Gly Phe Thr Leu Asp Tyr Tyr Ala Ile Asn
1   5   10

<210> 795
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 795

Gly Thr Ile Phe Ser Ile Asn Arg Met Asp
1   5   10

<210> 796
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 796

Gly Phe Thr Phe Ser Ser Tyr Gly Met Ser
1   5   10

<210> 797
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 797

Gly Lys Ile Phe Ser Gly Asn Asp Met Gly
1   5   10

<210> 798
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 798

Gly Thr Ile Phe Ser Ile Asn Arg Met Asp
1   5   10

<210> 799
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 799

Gly Phe Thr Phe Ser Ser Tyr Gly Met Ser
1   5   10

<210> 800
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 800

Gly Phe Thr Phe Asn Asp Tyr Ala Met Ser
1   5   10

<210> 801
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 801

Gly Phe Asn Leu Asp Pro Tyr Ala Ile Ala
1   5   10

<210> 802
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 802

Gly Phe Thr Phe Thr Ala Tyr Ala Met Ser
1   5   10

<210> 803
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 803

Gly Phe Thr Phe Asp Tyr Tyr Ala Ile Gly
1   5   10

<210> 804
<211> 10

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 804

Gly Phe Asn Leu Asp Pro Tyr Ala Ile Ala
1   5   10

<210> 805
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 805

Gly Thr Ile Phe Ser Ile Asn Arg Met Asp
1   5   10

<210> 806
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 806

Gly Thr Ile Phe Ser Ile Asn Arg Met Asp
1   5   10

<210> 807
<211> 10
<212> PRT
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<220>
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<400> 807

Gly Phe Thr Phe Ser Ser Tyr Gly Met Ser
1 5 10

<210> 808
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 808

Gly Phe Asn Leu Asp Pro Tyr Ala Ile Gly
1 5 10

<210> 809
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 809

Gly Phe Asn Leu Asp Pro Tyr Ala Ile Ala
1 5 10

<210> 810
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 810

Glu Ser Ile Phe Ser Ile Glu Ala Met Gly
1 5 10

<210> 811
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 811

Gly Lys Ile Phe Ser Gly Asn Asp Met Gly
1   5   10

<210> 812
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 812

Gly Phe Thr Leu Asp Tyr Tyr Ala Ile Gly
1   5   10

<210> 813
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 813

Gly Phe Thr Phe Ser Ser Tyr Gly Met Ser
1   5   10

<210> 814
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 814

Gly Thr Ile Phe Ser Ile Asn Arg Met Asp
1   5   10

<210> 815
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 815

Gly Phe Thr Phe Ser Ser Tyr Gly Met Ser
1   5   10

<210> 816
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 816

Gly Phe Asn Leu Asp Pro Tyr Ala Ile Ala
1   5   10

<210> 817
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 817

Gly Arg Thr Phe Ser Ile Ser Ala Met Gly
1   5   10

<210> 818
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 818

Gly Phe Thr Leu Asp Tyr Tyr Ala Ile Asn
1   5   10

<210> 819
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 819

Gly Phe Thr Phe Ser Ser Tyr Gly Met Ser
1   5   10

<210> 820
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 820

Gly Phe Thr Phe Asn Asp Tyr Ala Met Ser
1   5   10

<210> 821
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 821

Gly Phe Thr Leu Asp Tyr Tyr Ala Ile Gly
1   5   10

<210> 822
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 822

Ile Ser Ser Ser Asp Gly Ser Thr Tyr
1   5

<210> 823
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 823

Ile Thr Ser Asp Gly Phe Pro Thr
1   5

<210> 824
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 824

Ile Arg Trp Asn Gly Gly Ser Thr Asn
1   5

<210> 825
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 825

Ile Ser Ser Ser Asp Gly Ser Thr Tyr
1   5

<210> 826
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 826

Ile Thr Ser Asp Gly Thr Pro Thr
1   5

<210> 827
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 827

Ile Asp Ser Gly Gly Gly Ser Thr Ser
1   5

<210> 828
<211> 8

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 828

Ile Thr Ser Gly Gly Ile Thr Asp
1   5

<210> 829
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
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<400> 829

Ile Thr Ser Asp Gly Thr Pro Thr
1   5

<210> 830
<211> 9
<212> PRT
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<220>
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<400> 830

Ile Asp Ser Gly Gly Gly Ser Thr Ser
1   5

<210> 831
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 831

Ile Arg Ser Asn Gly Gly Tyr Thr Asn
1 5

<210> 832
<211> 9
<212> PRT
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<220>
<223> Synthetic Sequence

<400> 832

Ile Ser Ser Ser Asp Val Gly Thr Tyr
1 5

<210> 833
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 833

Ile Asn Ser Ser Asp Gly Ser Thr Tyr
1 5

<210> 834
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 834

Ile Ser Gly Ser Asp Ser Ser Thr Tyr
1 5

<210> 835
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 835

Ile Ser Ser Ser Asp Val Gly Thr Tyr
1   5

<210> 836
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 836

Ile Thr Ser Asp Gly Thr Pro Thr
1   5

<210> 837
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 837

Ile Thr Ser Asp Gly Thr Pro Ala
1   5

<210> 838
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 838

Ile Asp Ser Gly Gly Gly Ser Thr Ser
1   5

<210> 839
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 839

Ile Ser Ser Gly Asp Gly Ser Lys Tyr
1   5

<210> 840
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 840

Ile Ser Ser Ser Asp Val Gly Thr Tyr
1   5

<210> 841
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 841

Ile Phe Gly Gly Gly Phe Thr Asn
1   5

<210> 842
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 842

Ile Thr Ser Gly Gly Ile Thr Asp
1   5

<210> 843
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 843

Ile Ser Ser Ser Asp Gly Ser Thr Tyr
1   5

<210> 844
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 844

Ile Asp Ser Gly Gly Gly Ser Thr Ser
1   5

<210> 845
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 845

Ile Thr Ser Asp Gly Thr Pro Thr
1   5

<210> 846
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 846

Ile Asp Ser Gly Gly Gly Ser Thr Ser
1   5

<210> 847
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 847

Ile Ser Ser Ser Asp Val Gly Thr Tyr
1   5

<210> 848
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 848

Ile Thr Trp Ser Gly Gly Ser Thr Ser
1   5

<210> 849
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 849

Ile Ser Ser Ser Asp Gly Ser Thr Tyr
1   5

<210> 850
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 850

Ile Asp Ser Gly Gly Gly Ser Thr Ser
1   5

<210> 851
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 851

Ile Arg Ser Asn Gly Gly Tyr Thr Asn
1   5

<210> 852
<211> 9

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 852

Ile Ser Ser Ser Asp Gly Ser Thr Tyr
1 5

<210> 853
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 853

Asp Gly Trp Ser Ser Cys Arg His Gly Ile Asn Glu Tyr Leu Tyr Trp
1 5 10 15

<210> 854
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 854

Ser Ser Gly Val Tyr Asn Tyr Trp
1 5

<210> 855
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 855

Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Pro Arg
1 5 10

<210> 856
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 856

Ser Gly Trp Arg Leu Cys Arg Pro Thr Asp Glu Tyr Asp Tyr Ser Tyr
1 5 10 15

Trp

<210> 857
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 857

Ser Ser Gly Val Tyr Asn Tyr Trp
1 5

<210> 858
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 858

Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Ser Asp Tyr Trp
1   5   10

<210> 859
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 859

Arg Asp Arg Thr Ile Trp Trp
1   5

<210> 860
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 860

Ser Ser Gly Val Tyr Asn Tyr Trp
1   5

<210> 861
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 861

Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Ser Asp Tyr Trp
1   5   10

<210> 862
<211> 12

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 862

Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Tyr Pro
1 5 10

<210> 863
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 863

Asp Gly Tyr Tyr Tyr Cys Ser Asp Tyr Pro His Pro Leu Tyr Trp
1 5 10 15

<210> 864
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 864

Asp Gly Trp Arg Asp Cys Thr Trp Ser Asn Glu Tyr Ala Tyr Trp
1 5 10 15

<210> 865
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 865

Thr Gly Trp Arg Thr Cys Arg Gly Leu Asn Glu Tyr Asp Tyr Trp
1 5 10 15

<210> 866
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 866

Asp Gly Tyr Tyr Tyr Cys Ser Asp Tyr Pro His Pro Leu Tyr Trp
1 5 10 15

<210> 867
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 867

Ser Ser Gly Val Tyr Asn Tyr Trp
1 5

<210> 868
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 868

Ser Ser Gly Val Tyr Asn Tyr Trp
1 5

<210> 869
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 869

Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Ser Asp Tyr Trp
1   5   10

<210> 870
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 870

Asp Gly Tyr Tyr Tyr Cys Ser Asp Tyr Pro His Pro Leu Tyr Trp
1   5   10   15

<210> 871
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 871

Asp Gly Tyr Tyr Tyr Cys Ser Asp Tyr Pro His Pro Leu Tyr Trp
1   5   10   15

<210> 872
<211> 13
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 872

Asp Leu Val Ser Gly Ser Ser Arg Leu Tyr Asp Tyr Trp
1 5 10

<210> 873
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 873

Arg Asp Arg Thr Ile Trp Trp
1 5

<210> 874
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<400> 874

Asp Gly Trp Ser Ser Cys Arg His Gly Ile Asn Glu Tyr Leu Tyr Trp
1 5 10 15

<210> 875
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 875

Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Ser Asp Tyr Trp
1 5 10

<210> 876
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 876

Ser Ser Gly Val Tyr Asn Tyr Trp
1 5

<210> 877
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 877

Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Ser Asp Tyr Trp
1 5 10

<210> 878
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<400> 878

Asp Gly Tyr Tyr Tyr Cys Ser Asp Tyr Pro His Pro Leu Tyr Trp
1 5 10 15

<210> 879
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 879

Met Gly Arg Thr Asn Tyr Gly Val Ile Tyr Asp Pro Asn Met Tyr Asn
1   5   10   15

Tyr Trp

<210> 880
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 880

Ser Gly Trp Arg Leu Cys Arg Pro Thr Asp Glu Tyr Asp Tyr Leu Tyr
1   5   10   15

Trp

<210> 881
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 881

Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Ser Asp Tyr Trp
1   5   10

<210> 882
<211> 12

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 882

Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Tyr Pro
1 5 10

<210> 883
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 883

Asp Gly Trp Ser Ser Cys Arg His Gly Ile Asn Glu Tyr Leu Tyr Trp
1 5 10 15

<210> 884
<211> 143
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 884

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
20 25 30

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Val
35 40 45

```
Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Asn
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Thr Asp Gly Trp Ser Ser Cys Arg His Gly Ile Asn Glu Tyr Leu
            100                 105                 110


Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr
        115                 120                 125


Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  885
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  885

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn
            20                  25                  30


His Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Leu Ile Thr Ser Asp Gly Phe Pro Thr Tyr Ala Asp Ser Ala Lys
    50                  55                  60
```

```
Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His
                85                  90                  95


Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130


<210>  886
<211>  138
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  886

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30


Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ala Ile Arg Trp Asn Gly Gly Ser Thr Asn Tyr Ala Asp Ser Val
    50                  55                  60
```

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Pro Arg Gly Gln Gly
            100                 105                 110


Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro
        115                 120                 125


Asp Tyr Gly Ser His His His His His His
    130                 135


<210>  887
<211>  144
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  887

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
            20                  25                  30


Ala Ile Asn Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Val
        35                  40                  45


Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Thr Ser Gly Trp Arg Leu Cys Arg Pro Thr Asp Glu Tyr Asp Tyr
            100                 105                 110


Ser Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala
        115                 120                 125


Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  888
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  888

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Val Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn
            20                  25                  30


Arg Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Leu Ile Thr Ser Asp Gly Thr Pro Thr Tyr Ala Asp Ser Ala Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu
65                  70                  75                  80
```

```
Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His
                85                  90                  95


Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130


<210>  889
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  889

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Gly Met Ser Trp Val Arg Gln Thr Pro Gly Lys Gly Pro Glu Trp Val
        35                  40                  45


Ser Ala Ile Asp Ser Gly Gly Gly Ser Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Ser Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  890
<211>  133
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  890

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Lys Ile Phe Ser Gly Asn
            20                  25                  30


Asp Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Gly Ile Ile Thr Ser Gly Gly Ile Thr Asp Tyr Ala Asp Ala Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Met Met Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95
```

Met Arg Asp Arg Thr Ile Trp Trp Gly Gln Gly Thr Gln Val Thr Val
100 105 110

Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His
115 120 125

His His His His His
130

<210> 891
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 891

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn
20 25 30

Arg Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Leu Ile Thr Ser Asp Gly Thr Pro Thr Tyr Ala Asp Ser Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His
85 90 95

Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

```
Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130


<210>  892
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  892

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Gly Met Ser Trp Val Arg Gln Thr Pro Gly Lys Gly Pro Glu Trp Val
        35                  40                  45


Ser Ala Ile Asp Ser Gly Gly Gly Ser Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Thr Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Ser Asp Tyr Trp Gly
            100                 105                 110
```

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115   120   125

Val Pro Asp Tyr Gly Ser His His His His His His
    130   135   140

<210> 893
<211> 138
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 893

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asp Tyr
            20   25   30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Gly Ile Arg Ser Asn Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Tyr Pro Gly Gln Gly
            100   105   110

Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro
        115   120   125

```
Asp Tyr Gly Ser His His His His His His
    130                 135


<210>  894
<211>  142
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  894

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Leu Asp Pro Tyr
            20                  25                  30


Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Val
        35                  40                  45


Ser Cys Ile Ser Ser Ser Asp Val Gly Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys 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


Ala Thr Asp Gly Tyr Tyr Tyr Cys Ser Asp Tyr Pro His Pro Leu Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125
```

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 895
<211> 142
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 895

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Ala Tyr
20 25 30

Ala Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Val
35 40 45

Ser Cys Ile Asn Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr His Cys
85 90 95

Ala Thr Asp Gly Trp Arg Asp Cys Thr Trp Ser Asn Glu Tyr Ala Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 896
<211> 142
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 896

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Tyr Tyr
            20                  25                  30


Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Val
        35                  40                  45


Ser Cys Ile Ser Gly Ser Asp Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Val Arg Asp Asn Ala Gln Asn Thr Val Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95


Ala Val Thr Gly Trp Arg Thr Cys Arg Gly Leu Asn Glu Tyr Asp Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 897
<211> 142
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 897

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Leu Asp Pro Tyr
            20                  25                  30


Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Val
        35                  40                  45


Ser Cys Ile Ser Ser Ser Asp Val Gly Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys 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


Ala Thr Asp Gly Tyr Tyr Tyr Cys Ser Asp Tyr Pro His Pro Leu Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 898
<211> 134

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 898

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Glu
1   5   10   15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn
            20   25   30

Arg Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35   40   45

Ala Leu Ile Thr Ser Asp Gly Thr Pro Thr Tyr Ala Asp Ser Ala Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu
65   70   75   80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His
                85   90   95

Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100   105   110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115   120   125

His His His His His His
    130

<210> 899
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 899

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn
            20   25   30

Arg Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35   40   45

Ala Leu Ile Thr Ser Asp Gly Thr Pro Ala Tyr Ala Asp Ser Ala Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu
65   70   75   80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His
                85   90   95

Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100   105   110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115   120   125

His His His His His His
    130

<210> 900
<211> 140
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 900

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ser Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Lys Thr Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Thr Pro Gly Lys Gly Pro Glu Trp Val
35 40 45

Ser Ala Ile Asp Ser Gly Gly Gly Ser Thr Ser Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Ser Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
115 120 125

Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 901
<211> 142
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 901

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Leu Asp Pro Tyr
            20                  25                  30


Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Val
        35                  40                  45


Ser Cys Ile Ser Ser Gly Asp Gly Ser Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ala Lys Lys 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


Ala Thr Asp Gly Tyr Tyr Tyr Cys Ser Asp Tyr Pro His Pro Leu Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 902
<211> 142
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 902

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Asn Leu Asp Pro Tyr
            20                  25                  30


Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Val
        35                  40                  45


Ser Cys Ile Ser Ser Ser Asp Val Gly Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys 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


Ala Thr Asp Gly Tyr Tyr Tyr Cys Ser Asp Tyr Pro His Pro Leu Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  903
<211>  139
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  903

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Ser Ile Phe Ser Ile Glu
            20                  25                  30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45

Ala Ala Ile Phe Gly Gly Gly Phe Thr Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Asn Arg Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Ala Asp Leu Val Ser Gly Ser Ser Arg Leu Tyr Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val
        115                 120                 125

Pro Asp Tyr Gly Ser His His His His His His
    130                 135


<210>  904
<211>  133
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  904

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Lys Ile Phe Ser Gly Asn
            20                  25                  30


Asp Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Gly Ile Ile Thr Ser Gly Gly Ile Thr Asp Tyr Ala Asp Ala Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Met Met Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Met Arg Asp Arg Thr Ile Trp Trp Gly Gln Gly Thr Gln Val Thr Val
            100                 105                 110


Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His
        115                 120                 125


His His His His His
    130


<210>  905
<211>  143
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  905

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
            20                  25                  30
```

```
Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Val
        35                  40                  45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Asn
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Asp Gly Trp Ser Ser Cys Arg His Gly Ile Asn Glu Tyr Leu
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr
        115                 120                 125

Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 906
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 906

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30
```

```
Gly Met Ser Trp Val Arg Gln Thr Pro Gly Lys Gly Pro Glu Trp Val
        35                  40                  45


Ser Ala Ile Asp Ser Gly Gly Gly Ser Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Ser Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  907
<211>  134
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  907

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn
            20                  25                  30


Arg Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45
```

```
Ala Leu Ile Thr Ser Asp Gly Thr Pro Thr Tyr Ala Asp Ser Ala Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His
                85                  90                  95

Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125

His His His His His His
    130


<210>  908
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  908

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Gly Met Ser Trp Val Arg Gln Thr Pro Gly Lys Gly Pro Glu Trp Val
        35                  40                  45
```

```
Ser Ala Ile Asp Ser Gly Gly Gly Ser Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Ser Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  909
<211>  142
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  909

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Leu Asp Pro Tyr
            20                  25                  30


Ala Ile Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Val
        35                  40                  45


Ser Cys Ile Ser Ser Ser Asp Val Gly Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
```

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys 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


Ala Thr Asp Gly Tyr Tyr Tyr Cys Ser Asp Tyr Pro His Pro Leu Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  910
<211>  145
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence


<220>
<221>  misc_feature
<222>  (13)..(13)
<223>  Xaa can be any naturally occurring amino acid

<400>  910

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Xaa Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ile Ser
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45
```

```
Ala Ala Ile Thr Trp Ser Gly Gly Ser Thr Ser Tyr Thr Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Ala Ala Met Gly Arg Thr Asn Tyr Gly Val Ile Tyr Asp Pro Asn Met
            100                 105                 110

Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala
        115                 120                 125

Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His
    130                 135                 140

His
145
```

<210> 911
<211> 144
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 911

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
            20                  25                  30
```

```
Ala Ile Asn Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Val
        35                  40                  45


Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Thr Ser Gly Trp Arg Leu Cys Arg Pro Thr Asp Glu Tyr Asp Tyr
            100                 105                 110


Leu Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala
        115                 120                 125


Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  912
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  912

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Met Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Gly Met Ser Trp Val Arg Gln Thr Pro Gly Lys Gly Pro Glu Trp Val
        35                  40                  45
```

```
Ser Ala Ile Asp Ser Gly Gly Gly Ser Thr Ser Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Ser Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125

Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  913
<211>  138
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  913

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Thr Val Gln Ala Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asp Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

```
Ser Gly Ile Arg Ser Asn Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Gln Gly Tyr Tyr Cys Ser Gly Tyr Gly Cys Tyr Pro Gly Gln Gly
            100                 105                 110


Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro
        115                 120                 125


Asp Tyr Gly Ser His His His His His His
    130                 135


<210>  914
<211>  143
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  914

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Thr
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
            20                  25                  30


Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Glu Val
        35                  40                  45


Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
```

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Asn
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Thr Asp Gly Trp Ser Ser Cys Arg His Gly Ile Asn Glu Tyr Leu
            100                 105                 110


Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr
        115                 120                 125


Pro Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  915
<211>  451
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  915

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60
```

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255
```

```
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile
                325                 330                 335


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350


Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365


Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445
```

Pro Gly Lys
    450

<210> 916
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 916

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ser Ser Ser
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

Ile Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50   55   60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65   70   75   80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Leu Pro
                85   90   95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100   105   110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115   120   125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130   135   140

```
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160


Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175


Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190


Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205


Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  917
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  917

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60
```

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  918
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  918

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ser Ser Ser
            20                  25                  30


Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


Ile Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80


Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Leu Pro
                85                  90                  95
```

```
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210>  919
<211>  448
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  919

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser
            20                  25                  30


Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125
```

```
Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320
```

```
Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335


Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350


Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365


Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380


Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400


Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415


Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430


Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210>  920
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  920

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
            20                  25                  30
```

```
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> 921
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 921

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Ile Met Met Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Thr Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125


Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
```

```
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160


Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175


Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190


Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205


Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220


Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240


Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255


Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270


Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285


Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300


Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320


Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335
```

```
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350


Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        355                 360                 365


Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380


Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400


Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415


Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430


Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445


Gly Lys
    450


<210>  922
<211>  216
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  922

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
```

```
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
                85                  90                  95

Ser Thr Arg Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215
```

<210> 923
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 923

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Gly Asp Thr Phe Ser Thr Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Lys Ala His Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Lys Phe His Phe Val Ser Gly Ser Pro Phe Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 924
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 924

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Thr
                85   90   95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 925
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 925

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30


Gly Phe Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Trp Ile Thr Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80


Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Tyr Phe Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  926
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  926

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30


Leu Val Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
```

```
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Arg
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 927
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 927

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Asp Val His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45

Gly Trp Leu His Ala Asp Thr Gly Ile Thr Lys Phe Ser Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu Arg Ile Gln Leu Trp Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser
        115


<210>  928
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  928

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 929
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 929

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Val Ser Gly Gly Ile Phe Ser Thr Tyr
            20                  25                  30


Ala Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn His Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Gln Gly Ile Ala Ala Ala Leu Phe Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 930
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 930

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50   55   60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65   70   75   80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
                85   90   95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 931
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 931

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Val Val His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Gly Asn Ser Gly Asn Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Val Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser

<210> 932
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 932

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
35 40 45

```
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  933
<211>  123
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  933

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Thr Ser Gly Asp Thr Phe Ser Ser Tyr
            20                  25                  30


Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Gly Ile Ile Pro Ile Phe Gly Arg Ala His Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95


Ala Arg Lys Phe His Phe Val Ser Gly Ser Pro Phe Gly Met Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  934
<211>  106
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  934

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Thr
                85                  90                  95


Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 935
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 935

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Lys Ala His Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Lys Tyr Asp Tyr Val Ser Gly Ser Pro Phe Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 936
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 936

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Thr
                85   90   95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 937
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 937

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20   25   30

Ala Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Gly Ile Ile Pro Ile Phe Gly Ser Ala Asn Tyr Ala Gln Lys Phe
    50   55   60

Gln Asp Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Ala Ala Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Ser Ser Gly Trp Ser Arg Tyr Tyr Met Asp Val Trp Gly
            100   105   110

Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 938
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 938

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

```
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
                85                  90                  95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 939
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 939

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Glu Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Asn Ser Tyr
            20                  25                  30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Gly Ile Ile Pro Leu Phe Gly Ile Ala His Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65                  70                  75                  80
```

Met Asp Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Lys Tyr Ser Tyr Val Ser Gly Ser Pro Phe Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 940
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 940

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Thr
85 90 95

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 941
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 941

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Thr Phe Asp Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Arg Gly Arg Ile Glu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Gly Arg Phe Arg Tyr Phe Asp Trp Phe Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 942
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 942

Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Ala
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Phe
                85   90   95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100   105

<210> 943
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 943

Glu Val Lys Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
1   5   10   15

```
Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Thr Ser Asp
            20                  25                  30


Tyr Trp Asn Trp Ile Arg Lys Phe Pro Gly Asn Lys Leu Glu Tyr Val
        35                  40                  45


Gly Tyr Ile Ser Tyr Thr Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Tyr Tyr Leu
65                  70                  75                  80


Gln Leu Asn Ser Val Thr Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
                85                  90                  95


Arg Tyr Gly Gly Trp Leu Ser Pro Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Thr Leu Thr Val Ser Ser
        115
```

<210> 944
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 944

```
Asp Ile Val Met Thr Gln Ser His Lys Leu Met Ser Thr Ser Val Gly
1               5                   10                  15


Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20                  25                  30


Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45
```

```
Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65                  70                  75                  80

Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Asp Ser Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Val Glu Leu Lys
            100                 105
```

<210> 945
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 945

```
Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1               5                   10                  15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Thr Tyr
            20                  25                  30

Ser Ile Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
        35                  40                  45

Gly Val Met Trp Ala Gly Gly Gly Thr Asn Ser Asn Ser Val Leu Lys
    50                  55                  60

Ser Arg Leu Ile Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65                  70                  75                  80
```

```
Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Arg Tyr Tyr Cys Ala
                85                  90                  95


Arg Tyr Tyr Gly Asn Ser Pro Tyr Tyr Ala Ile Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Ser Val Thr Val Ser Ser
        115                 120


<210>  946
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  946

Asp Ile Val Thr Thr Gln Ser His Lys Leu Met Ser Thr Ser Val Gly
1               5                   10                  15


Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20                  25                  30


Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65                  70                  75                  80


Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Asp Ser Ser Tyr Pro Leu
                85                  90                  95


Thr Phe Gly Ala Gly Thr Lys Val Glu Leu Lys
            100                 105
```

<210> 947
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 947

```
Glu Val Lys Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Ile Ser Asp
            20                  25                  30


Tyr Trp Asn Trp Ile Arg Lys Phe Pro Gly Asn Lys Leu Glu Tyr Leu
        35                  40                  45


Gly Tyr Ile Ser Tyr Thr Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Tyr Tyr Leu
65                  70                  75                  80


Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
                85                  90                  95


Arg Arg Gly Gly Trp Leu Leu Pro Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Thr Leu Thr Val Ser Ser
        115
```

<210> 948
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 948

```
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Val Ser Val Gly
1               5                   10                  15


Glu Lys Val Ser Met Gly Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30


Ser Asn Gln Lys Asn Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45


Ser Pro Lys Leu Leu Ile Asp Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60


Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80


Ile Ser Ser Val Lys Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
                85                  90                  95


Tyr Tyr Gly Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110


Lys
```

<210> 949
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 949

```
Glu Val Lys Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Asp Ile Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Trp Ile Phe Pro Arg Asp Asn Asn Thr Lys Tyr Asn Glu Asn Phe
    50                  55                  60


Lys Gly Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Thr Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu His Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95


Thr Lys Glu Asn Trp Val Gly Asp Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Thr Leu Thr Leu Ser Ser
        115


<210>  950
<211>  106
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  950

Asp Ile Val Met Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1               5                   10                  15


Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Ile Arg Tyr Met
            20                  25                  30
```

```
His Trp Tyr Gln Gln Lys Pro Gly Thr Ser Pro Lys Arg Trp Ile Ser
        35                  40                  45


Asp Thr Ser Lys Leu Thr Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
    50                  55                  60


Gly Ser Gly Thr Ser Tyr Ala Leu Thr Ile Ser Ser Met Glu Ala Glu
65                  70                  75                  80


Asp Ala Ala Thr Tyr Tyr Cys His Gln Arg Ser Ser Tyr Pro Trp Thr
                85                  90                  95


Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  951
<211>  114
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  951

Glu Val Gln Leu Gln Gln Ser Gly Pro Asp Leu Val Thr Pro Gly Ala
1               5                   10                  15


Ser Val Arg Ile Ser Cys Gln Ala Ser Gly Tyr Thr Phe Pro Asp Tyr
            20                  25                  30


Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45


Gly Asp Ile Asp Pro Asn Tyr Gly Gly Thr Thr Tyr Asn Gln Lys Phe
    50                  55                  60
```

```
Lys Gly Lys Ala Ile Leu Thr Val Asp Arg Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Ala Leu Thr Asp Trp Gly Gln Gly Thr Ser Leu Thr Val
            100                 105                 110


Ser Ser
```

<210> 952
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 952

```
Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1               5                   10                  15


Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
            20                  25                  30


Tyr Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45


Ala Thr Phe Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
    50                  55                  60


Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Thr Glu
65                  70                  75                  80


Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Asn Asn Pro Leu Thr
                85                  90                  95
```

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 953
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 953

Glu Val Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Val Met His Trp Val Lys Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Tyr Val Asn Pro Phe Asn Asp Gly Thr Lys Tyr Asn Glu Met Phe
50 55 60

Lys Gly Arg Ala Thr Leu Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gln Ala Trp Gly Tyr Pro Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 954
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 954

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Val Met His Trp Val Lys Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Tyr Val Asn Pro Phe Asn Asp Gly Thr Lys Tyr Asn Glu Met Phe
50 55 60

Lys Gly Arg Ala Thr Leu Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gln Ala Trp Gly Tyr Pro Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 955
<211> 115
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 955

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Val Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
        35   40   45

Gly Tyr Val Asn Pro Phe Asn Asp Gly Thr Lys Tyr Asn Glu Met Phe
    50   55   60

Lys Gly Arg Ala Thr Leu Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gln Ala Trp Gly Tyr Pro Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 956
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 956

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Val Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
        35                  40                  45


Gly Tyr Val Asn Pro Phe Asn Asp Gly Thr Lys Tyr Asn Glu Met Phe
    50                  55                  60


Lys Gly Arg Ala Thr Leu Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gln Ala Trp Gly Tyr Pro Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  957
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  957

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
```

```
Val Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
        35                  40                  45

Gly Tyr Val Asn Pro Phe Asn Asp Gly Thr Lys Tyr Asn Glu Met Phe
    50                  55                  60

Lys Gly Arg Ala Thr Ile Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gln Ala Trp Gly Tyr Pro Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser
        115


<210>  958
<211>  111
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  958

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Thr Glu Ser Val Glu Tyr Tyr
            20                  25                  30

Gly Thr Ser Leu Val Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Leu Leu Ile Tyr Ala Ala Ser Ser Val Asp Ser Gly Val Pro Ser
    50                  55                  60
```

```
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65                  70                  75                  80


Ser Leu Glu Glu Glu Asp Ala Ala Met Tyr Phe Cys Gln Gln Ser Arg
                85                  90                  95


Arg Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210>  959
<211>  111
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  959

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Thr Glu Ser Val Glu Tyr Tyr
            20                  25                  30


Gly Thr Ser Leu Val Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


Lys Leu Leu Ile Tyr Ala Ala Ser Ser Val Asp Ser Gly Val Pro Ser
    50                  55                  60


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65                  70                  75                  80


Ser Leu Glu Ala Glu Asp Ala Ala Met Tyr Phe Cys Gln Gln Ser Arg
                85                  90                  95
```

Arg Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 960
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 960

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Thr Glu Ser Val Glu Tyr Tyr
20 25 30

Gly Thr Ser Leu Val Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Ser Val Asp Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65 70 75 80

Ser Leu Glu Ala Glu Asp Ala Ala Met Tyr Phe Cys Gln Gln Ser Arg
85 90 95

Arg Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 961
<211> 111
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 961

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Thr Glu Ser Val Glu Tyr Tyr
            20   25   30

Gly Thr Ser Leu Val Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35   40   45

Lys Leu Leu Ile Tyr Ala Ala Ser Ser Val Asp Ser Gly Val Pro Ser
    50   55   60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65   70   75   80

Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Phe Cys Gln Gln Ser Arg
                85   90   95

Arg Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100   105   110

<210> 962
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 962

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
            20   25   30

```
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ser Ile Ser Ser Ser Gly Asp Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Leu Val Thr Ser Met Val Ala Phe Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  963
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  963

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1               5                   10                  15


Ala Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Gln Lys Tyr Val
            20                  25                  30


Phe Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45
```

Glu Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Val Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Arg Ser Gly Asn His
85 90 95

Arg Val Phe Gly Gly Gly Thr Arg Leu Thr Val Leu
100 105

<210> 964
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 964

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Gly Glu Gln Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

```
Ala Arg Asp Trp Asn Tyr Gly Tyr Tyr Asp Met Asp Val Trp Gly Gln
            100                 105                 110


Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  965
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  965

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
            20                  25                  30


Tyr Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


Ile Phe Gly Thr Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80


Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Ile
                85                  90                  95


Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105
```

<210> 966
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 966

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 967
<211> 108
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 967

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ser Ser Ser
            20   25   30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35   40   45

Ile Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50   55   60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65   70   75   80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Leu Pro
                85   90   95

Trp Thr Phe Gly Gln Gly Thr Glu Val Glu Ile Lys
            100   105

<210> 968
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 968

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20   25   30

```
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ala Ile Arg Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Lys Asp Leu His Tyr Asp Ser Ser Gly Tyr Leu Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  969
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  969

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Ser Trp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
```

Tyr Ala Ile Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Leu
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 970
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 970

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Asn Ile Lys Gln Asp Gly Gly Glu Lys Tyr Tyr Val Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

```
Ala Arg Val Gln Leu Tyr Ser Asp Tyr Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser
        115


<210>  971
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  971

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Ser Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Gly Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln Ser His Ser Leu Pro Pro
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 972
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 972

Glu Val Gln Leu Leu Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Gly Ser Gly Gly Phe Thr Phe Ser Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Val Glu Asp Ser Ala Val Tyr Ser Cys
85 90 95

Ala Lys Val Leu Val Gly Phe Asn Asn Gly Cys Trp Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 973
<211> 108
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 973

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1   5   10   15

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val
            20   25   30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
        35   40   45

Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50   55   60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65   70   75   80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Asn Asp His
                85   90   95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100   105

<210> 974
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 974

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
            20   25   30

```
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ser Ile Ser Ser Ser Gly Asp Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Leu Val Thr Ser Met Val Ala Phe Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  975
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  975

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1               5                   10                  15


Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Gln Lys Tyr Val
            20                  25                  30


Phe Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45
```

```
Glu Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60


Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Val Glu
65                  70                  75                  80


Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Arg Ser Gly Asn His
                85                  90                  95


Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210>  976
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  976

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  977
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  977

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ser Ser Ser
            20                  25                  30


Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


Ile Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80


Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Leu Pro
                85                  90                  95


Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 978
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 978

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Tyr Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
    50                  55                  60


Lys Asn Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 979
<211> 120
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 979

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Trp Met Tyr Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
    50   55   60

Lys Asn Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
            100   105   110

Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 980
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 980

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1   5   10   15

```
Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
    50                  55                  60


Lys Asn Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  981
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  981

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
```

```
Trp Met Tyr Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu Trp Leu
        35                  40                  45


Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
    50                  55                  60


Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val Val
65                  70                  75                  80


Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  982
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  982

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15


Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Tyr Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
    50                  55                  60
```

```
Lys Asn Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  983
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  983

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Tyr Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu Trp Leu
        35                  40                  45


Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
    50                  55                  60


Lys Asn Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80
```

```
Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  984
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  984

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15


Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Tyr Trp Val Arg Gln Ala Arg Gly Gln Arg Leu Glu Trp Ile
        35                  40                  45


Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
    50                  55                  60


Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val Val
65                  70                  75                  80


Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110
```

Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 985
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 985

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1   5   10   15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Trp Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
    50   55   60

Lys Asn Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
            100   105   110

Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 986
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 986

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Tyr Trp Val Arg Gln Ala Arg Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asn Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 987
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 987

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1   5   10   15

Glu Pro Ala Ser Ile Ser Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20   25   30

Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
        35   40   45

Tyr Trp Ala Ser Thr Arg His Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 988
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 988

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20   25   30

```
Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
        35                  40                  45


Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210>  989
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  989

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1               5                   10                  15


Glu Lys Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20                  25                  30


Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
        35                  40                  45


Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60
```

Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80

Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 990
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 990

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
20 25 30

Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 991
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 991

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                  10                  15


Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20                  25                  30


Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
        35                  40                  45


Tyr Trp Ala Ser Thr Arg His Thr Gly Ile Pro Pro Arg Phe Ser Gly
    50                  55                  60


Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Asn Asn Ile Glu Ser
65                  70                  75                  80


Glu Asp Ala Ala Tyr Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 992
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 992

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1               5                   10                  15


Gln Pro Ala Ser Ile Ser Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20                  25                  30


Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 993
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 993

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20                  25                  30
```

```
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210>  994
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  994

Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20                  25                  30


Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
        35                  40                  45


Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala
65                  70                  75                  80
```

```
Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210>  995
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  995

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1               5                   10                  15


Glu Lys Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20                  25                  30


Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 996
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 996

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Arg Ser Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Ser Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu
65 70 75 80

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Asp Cys Ala
85 90 95

Arg Gly Tyr Asp Ser Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Glu
115

<210> 997
<211> 116
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 997

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Tyr
            20   25   30

Gly Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
        35   40   45

Ala Ser Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Pro Asp Ser Val Lys
    50   55   60

Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu
65   70   75   80

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
                85   90   95

Lys Gly Tyr Asp Ser Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
            100   105   110

Ile Val Ser Ala
        115

<210> 998
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 998

Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1   5   10   15

```
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Thr Tyr
            20                  25                  30


Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
        35                  40                  45


Gly Val Ile Trp Arg Gly Val Thr Thr Asp Tyr Asn Ala Ala Phe Met
    50                  55                  60


Ser Arg Leu Thr Ile Thr Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65                  70                  75                  80


Lys Met Asn Ser Leu Gln Ala Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
                85                  90                  95


Arg Leu Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
            100                 105                 110


Thr Val Ser Ser
        115


<210>  999
<211>  116
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  999

Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1               5                   10                  15


Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
            20                  25                  30
```

```
Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
        35                  40                  45


Gly Val Ile Trp Ser Gly Gly Val Thr Asp Tyr Asn Ala Ala Phe Ile
    50                  55                  60


Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65                  70                  75                  80


Lys Met Asn Ser Leu Gln Ala Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
                85                  90                  95


Arg Leu Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
            100                 105                 110


Thr Val Ser Ser
        115


<210>  1000
<211>  119
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1000

Glu Val Lys Leu Phe Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Asp Phe Ser Thr Tyr
            20                  25                  30


Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Gln Ile Asn Pro Asp Ser Thr Thr Ile Asn Tyr Ala Pro Ser Leu
    50                  55                  60
```

```
Lys Asp Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe
65                  70                  75                  80


Leu Gln Met Ser Lys Val Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95


Ala Lys Pro Gly Asp Tyr Gly Tyr Asp Phe Asp Cys Trp Gly Gln Gly
            100                 105                 110


Thr Thr Leu Thr Val Ser Ser
        115


<210>  1001
<211>  119
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1001

Glu Val Gln Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Asp Ser Ile Thr Ser Gly
            20                  25                  30


Tyr Trp Asn Trp Ile Arg Lys Phe Pro Gly Asn Lys Leu Glu Tyr Met
        35                  40                  45


Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Tyr Tyr Leu
65                  70                  75                  80
```

```
Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
                85                  90                  95


Arg Ser Leu Leu Trp Phe Ser Thr Gly Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ala
        115


<210>  1002
<211>  116
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1002

Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1               5                   10                  15


Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
            20                  25                  30


Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
        35                  40                  45


Gly Val Ile Trp Ser Gly Gly Ile Thr Asp Tyr Asn Ala Ala Phe Lys
    50                  55                  60


Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65                  70                  75                  80


Lys Met Asn Ser Leu Gln Ala Asn Asp Thr Ala Ile Tyr Phe Cys Ala
                85                  90                  95


Arg Leu Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
            100                 105                 110
```

Thr Val Ser Ser
        115

<210> 1003
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1003

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Tyr
            20   25   30

Gly Met Ser Trp Ala Arg Gln Ile Pro Glu Lys Arg Leu Glu Trp Val
        35   40   45

Ala Ser Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Leu Gly Ser Val Gln
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu
65   70   75   80

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
                85   90   95

Arg Gly Tyr Asp Ala Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
            100   105   110

Ser Val Ser Glu
        115

<210> 1004
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1004

```
Glu Val Gln Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Asp Ser Ile Thr Ser Gly
            20                  25                  30


Tyr Trp Thr Trp Ile Arg Lys Phe Pro Gly Asn Lys Leu Glu Tyr Met
        35                  40                  45


Gly Tyr Ile Ser Tyr Thr Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Ile Ser Ile Ser Arg Asp Thr Ser Lys Ser Gln Tyr Tyr Leu
65                  70                  75                  80


Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
                85                  90                  95


Arg Gln Arg Asp Trp Leu Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ala
        115
```

<210> 1005
<211> 116
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 1005

Glu Glu Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Tyr
            20   25   30

Gly Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
        35   40   45

Ala Ser Ile Ser Ser Gly Gly Ser Ile Tyr Tyr Pro Asp Ser Val Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu
65   70   75   80

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
                85   90   95

Arg Gly Tyr Asp Ala Gly Phe Ala Phe Trp Gly Gln Gly Thr Leu Val
            100   105   110

Thr Ala Ser Ala
        115

<210> 1006
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1006

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1   5   10   15

```
Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Thr Tyr
            20                  25                  30


Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu
        35                  40                  45


Gly Val Ile Trp Arg Gly Val Thr Thr Asp Tyr Asn Ala Ala Phe Met
    50                  55                  60


Ser Arg Leu Thr Ile Thr Lys Asp Asn Ser Lys Asn Gln Val Val Leu
65                  70                  75                  80


Thr Met Asn Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
                85                  90                  95


Arg Leu Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110


Thr Val Ser Ser
        115


<210>  1007
<211>  116
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1007

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Arg Ser Tyr
            20                  25                  30
```

```
Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Ser Ile Ser Ser Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Asp Cys Ala
                85                  90                  95


Arg Gly Tyr Asp Ser Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110


Thr Val Ser Ser
        115


<210>  1008
<211>  112
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1008

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15


Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
            20                  25                  30


Ser Ser Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


Lys Leu Leu Ile Lys Tyr Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
    50                  55                  60
```

```
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80


Pro Val Glu Glu Glu Asp Thr Ala Thr Tyr Tyr Cys Gln His Ser Trp
                85                  90                  95


Glu Ile Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105                 110


<210>  1009
<211>  111
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1009

Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15


Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
            20                  25                  30


Ser Ser Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


Lys Leu Leu Ile Lys Tyr Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
    50                  55                  60


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80


Pro Val Glu Glu Glu Asp Thr Ala Thr Tyr Tyr Cys Gln His Ser Trp
                85                  90                  95
```

Glu Ile Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105   110

<210> 1010
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1010

Ser Ile Val Met Thr Gln Thr Pro Lys Phe Leu Leu Val Ser Ala Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
            20   25   30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35   40   45

Tyr Tyr Ala Ala Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
    50   55   60

Ser Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Ile Val Gln Ala
65   70   75   80

Glu Asp Leu Ala Val Tyr Phe Cys Gln Gln Asp Tyr Thr Ser Pro Tyr
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 1011
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 1011

Ser Ile Val Met Thr Gln Thr Pro Lys Phe Leu Leu Val Ser Ala Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
            20   25   30

Val Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35   40   45

Tyr Tyr Ala Ser Asn Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
    50   55   60

Ser Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Thr Val Gln Ala
65   70   75   80

Glu Asp Leu Ala Val Tyr Phe Cys Gln Gln Asp Tyr Thr Ser Pro Tyr
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 1012
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1012

Asp Val Leu Met Thr Gln Thr Pro Leu Tyr Leu Pro Val Ser Leu Gly
1   5   10   15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ile Ile Val His Ser
            20   25   30

```
Asn Ala Asn Thr Tyr Leu Glu Trp Phe Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
                85                  90                  95

Ser His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110
```

<210> 1013
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1013

```
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1               5                   10                  15

Glu Lys Val Thr Leu Thr Cys Ser Ala Ser Ser Ser Val Ser Ser Ser
            20                  25                  30

Tyr Leu Tyr Trp Asn Gln Gln Lys Pro Gly Ser Ser Pro Lys Val Trp
        35                  40                  45

Ile Tyr Asn Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
    50                  55                  60
```

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Ser Tyr Phe Cys His Gln Trp Arg Ser Tyr Pro
85 90 95

Pro Thr Leu Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 1014
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1014

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Asn Ser Ser Val Ser Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Gly Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Trp Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 1015
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1015

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

Ser Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Lys Tyr Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Glu Glu Asp Thr Ala Thr Tyr Tyr Cys Gln Asn Ser Trp
85 90 95

Glu Ile Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 1016
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1016

Asp Ile Val Met Thr Gln Thr Pro Ser Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Ser Asn Gln Lys Asn Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Asn Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Ser Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Lys Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 1017
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1017

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

```
Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
            20                  25                  30


Ser Tyr Ser Tyr Val His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


Lys Leu Leu Ile Lys Tyr Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
    50                  55                  60


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80


Pro Val Glu Glu Glu Asp Thr Ala Thr Tyr Tyr Cys Gln His Ser Trp
                85                  90                  95


Glu Ile Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210>  1018
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1018

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
            20                  25                  30


Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Tyr Ala Ala Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60
```

```
Ser Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Asp Tyr Thr Ser Pro Tyr
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  1019
<211>  111
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1019

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Gly
1               5                   10                  15


Gln Arg Ala Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
            20                  25                  30


Ser Ser Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45


Lys Leu Leu Ile Lys Tyr Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
    50                  55                  60


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65                  70                  75                  80


Pro Val Glu Ala Asn Asp Thr Ala Asn Tyr Tyr Cys Gln His Ser Trp
                85                  90                  95
```

Glu Ile Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 1020
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1020

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Thr Tyr
20 25 30

Trp Met His Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asn Ile Tyr Pro Gly Thr Gly Gly Ser Asn Phe Asp Glu Lys Phe
50 55 60

Lys Asn Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Trp Thr Thr Gly Thr Gly Ala Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> 1021
<211> 117

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1021

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1   5   10   15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Thr Tyr
            20   25   30

Trp Met His Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu Trp Leu
        35   40   45

Gly Asn Ile Tyr Pro Gly Thr Gly Gly Ser Asn Phe Asp Glu Lys Phe
    50   55   60

Lys Asn Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Thr Arg Trp Thr Thr Gly Thr Gly Ala Tyr Trp Gly Gln Gly Thr Thr
            100   105   110

Val Thr Val Ser Ser
        115

<210> 1022
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1022

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
            20                  25                  30


Trp Met His Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu Trp Leu
        35                  40                  45


Gly Asn Ile Tyr Pro Gly Thr Gly Gly Ser Asn Phe Asp Glu Lys Phe
    50                  55                  60


Lys Asn Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Arg Trp Thr Thr Gly Thr Gly Ala Tyr Trp Gly Gln Gly Thr Thr
            100                 105                 110


Val Thr Val Ser Ser
        115
```

<210> 1023
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1023

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15
```

```
Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Thr Tyr
            20                  25                  30


Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Asn Ile Tyr Pro Gly Thr Gly Gly Ser Asn Phe Asp Glu Lys Phe
    50                  55                  60


Lys Asn Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Arg Trp Thr Thr Gly Thr Gly Ala Tyr Trp Gly Gln Gly Thr Thr
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  1024
<211>  113
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1024

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
            20                  25                  30


Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45
```

```
Ala Pro Arg Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Asn
                85                  90                  95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110

Lys
```

<210> 1025
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1025

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
            20                  25                  30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ala Pro Arg Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Ile
    50                  55                  60
```

```
Pro Pro Arg Phe Ser Gly Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80


Ile Asn Asn Ile Glu Ser Glu Asp Ala Ala Tyr Tyr Phe Cys Gln Asn
                85                  90                  95


Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110


Lys



<210>  1026
<211>  113
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1026

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
            20                  25                  30


Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys
        35                  40                  45


Ala Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60


Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65                  70                  75                  80


Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Asn
                85                  90                  95
```

```
Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110


Lys



<210>  1027
<211>  113
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1027

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
            20                  25                  30


Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45


Ala Pro Arg Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60


Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65                  70                  75                  80


Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Asn
                85                  90                  95


Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110
```

Lys

<210> 1028
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1028

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys
35 40 45

Ala Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65 70 75 80

Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 1029
<211> 113

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1029

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ala Pro Arg Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65 70 75 80

Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 1030
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1030

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ala Pro Arg Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65 70 75 80

Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 1031
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1031

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

```
Asp Arg Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
            20                  25                  30


Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Leu Gln Lys Pro Gly Gln
        35                  40                  45


Ser Pro Gln Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60


Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65                  70                  75                  80


Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Asn
                85                  90                  95


Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110


Lys



<210>  1032
<211>  113
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1032

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1               5                   10                  15


Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
            20                  25                  30


Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys
        35                  40                  45
```

```
Ala Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65                  70                  75                  80

Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Asn
                85                  90                  95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110

Lys
```

<210> 1033
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1033

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser
            20                  25                  30

Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
```

```
Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ala
        115


<210>  1034
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1034

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
            20                  25                  30


Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala
                85                  90                  95
```

```
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100                 105


<210>  1035
<211>  126
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1035

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
            20                  25                  30


Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Trp Ala
        35                  40                  45


Ser Ser Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Phe
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
                85                  90                  95


Ala Ala Ser Gln Ala Pro Ile Thr Ile Ala Thr Met Met Lys Pro Phe
            100                 105                 110


Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120                 125
```

<210> 1036
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1036

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
            20                  25                  30


Ala Lys Cys Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Trp Val
        35                  40                  45


Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95


Ala Ala Arg His Gly Gly Pro Leu Thr Val Glu Tyr Phe Phe Asp Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120
```

<210> 1037
<211> 124
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 1037

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Tyr Tyr
            20   25   30

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Ala Arg Glu Gly Val
        35   40   45

Ser Cys Ile Ser Gly Gly Asp Asn Ser Thr Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

Ala Thr Gly Gly Trp Lys Tyr Cys Ser Gly Tyr Asp Pro Glu Tyr Ile
            100   105   110

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115   120

<210> 1038
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1038

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1   5   10   15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Gln Tyr
            20                  25                  30


Asp Val Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Phe Ser Ser Ser Gly Gly Arg Thr Ile Tyr Pro Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Phe Ser Arg Asp Asn Thr Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
                85                  90                  95


Ile Asp Trp Tyr Leu Asn Ser Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  1039
<211>  114
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1039

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Val Asp Ala Ser Asn Ser
            20                  25                  30
```

```
Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Trp Val
        35                  40                  45

Ala Arg Ile Thr Gly Gly Gly Leu Ile Ala Tyr Thr Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Glu Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Thr Ile Asn Ser Arg Asp Gly Trp Gly Gln Gly Thr Gln Val Thr Val
            100                 105                 110

Ser Ser
```

<210> 1040
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1040

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15

Ser Leu Thr Ile Ser Cys Ala Ala Ser Gly Ile Thr Phe Ser Asp Ser
            20                  25                  30

Ile Val Ser Trp Tyr Arg Arg Ala Arg Gly Lys Gln Arg Glu Trp Val
        35                  40                  45

Ala Gly Ile Ser Asn Gly Gly Thr Thr Lys Tyr Ala Glu Ser Val Leu
    50                  55                  60
```

```
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Asn Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Gly Leu Asn Pro Glu Asp Thr Ala Val Tyr Leu Cys Lys
                85                  90                  95


Val Arg Gln Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
            100                 105                 110


<210>  1041
<211>  130
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1041

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Ser Thr Val Leu Ile Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Ser Ile Ser Ser Gly 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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95
```

Ala Asp Val Tyr Pro Gln Asp Tyr Gly Leu Gly Tyr Val Glu Gly Lys
100 105 110

Val Tyr Tyr Gly His Asp Tyr Trp Gly Thr Gly Thr Leu Val Thr Val
115 120 125

Ser Ser
130

<210> 1042
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1042

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Asn Tyr
20 25 30

Val Ser Asn Tyr Ala Met Gly Trp Gly Arg Gln Ala Pro Gly Thr Gln
35 40 45

Arg Glu Leu Val Ala Ser Ile Ser Asn Gly Asp Thr Thr Asn Tyr Ala
50 55 60

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
65 70 75 80

Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Phe Glu His Gln Val Ala Gly Leu Thr Trp Gly Gln Gly
100 105 110

Thr Gln Val Thr Val Ser Ser
        115

<210> 1043
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<220>
<221> misc_feature
<222> (27)..(27)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (32)..(32)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (75)..(75)
<223> Xaa can be any naturally occurring amino acid

<400> 1043

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Xaa Ala Leu Lys Ile Xaa
            20   25   30

Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35   40   45

Ala Ala Ile Thr Ser Gly Gly Arg Thr Asn Tyr Ser Asp Ser Val Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Gly Asp Asn Ala Xaa Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys Arg
85 90 95

Glu Trp Asn Ser Gly Tyr Pro Pro Val Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Gln Val Thr Val Ser Ser
115

<210> 1044
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1044

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Gly
20 25 30

Thr Met Gly Trp Phe Arg Arg Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Ser Ile Pro Trp Ser Gly Gly Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ala Gln Asn Thr Val Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

```
Ala Phe Lys Glu Arg Ser Thr Gly Trp Asp Phe Ala Ser Trp Gly Gln
            100                 105                 110


Gly Ile Gln Val Thr Val Ser Ser
        115                 120


<210>  1045
<211>  127
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1045

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
            20                  25                  30


Gly Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35                  40                  45


Ser Phe Ile Ser Gly Ser Asp Gly Ser Thr Tyr Tyr Ala Glu Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Lys Ala Lys 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


Ala Ala Asp Pro Trp Gly Pro Pro Ser Ile Ala Thr Met Thr Ser Tyr
            100                 105                 110
```

Glu Tyr Lys His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115   120   125

<210> 1046
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1046

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
            20   25   30

Thr Met Ile Trp Leu Arg Arg Ala Pro Gly Lys Gly Phe Glu Trp Val
        35   40   45

Ser Thr Ile Asp Lys Asp Gly Asn Thr Asn Tyr Val Asp Ser Val Lys
    50   55   60

Gly Arg Phe Ala Val Ser Arg Asp Asn Thr Lys Asn Thr Leu Tyr Leu
65   70   75   80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Met Tyr Tyr Cys Thr
                85   90   95

Lys His Gly Ser Ser Ala Arg Gly Gln Gly Thr Arg Val Thr Val Ser
            100   105   110

Ser

<210> 1047
<211> 114

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1047

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Glu Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Asn Ser Gly Gly Gly Ile Thr Tyr Arg Gly Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Glu
85 90 95

Asn Gly Gly Ser Ser Tyr Arg Arg Gly Gln Gly Thr Gln Val Thr Val
100 105 110

Ser Ser

<210> 1048
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1048

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20                  25                  30


Thr Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Thr Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Pro Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110


Ser Ser
```

<210> 1049
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1049

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15
```

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20   25   30

Thr Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45

Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
    50   55   60

Lys Asp Arg Thr Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Pro Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100   105   110

Ser Ser

<210> 1050
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1050

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20   25   30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45

```
Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Thr Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Pro Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110

Ser Ser
```

<210> 1051
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1051

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20                  25                  30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
    50                  55                  60
```

```
Lys Asp Arg Thr Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Pro Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110


Ser Ser
```

<210> 1052
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1052

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20                  25                  30


Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Thr Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Pro Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            100                 105                 110


Ser Ser



<210>  1053
<211>  113
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1053

Asp Ile Val Met Thr Gln Ser Pro Ala Ser Leu Thr Val Thr Pro Gly
1               5                   10                  15


Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20                  25                  30


Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45


Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60


Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80


Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn
                85                  90                  95


Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
            100                 105                 110
```

Lys

<210> 1054
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1054

Asp Ile Val Met Thr Gln Ser Pro Ala Ser Leu Ser Val Thr Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 1055
<211> 113

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1055

Asp Ile Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1   5   10   15

Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20   25   30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
        35   40   45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50   55   60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65   70   75   80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn
                85   90   95

Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
            100   105   110

Lys

<210> 1056
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1056

```
Asp Ile Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1               5                  10                  15


Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20                  25                  30


Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45


Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60


Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80


Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn
                85                  90                  95


Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
            100                 105                 110


Lys
```

<210> 1057
<211> 504
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> exemplary human SIRP1alpha polypeptide

<220>
<221> MISC_FEATURE
<223> exemplary human SIRP1alpha polypeptide with a signal peptide sequence

<400> 1057

```
Met Glu Pro Ala Gly Pro Ala Pro Gly Arg Leu Gly Pro Leu Leu Cys
1               5                  10                  15

Leu Leu Leu Ala Ala Ser Cys Ala Trp Ser Gly Val Ala Gly Glu Glu
            20                  25                  30

Glu Leu Gln Val Ile Gln Pro Asp Lys Ser Val Leu Val Ala Ala Gly
        35                  40                  45

Glu Thr Ala Thr Leu Arg Cys Thr Ala Thr Ser Leu Ile Pro Val Gly
    50                  55                  60

Pro Ile Gln Trp Phe Arg Gly Ala Gly Pro Gly Arg Glu Leu Ile Tyr
65                  70                  75                  80

Asn Gln Lys Glu Gly His Phe Pro Arg Val Thr Thr Val Ser Asp Leu
                85                  90                  95

Thr Lys Arg Asn Asn Met Asp Phe Ser Ile Arg Ile Gly Asn Ile Thr
            100                 105                 110

Pro Ala Asp Ala Gly Thr Tyr Tyr Cys Val Lys Phe Arg Lys Gly Ser
        115                 120                 125

Pro Asp Asp Val Glu Phe Lys Ser Gly Ala Gly Thr Glu Leu Ser Val
    130                 135                 140

Arg Ala Lys Pro Ser Ala Pro Val Val Ser Gly Pro Ala Ala Arg Ala
145                 150                 155                 160

Thr Pro Gln His Thr Val Ser Phe Thr Cys Glu Ser His Gly Phe Ser
                165                 170                 175

Pro Arg Asp Ile Thr Leu Lys Trp Phe Lys Asn Gly Asn Glu Leu Ser
```

```
            180                 185                 190

Asp Phe Gln Thr Asn Val Asp Pro Val Gly Glu Ser Val Ser Tyr Ser
        195                 200                 205

Ile His Ser Thr Ala Lys Val Val Leu Thr Arg Glu Asp Val His Ser
    210                 215                 220

Gln Val Ile Cys Glu Val Ala His Val Thr Leu Gln Gly Asp Pro Leu
225                 230                 235                 240

Arg Gly Thr Ala Asn Leu Ser Glu Thr Ile Arg Val Pro Pro Thr Leu
                245                 250                 255

Glu Val Thr Gln Gln Pro Val Arg Ala Glu Asn Gln Val Asn Val Thr
            260                 265                 270

Cys Gln Val Arg Lys Phe Tyr Pro Gln Arg Leu Gln Leu Thr Trp Leu
        275                 280                 285

Glu Asn Gly Asn Val Ser Arg Thr Glu Thr Ala Ser Thr Val Thr Glu
    290                 295                 300

Asn Lys Asp Gly Thr Tyr Asn Trp Met Ser Trp Leu Leu Val Asn Val
305                 310                 315                 320

Ser Ala His Arg Asp Asp Val Lys Leu Thr Cys Gln Val Glu His Asp
                325                 330                 335

Gly Gln Pro Ala Val Ser Lys Ser His Asp Leu Lys Val Ser Ala His
            340                 345                 350

Pro Lys Glu Gln Gly Ser Asn Thr Ala Ala Glu Asn Thr Gly Ser Asn
        355                 360                 365

Glu Arg Asn Ile Tyr Ile Val Val Gly Val Val Cys Thr Leu Leu Val
```

```
    370                 375                 380

Ala Leu Leu Met Ala Ala Leu Tyr Leu Val Arg Ile Arg Gln Lys Lys
385                 390                 395                 400

Ala Gln Gly Ser Thr Ser Ser Thr Arg Leu His Glu Pro Glu Lys Asn
                405                 410                 415

Ala Arg Glu Ile Thr Gln Asp Thr Asn Asp Ile Thr Tyr Ala Asp Leu
            420                 425                 430

Asn Leu Pro Lys Gly Lys Lys Pro Ala Pro Gln Ala Ala Glu Pro Asn
        435                 440                 445

Asn His Thr Glu Tyr Ala Ser Ile Gln Thr Ser Pro Gln Pro Ala Ser
    450                 455                 460

Glu Asp Thr Leu Thr Tyr Ala Asp Leu Asp Met Val His Leu Asn Arg
465                 470                 475                 480

Thr Pro Lys Gln Pro Ala Pro Lys Pro Glu Pro Ser Phe Ser Glu Tyr
                485                 490                 495

Ala Ser Val Gln Val Pro Arg Lys
            500

<210>  1058
<211>  474
<212>  PRT
<213>  Homo sapiens

<220>
<221>  MISC_FEATURE
<223>  exemplary human SIRP1alpha polypeptide without a signal peptide
       sequence

<400>  1058
```

```
Glu Glu Glu Leu Gln Val Ile Gln Pro Asp Lys Ser Val Leu Val Ala
1               5                  10                  15

Ala Gly Glu Thr Ala Thr Leu Arg Cys Thr Ala Thr Ser Leu Ile Pro
            20                  25                  30

Val Gly Pro Ile Gln Trp Phe Arg Gly Ala Gly Pro Gly Arg Glu Leu
        35                  40                  45

Ile Tyr Asn Gln Lys Glu Gly His Phe Pro Arg Val Thr Thr Val Ser
    50                  55                  60

Asp Leu Thr Lys Arg Asn Asn Met Asp Phe Ser Ile Arg Ile Gly Asn
65                  70                  75                  80

Ile Thr Pro Ala Asp Ala Gly Thr Tyr Tyr Cys Val Lys Phe Arg Lys
                85                  90                  95

Gly Ser Pro Asp Asp Val Glu Phe Lys Ser Gly Ala Gly Thr Glu Leu
            100                 105                 110

Ser Val Arg Ala Lys Pro Ser Ala Pro Val Val Ser Gly Pro Ala Ala
        115                 120                 125

Arg Ala Thr Pro Gln His Thr Val Ser Phe Thr Cys Glu Ser His Gly
    130                 135                 140

Phe Ser Pro Arg Asp Ile Thr Leu Lys Trp Phe Lys Asn Gly Asn Glu
145                 150                 155                 160

Leu Ser Asp Phe Gln Thr Asn Val Asp Pro Val Gly Glu Ser Val Ser
                165                 170                 175

Tyr Ser Ile His Ser Thr Ala Lys Val Val Leu Thr Arg Glu Asp Val
            180                 185                 190
```

```
His Ser Gln Val Ile Cys Glu Val Ala His Val Thr Leu Gln Gly Asp
        195                 200                 205


Pro Leu Arg Gly Thr Ala Asn Leu Ser Glu Thr Ile Arg Val Pro Pro
    210                 215                 220


Thr Leu Glu Val Thr Gln Gln Pro Val Arg Ala Glu Asn Gln Val Asn
225                 230                 235                 240


Val Thr Cys Gln Val Arg Lys Phe Tyr Pro Gln Arg Leu Gln Leu Thr
                245                 250                 255


Trp Leu Glu Asn Gly Asn Val Ser Arg Thr Glu Thr Ala Ser Thr Val
            260                 265                 270


Thr Glu Asn Lys Asp Gly Thr Tyr Asn Trp Met Ser Trp Leu Leu Val
        275                 280                 285


Asn Val Ser Ala His Arg Asp Asp Val Lys Leu Thr Cys Gln Val Glu
    290                 295                 300


His Asp Gly Gln Pro Ala Val Ser Lys Ser His Asp Leu Lys Val Ser
305                 310                 315                 320


Ala His Pro Lys Glu Gln Gly Ser Asn Thr Ala Ala Glu Asn Thr Gly
                325                 330                 335


Ser Asn Glu Arg Asn Ile Tyr Ile Val Val Gly Val Val Cys Thr Leu
            340                 345                 350


Leu Val Ala Leu Leu Met Ala Ala Leu Tyr Leu Val Arg Ile Arg Gln
        355                 360                 365


Lys Lys Ala Gln Gly Ser Thr Ser Ser Thr Arg Leu His Glu Pro Glu
    370                 375                 380
```

```
Lys Asn Ala Arg Glu Ile Thr Gln Asp Thr Asn Asp Ile Thr Tyr Ala
385                 390                 395                 400


Asp Leu Asn Leu Pro Lys Gly Lys Lys Pro Ala Pro Gln Ala Ala Glu
                405                 410                 415


Pro Asn Asn His Thr Glu Tyr Ala Ser Ile Gln Thr Ser Pro Gln Pro
            420                 425                 430


Ala Ser Glu Asp Thr Leu Thr Tyr Ala Asp Leu Asp Met Val His Leu
        435                 440                 445


Asn Arg Thr Pro Lys Gln Pro Ala Pro Lys Pro Glu Pro Ser Phe Ser
    450                 455                 460


Glu Tyr Ala Ser Val Gln Val Pro Arg Lys
465                 470


<210>  1059
<211>  508
<212>  PRT
<213>  Homo sapiens


<220>
<221>  MISC_FEATURE
<223>  SIRP1alpha targeting moiety

<400>  1059

Met Glu Pro Ala Gly Pro Ala Pro Gly Arg Leu Gly Pro Leu Leu Cys
1               5                   10                  15


Leu Leu Leu Ala Ala Ser Cys Ala Trp Ser Gly Val Ala Gly Glu Glu
            20                  25                  30


Glu Leu Gln Val Ile Gln Pro Asp Lys Ser Val Leu Val Ala Ala Gly
        35                  40                  45
```

```
Glu Thr Ala Thr Leu Arg Cys Thr Ala Thr Ser Leu Ile Pro Val Gly
    50                  55                  60

Pro Ile Gln Trp Phe Arg Gly Ala Gly Pro Gly Arg Glu Leu Ile Tyr
65                  70                  75                  80

Asn Gln Lys Glu Gly His Phe Pro Arg Val Thr Thr Val Ser Asp Leu
                85                  90                  95

Thr Lys Arg Asn Asn Met Asp Phe Ser Ile Arg Ile Gly Asn Ile Thr
            100                 105                 110

Pro Ala Asp Ala Gly Thr Tyr Tyr Cys Val Lys Phe Arg Lys Gly Ser
        115                 120                 125

Pro Asp Asp Val Glu Phe Lys Ser Gly Ala Gly Thr Glu Leu Ser Val
    130                 135                 140

Arg Ala Lys Pro Ser Ala Pro Val Val Ser Gly Pro Ala Ala Arg Ala
145                 150                 155                 160

Thr Pro Gln His Thr Val Ser Phe Thr Cys Glu Ser His Gly Phe Ser
                165                 170                 175

Pro Arg Asp Ile Thr Leu Lys Trp Phe Lys Asn Gly Asn Glu Leu Ser
            180                 185                 190

Asp Phe Gln Thr Asn Val Asp Pro Val Gly Glu Ser Val Ser Tyr Ser
        195                 200                 205

Ile His Ser Thr Ala Lys Val Val Leu Thr Arg Glu Asp Val His Ser
    210                 215                 220

Gln Val Ile Cys Glu Val Ala His Val Thr Leu Gln Gly Asp Pro Leu
225                 230                 235                 240
```

```
Arg Gly Thr Ala Asn Leu Ser Glu Thr Ile Arg Val Pro Pro Thr Leu
                245                 250                 255

Glu Val Thr Gln Gln Pro Val Arg Ala Glu Asn Gln Val Asn Val Thr
            260                 265                 270

Cys Gln Val Arg Lys Phe Tyr Pro Gln Arg Leu Gln Leu Thr Trp Leu
        275                 280                 285

Glu Asn Gly Asn Val Ser Arg Thr Glu Thr Ala Ser Thr Val Thr Glu
    290                 295                 300

Asn Lys Asp Gly Thr Tyr Asn Trp Met Ser Trp Leu Leu Val Asn Val
305                 310                 315                 320

Ser Ala His Arg Asp Asp Val Lys Leu Thr Cys Gln Val Glu His Asp
                325                 330                 335

Gly Gln Pro Ala Val Ser Lys Ser His Asp Leu Lys Val Ser Ala His
            340                 345                 350

Pro Lys Glu Gln Gly Ser Asn Thr Ala Ala Glu Asn Thr Gly Ser Asn
        355                 360                 365

Glu Arg Asn Ile Tyr Ile Val Val Gly Val Val Cys Thr Leu Leu Val
    370                 375                 380

Ala Leu Leu Met Ala Ala Leu Tyr Leu Val Arg Ile Arg Gln Lys Lys
385                 390                 395                 400

Ala Gln Gly Ser Thr Ser Ser Thr Arg Leu His Glu Pro Glu Lys Asn
                405                 410                 415

Ala Arg Glu Ile Thr Gln Val Gln Ser Leu Asp Thr Asn Asp Ile Thr
            420                 425                 430
```

```
Tyr Ala Asp Leu Asn Leu Pro Lys Gly Lys Lys Pro Ala Pro Gln Ala
        435                 440                 445


Ala Glu Pro Asn Asn His Thr Glu Tyr Ala Ser Ile Gln Thr Ser Pro
    450                 455                 460


Gln Pro Ala Ser Glu Asp Thr Leu Thr Tyr Ala Asp Leu Asp Met Val
465                 470                 475                 480


His Leu Asn Arg Thr Pro Lys Gln Pro Ala Pro Lys Pro Glu Pro Ser
                485                 490                 495


Phe Ser Glu Tyr Ala Ser Val Gln Val Pro Arg Lys
            500                 505


<210>  1060
<211>  503
<212>  PRT
<213>  Homo sapiens


<220>
<221>  MISC_FEATURE
<223>  a polypeptide encoding human SIRP1alpha isoform 4

<220>
<221>  MISC_FEATURE
<223>  polypeptide encoding human SIRP1alpha isoform 4

<400>  1060

Met Glu Pro Ala Gly Pro Ala Pro Gly Arg Leu Gly Pro Leu Leu Cys
1               5                   10                  15


Leu Leu Leu Ala Ala Ser Cys Ala Trp Ser Gly Val Ala Gly Glu Glu
            20                  25                  30


Glu Leu Gln Val Ile Gln Pro Asp Lys Ser Val Leu Val Ala Ala Gly
        35                  40                  45
```

```
Glu Thr Ala Thr Leu Arg Cys Thr Ala Thr Ser Leu Ile Pro Val Gly
    50                  55                  60

Pro Ile Gln Trp Phe Arg Gly Ala Gly Pro Gly Arg Glu Leu Ile Tyr
65                  70                  75                  80

Asn Gln Lys Glu Gly His Phe Pro Arg Val Thr Thr Val Ser Asp Leu
                85                  90                  95

Thr Lys Arg Asn Asn Met Asp Phe Ser Ile Arg Ile Gly Asn Ile Thr
            100                 105                 110

Pro Ala Asp Ala Gly Thr Tyr Tyr Cys Val Lys Phe Arg Lys Gly Ser
        115                 120                 125

Pro Asp Val Glu Phe Lys Ser Gly Ala Gly Thr Glu Leu Ser Val Arg
    130                 135                 140

Ala Lys Pro Ser Ala Pro Val Val Ser Gly Pro Ala Ala Arg Ala Thr
145                 150                 155                 160

Pro Gln His Thr Val Ser Phe Thr Cys Glu Ser His Gly Phe Ser Pro
                165                 170                 175

Arg Asp Ile Thr Leu Lys Trp Phe Lys Asn Gly Asn Glu Leu Ser Asp
            180                 185                 190

Phe Gln Thr Asn Val Asp Pro Val Gly Glu Ser Val Ser Tyr Ser Ile
        195                 200                 205

His Ser Thr Ala Lys Val Val Leu Thr Arg Glu Asp Val His Ser Gln
    210                 215                 220

Val Ile Cys Glu Val Ala His Val Thr Leu Gln Gly Asp Pro Leu Arg
225                 230                 235                 240
```

```
Gly Thr Ala Asn Leu Ser Glu Thr Ile Arg Val Pro Pro Thr Leu Glu
                245                 250                 255

Val Thr Gln Gln Pro Val Arg Ala Glu Asn Gln Val Asn Val Thr Cys
            260                 265                 270

Gln Val Arg Lys Phe Tyr Pro Gln Arg Leu Gln Leu Thr Trp Leu Glu
        275                 280                 285

Asn Gly Asn Val Ser Arg Thr Glu Thr Ala Ser Thr Val Thr Glu Asn
    290                 295                 300

Lys Asp Gly Thr Tyr Asn Trp Met Ser Trp Leu Leu Val Asn Val Ser
305                 310                 315                 320

Ala His Arg Asp Asp Val Lys Leu Thr Cys Gln Val Glu His Asp Gly
                325                 330                 335

Gln Pro Ala Val Ser Lys Ser His Asp Leu Lys Val Ser Ala His Pro
            340                 345                 350

Lys Glu Gln Gly Ser Asn Thr Ala Ala Glu Asn Thr Gly Ser Asn Glu
        355                 360                 365

Arg Asn Ile Tyr Ile Val Val Gly Val Val Cys Thr Leu Leu Val Ala
    370                 375                 380

Leu Leu Met Ala Ala Leu Tyr Leu Val Arg Ile Arg Gln Lys Lys Ala
385                 390                 395                 400

Gln Gly Ser Thr Ser Ser Thr Arg Leu His Glu Pro Glu Lys Asn Ala
                405                 410                 415

Arg Glu Ile Thr Gln Asp Thr Asn Asp Ile Thr Tyr Ala Asp Leu Asn
            420                 425                 430
```

```
Leu Pro Lys Gly Lys Lys Pro Ala Pro Gln Ala Ala Glu Pro Asn Asn
        435                 440                 445


His Thr Glu Tyr Ala Ser Ile Gln Thr Ser Pro Gln Pro Ala Ser Glu
    450                 455                 460


Asp Thr Leu Thr Tyr Ala Asp Leu Asp Met Val His Leu Asn Arg Thr
465                 470                 475                 480


Pro Lys Gln Pro Ala Pro Lys Pro Glu Pro Ser Phe Ser Glu Tyr Ala
                485                 490                 495


Ser Val Gln Val Pro Arg Lys
            500


<210>  1061
<211>  760
<212>  PRT
<213>  Homo sapiens


<220>
<221>  MISC_FEATURE
<223>  human FAP

<400>  1061

Met Lys Thr Trp Val Lys Ile Val Phe Gly Val Ala Thr Ser Ala Val
1               5                   10                  15


Leu Ala Leu Leu Val Met Cys Ile Val Leu Arg Pro Ser Arg Val His
            20                  25                  30


Asn Ser Glu Glu Asn Thr Met Arg Ala Leu Thr Leu Lys Asp Ile Leu
        35                  40                  45


Asn Gly Thr Phe Ser Tyr Lys Thr Phe Phe Pro Asn Trp Ile Ser Gly
    50                  55                  60
```

```
Gln Glu Tyr Leu His Gln Ser Ala Asp Asn Asn Ile Val Leu Tyr Asn
65                  70                  75                  80


Ile Glu Thr Gly Gln Ser Tyr Thr Ile Leu Ser Asn Arg Thr Met Lys
                85                  90                  95


Ser Val Asn Ala Ser Asn Tyr Gly Leu Ser Pro Asp Arg Gln Phe Val
            100                 105                 110


Tyr Leu Glu Ser Asp Tyr Ser Lys Leu Trp Arg Tyr Ser Tyr Thr Ala
        115                 120                 125


Thr Tyr Tyr Ile Tyr Asp Leu Ser Asn Gly Glu Phe Val Arg Gly Asn
    130                 135                 140


Glu Leu Pro Arg Pro Ile Gln Tyr Leu Cys Trp Ser Pro Val Gly Ser
145                 150                 155                 160


Lys Leu Ala Tyr Val Tyr Gln Asn Asn Ile Tyr Leu Lys Gln Arg Pro
                165                 170                 175


Gly Asp Pro Pro Phe Gln Ile Thr Phe Asn Gly Arg Glu Asn Lys Ile
            180                 185                 190


Phe Asn Gly Ile Pro Asp Trp Val Tyr Glu Glu Glu Met Leu Pro Thr
        195                 200                 205


Lys Tyr Ala Leu Trp Trp Ser Pro Asn Gly Lys Phe Leu Ala Tyr Ala
    210                 215                 220


Glu Phe Asn Asp Lys Asp Ile Pro Val Ile Ala Tyr Ser Tyr Tyr Gly
225                 230                 235                 240


Asp Glu Gln Tyr Pro Arg Thr Ile Asn Ile Pro Tyr Pro Lys Ala Gly
                245                 250                 255
```

```
Ala Lys Asn Pro Val Val Arg Ile Phe Ile Ile Asp Thr Thr Tyr Pro
            260                 265                 270

Ala Tyr Val Gly Pro Gln Glu Val Pro Val Pro Ala Met Ile Ala Ser
        275                 280                 285

Ser Asp Tyr Tyr Phe Ser Trp Leu Thr Trp Val Thr Asp Glu Arg Val
    290                 295                 300

Cys Leu Gln Trp Leu Lys Arg Val Gln Asn Val Ser Val Leu Ser Ile
305                 310                 315                 320

Cys Asp Phe Arg Glu Asp Trp Gln Thr Trp Asp Cys Pro Lys Thr Gln
                325                 330                 335

Glu His Ile Glu Glu Ser Arg Thr Gly Trp Ala Gly Gly Phe Phe Val
            340                 345                 350

Ser Arg Pro Val Phe Ser Tyr Asp Ala Ile Ser Tyr Tyr Lys Ile Phe
        355                 360                 365

Ser Asp Lys Asp Gly Tyr Lys His Ile His Tyr Ile Lys Asp Thr Val
    370                 375                 380

Glu Asn Ala Ile Gln Ile Thr Ser Gly Lys Trp Glu Ala Ile Asn Ile
385                 390                 395                 400

Phe Arg Val Thr Gln Asp Ser Leu Phe Tyr Ser Ser Asn Glu Phe Glu
                405                 410                 415

Glu Tyr Pro Gly Arg Arg Asn Ile Tyr Arg Ile Ser Ile Gly Ser Tyr
            420                 425                 430

Pro Pro Ser Lys Lys Cys Val Thr Cys His Leu Arg Lys Glu Arg Cys
        435                 440                 445
```

```
Gln Tyr Tyr Thr Ala Ser Phe Ser Asp Tyr Ala Lys Tyr Tyr Ala Leu
    450                 455                 460

Val Cys Tyr Gly Pro Gly Ile Pro Ile Ser Thr Leu His Asp Gly Arg
465                 470                 475                 480

Thr Asp Gln Glu Ile Lys Ile Leu Glu Glu Asn Lys Glu Leu Glu Asn
                485                 490                 495

Ala Leu Lys Asn Ile Gln Leu Pro Lys Glu Glu Ile Lys Lys Leu Glu
            500                 505                 510

Val Asp Glu Ile Thr Leu Trp Tyr Lys Met Ile Leu Pro Pro Gln Phe
        515                 520                 525

Asp Arg Ser Lys Lys Tyr Pro Leu Leu Ile Gln Val Tyr Gly Gly Pro
    530                 535                 540

Cys Ser Gln Ser Val Arg Ser Val Phe Ala Val Asn Trp Ile Ser Tyr
545                 550                 555                 560

Leu Ala Ser Lys Glu Gly Met Val Ile Ala Leu Val Asp Gly Arg Gly
                565                 570                 575

Thr Ala Phe Gln Gly Asp Lys Leu Leu Tyr Ala Val Tyr Arg Lys Leu
            580                 585                 590

Gly Val Tyr Glu Val Glu Asp Gln Ile Thr Ala Val Arg Lys Phe Ile
        595                 600                 605

Glu Met Gly Phe Ile Asp Glu Lys Arg Ile Ala Ile Trp Gly Trp Ser
    610                 615                 620

Tyr Gly Gly Tyr Val Ser Ser Leu Ala Leu Ala Ser Gly Thr Gly Leu
625                 630                 635                 640
```

```
Phe Lys Cys Gly Ile Ala Val Ala Pro Val Ser Ser Trp Glu Tyr Tyr
                645                 650                 655


Ala Ser Val Tyr Thr Glu Arg Phe Met Gly Leu Pro Thr Lys Asp Asp
            660                 665                 670


Asn Leu Glu His Tyr Lys Asn Ser Thr Val Met Ala Arg Ala Glu Tyr
        675                 680                 685


Phe Arg Asn Val Asp Tyr Leu Leu Ile His Gly Thr Ala Asp Asp Asn
    690                 695                 700


Val His Phe Gln Asn Ser Ala Gln Ile Ala Lys Ala Leu Val Asn Ala
705                 710                 715                 720


Gln Val Asp Phe Gln Ala Met Trp Tyr Ser Asp Gln Asn His Gly Leu
                725                 730                 735


Ser Gly Leu Ser Thr Asn His Leu Tyr Thr His Met Thr His Phe Leu
            740                 745                 750


Lys Gln Cys Phe Ser Leu Ser Asp
        755                 760


<210>  1062
<211>  134
<212>  PRT
<213>  Homo sapiens

<400>  1062

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Gly Phe Asp Ser Arg Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Trp Val
```

        35   40   45

Ala Thr Ile Thr Ser Asp Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
    50   55   60

Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65   70   75   80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85   90   95

Ala Ala Pro Pro Ile Phe Gly Ser Trp Gly Gln Gly Thr Gln Val Thr
            100   105   110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115   120   125

His His His His His His
    130

<210> 1063
<211> 134
<212> PRT
<213> Homo sapiens

<400> 1063

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Arg Ala Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Thr Phe Asp Ser Arg Asn
            20   25   30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Trp Val
        35   40   45

Ala Thr Ile Thr Thr Asp Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
    50   55   60

```
Ala Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Ala Ala Pro Pro Ile Phe Gly Ser Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130


<210>  1064
<211>  134
<212>  PRT
<213>  Homo sapiens

<400>  1064

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Asp Ser Arg Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Trp Val
        35                  40                  45


Ala Thr Ile Thr Thr Asp Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60


Ala Arg Phe Thr Val Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65                  70                  75                  80
```

```
Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Ala Ala Pro Pro Ile Phe Asn Ser Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130


<210>  1065
<211>  134
<212>  PRT
<213>  Homo sapiens

<400>  1065

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Asp Ile Arg Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Thr Arg Arg Glu Trp Val
        35                  40                  45


Ala Thr Ile Thr Thr Asp Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60


Ala Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95
```

Leu Ala Pro Pro Ile Phe Gly Ser Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
115 120 125

His His His His His His
130

<210> 1066
<211> 134
<212> PRT
<213> Homo sapiens

<400> 1066

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Asp Ser Arg Asn
20 25 30

Thr Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Trp Val
35 40 45

Ala Thr Ile Thr Thr Gly Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Ala Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Leu Ala Pro Pro Ile Phe Asn Ser Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser

115 120 125

His His His His His His
130

<210> 1067
<211> 134
<212> PRT
<213> Homo sapiens

<400> 1067

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Val Ala Glu Ser Ile Asp Val Arg Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Trp Val
35 40 45

Ala Thr Ile Thr Thr Gly Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Ala Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Ala Ala Pro Pro Ile Leu Asn Ser Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
115 120 125

His His His His His His
130

<210> 1068
<211> 134
<212> PRT
<213> Homo sapiens

<400> 1068

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Arg Val Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ser Phe Asp Ser Arg Asn
20 25 30

Ser Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Trp Val
35 40 45

Ala Thr Ile Thr Ser Gly Ser Arg Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Ala Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asp Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Ala Ala Pro Pro Ile Phe Asn Ser Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
115 120 125

His His His His His His
130

<210> 1069
<211> 134
<212> PRT

<213> Homo sapiens

<400> 1069

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Arg Leu Phe Ser Ala Asn
20 25 30

Thr Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Leu Val
35 40 45

Ala Thr Ile Leu Ser Ser Gly Ser Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asp Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Leu Ala Pro Pro Pro Glu Gly Tyr Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
115 120 125

His His His His His His
130

<210> 1070
<211> 134
<212> PRT
<213> Homo sapiens

<400> 1070

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Arg Leu Phe Ser Ala Asn
20 25 30

Thr Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Leu Val
35 40 45

Ala Thr Ile Leu Ser Ser Gly Ser Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asp Gly Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Ala Pro Pro Pro Glu Gly Tyr Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
115 120 125

His His His His His His
130

<210> 1071
<211> 136
<212> PRT
<213> Homo sapiens

<400> 1071

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Val Gly Asn
20 25 30

```
Ala Met Gly Trp Tyr Arg Gln Ala Leu Gly Asn Gln Arg Glu Leu Val
        35                  40                  45


Ala Gly Ile Thr Ser Asp Gly Thr Thr Tyr Tyr Pro Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Asp Lys Asn Thr Ile Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Leu Trp Pro Pro Arg Ile Gly Phe Ala Ser Trp Gly Gln Gly Thr Gln
            100                 105                 110


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
        115                 120                 125


Gly Ser His His His His His His
    130                 135


<210>  1072
<211>  136
<212>  PRT
<213>  Homo sapiens

<400>  1072

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Val Gly Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Leu Gly Asn Gln Arg Glu Leu Val
        35                  40                  45
```

```
Ala Gly Ile Thr Ser Asp Gly Thr Thr Tyr Tyr Pro Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Asp Lys Asn Thr Ile Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Leu Trp Pro Pro Arg Ile Gly Phe Ala Ser Trp Gly Gln Gly Thr Gln
            100                 105                 110


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
        115                 120                 125


Gly Ser His His His His His His
    130                 135


<210>  1073
<211>  136
<212>  PRT
<213>  Homo sapiens

<400>  1073

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Arg Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Val Gly Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Leu Gly Asn Gln Arg Glu Leu Val
        35                  40                  45


Ala Gly Ile Thr Ser Asp Gly Thr Thr Tyr Tyr Pro Asp Ser Val Lys
    50                  55                  60
```

Gly Arg Phe Thr Ile Ser Arg Asp Asn Asp Lys Asn Thr Ile Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Leu Trp Pro Pro Arg Ile Gly Phe Ala Ser Trp Gly Gln Gly Thr Gln
100 105 110

Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
115 120 125

Gly Ser His His His His His His
130 135

<210> 1074
<211> 136
<212> PRT
<213> Homo sapiens

<400> 1074

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Val Gly Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Leu Gly Asn Gln Arg Glu Leu Val
35 40 45

Ala Gly Ile Thr Ser Asp Gly Thr Thr Tyr Tyr Pro Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Asp Lys Asn Thr Ile Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn

85 90 95

Leu Trp Pro Pro Arg Ile Gly Phe Ala Ser Trp Gly Gln Gly Thr Gln
100 105 110

Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
115 120 125

Gly Ser His His His His His His
130 135

<210> 1075
<211> 136
<212> PRT
<213> Homo sapiens

<400> 1075

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Ser Met Leu Asn
20 25 30

Ser Met Gly Trp Tyr Arg Gln Ala Leu Gly Lys Gln Arg Glu Phe Val
35 40 45

Ala Gly Ile Thr Ser Gly Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Ala Ile Ser Arg Asp Asn Asp Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Thr Trp Pro Pro Arg Ile Ala Phe Asp Ser Trp Gly Gln Gly Thr Gln
100 105 110

```
Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
        115                 120                 125


Gly Ser His His His His His His
    130                 135


<210>  1076
<211>  140
<212>  PRT
<213>  Homo sapiens

<400>  1076

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Ser Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Ala Gly Lys Arg Arg Glu Leu Val
        35                  40                  45


Ala Gly Ile Arg Ser Asp Gly Asn Thr Asn Tyr Val Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Arg Ala Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Tyr Trp Pro Pro Pro Leu Arg Gln Gly Gly Asp Tyr Ala Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125
```

```
Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1077
<211>  136
<212>  PRT
<213>  Homo sapiens

<400>  1077

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Val Val Ser Gly Ser Phe Asp Ser Arg Asn
            20                  25                  30


Ala Met Ala Trp Tyr Arg Gln Ala Leu Gly Lys Glu Arg Val Trp Val
        35                  40                  45


Ala Gly Ile Ile Ser Asp Gly Ser Thr Asn Tyr Ala Asp Ala Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Asp Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Ala Trp Pro Pro Arg Ile Gly Leu Gly Ser Trp Gly Gln Gly Thr Gln
            100                 105                 110


Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
        115                 120                 125


Gly Ser His His His His His His
    130                 135
```

<210> 1078
<211> 135
<212> PRT
<213> Homo sapiens

<400> 1078

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Thr Met Ser Ser Ile Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Gly Ile Leu Ser Asp Gly Thr Thr Lys Tyr Val Glu Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val His Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Val Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Phe Pro Pro Pro Val Pro Ala Ser Trp Gly Gln Gly Thr Gln Val
100 105 110

Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly
115 120 125

Ser His His His His His His
130 135

<210> 1079
<211> 134
<212> PRT
<213> Homo sapiens

<400> 1079

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Ile Ser Ser Met Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Leu Val
        35                  40                  45


Ala Gly Leu Gly Ser Gly Val Ser Thr Thr Tyr Ala Asp Ala Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Arg Trp Pro Pro Pro Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130
```

<210> 1080
<211> 137
<212> PRT
<213> Homo sapiens

<400> 1080

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Val Val Ser Gly Thr Ile Leu Ser Ser Asn
            20                  25                  30


Ser Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Leu Val
        35                  40                  45


Ala Ser Ile Ser Thr Asp Gly Ser Thr Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Val Phe Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Phe His Pro Pro Val Val Arg Asp Trp Gly Asp Thr Tyr Trp Gly Thr
            100                 105                 110


Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp
        115                 120                 125


Tyr Gly Ser His His His His His His
    130                 135


<210>  1081
<211>  136
<212>  PRT
<213>  Homo sapiens

<400>  1081

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Phe Ser Ile Gly
            20                  25                  30
```

```
Thr Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Leu Val
        35                  40                  45

Ala Phe Ile Thr Val Asp His Asn Thr Tyr Tyr Thr Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Thr Glu Asn Asp Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Arg Ala Pro Pro Ser Thr Asp Gly Asp Arg Trp Gly Gln Gly Thr Gln
            100                 105                 110

Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr
        115                 120                 125

Gly Ser His His His His His His
    130                 135


<210>  1082
<211>  142
<212>  PRT
<213>  Homo sapiens

<400>  1082

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Thr Tyr
            20                  25                  30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45

Ala Ala Ile Ser Asn Gly Gly Ser Ala Tyr Tyr Ala Asp Ser Val Lys
```

50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65 70 75 80

Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1083
<211> 142
<212> PRT
<213> Homo sapiens

<400> 1083

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Tyr
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Ala Ile Ser Asn Gly Gly Ser Ala Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65 70 75 80

```
Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1084
<211>  142
<212>  PRT
<213>  Homo sapiens

<400>  1084

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ile Ala Ser Gly Arg Thr Phe Gly Thr Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Ser Ser Gly Gly Ser Ala Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95
```

```
Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1085
<211>  142
<212>  PRT
<213>  Homo sapiens

<400>  1085

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ile Ala Ser Gly Arg Thr Phe Gly Thr Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Ser Thr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn His Val Asp Trp Pro Tyr
            100                 105                 110
```

```
Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1086
<211>  142
<212>  PRT
<213>  Homo sapiens

<400>  1086

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Ser Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Ala Arg Thr Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
```

130 135 140

<210> 1087
<211> 142
<212> PRT
<213> Homo sapiens

<400> 1087

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Ser Arg Glu Leu Val
35 40 45

Ala Ala Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65 70 75 80

Gln Thr Asn Ser Pro Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Thr Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1088
<211> 142

<212> PRT
<213> Homo sapiens

<400> 1088

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Thr Tyr
20 25 30

Ala Leu Ala Trp Phe Arg Gln Ala Pro Gly Lys Ser Arg Glu Leu Val
35 40 45

Ala Ala Ile Ser Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65 70 75 80

Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Lys Thr Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1089
<211> 142
<212> PRT
<213> Homo sapiens

<400> 1089

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ala Phe Gly Ser Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Leu Glu Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Ala Arg Thr Gly Gly Ala Ala Tyr Thr Arg Arg Ile Asp Trp Pro Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1090
<211>  142
<212>  PRT
<213>  Homo sapiens

<400>  1090

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
```

```
            20                  25                  30

Ala Met Gly Trp Phe Arg Gln Ala Ala Gly Lys Glu Arg Glu Leu Val
        35                  40                  45

Ala Ala Ile Ser Ala Gly Gly Ser Thr Leu Tyr Ala Asp Asn Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65                  70                  75                  80

Leu Ser Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn His Ile Asp Trp Pro Tyr
            100                 105                 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1091
<211>  142
<212>  PRT
<213>  Homo sapiens

<400>  1091

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
            20                  25                  30

Ala Met Gly Trp Phe Arg Gln Ala Ala Gly Lys Glu Arg Glu Leu Val
        35                  40                  45
```

```
Ala Ala Ile Ser Ala Gly Gly Ser Thr Leu Tyr Ala Asp Asn Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65                  70                  75                  80

Leu Ser Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn His Ile Asp Trp Pro Tyr
            100                 105                 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1092
<211>  142
<212>  PRT
<213>  Homo sapiens

<400>  1092

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
            20                  25                  30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45

Ala Ala Ile Ser Ser Gly Gly Ser Thr Leu 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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Ala Arg Ser Gly Gly Ala Tyr Tyr Thr Ala Arg Val Asp Trp Pro Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1093
<211>  142
<212>  PRT
<213>  Homo sapiens

<400>  1093

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Ser Ser Gly Gly Ser Thr Leu Tyr Ala Gly Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Lys Asp Asn Ala Lys Asn Thr Val Tyr Leu
65                  70                  75                  80
```

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Ser Gly Gly Ala Tyr Tyr Thr Ala Arg Val Asp Trp Pro Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1094
<211> 142
<212> PRT
<213> Homo sapiens

<400> 1094

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1 5 10 15

Ser Pro Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Ala Ile Ser Ser Gly Gly Ile Thr Tyr 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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Ser Gly Ser Ala Tyr Tyr Thr Thr Arg Val Asp Trp Pro Tyr

100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1095
<211> 142
<212> PRT
<213> Homo sapiens

<400> 1095

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Asn Ile Asp Ser Ile Ala
20 25 30

Ser Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Ala Ile Ser Val Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65 70 75 80

Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Ser Arg Ile Asp Trp Pro Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

```
Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1096
<211>  142
<212>  PRT
<213>  Homo sapiens

<400>  1096

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Glu Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Gly Ile Ser Ser Gly Gly Ile Thr Asn Tyr Ala His Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Ile Asp Lys Asn Thr Val Phe Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Ala Arg Ser Gly Gly Ala Tyr Tyr Thr Ser Arg Val Asp Trp Pro Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 1097
<211> 142
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (13)..(13)
<223> Xaa can be any naturally occurring amino acid

<400> 1097

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Xaa Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Asp Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Ile
        35                  40                  45


Ala Gly Ile Ser Trp Gly Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Met Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Ala Arg Leu Ser Gly Val Ser Arg Ser Asp Arg Pro Tyr Asp Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 1098
<211> 142
<212> PRT
<213> Homo sapiens

<400> 1098

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Met Tyr
20 25 30

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Ser Ile Ser Ser Gly Gly Ser Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Lys Thr Val Tyr Leu
65 70 75 80

Gln Met Met Ser Leu Glu Pro Glu Ala Thr Gly Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Asp Gly Ser Ala Leu Tyr Thr Ala His Ser Asp Trp Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1099
<211> 142
<212> PRT

<213> Homo sapiens

<400> 1099

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asp
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Arg Thr Phe Ser Met Tyr
20 25 30

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Gly Ile Ser Ser Gly Gly Ser Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Lys Lys Thr Val Tyr Leu
65 70 75 80

Gln Met Met Ser Leu Glu Pro Glu Asp Thr Gly Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Ser Gly Ser Ala Tyr Phe Ser Gly Arg Tyr Tyr Trp Asn Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1100
<211> 142
<212> PRT
<213> Homo sapiens

<400> 1100

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Tyr
20 25 30

Val Met Gly Trp Phe Arg Gln Val Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Ala Ile Thr Ser Gly Leu Ser Thr Tyr Tyr Ala Asp Ser Leu Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Met Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Leu Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Glu Gly Gly Gly Ile Trp Thr Ser Ser Thr Gln Tyr Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1101
<211> 137
<212> PRT
<213> Homo sapiens

<400> 1101

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Thr Ile Phe Ser Ser Gly
20 25 30

```
Ala Met Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu
        35                  40                  45


Trp Val Ala Gly Ile Thr Gly Ser Arg Thr Thr Thr Tyr Ala Asp Ser
    50                  55                  60


Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Thr Val
65                  70                  75                  80


Phe Leu Gln Met Asn Asn Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr
                85                  90                  95


Cys Asn Leu Trp Pro Pro Ser Arg Pro Asp His Trp Gly Gln Gly Thr
            100                 105                 110


Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp
        115                 120                 125


Tyr Gly Ser His His His His His His
    130                 135


<210>  1102
<211>  134
<212>  PRT
<213>  Homo sapiens

<400>  1102

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Thr Ile Ser Ser Gly Ala
            20                  25                  30


Met Gly Trp Tyr Arg Gln Val Pro Gly Lys Gln Arg Glu Trp Val Ala
        35                  40                  45
```

```
Gly Ile Thr Gly Ser Arg Thr Thr Met Tyr Thr Glu Ser Val Lys Gly
    50                  55                  60


Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Thr Val Phe Leu Gln
65                  70                  75                  80


Met Asn Asn Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys Asn Leu
                85                  90                  95


Trp Pro Pro Ser Arg Pro Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
        115                 120                 125


His His His His His His
    130


<210>  1103
<211>  115
<212>  PRT
<213>  Homo sapiens

<400>  1103

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Gly Phe Asp Ser Arg Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Trp Val
        35                  40                  45


Ala Thr Ile Thr Ser Asp Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60
```

```
Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Ala Ala Pro Pro Ile Phe Gly Ser Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  1104
<211>  115
<212>  PRT
<213>  Homo sapiens

<400>  1104

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Arg Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Thr Phe Asp Ser Arg Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Trp Val
        35                  40                  45


Ala Thr Ile Thr Thr Asp Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60


Ala Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Ala Ala Pro Pro Ile Phe Gly Ser Trp Gly Gln Gly Thr Gln Val Thr
```

100 105 110

Val Ser Ser
115

<210> 1105
<211> 115
<212> PRT
<213> Homo sapiens

<400> 1105

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Asp Ser Arg Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Trp Val
35 40 45

Ala Thr Ile Thr Thr Asp Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Ala Arg Phe Thr Val Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Ala Ala Pro Pro Ile Phe Asn Ser Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser
115

<210> 1106
<211> 115

<212> PRT
<213> Homo sapiens

<400> 1106

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Asp Ile Arg Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Thr Arg Arg Glu Trp Val
35 40 45

Ala Thr Ile Thr Thr Asp Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Ala Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Leu Ala Pro Pro Ile Phe Gly Ser Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser
115

<210> 1107
<211> 115
<212> PRT
<213> Homo sapiens

<400> 1107

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Asp Ser Arg Asn
            20                  25                  30


Thr Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Trp Val
        35                  40                  45


Ala Thr Ile Thr Thr Gly Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60


Ala Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Leu Ala Pro Pro Ile Phe Asn Ser Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  1108
<211>  115
<212>  PRT
<213>  Homo sapiens

<400>  1108

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Thr Val Ala Glu Ser Ile Asp Val Arg Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Trp Val
        35                  40                  45


Ala Thr Ile Thr Thr Gly Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
```

50 55 60

Ala Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Ala Ala Pro Pro Ile Leu Asn Ser Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser
115

<210> 1109
<211> 115
<212> PRT
<213> Homo sapiens

<400> 1109

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Arg Val Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ser Phe Asp Ser Arg Asn
20 25 30

Ser Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Trp Val
35 40 45

Ala Thr Ile Thr Ser Gly Ser Arg Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Ala Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asp Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

```
Ala Ala Pro Pro Ile Phe Asn Ser Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  1110
<211>  115
<212>  PRT
<213>  Homo sapiens

<400>  1110

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Arg Leu Phe Ser Ala Asn
            20                  25                  30


Thr Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Leu Val
        35                  40                  45


Ala Thr Ile Leu Ser Ser Gly Ser Thr Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asp Ala Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Leu Ala Pro Pro Pro Glu Gly Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser
        115
```

<210> 1111
<211> 115
<212> PRT
<213> Homo sapiens

<400> 1111

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Arg Leu Phe Ser Ala Asn
20 25 30

Thr Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Leu Val
35 40 45

Ala Thr Ile Leu Ser Ser Gly Ser Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asp Gly Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe Ala Pro Pro Pro Glu Gly Tyr Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser
115

<210> 1112
<211> 117
<212> PRT
<213> Homo sapiens

<400> 1112

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Val Gly Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Leu Gly Asn Gln Arg Glu Leu Val
35 40 45

Ala Gly Ile Thr Ser Asp Gly Thr Thr Tyr Tyr Pro Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Asp Lys Asn Thr Ile Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Leu Trp Pro Pro Arg Ile Gly Phe Ala Ser Trp Gly Gln Gly Thr Gln
100 105 110

Val Thr Val Ser Ser
115

<210> 1113
<211> 117
<212> PRT
<213> Homo sapiens

<400> 1113

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Val Gly Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Leu Gly Asn Gln Arg Glu Leu Val
35 40 45

```
Ala Gly Ile Thr Ser Asp Gly Thr Thr Tyr Tyr Pro Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Asp Lys Asn Thr Ile Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Leu Trp Pro Pro Arg Ile Gly Phe Ala Ser Trp Gly Gln Gly Thr Gln
            100                 105                 110

Val Thr Val Ser Ser
        115
```

<210> 1114
<211> 117
<212> PRT
<213> Homo sapiens

<400> 1114

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Arg Ala Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Val Gly Asn
            20                  25                  30

Ala Met Gly Trp Tyr Arg Gln Ala Leu Gly Asn Gln Arg Glu Leu Val
        35                  40                  45

Ala Gly Ile Thr Ser Asp Gly Thr Thr Tyr Tyr Pro Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Asp Lys Asn Thr Ile Tyr Leu
65                  70                  75                  80
```

```
Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Leu Trp Pro Pro Arg Ile Gly Phe Ala Ser Trp Gly Gln Gly Thr Gln
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  1115
<211>  117
<212>  PRT
<213>  Homo sapiens

<400>  1115

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Val Gly Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Leu Gly Asn Gln Arg Glu Leu Val
        35                  40                  45


Ala Gly Ile Thr Ser Asp Gly Thr Thr Tyr Tyr Pro Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Asp Lys Asn Thr Ile Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Leu Trp Pro Pro Arg Ile Gly Phe Ala Ser Trp Gly Gln Gly Thr Gln
            100                 105                 110
```

Val Thr Val Ser Ser
        115

<210> 1116
<211> 117
<212> PRT
<213> Homo sapiens

<400> 1116

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Ser Met Leu Asn
            20   25   30

Ser Met Gly Trp Tyr Arg Gln Ala Leu Gly Lys Gln Arg Glu Phe Val
        35   40   45

Ala Gly Ile Thr Ser Gly Gly Arg Thr Asn Tyr Ala Asp Ser Val Lys
    50   55   60

Gly Arg Phe Ala Ile Ser Arg Asp Asn Asp Lys Asn Thr Val Tyr Leu
65   70   75   80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85   90   95

Thr Trp Pro Pro Arg Ile Ala Phe Asp Ser Trp Gly Gln Gly Thr Gln
            100   105   110

Val Thr Val Ser Ser
        115

<210> 1117
<211> 121
<212> PRT
<213> Homo sapiens

<400> 1117

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Ser Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Ala Gly Lys Arg Arg Glu Leu Val
35 40 45

Ala Gly Ile Arg Ser Asp Gly Asn Thr Asn Tyr Val Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Arg Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Tyr Trp Pro Pro Pro Leu Arg Gln Gly Gly Asp Tyr Ala Tyr Trp Gly
100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 1118
<211> 117
<212> PRT
<213> Homo sapiens

<400> 1118

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Val Ser Gly Ser Phe Asp Ser Arg Asn
20 25 30

```
Ala Met Ala Trp Tyr Arg Gln Ala Leu Gly Lys Glu Arg Val Trp Val
        35                  40                  45


Ala Gly Ile Ile Ser Asp Gly Ser Thr Asn Tyr Ala Asp Ala Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Asp Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Ala Trp Pro Pro Arg Ile Gly Leu Gly Ser Trp Gly Gln Gly Thr Gln
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  1119
<211>  116
<212>  PRT
<213>  Homo sapiens

<400>  1119

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Thr Met Ser Ser Ile Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Gly Ile Leu Ser Asp Gly Thr Thr Lys Tyr Val Glu Ser Val Lys
    50                  55                  60
```

```
Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val His Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Val Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Phe Phe Pro Pro Pro Val Pro Ala Ser Trp Gly Gln Gly Thr Gln Val
            100                 105                 110


Thr Val Ser Ser
        115


<210>  1120
<211>  115
<212>  PRT
<213>  Homo sapiens

<400>  1120

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Ile Ser Ser Met Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Leu Val
        35                  40                  45


Ala Gly Leu Gly Ser Gly Val Ser Thr Thr Tyr Ala Asp Ala Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Arg Trp Pro Pro Pro Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
```

100 105 110

Val Ser Ser
115

<210> 1121
<211> 120
<212> PRT
<213> Homo sapiens

<400> 1121

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Val Ser Gly Thr Ile Leu Ser Ser Asn
20 25 30

Ser Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Leu Val
35 40 45

Ala Ser Ile Ser Thr Asp Gly Ser Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Val Phe Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Phe His Pro Pro Val Val Arg Asp Trp Gly Asp Thr Tyr Trp Gly Thr
100 105 110

Gln Val Thr Val Ser Ser Gln Gly
115 120

<210> 1122
<211> 117

<212> PRT
<213> Homo sapiens

<400> 1122

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Ser Ile Phe Ser Ile Gly
            20                  25                  30


Thr Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Leu Val
        35                  40                  45


Ala Phe Ile Thr Val Asp His Asn Thr Tyr Tyr Thr Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Thr Glu Asn Asp Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Arg Ala Pro Pro Ser Thr Asp Gly Asp Arg Trp Gly Gln Gly Thr Gln
            100                 105                 110


Val Thr Val Ser Ser
        115
```

<210> 1123
<211> 123
<212> PRT
<213> Homo sapiens

<400> 1123

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Thr Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Ser Asn Gly Gly Ser Ala Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120


<210>  1124
<211>  123
<212>  PRT
<213>  Homo sapiens

<400>  1124

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Ser Asn Gly Gly Ser Ala Tyr Tyr Ala Asp Ser Val Lys
```

50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65 70 75 80

Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 1125
<211> 123
<212> PRT
<213> Homo sapiens

<400> 1125

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ile Ala Ser Gly Arg Thr Phe Gly Thr Tyr
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Ala Ile Ser Ser Gly Gly Ser Ala Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65 70 75 80

Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

```
Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120


<210>  1126
<211>  123
<212>  PRT
<213>  Homo sapiens

<400>  1126

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ile Ala Ser Gly Arg Thr Phe Gly Thr Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Ser Thr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn His Val Asp Trp Pro Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120
```

<210> 1127
<211> 123
<212> PRT
<213> Homo sapiens

<400> 1127

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Ser Arg Glu Leu Val
35 40 45

Ala Ala Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65 70 75 80

Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Thr Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 1128
<211> 123
<212> PRT
<213> Homo sapiens

<400> 1128

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Ser Arg Glu Leu Val
35 40 45

Ala Ala Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65 70 75 80

Gln Thr Asn Ser Pro Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Thr Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 1129
<211> 123
<212> PRT
<213> Homo sapiens

<400> 1129

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Thr Tyr
20 25 30

Ala Leu Ala Trp Phe Arg Gln Ala Pro Gly Lys Ser Arg Glu Leu Val
35 40 45

```
Ala Ala Ile Ser Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Ala Lys Thr Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro Tyr
            100                 105                 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120
```

<210> 1130
<211> 123
<212> PRT
<213> Homo sapiens

<400> 1130

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ala Phe Gly Ser Tyr
            20                  25                  30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Leu Glu Arg Glu Leu Val
        35                  40                  45

Ala Ala Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65                  70                  75                  80
```

```
Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Ala Arg Thr Gly Gly Ala Ala Tyr Thr Arg Arg Ile Asp Trp Pro Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120


<210>  1131
<211>  123
<212>  PRT
<213>  Homo sapiens

<400>  1131

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Ala Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Ser Ala Gly Gly Ser Thr Leu Tyr Ala Asp Asn Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65                  70                  75                  80


Leu Ser Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn His Ile Asp Trp Pro Tyr
            100                 105                 110
```

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115   120

<210> 1132
<211> 123
<212> PRT
<213> Homo sapiens

<400> 1132

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
            20   25   30

Ala Met Gly Trp Phe Arg Gln Ala Ala Gly Lys Glu Arg Glu Leu Val
        35   40   45

Ala Ala Ile Ser Ala Gly Gly Ser Thr Leu Tyr Ala Asp Asn Val Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65   70   75   80

Leu Ser Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn His Ile Asp Trp Pro Tyr
            100   105   110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115   120

<210> 1133
<211> 123
<212> PRT
<213> Homo sapiens

<400> 1133

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Ala Ile Ser Ser Gly Gly Ser Thr Leu 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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Ser Gly Gly Ala Tyr Tyr Thr Ala Arg Val Asp Trp Pro Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 1134
<211> 123
<212> PRT
<213> Homo sapiens

<400> 1134

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
20 25 30

```
Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Ser Ser Gly Gly Ser Thr Leu Tyr Ala Gly Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Lys Asp Asn Ala Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Ala Arg Ser Gly Gly Ala Tyr Tyr Thr Ala Arg Val Asp Trp Pro Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120


<210>  1135
<211>  123
<212>  PRT
<213>  Homo sapiens

<400>  1135

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Glu Ala Glu Gly
1               5                   10                  15


Ser Pro Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Ser Ser Gly Gly Ile Thr Tyr 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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Ser Gly Ser Ala Tyr Tyr Thr Thr Arg Val Asp Trp Pro Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 1136
<211> 123
<212> PRT
<213> Homo sapiens

<400> 1136

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Asn Ile Asp Ser Ile Ala
20 25 30

Ser Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Ala Ile Ser Val Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr Leu
65 70 75 80

Gln Thr Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Ser Arg Ile Asp Trp Pro Tyr

100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 1137
<211> 123
<212> PRT
<213> Homo sapiens

<400> 1137

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Glu Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Gly Ser Tyr
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Gly Ile Ser Ser Gly Gly Ile Thr Asn Tyr Ala His Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Ile Asp Lys Asn Thr Val Phe Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Ser Gly Gly Ala Tyr Tyr Thr Ser Arg Val Asp Trp Pro Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 1138
<211> 123

<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (13)..(13)
<223> Xaa can be any naturally occurring amino acid

<400> 1138

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Xaa Ala Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Asp Tyr
            20   25   30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Ile
        35   40   45

Ala Gly Ile Ser Trp Gly Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Met Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Ala Arg Leu Ser Gly Val Ser Arg Ser Asp Arg Pro Tyr Asp Tyr
            100   105   110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115   120

<210> 1139
<211> 123
<212> PRT
<213> Homo sapiens

<400> 1139

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Met Tyr
20 25 30

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Ser Ile Ser Ser Gly Gly Ser Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Lys Thr Val Tyr Leu
65 70 75 80

Gln Met Met Ser Leu Glu Pro Glu Ala Thr Gly Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Asp Gly Ser Ala Leu Tyr Thr Ala His Ser Asp Trp Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 1140
<211> 123
<212> PRT
<213> Homo sapiens

<400> 1140

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asp
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Arg Thr Phe Ser Met Tyr
20 25 30

```
Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Gly Ile Ser Ser Gly Gly Ser Thr Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Lys Lys Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Met Ser Leu Glu Pro Glu Asp Thr Gly Val Tyr Tyr Cys Ala
                85                  90                  95


Ala Arg Ser Gly Ser Ala Tyr Phe Ser Gly Arg Tyr Tyr Trp Asn Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120


<210>  1141
<211>  123
<212>  PRT
<213>  Homo sapiens

<400>  1141

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Tyr
            20                  25                  30


Val Met Gly Trp Phe Arg Gln Val Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Thr Ser Gly Leu Ser Thr Tyr Tyr Ala Asp Ser Leu Lys
    50                  55                  60
```

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Met Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Leu Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ala Arg Glu Gly Gly Gly Ile Trp Thr Ser Ser Thr Gln Tyr Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 1142
<211> 118
<212> PRT
<213> Homo sapiens

<400> 1142

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Thr Ile Phe Ser Ser Gly
20 25 30

Ala Met Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu
35 40 45

Trp Val Ala Gly Ile Thr Gly Ser Arg Thr Thr Thr Tyr Ala Asp Ser
50 55 60

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Thr Val
65 70 75 80

Phe Leu Gln Met Asn Asn Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Asn Leu Trp Pro Pro Ser Arg Pro Asp His Trp Gly Gln Gly Thr

100 105 110

Gln Val Thr Val Ser Ser
115

<210> 1143
<211> 115
<212> PRT
<213> Homo sapiens

<400> 1143

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Thr Ile Ser Ser Gly Ala
20 25 30

Met Gly Trp Tyr Arg Gln Val Pro Gly Lys Gln Arg Glu Trp Val Ala
35 40 45

Gly Ile Thr Gly Ser Arg Thr Thr Met Tyr Thr Glu Ser Val Lys Gly
50 55 60

Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Thr Val Phe Leu Gln
65 70 75 80

Met Asn Asn Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys Asn Leu
85 90 95

Trp Pro Pro Ser Arg Pro Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser
115

<210> 1144
<211> 10

<212> PRT
<213> Homo sapiens

<400> 1144

Gly Gly Phe Asp Ser Arg Asn Ala Met Gly
1   5   10

<210> 1145
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1145

Gly Thr Phe Asp Ser Arg Asn Ala Met Gly
1   5   10

<210> 1146
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1146

Gly Ser Phe Asp Ser Arg Asn Ala Met Gly
1   5   10

<210> 1147
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1147

Gly Ser Ile Asp Ile Arg Asn Ala Met Gly
1   5   10

<210> 1148
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1148

Gly Ser Ile Asp Ser Arg Asn Thr Met Gly
1   5   10

<210> 1149
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1149

Glu Ser Ile Asp Val Arg Asn Ala Met Gly
1   5   10

<210> 1150
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1150

Gly Ser Phe Asp Ser Arg Asn Ser Met Gly
1   5   10

<210> 1151
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1151

Gly Arg Leu Phe Ser Ala Asn Thr Met Gly
1   5   10

<210> 1152
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1152

Gly Ser Ile Phe Val Gly Asn Ala Met Gly
1   5   10

<210> 1153
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1153

Gly Ser Ile Ser Met Leu Asn Ser Met Gly
1 5 10

<210> 1154
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1154

Gly Ser Ile Phe Ser Ser Asn Ala Met Gly
1 5 10

<210> 1155
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1155

Gly Ser Phe Asp Ser Arg Asn Ala Met Ala
1 5 10

<210> 1156
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1156

Gly Thr Met Ser Ser Ile Asn Ala Met Gly
1 5 10

<210> 1157
<211> 10
<212> PRT

<213> Homo sapiens

<400> 1157

Gly Ile Ile Ser Ser Met Asn Ala Met Gly
1 5 10

<210> 1158
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1158

Gly Thr Ile Leu Ser Ser Asn Ser Met Gly
1 5 10

<210> 1159
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1159

Arg Ser Ile Phe Ser Ile Gly Thr Met Gly
1 5 10

<210> 1160
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1160

Gly Arg Thr Phe Ser Thr Tyr Ala Met Gly
1 5 10

<210> 1161
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1161

Gly Arg Thr Phe Ser Ser Tyr Ala Met Gly
1   5   10

<210> 1162
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1162

Gly Arg Thr Phe Gly Thr Tyr Ala Met Gly
1   5   10

<210> 1163
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1163

Gly Arg Thr Phe Gly Ser Tyr Ala Met Gly
1   5   10

<210> 1164
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1164

Gly Arg Thr Phe Gly Thr Tyr Ala Leu Ala
1   5   10

<210> 1165
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1165

Gly Arg Ala Phe Gly Ser Tyr Ala Met Gly
1   5   10

<210> 1166
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1166

Gly Asn Ile Asp Ser Ile Ala Ser Met Gly
1   5   10

<210> 1167
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1167

Gly Arg Thr Phe Ser Asp Tyr Ala Met Gly
1   5   10

<210> 1168
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1168

Gly Arg Thr Phe Ser Met Tyr Ala Ile Gly
1   5   10

<210> 1169
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1169

Glu Arg Thr Phe Ser Met Tyr Ala Ile Gly
1   5   10

<210> 1170
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1170

Gly Arg Thr Phe Ser Ser Tyr Val Met Gly
1 5 10

<210> 1171
<211> 12
<212> PRT
<213> Homo sapiens

<400> 1171

Gly Thr Ile Phe Ser Ser Gly Ala Met Ala Met Gly
1 5 10

<210> 1172
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1172

Gly Thr Ile Ser Ser Gly Ala Met Gly
1 5

<210> 1173
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1173

Thr Ile Thr Ser Asp Gly Arg Thr Asn
1 5

<210> 1174
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1174

Thr Ile Thr Thr Asp Gly Arg Thr Asn

1 5

<210> 1175
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1175

Thr Ile Thr Thr Gly Gly Arg Thr Asn
1 5

<210> 1176
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1176

Thr Ile Thr Ser Gly Ser Arg Thr Asn
1 5

<210> 1177
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1177

Thr Ile Leu Ser Ser Gly Ser Thr Asn
1 5

<210> 1178
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1178

Gly Ile Thr Ser Asp Gly Thr Thr Tyr
1 5

<210> 1179

<211> 9
<212> PRT
<213> Homo sapiens

<400> 1179

Gly Ile Thr Ser Gly Gly Arg Thr Asn
1 5

<210> 1180
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1180

Gly Ile Arg Ser Asp Gly Asn Thr Asn
1 5

<210> 1181
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1181

Gly Ile Ile Ser Asp Gly Ser Thr Asn
1 5

<210> 1182
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1182

Gly Ile Leu Ser Asp Gly Thr Thr Lys
1 5

<210> 1183
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1183

Gly Leu Gly Ser Gly Val Ser Thr Thr
1 5

<210> 1184
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1184

Ser Ile Ser Thr Asp Gly Ser Thr Asn
1 5

<210> 1185
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1185

Phe Ile Thr Val Asp His Asn Thr Tyr
1 5

<210> 1186
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1186

Ala Ile Ser Asn Gly Gly Ser Ala Tyr
1 5

<210> 1187
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1187

Ala Ile Ser Ser Gly Gly Ser Ala Tyr
1 5

<210> 1188
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1188

Ala Ile Ser Thr Gly Gly Ser Thr Tyr
1 5

<210> 1189
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1189

Ala Ile Ser Ser Gly Gly Thr Thr Tyr
1 5

<210> 1190
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1190

Ala Ile Ser Ser Gly Gly Ser Thr Tyr
1 5

<210> 1191
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1191

Ala Ile Ser Ala Gly Gly Ser Thr Leu
1 5

<210> 1192
<211> 9

<212> PRT
<213> Homo sapiens

<400> 1192

Ala Ile Ser Ser Gly Gly Ser Thr Leu
1 5

<210> 1193
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1193

Ala Ile Ser Ser Gly Gly Ile Thr Tyr
1 5

<210> 1194
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1194

Ala Ile Ser Val Gly Gly Ser Thr Tyr
1 5

<210> 1195
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1195

Gly Ile Ser Ser Gly Gly Ile Thr Asn
1 5

<210> 1196
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1196

Gly Ile Ser Trp Gly Gly Ser Ser Thr Tyr
1 5 10

<210> 1197
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1197

Ser Ile Ser Ser Gly Gly Ser Thr Asn
1 5

<210> 1198
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1198

Gly Ile Ser Ser Gly Gly Ser Thr Asn
1 5

<210> 1199
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1199

Ala Ile Thr Ser Gly Leu Ser Thr Tyr
1 5

<210> 1200
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1200

Gly Ile Thr Gly Ser Arg Thr Thr Thr
1 5

<210> 1201
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1201

Gly Ile Thr Gly Ser Arg Thr Thr Met
1   5

<210> 1202
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1202

Asn Ala Ala Pro Pro Ile Phe Gly Ser
1   5

<210> 1203
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1203

Asn Ala Ala Pro Pro Ile Phe Asn Ser
1   5

<210> 1204
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1204

Asn Leu Ala Pro Pro Ile Phe Gly Ser
1   5

<210> 1205
<211> 9
<212> PRT

<213> Homo sapiens

<400> 1205

Asn Leu Ala Pro Pro Ile Phe Asn Ser
1 5

<210> 1206
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1206

Asn Ala Ala Pro Pro Ile Leu Asn Ser
1 5

<210> 1207
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1207

Asn Leu Ala Pro Pro Pro Glu Gly Tyr
1 5

<210> 1208
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1208

Asn Phe Ala Pro Pro Pro Glu Gly Tyr
1 5

<210> 1209
<211> 11
<212> PRT
<213> Homo sapiens

<400> 1209

Asn Leu Trp Pro Pro Arg Ile Gly Phe Ala Ser
1   5   10

<210> 1210
<211> 11
<212> PRT
<213> Homo sapiens

<400> 1210

Asn Thr Trp Pro Pro Arg Ile Ala Phe Asp Ser
1   5   10

<210> 1211
<211> 15
<212> PRT
<213> Homo sapiens

<400> 1211

Asn Tyr Trp Pro Pro Pro Leu Arg Gln Gly Gly Asp Tyr Ala Tyr
1   5   10   15

<210> 1212
<211> 11
<212> PRT
<213> Homo sapiens

<400> 1212

Asn Ala Trp Pro Pro Arg Ile Gly Leu Gly Ser
1   5   10

<210> 1213
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1213

Asn Phe Phe Pro Pro Pro Val Pro Ala Ser
1   5   10

<210> 1214
<211> 9
<212> PRT
<213> Homo sapiens

<400> 1214

Asn Arg Trp Pro Pro Pro Tyr Asp Tyr
1 5

<210> 1215
<211> 14
<212> PRT
<213> Homo sapiens

<400> 1215

Asn Phe His Pro Pro Val Val Arg Asp Trp Gly Asp Thr Tyr
1 5 10

<210> 1216
<211> 11
<212> PRT
<213> Homo sapiens

<400> 1216

Asn Arg Ala Pro Pro Ser Thr Asp Gly Asp Arg
1 5 10

<210> 1217
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1217

Ala Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro
1 5 10 15

Tyr

<210> 1218
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1218

Ala Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn His Val Asp Trp Pro
1   5   10   15

Tyr

<210> 1219
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1219

Ala Ala Arg Thr Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro
1   5   10   15

Tyr

<210> 1220
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1220

Ala Ala Lys Thr Gly Ser Ala Tyr Tyr Thr Asn Arg Ile Asp Trp Pro
1   5   10   15

Tyr

<210> 1221
<211> 17
<212> PRT

<213> Homo sapiens

<400> 1221

Ala Ala Arg Thr Gly Gly Ala Ala Tyr Thr Arg Arg Ile Asp Trp Pro
1 5 10 15

Tyr

<210> 1222
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1222

Ala Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Asn His Ile Asp Trp Pro
1 5 10 15

Tyr

<210> 1223
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1223

Ala Ala Arg Ser Gly Gly Ala Tyr Tyr Thr Ala Arg Val Asp Trp Pro
1 5 10 15

Tyr

<210> 1224
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1224

Ala Ala Arg Ser Gly Ser Ala Tyr Tyr Thr Thr Arg Val Asp Trp Pro
1 5 10 15

Tyr

<210> 1225
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1225

Ala Ala Arg Arg Gly Ser Ala Tyr Tyr Thr Ser Arg Ile Asp Trp Pro
1 5 10 15

Tyr

<210> 1226
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1226

Ala Ala Arg Ser Gly Gly Ala Tyr Tyr Thr Ser Arg Val Asp Trp Pro
1 5 10 15

Tyr

<210> 1227
<211> 16
<212> PRT
<213> Homo sapiens

<400> 1227

Ala Ala Arg Leu Ser Gly Val Ser Arg Ser Asp Arg Pro Tyr Asp Tyr
1 5 10 15

<210> 1228
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1228

Ala Ala Arg Asp Gly Ser Ala Leu Tyr Thr Ala His Ser Asp Trp Asp
1 5 10 15

Tyr

<210> 1229
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1229

Ala Ala Arg Ser Gly Ser Ala Tyr Phe Ser Gly Arg Tyr Tyr Trp Asn
1 5 10 15

Tyr

<210> 1230
<211> 17
<212> PRT
<213> Homo sapiens

<400> 1230

Ala Ala Arg Glu Gly Gly Gly Ile Trp Thr Ser Ser Thr Gln Tyr Asp
1 5 10 15

Tyr

<210> 1231

<211> 10
<212> PRT
<213> Homo sapiens

<400> 1231

Asn Leu Trp Pro Pro Ser Arg Pro Asp His
1 5 10

<210> 1232
<211> 10
<212> PRT
<213> Homo sapiens

<400> 1232

Asn Leu Trp Pro Pro Ser Arg Pro Asp Tyr
1 5 10

<210> 1233
<211> 333
<212> PRT
<213> Homo sapiens

<400> 1233

Met Glu Ser Ser Gly Asn Pro Glu Ser Thr Thr Phe Phe Tyr Tyr Asp
1 5 10 15

Leu Gln Ser Gln Pro Cys Glu Asn Gln Ala Trp Val Phe Ala Thr Leu
20 25 30

Ala Thr Thr Val Leu Tyr Cys Leu Val Phe Leu Leu Ser Leu Val Gly
35 40 45

Asn Ser Leu Val Leu Trp Val Leu Val Lys Tyr Glu Ser Leu Glu Ser
50 55 60

Leu Thr Asn Ile Phe Ile Leu Asn Leu Cys Leu Ser Asp Leu Val Phe
65 70 75 80

```
Ala Cys Leu Leu Pro Val Trp Ile Ser Pro Tyr His Trp Gly Trp Val
                85                  90                  95

Leu Gly Asp Phe Leu Cys Lys Leu Leu Asn Met Ile Phe Ser Ile Ser
            100                 105                 110

Leu Tyr Ser Ser Ile Phe Phe Leu Thr Ile Met Thr Ile His Arg Tyr
        115                 120                 125

Leu Ser Val Val Ser Pro Leu Ser Thr Leu Arg Val Pro Thr Leu Arg
    130                 135                 140

Cys Arg Val Leu Val Thr Met Ala Val Trp Val Ala Ser Ile Leu Ser
145                 150                 155                 160

Ser Ile Leu Asp Thr Ile Phe His Lys Val Leu Ser Ser Gly Cys Asp
                165                 170                 175

Tyr Ser Glu Leu Thr Trp Tyr Leu Thr Ser Val Tyr Gln His Asn Leu
            180                 185                 190

Phe Phe Leu Leu Ser Leu Gly Ile Ile Leu Phe Cys Tyr Val Glu Ile
        195                 200                 205

Leu Arg Thr Leu Phe Arg Ser Arg Ser Lys Arg Arg His Arg Thr Val
    210                 215                 220

Lys Leu Ile Phe Ala Ile Val Val Ala Tyr Phe Leu Ser Trp Gly Pro
225                 230                 235                 240

Tyr Asn Phe Thr Leu Phe Leu Gln Thr Leu Phe Arg Thr Gln Ile Ile
                245                 250                 255

Arg Ser Cys Glu Ala Lys Gln Gln Leu Glu Tyr Ala Leu Leu Ile Cys
            260                 265                 270
```

```
Arg Asn Leu Ala Phe Ser His Cys Cys Phe Asn Pro Val Leu Tyr Val
        275                 280                 285


Phe Val Gly Val Lys Phe Arg Thr His Leu Lys His Val Leu Arg Gln
    290                 295                 300


Phe Trp Phe Cys Arg Leu Gln Ala Pro Ser Pro Ala Ser Ile Pro His
305                 310                 315                 320


Ser Pro Gly Ala Phe Ala Tyr Glu Gly Ala Ser Phe Tyr
                325                 330


<210>  1234
<211>  450
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (muromonab-CD3 heavy chain)

<400>  1234

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1               5                   10                  15


Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
            20                  25                  30


Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80


Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr
        115                 120                 125

Pro Leu Ala Pro Val Cys Gly Gly Thr Thr Gly Ser Ser Val Thr Leu
    130                 135                 140

Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp
145                 150                 155                 160

Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser
            180                 185                 190

Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser
        195                 200                 205

Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285
```

```
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210>  1235
<211>  213
```

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (muromonab-CD3 light chain)

<400> 1235

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala His Phe Arg Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
85 90 95

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg Ala Asp Thr Ala Pro
100 105 110

Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
115 120 125

Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
130 135 140

Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn
145 150 155 160

```
Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
                165                 170                 175


Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
            180                 185                 190


Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
        195                 200                 205


Asn Arg Asn Glu Cys
    210


<210>  1236
<211>  449
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (otelixizumab heavy chain)

<400>  1236

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
            20                  25                  30


Pro Met Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Thr Ile Ser Thr Ser Gly Gly Arg Thr Tyr Tyr Arg Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Lys Phe Arg Gln Tyr Ser Gly Gly Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285
```

```
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445

Lys
```

<210> 1237
<211> 216

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (otelixizumab light chain)

<400> 1237

Asp Ile Gln Leu Thr Gln Pro Asn Ser Val Ser Thr Ser Leu Gly Ser
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Leu Ser Ser Gly Asn Ile Glu Asn Asn
20 25 30

Tyr Val His Trp Tyr Gln Leu Tyr Glu Gly Arg Ser Pro Thr Thr Met
35 40 45

Ile Tyr Asp Asp Asp Lys Arg Pro Asp Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Ile Asp Arg Ser Ser Asn Ser Ala Phe Leu Thr Ile His Asn
65 70 75 80

Val Ala Ile Glu Asp Glu Ala Ile Tyr Phe Cys His Ser Tyr Val Ser
85 90 95

Ser Phe Asn Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Arg Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160

```
Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175


Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190


Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205


Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210>  1238
<211>  449
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (teplizumab heavy chain)

<400>  1238

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
            20                  25                  30


Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Val
    50                  55                  60


Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Ala Phe
65                  70                  75                  80


Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
                85                  90                  95
```

```
Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Pro Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285
```

```
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445

Lys
```

<210> 1239
<211> 213

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (teplizumab light chain)

<400> 1239

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15


Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30


Asn Trp Tyr Gln Gln Thr Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
        35                  40                  45


Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60


Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu
65                  70                  75                  80


Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
                85                  90                  95


Phe Gly Gln Gly Thr Lys Leu Gln Ile Thr Arg Thr Val Ala Ala Pro
            100                 105                 110


Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125


Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140


Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160
```

```
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175


Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190


Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205


Asn Arg Gly Glu Cys
    210


<210>  1240
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (visilizumab heavy chain variable region)

<400>  1240

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ile Ser Tyr
            20                  25                  30


Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr His Tyr Asn Gln Lys Leu
    50                  55                  60


Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Ser Ala Tyr Tyr Asp Tyr Asp Gly Phe Ala Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  1241
<211>  106
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (visilizumab heavy chain variable region)

<400>  1241

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30


Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile Tyr
        35                  40                  45


Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60


Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65                  70                  75                  80


Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Pro Thr
                85                  90                  95


Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 1242
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1242

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Gly Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gln Met Gly Tyr Trp His Phe Asp Leu Trp Gly Arg Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 1243
<211> 118
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 1243

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Ser Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Gly Tyr
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Lys Tyr Tyr Val Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Gly Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gln Met Gly Tyr Trp His Phe Asp Leu Trp Gly Arg Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 1244
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1244

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

```
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210>  1245
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1245

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
```

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1246
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1246

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Met Tyr
85 90 95

```
Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
            100                 105                 110


Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210>  1247
<211>  125
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1247

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
            20                  25                  30


Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60


Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ile
65                  70                  75                  80


Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Met Tyr
                85                  90                  95


Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
            100                 105                 110
```

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120   125

<210> 1248
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1248

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
            20   25   30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50   55   60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ile
65   70   75   80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Met Tyr
                85   90   95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
            100   105   110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120   125

<210> 1249
<211> 125

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1249

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
            20   25   30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50   55   60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ile
65   70   75   80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Met Tyr
                85   90   95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
            100   105   110

Ala Tyr Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115   120   125

<210> 1250
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1250

Gln Ala Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Gln Thr Pro Gly Gln Ala Phe Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Val Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Ile Tyr Phe Cys Ala Leu Trp Tyr Ser Asn
85 90 95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 1251
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1251

Gln Ala Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

```
Asn Tyr Ala Asn Trp Val Gln Gln Thr Pro Gly Gln Ala Phe Arg Gly
        35                  40                  45


Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Val Pro Ala Arg Phe
    50                  55                  60


Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80


Gln Ala Asp Asp Glu Ser Ile Tyr Phe Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95


Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210>  1252
<211>  109
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1252

Gln Ala Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1               5                   10                  15


Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30


Asn Tyr Ala Asn Trp Val Gln Gln Thr Pro Gly Gln Ala Phe Arg Gly
        35                  40                  45


Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Val Pro Ala Arg Phe
    50                  55                  60


Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
```

```
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95


Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210>  1253
<211>  119
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1253

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
            20                  25                  30


Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Ala Thr Leu Thr Thr Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Gln Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110
```

Thr Leu Val Thr Val Ser Ser
        115

<210> 1254
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1254

Gln Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Met Ser Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20   25   30

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
        35   40   45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Arg Gly Ser
    50   55   60

Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65   70   75   80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
                85   90   95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 1255
<211> 125
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 1255

Glu Leu Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Leu Ser Pro Tyr Cys Thr Asn Gly Val Cys Trp Asp Ala Phe
            100   105   110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115   120   125

<210> 1256
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1256

Glu Leu Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Arg
1   5   10   15

```
Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Gly Asp Tyr
            20                  25                  30

Ala Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Phe Ile Arg Ser Lys Ala Tyr Gly Gly Thr Thr Glu Tyr Ala Ala
    50                  55                  60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ile
65                  70                  75                  80

Ala Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Thr Pro Gln Leu Trp Leu Leu Gln Asp Ala Phe Asp Ile Trp
            100                 105                 110

Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210>  1257
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1257

Glu Leu Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Arg
            20                  25                  30
```

```
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Asp Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Ser Gly Tyr Thr Ser Cys Arg Asp Ala Phe Asp Ile Trp Gly Gln
            100                 105                 110


Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210>  1258
<211>  126
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1258

Glu Leu Gln Leu Val Glu Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
            20                  25                  30


Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60
```

```
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80


Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Arg Gly Arg Gly Arg Phe Leu Gly Trp Leu Leu Gly Gly Ser Asn Trp
            100                 105                 110


Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210>  1259
<211>  119
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1259

Glu Leu Gln Leu Val Glu Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
            20                  25                  30


Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80
```

```
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Arg Gly Pro Asp Arg Met Gly His Gly Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110


Thr Met Val Thr Val Ser Ser
        115


<210>  1260
<211>  127
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1260

Glu Leu Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30


Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45


Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50                  55                  60


Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80


Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95


Tyr Tyr Cys Ala Arg Asp Arg Arg Arg Ile Ala Ala Arg Gln Tyr Tyr
            100                 105                 110
```

```
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125


<210>  1261
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1261

Glu Leu Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Ala Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ala Val Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Lys Ala Lys Phe Leu Gly His Tyr Tyr Gly Met Asp Val Trp Gly
            100                 105                 110


Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 1262
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1262

Glu Leu Gln Leu Val Glu Ser Gly Pro Val Leu Val Lys Pro Thr Asp
1   5   10   15

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Asn Asn Pro
            20   25   30

Arg Met Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Thr Leu Glu
        35   40   45

Trp Leu Ala His Ile Phe Pro Ser Asp Ala Lys Ala His Ser Ala Ser
    50   55   60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Ser Gln Val
65   70   75   80

Val Pro Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85   90   95

Cys Ala Arg Ile Leu Gly Glu Tyr Tyr Pro Pro Ala Trp Phe Asp Pro
            100   105   110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 1263
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 1263

Glu Leu Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Thr Ile Ser Asn Tyr
            20   25   30

Leu Asn Trp Tyr Gln Leu Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser Thr Leu Gln Ser Glu Val Pro Thr Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Gly Leu His Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Arg
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 1264
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1264

Glu Leu Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
            20   25   30

```
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  1265
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1265

Glu Leu Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Gly Asn Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Met Leu Ile
        35                  40                  45


Tyr Trp Ala Ser Ile Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60
```

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Asn Pro Gln
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1266
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1266

Glu Leu Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105

<210> 1267
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1267

```
Glu Leu Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30


Leu Asn Trp Tyr Gln Gln Lys Ser Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ser Pro Trp
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 1268
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1268

```
Glu Leu Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                  10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
            20                  25                  30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65                  70                  75                  80

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro
                85                  90                  95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 1269
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1269

```
Glu Leu Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30
```

```
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ala Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 1270
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1270

```
Glu Leu Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
            20                  25                  30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80
```

```
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
                85                  90                  95


Tyr Leu Lys Ile Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110


Lys



<210>  1271
<211>  119
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1271

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
            20                  25                  30


Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Val Thr Met Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 1272
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1272

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Val Thr Met Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 1273
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1273

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                  10                  15


Glu Arg Ala Thr Leu Ser Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30


Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
        35                  40                  45


Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala His Phe Arg Gly Ser
    50                  55                  60


Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu
65                  70                  75                  80


Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
                85                  90                  95


Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 1274
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1274

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 1275
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1275

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
            20                  25                  30


Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60


Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65                  70                  75                  80


Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Ala Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
            100                 105                 110


Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210>  1276
<211>  125
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1276

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
            20                  25                  30


Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

```
Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60


Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65                  70                  75                  80


Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Ala Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Tyr Phe
            100                 105                 110


Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210>  1277
<211>  125
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1277

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
            20                  25                  30


Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60
```

```
Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65                  70                  75                  80


Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Ala Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser His Phe
            100                 105                 110


Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210>  1278
<211>  110
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1278

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr
            20                  25                  30


Ser Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Lys Ala Pro Lys
        35                  40                  45


Gly Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Val Pro Ser Arg
    50                  55                  60


Phe Ser Gly Ser Leu Ile Gly Asp Lys Ala Thr Leu Thr Ile Ser Ser
65                  70                  75                  80


Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Leu Trp Tyr Ser
                85                  90                  95
```

```
Asn Leu Trp Val Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  1279
<211>  110
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1279

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr
            20                  25                  30


Ser Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Lys Ala Pro Lys
        35                  40                  45


Gly Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Val Pro Ala Arg
    50                  55                  60


Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
65                  70                  75                  80


Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Leu Trp Tyr Ser
                85                  90                  95


Asn Leu Trp Val Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  1280
<211>  110
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> Synthetic Sequence

<400> 1280

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr
            20   25   30

Ser Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Lys Ala Pro Lys
        35   40   45

Ala Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Val Pro Ser Arg
    50   55   60

Phe Ser Gly Ser Leu Ile Gly Asp Lys Ala Thr Leu Thr Ile Ser Ser
65   70   75   80

Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Leu Trp Tyr Ser
                85   90   95

Asn Leu Trp Val Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105   110

<210> 1281
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1281

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

```
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr
            20                  25                  30


Ser Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Lys Ala Pro Lys
        35                  40                  45


Gly Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Val Pro Ser Arg
    50                  55                  60


Phe Ser Gly Ser Leu Ile Gly Asp Lys Ala Thr Leu Thr Ile Ser Ser
65                  70                  75                  80


Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Leu Trp Tyr Ser
                85                  90                  95


Asn Leu Trp Val Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  1282

<400>  1282
000

<210>  1283
<211>  5
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (linker sequence)

<400>  1283

Gly Gly Gly Gly Ser
1               5


<210>  1284
<211>  10
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1284

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1   5   10

<210> 1285
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1285

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1   5   10   15

<210> 1286
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1286

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1   5   10   15

Gly Gly Gly Ser
            20

<210> 1287
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1287

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> 1288
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1288

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

<210> 1289
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1289

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser

35

<210> 1290
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1290

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser
35 40

<210> 1291
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1291

Gly Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 1292
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1292

Gly Gly Gly Gly Gly Gly Gly Gly
1   5

<210> 1293
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1293

Gly Gly Gly Gly Gly Gly
1   5

<210> 1294
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1294

Glu Ala Ala Ala Lys
1   5

<210> 1295
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1295

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys
1   5   10

<210> 1296

<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1296

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys
1 5 10 15

<210> 1297
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1297

Ala Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Ala
1 5 10

<210> 1298
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1298

Ala Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys
1 5 10 15

Ala

<210> 1299
<211> 22
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1299

Ala Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys
1   5   10   15

Glu Ala Ala Ala Lys Ala
            20

<210> 1300
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1300

Ala Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys
1   5   10   15

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Ala
            20   25

<210> 1301
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1301

Ala Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys
1   5   10   15

Glu Ala Ala Ala Lys Ala Leu Glu Ala Glu Ala Ala Ala Lys Glu Ala

20 25 30

Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Ala
35 40 45

<210> 1302
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1302

Pro Ala Pro Ala Pro
1 5

<210> 1303
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1303

Lys Glu Ser Gly Ser Val Ser Ser Glu Gln Leu Ala Gln Phe Arg Ser
1 5 10 15

Leu Asp

<210> 1304
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1304

Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr
1   5   10

<210> 1305
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1305

Gly Ser Ala Gly Ser Ala Ala Gly Ser Gly Glu Phe
1   5   10

<210> 1306
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1306

Gly Gly Ser Gly Gly Ser
1   5

<210> 1307
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1307

Gly Gly Ser Gly Gly Ser Gly Gly Ser
1   5

<210> 1308

<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1308

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
1 5 10

<210> 1309
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1309

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
1 5 10 15

<210> 1310
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1310

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1 5 10 15

Gly Ser

<210> 1311
<211> 21
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1311

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1   5   10   15

Gly Ser Gly Gly Ser
            20

<210> 1312
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1312

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1   5   10   15

Gly Ser Gly Gly Ser Gly Gly Ser
            20

<210> 1313
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1313

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1   5   10   15

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser

20 25

<210> 1314
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1314

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1 5 10 15

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
20 25 30

<210> 1315
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1315

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1 5 10 15

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
20 25 30

Ser

<210> 1316
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1316

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1   5   10   15

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            20   25   30

Ser Gly Gly Ser
        35

<210> 1317
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1317

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1   5   10   15

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            20   25   30

Ser Gly Gly Ser Gly Gly Ser
        35

<210> 1318
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1318

```
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1               5                   10                  15


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            20                  25                  30


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        35                  40


<210>  1319
<211>  45
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (linker sequence)

<400>  1319

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1               5                   10                  15


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            20                  25                  30


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        35                  40                  45


<210>  1320
<211>  48
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (linker sequence)

<400>  1320

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1               5                   10                  15
```

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            20   25   30

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        35   40   45

<210> 1321
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1321

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1   5   10   15

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            20   25   30

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        35   40   45

Gly Gly Ser
    50

<210> 1322
<211> 54
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1322

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1   5   10   15

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            20   25   30

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        35   40   45

Gly Gly Ser Gly Gly Ser
    50

<210> 1323
<211> 57
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1323

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1   5   10   15

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            20   25   30

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        35   40   45

Gly Gly Ser Gly Gly Ser Gly Gly Ser
    50   55

<210> 1324
<211> 60
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1324

```
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
1               5                   10                  15


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            20                  25                  30


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        35                  40                  45


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
    50                  55                  60


<210>  1325
<211>  45
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (linker sequence)

<400>  1325

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1               5                   10                  15


Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            20                  25                  30


Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        35                  40                  45


<210>  1326
<211>  50
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (linker sequence)

<400>  1326
```

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1               5                   10                  15


Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            20                  25                  30


Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        35                  40                  45


Gly Ser
    50


<210>  1327
<211>  55
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (linker sequence)

<400>  1327

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1               5                   10                  15


Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            20                  25                  30


Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        35                  40                  45


Gly Ser Gly Gly Gly Gly Ser
    50                  55


<210>  1328
<211>  60
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1328

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1   5   10   15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            20   25   30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    50   55   60

<210> 1329
<211> 65
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1329

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1   5   10   15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            20   25   30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    50   55   60

Ser

65

<210> 1330
<211> 70
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1330

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
50 55 60

Ser Gly Gly Gly Gly Ser
65 70

<210> 1331
<211> 75
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1331

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly

            20   25   30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    50   55   60

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65   70   75

<210> 1332
<211> 80
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1332

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1   5   10   15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            20   25   30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    50   55   60

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65   70   75   80

<210> 1333
<211> 85
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1333

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1   5   10   15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            20   25   30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    50   55   60

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65   70   75   80

Gly Gly Gly Gly Ser
                85

<210> 1334
<211> 90
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1334

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1   5   10   15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            20   25   30

```
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        35                  40                  45


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    50                  55                  60


Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65                  70                  75                  80


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
                85                  90


<210>  1335
<211>  95
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (linker sequence)

<400>  1335

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1               5                   10                  15


Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            20                  25                  30


Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        35                  40                  45


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    50                  55                  60


Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65                  70                  75                  80


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
```

85 90 95

<210> 1336
<211> 100
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1336

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
50 55 60

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65 70 75 80

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
85 90 95

Gly Gly Gly Ser
100

<210> 1337
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1337

Gly Gly Gly Ser Glu
1 5

<210> 1338
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1338

Gly Ser Glu Ser Gly
1 5

<210> 1339
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1339

Gly Ser Glu Gly Ser
1 5

<210> 1340
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (linker sequence)

<400> 1340

Gly Glu Gly Gly Ser Gly Glu Gly Ser Ser Gly Glu Gly Ser Ser Ser
1 5 10 15

Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu Gly Gly Gly Ser Glu
            20   25   30

Gly Gly Ser
        35

<210> 1341
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1341

Cys Pro Pro Cys
1

<210> 1342
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1342

Asp Lys Thr His Thr Cys Pro Pro Cys
1   5

<210> 1343
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1343

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys

1 5 10

<210> 1344
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1344

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10

<210> 1345

<400> 1345
000

<210> 1346
<211> 297
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1346

Met Thr Thr Pro Arg Asn Ser Val Asn Gly Thr Phe Pro Ala Glu Pro
1 5 10 15

Met Lys Gly Pro Ile Ala Met Gln Ser Gly Pro Lys Pro Leu Phe Arg
20 25 30

Arg Met Ser Ser Leu Val Gly Pro Thr Gln Ser Phe Phe Met Arg Glu
35 40 45

Ser Lys Thr Leu Gly Ala Val Gln Ile Met Asn Gly Leu Phe His Ile
50 55 60

```
Ala Leu Gly Gly Leu Leu Met Ile Pro Ala Gly Ile Tyr Ala Pro Ile
65                  70                  75                  80


Cys Val Thr Val Trp Tyr Pro Leu Trp Gly Gly Ile Met Tyr Ile Ile
                85                  90                  95


Ser Gly Ser Leu Leu Ala Ala Thr Glu Lys Asn Ser Arg Lys Cys Leu
            100                 105                 110


Val Lys Gly Lys Met Ile Met Asn Ser Leu Ser Leu Phe Ala Ala Ile
        115                 120                 125


Ser Gly Met Ile Leu Ser Ile Met Asp Ile Leu Asn Ile Lys Ile Ser
    130                 135                 140


His Phe Leu Lys Met Glu Ser Leu Asn Phe Ile Arg Ala His Thr Pro
145                 150                 155                 160


Tyr Ile Asn Ile Tyr Asn Cys Glu Pro Ala Asn Pro Ser Glu Lys Asn
                165                 170                 175


Ser Pro Ser Thr Gln Tyr Cys Tyr Ser Ile Gln Ser Leu Phe Leu Gly
            180                 185                 190


Ile Leu Ser Val Met Leu Ile Phe Ala Phe Phe Gln Glu Leu Val Ile
        195                 200                 205


Ala Gly Ile Val Glu Asn Glu Trp Lys Arg Thr Cys Ser Arg Pro Lys
    210                 215                 220


Ser Asn Ile Val Leu Leu Ser Ala Glu Glu Lys Lys Glu Gln Thr Ile
225                 230                 235                 240


Glu Ile Lys Glu Glu Val Val Gly Leu Thr Glu Thr Ser Ser Gln Pro
                245                 250                 255
```

```
Lys Asn Glu Glu Asp Ile Glu Ile Ile Pro Ile Gln Glu Glu Glu Glu
            260                 265                 270


Glu Glu Thr Glu Thr Asn Phe Pro Glu Pro Pro Gln Asp Gln Glu Ser
        275                 280                 285


Ser Pro Ile Glu Asn Asp Ser Ser Pro
    290                 295


<210>  1347
<211>  10
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1347

Gly Arg Thr Phe Ser Arg Gln Ser Met Gly
1               5                   10


<210>  1348
<211>  10
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1348

Gly Arg Thr Phe Ser Gly Gln Ser Met Gly
1               5                   10


<210>  1349
<211>  10
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence
```

<400> 1349

Gly Arg Thr Phe Ser Ser Tyr Ala Met Gly
1 5 10

<210> 1350
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1350

Gly Arg Thr Phe Ser Ser Tyr Asn Met Gly
1 5 10

<210> 1351
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1351

Gly Arg Thr Phe Ser Asn Tyr Asn Met Gly
1 5 10

<210> 1352
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1352

Gly Arg Thr Phe Ser Asn Ser Asn Met Gly
1 5 10

<210> 1353
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1353

Gly Arg Ser Phe Ser Ser Val Asn Met Gly
1   5   10

<210> 1354
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1354

Gly Arg Thr Phe Ser Met Gly
1   5

<210> 1355
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1355

Gly Arg Thr Val Gly Ser Tyr Ser Met Gly
1   5   10

<210> 1356
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 1356

Arg Phe Thr Leu Asp Tyr Tyr Ala Ile Gly
1   5   10

<210> 1357
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1357

Gly Phe Thr Leu Asp Tyr Tyr Ala Ile Gly
1   5   10

<210> 1358
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1358

Gly Arg Asp Phe Ala Thr Tyr Ser Met Ala
1   5   10

<210> 1359
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1359

Gly Arg Asp Phe Ala Thr Tyr Ser Met Thr
1   5   10

<210> 1360
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1360

Gly Arg Asp Phe Ser Thr Tyr Ser Met Gly
1   5   10

<210> 1361
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1361

Gly Arg Thr Phe Asn Thr Tyr Ser Met Gly
1   5   10

<210> 1362
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1362

Gly Arg Thr Phe Ser Thr Tyr Ser Met Gly
1   5   10

<210> 1363
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1363

Gly Arg Asp Phe Ser Thr Tyr Ser Met Gly
1   5   10

<210> 1364
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1364

Gly Asn Thr Phe Asp Thr Arg Ala Met Gly
1   5   10

<210> 1365
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1365

Gly Arg Thr Arg Asp Ala Asn Ala Met Gly
1   5   10

<210> 1366
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1366

Gly Ser Thr Phe Ser Ile Lys Ala Met Gly
1   5   10

<210> 1367
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1367

Val Ile Thr Trp Ser Gly Gly Ser Pro Tyr Tyr Ala Asp Ser Val Arg
1   5   10   15

Gly

<210> 1368
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1368

Val Ile Thr Trp Ser Gly Gly Ser Pro Tyr Tyr Ala Asp Ser Val Lys
1   5   10   15

Gly

<210> 1369
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1369

Val Ile Ser Trp Ser Gly Gly Ser Pro Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1370
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1370

Ala Ile Asp Trp Ser Gly Gly Ser Pro Tyr Tyr Ala Ala Ser Val Arg
1 5 10 15

Gly

<210> 1371
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1371

Val Ile Asp Trp Ser Gly Gly Ser Pro Tyr Tyr Thr Asp Ser Val Arg
1 5 10 15

Gly

<210> 1372
<211> 17

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1372

Ala Ile Thr Tyr Ser Gly Gly Ser Pro Tyr Tyr Ala Ser Ser Val Arg
1 5 10 15

Gly

<210> 1373
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1373

Ala Val Ile Trp Ser Gly Ala Ser Pro Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1374
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1374

Ala Val Thr Trp Ser Gly Ala Ser Pro Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1375
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1375

Ala Val Thr Arg Ser Gly Ala Ser Pro Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1376
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1376

Cys Ile Ser Ser Ser Gly Gly Ser Thr Asn Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1377
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1377

Thr Ile Ser Trp Ser Gly Gln Arg Thr Arg Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1378
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1378

Ser Ile Ser Trp Ser Gly Gln Arg Ser Arg Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1379
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1379

Ile Ile Ser Trp Ser Gly Gln Arg Thr Arg Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1380
<211> 17

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1380

Ala Ile Ser Arg Ser Ser Phe Asn Thr Tyr Tyr Ser Asp Ser Val Thr
1 5 10 15

Gly

<210> 1381
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1381

Ala Ile Ser Trp Ser Gly Ser Arg Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1382
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1382

Ala Phe Ile Ser Gly Arg Gly Ser Thr Lys Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1383
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1383

Gly Phe Ile Ser Gly Arg Gly Ser Ala Lys Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1384
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1384

Pro Val Ser Tyr Gly Ser Gln Trp Leu Ala Asp Tyr
1 5 10

<210> 1385
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1385

Pro Val Ser Tyr Gly Ser Ser Trp Leu Ala Asp Tyr
1 5 10

<210> 1386
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1386

Pro Leu Ser Tyr Gly Ser Thr Trp Leu Ala Asp Tyr
1 5 10

<210> 1387
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1387

Gly Val Ser Phe Gly Ser Arg Trp Leu Ser Asp Tyr
1 5 10

<210> 1388
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1388

Gly Val Ser Tyr Gly Ser Arg Trp Leu Gly Asp Tyr
1 5 10

<210> 1389
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1389

Asn Pro Thr Tyr Gly Ser Asp Trp Asn Ala Glu Asn
1   5   10

<210> 1390
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1390

Asn Pro Thr Tyr Ser Gly Gly Trp His Ala Glu Tyr
1   5   10

<210> 1391
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1391

Glu Arg Thr Trp Val Ser Asn Tyr Tyr Cys Ser Gly Asp Gly Asp Gly
1   5   10   15

Tyr Asp Tyr Asp
            20

<210> 1392
<211> 14
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 1392

Pro Arg Thr Trp Gly Glu Phe Pro Pro Thr Gln Tyr Asp Ser
1   5   10

<210> 1393
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1393

Gly Lys Tyr Gly Met Lys Trp Arg Asp Gly Ala Asp Tyr
1   5   10

<210> 1394
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1394

Asp Arg Ser Ile Glu Val Gln Ile Ala Asp Tyr Asp Tyr
1   5   10

<210> 1395
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1395

Val Leu Pro Thr Gly Gly Gly Ser Ala Met Asp Tyr
1   5   10

<210> 1396
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1396

Val Leu Thr Thr Gly Gly Gly Ser Ala Met Asp Tyr
1 5 10

<210> 1397
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1397

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Arg Gln
20 25 30

Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Val Ile Thr Trp Ser Gly Gly Ser Pro Tyr Tyr Ala Asp Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

```
Ala Ala Pro Val Ser Tyr Gly Ser Gln Trp Leu Ala Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1398
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1398

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Arg Gln
            20                  25                  30


Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Val Ile Thr Trp Ser Gly Gly Ser Pro Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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
```

Ala Ala Pro Val Ser Tyr Gly Ser Gln Trp Leu Ala Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
115 120 125

Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1399
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1399

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Gly Gln
20 25 30

Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Val Ile Thr Trp Ser Gly Gly Ser Pro Tyr Tyr Ala Asp Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val His
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Pro Val Ser Tyr Gly Ser Gln Trp Leu Ala Asp Tyr Trp Gly
100 105 110

```
Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1400
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1400

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Val Ile Thr Trp Ser Gly Gly Ser Pro Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Pro Val Ser Tyr Gly Ser Gln Trp Leu Ala Asp Tyr Trp Gly
            100                 105                 110
```

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115   120   125

Val Pro Asp Tyr Gly Ser His His His His His His
    130   135   140

<210> 1401
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1401

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Arg Gln
            20   25   30

Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Glu Glu Arg Glu Phe Val
        35   40   45

Ala Val Ile Thr Trp Ser Gly Gly Ser Pro Tyr Tyr Ala Asp Ser Val
    50   55   60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

Ala Ala Pro Val Ser Tyr Gly Ser Gln Trp Leu Ala Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115   120   125

```
Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1402
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1402

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Tyr
            20                  25                  30


Asn Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Val Ile Ser Trp Ser Gly Gly Ser Pro Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Pro Val Ser Tyr Gly Ser Ser Trp Leu Ala Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125
```

Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1403
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1403

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Asn Tyr
20 25 30

Asn Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Ala Ile Asp Trp Ser Gly Gly Ser Pro Tyr Tyr Ala Ala Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu 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

Ala Ala Pro Leu Ser Tyr Gly Ser Thr Trp Leu Ala Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
115 120 125

Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1404
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1404

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Asn Ser
            20                  25                  30


Asn Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Val Ile Asp Trp Ser Gly Gly Ser Pro Tyr Tyr Thr Asp Ser Val
    50                  55                  60


Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65                  70                  75                  80


Leu Gln Met Asn Arg Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Gly Gly Val Ser Phe Gly Ser Arg Trp Leu Ser Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 1405
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1405

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ser Phe Ser Ser Val
20 25 30

Asn Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Val Ile Asp Trp Ser Gly Gly Ser Pro Tyr Tyr Thr Asp Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Gly Val Ser Tyr Gly Ser Arg Trp Leu Gly Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
115 120 125

Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1406
<211> 137

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1406

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Ala Gln Ala Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Met Gly
            20   25   30

Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val Ala Ala Ile
        35   40   45

Thr Tyr Ser Gly Gly Ser Pro Tyr Tyr Ala Ser Ser Val Arg Gly Arg
    50   55   60

Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln Met
65   70   75   80

Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala Asn
                85   90   95

Pro Thr Tyr Gly Ser Asp Trp Asn Ala Glu Asn Trp Gly Gln Gly Thr
            100   105   110

Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp
        115   120   125

Tyr Gly Ser His His His His His His
    130   135

<210> 1407
<211> 137
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1407

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Met Gly
            20                  25                  30


Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val Ala Ala Ile
        35                  40                  45


Thr Tyr Ser Gly Gly Ser Pro Tyr Tyr Ala Ser Ser Val Arg Gly Arg
    50                  55                  60


Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln Met
65                  70                  75                  80


Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala Asn
                85                  90                  95


Pro Thr Tyr Gly Ser Asp Trp Asn Ala Glu Asn Trp Gly Gln Gly Thr
            100                 105                 110


Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp
        115                 120                 125


Tyr Gly Ser His His His His His His
    130                 135
```

<210> 1408
<211> 140
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 1408

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Val Gly Ser Tyr
            20                  25                  30


Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Ala Val Ile Trp Ser Gly Ala Ser Pro Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Asn Pro Thr Tyr Ser Gly Gly Trp His Ala Glu Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 1409
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1409

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Val Gly Ser Tyr
            20                  25                  30


Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Ala Val Thr Trp Ser Gly Ala Ser Pro Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Asn Pro Thr Tyr Ser Gly Gly Trp His Ala Glu Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 1410
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1410

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Val Gly Ser Tyr
            20                  25                  30


Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Ala Val Thr Trp Ser Gly Ala Ser Pro Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Asn Pro Thr Tyr Ser Gly Gly Trp His Ala Glu Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1411
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1411

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Glu Gln Pro Gly Gly
1               5                  10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Val Gly Ser Tyr
            20                  25                  30


Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Ala Val Thr Arg Ser Gly Ala Ser Pro Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Asn Pro Thr Tyr Ser Gly Gly Trp His Ala Glu Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1412
<211>  140
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1412

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Leu Asp Tyr Tyr
            20                  25                  30


Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Ala Val Thr Trp Ser Gly Ala Ser Pro Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Asn Pro Thr Tyr Ser Gly Gly Trp His Ala Glu Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1413
<211>  149
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1413

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
            20                  25                  30
```

```
Ala Ile Gly Trp Leu Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
        35                  40                  45


Ser Cys Ile Ser Ser Ser Gly Gly Ser Thr Asn Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65                  70                  75                  80


Leu Leu Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Ala Glu Arg Thr Trp Val Ser Asn Tyr Tyr Cys Ser Gly Asp Gly
            100                 105                 110


Asp Gly Tyr Asp Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
        115                 120                 125


Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser His
    130                 135                 140


His His His His His
145


<210>  1414
<211>  142
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1414

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15
```

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Asp Phe Ala Thr Tyr
20 25 30

Ser Met Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
35 40 45

Ala Thr Ile Ser Trp Ser Gly Gln Arg Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

Ala Met Pro Arg Thr Trp Gly Glu Phe Pro Pro Thr Gln Tyr Asp Ser
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1415
<211> 142
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1415

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Asp Phe Ala Thr Tyr
20 25 30

```
Ser Met Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
        35                  40                  45


Ala Thr Ile Ser Trp Ser Gly Gln Arg Thr Arg Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Pro Arg Thr Trp Gly Glu Phe Pro Pro Thr Gln Tyr Asp Ser
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1416
<211>  142
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1416

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Pro Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Asp Phe Ala Thr Tyr
            20                  25                  30
```

```
Ser Met Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
        35                  40                  45


Ala Thr Ile Ser Trp Ser Gly Gln Arg Thr Arg Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Pro Arg Thr Trp Gly Glu Phe Pro Pro Thr Gln Tyr Asp Ser
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1417
<211>  142
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1417

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Asp Phe Ala Thr Tyr
            20                  25                  30


Ser Met Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
        35                  40                  45
```

```
Ala Thr Ile Ser Trp Ser Gly Gln Arg Thr Arg Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

Ala Ala Pro Arg Thr Trp Gly Glu Phe Pro Pro Thr Gln Tyr Asp Ser
            100                 105                 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1418
<211>  142
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1418

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Asp Phe Ala Thr Tyr
            20                  25                  30

Ser Met Ala Trp Phe Arg Gln Ala Pro Gly Glu Glu Arg Glu Ser Val
        35                  40                  45
```

Ala Thr Ile Ser Trp Ser Gly Gln Arg Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

Ala Ala Pro Arg Thr Trp Gly Glu Phe Pro Pro Thr Gln Tyr Asp Ser
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1419
<211> 142
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1419

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Asp Phe Ala Thr Tyr
20 25 30

Ser Met Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
35 40 45

Ala Thr Ile Ser Trp Ser Gly Gln Arg Thr Arg Tyr Ala Asp Ser Val
50 55 60

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Pro Arg Thr Trp Gly Glu Phe Pro Pro Thr Gln Tyr Asp Ser
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1420
<211>  142
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1420

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Arg Asp Phe Ala Thr Tyr
            20                  25                  30


Ser Met Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
        35                  40                  45


Ala Thr Ile Ser Trp Ser Gly Gln Arg Thr Arg Tyr Ala Asp Ser Val
    50                  55                  60
```

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Pro Arg Thr Trp Gly Glu Phe Pro Pro Thr Gln Tyr Asp Ser
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1421
<211>  142
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1421

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Asp Phe Ala Thr Tyr
            20                  25                  30


Ser Met Thr Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
        35                  40                  45


Ala Thr Ile Ser Trp Ser Gly Gln Arg Thr Arg Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65                  70                  75                  80
```

```
Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Ala Pro Arg Thr Trp Gly Glu Phe Pro Pro Thr Gln Tyr Asp Ser
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1422
<211>  142
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1422

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Asp Phe Ser Thr Tyr
            20                  25                  30


Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
        35                  40                  45


Ala Thr Ile Ser Trp Ser Gly Gln Arg Thr Arg Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

Ala Ala Pro Arg Thr Trp Gly Glu Phe Pro Pro Thr Gln Tyr Asp Ser
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1423
<211> 142
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1423

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Arg Thr Phe Asn Thr Tyr
20 25 30

Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Ser Ile Ser Trp Ser Gly Gln Arg Ser Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

```
Ala Ser Pro Arg Thr Trp Gly Glu Phe Pro Pro Thr Gln Tyr Asp Ser
            100                 105                 110


Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1424
<211>  142
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1424

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Thr Tyr
            20                  25                  30


Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Ile Ile Ser Trp Ser Gly Gln Arg Thr Arg Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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
```

Ala Ala Pro Arg Thr Trp Gly Glu Phe Pro Pro Thr Gln Tyr Asp Ser
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
115 120 125

Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1425
<211> 142
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1425

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Thr Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Asp Phe Ser Thr Tyr
20 25 30

Ser Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Ser Val
35 40 45

Ala Thr Ile Ser Trp Ser Gly Gln Arg Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

Ala Ala Pro Arg Thr Trp Gly Glu Phe Pro Pro Thr Gln Tyr Asp Ser
100 105 110

```
Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro
        115                 120                 125


Tyr Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1426
<211>  141
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1426

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Ala Gln Ala Gly Asn
1               5                   10                  15


Ser Leu Arg Ile Ser Cys Val Ala Ser Gly Asn Thr Phe Asp Thr Arg
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Ala Ile Ser Arg Ser Ser Phe Asn Thr Tyr Tyr Ser Asp Ser Val
    50                  55                  60


Thr Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Gly Lys Tyr Gly Met Lys Trp Arg Asp Gly Ala Asp Tyr Trp
            100                 105                 110
```

Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr
115 120 125

Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1427
<211> 141
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1427

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Ala Gln Ala Gly Asn
1 5 10 15

Ser Leu Arg Ile Ser Cys Val Ala Ser Gly Asn Thr Phe Asp Thr Arg
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Ala Ile Ser Arg Ser Ser Phe Asn Thr Tyr Tyr Ser Asp Ser Val
50 55 60

Thr Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

Val Ala Gly Lys Tyr Gly Met Lys Trp Arg Asp Gly Ala Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr
115 120 125

```
Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140


<210>  1428
<211>  141
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1428

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Glu
1               5                   10                  15


Ser Leu Arg Ile Ser Cys Val Ala Ser Gly Asn Thr Phe Asp Thr Arg
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Ala Ile Ser Arg Ser Ser Phe Asn Thr Tyr Tyr Ser Asp Ser Val
    50                  55                  60


Thr Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Val Ala Gly Lys Tyr Gly Met Lys Trp Arg Asp Gly Ala Asp Tyr Trp
            100                 105                 110


Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr
        115                 120                 125
```

Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1429
<211> 141
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1429

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Ala Gln Glu Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Asn Thr Phe Asp Thr Arg
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Ala Ile Ser Arg Ser Ser Phe Asn Thr Tyr Tyr Ser Asp Ser Val
50 55 60

Thr Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Met 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

Ala Ala Gly Lys Tyr Gly Met Lys Trp Arg Asp Gly Ala Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr
115 120 125

Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1430
<211> 141
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1430

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Asn Thr Phe Asp Thr Arg
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Ala Ile Ser Arg Ser Ser Phe Asn Thr Tyr Tyr Ser Asp Ser Val
    50                  55                  60


Thr Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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


Ala Ala Gly Lys Tyr Gly Met Lys Trp Arg Asp Gly Ala Asp Tyr Trp
            100                 105                 110


Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr
        115                 120                 125


Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 1431
<211> 141
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1431

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Thr Gly Gly
1   5   10   15

Thr Leu Thr Leu Ser Cys Val Ala Ser Gly Asn Thr Phe Asp Thr Arg
            20   25   30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Glu Glu Arg Glu Phe Val
        35   40   45

Ala Ala Ile Ser Arg Ser Ser Phe Asn Thr Tyr Tyr Ser Asp Ser Val
    50   55   60

Thr Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

Ala Ala Gly Lys Tyr Gly Met Lys Trp Arg Asp Gly Ala Asp Tyr Trp
            100   105   110

Gly Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr
        115   120   125

Asp Val Pro Asp Tyr Gly Ser His His His His His His
    130   135   140

<210> 1432
<211> 141

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1432

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Glu Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Arg Asp Ala Asn
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Ala Ile Ser Trp Ser Gly Ser Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Met His Thr Val Tyr
65 70 75 80

Leu Ser Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Asp Arg Ser Ile Glu Val Gln Ile Ala Asp Tyr Asp Tyr Trp
100 105 110

Gly Arg Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr
115 120 125

Asp Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1433
<211> 140
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1433

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Ile Lys
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Ala Phe Ile Ser Gly Arg Gly Ser Thr Lys Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Ala Ile Ser Arg Asp Asn Ala Lys Asn Thr Met Tyr
65                  70                  75                  80


Leu Gln Met Asp Ser Leu Glu Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Tyr Ile Val Leu Pro Thr Gly Gly Gly Ser Ala Met Asp Tyr Trp Gly
            100                 105                 110


Glu Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
        115                 120                 125


Val Pro Asp Tyr Gly Ser His His His His His His
    130                 135                 140
```

<210> 1434
<211> 140
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 1434

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Val Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Ile Lys
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Asp Leu Val
35 40 45

Ala Gly Phe Ile Ser Gly Arg Gly Ser Ala Lys Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ala Ile Ser Arg Asp Asn Ala Lys Asn Thr Met Tyr
65 70 75 80

Leu Gln Met Asp Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Tyr Ile Val Leu Thr Thr Gly Gly Gly Ser Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp
115 120 125

Val Pro Asp Tyr Gly Ser His His His His His His
130 135 140

<210> 1435
<211> 647
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE

<223> pcDNA3.4-mouse light chain
kappa-hIgG1-LALA-PG-20*GGS-3LEC89-20*GGS+G-IFNa2_R149A

<220>
<221> MISC_FEATURE
<223> P-956: pcDNA3.4-mouse light chain
kappa-hIgG1-LALA-PG-20*GGS-3LEC89-20*GGS+G-IFNa2_R149A

<400> 1435

```
Met Lys Leu Pro Val Arg Leu Leu Val Leu Met Phe Trp Ile Pro Ala
1               5                  10                  15


Ser Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
            20                  25                  30


Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
        35                  40                  45


Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
    50                  55                  60


Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
65                  70                  75                  80


Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
                85                  90                  95


Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
            100                 105                 110


Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly
        115                 120                 125


Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
    130                 135                 140


Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
145                 150                 155                 160
```

```
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
                165                 170                 175

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
            180                 185                 190

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
        195                 200                 205

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
    210                 215                 220

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
225                 230                 235                 240

Ser Leu Ser Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                245                 250                 255

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            260                 265                 270

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        275                 280                 285

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    290                 295                 300

Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro
305                 310                 315                 320

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser
                325                 330                 335

Val Asn Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu
            340                 345                 350
```

```
Leu Val Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser
        355                 360                 365

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr Val
    370                 375                 380

Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr
385                 390                 395                 400

Cys Lys Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Gln
                405                 410                 415

Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            420                 425                 430

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        435                 440                 445

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    450                 455                 460

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
465                 470                 475                 480

Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
                485                 490                 495

Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu
            500                 505                 510

Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
        515                 520                 525

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
    530                 535                 540
```

```
Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
545                 550                 555                 560


Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
                565                 570                 575


Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu
            580                 585                 590


Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
        595                 600                 605


Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
    610                 615                 620


Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
625                 630                 635                 640


Glu Ser Leu Arg Ser Lys Glu
                645


<210>  1436
<211>  647
<212>  PRT
<213>  Mus musculus


<220>
<221>  MISC_FEATURE
<223>  P-957: pcDNA3.4-mouse Ig heavy
       chain-3LEC89-20*GGS-hIgG1-LALA-PG-20*GGS+G-IFNa2_R149A

<400>  1436

Met Gly Trp Ser Cys Ile Ile Phe Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15


Val His Ser Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln
```

```
            20                  25                  30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe
        35                  40                  45

Ser Val Asn Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg
    50                  55                  60

Glu Leu Val Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp
65                  70                  75                  80

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr
                85                  90                  95

Val Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr
            100                 105                 110

Tyr Cys Lys Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr
        115                 120                 125

Gln Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    130                 135                 140

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
145                 150                 155                 160

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
                165                 170                 175

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
            180                 185                 190

Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
        195                 200                 205

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
```

```
    210                 215                 220

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
225                 230                 235                 240

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
                245                 250                 255

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
            260                 265                 270

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
        275                 280                 285

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala
    290                 295                 300

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
305                 310                 315                 320

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
                325                 330                 335

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            340                 345                 350

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        355                 360                 365

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
    370                 375                 380

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
385                 390                 395                 400

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
```

```
                405                 410                 415

Leu Ser Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            420                 425                 430

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        435                 440                 445

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    450                 455                 460

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
465                 470                 475                 480

Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
                485                 490                 495

Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu
            500                 505                 510

Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
        515                 520                 525

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
    530                 535                 540

Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
545                 550                 555                 560

Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
                565                 570                 575

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu
            580                 585                 590

Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
```

595 600 605

Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
610 615 620

Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
625 630 635 640

Glu Ser Leu Arg Ser Lys Glu
645

<210> 1437
<211> 421
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> P-958: pcDNA3.4-mouse Ig heavy chain-3LEC89-20*GGS-hIgG1-LALA-PG-YT (hole)

<400> 1437

Met Gly Trp Ser Cys Ile Ile Phe Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe
35 40 45

Ser Val Asn Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg
50 55 60

Glu Leu Val Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp
65 70 75 80

```
Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr
                85                  90                  95

Val Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr
            100                 105                 110

Tyr Cys Lys Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr
        115                 120                 125

Gln Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    130                 135                 140

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
145                 150                 155                 160

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
                165                 170                 175

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
            180                 185                 190

Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
        195                 200                 205

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    210                 215                 220

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
225                 230                 235                 240

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
                245                 250                 255

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
            260                 265                 270
```

```
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
        275                 280                 285

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala
    290                 295                 300

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
305                 310                 315                 320

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
                325                 330                 335

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            340                 345                 350

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        355                 360                 365

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu
    370                 375                 380

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
385                 390                 395                 400

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
                405                 410                 415

Leu Ser Pro Gly Lys
            420


<210>  1438
<211>  472
<212>  PRT
<213>  Mus musculus


<220>
<221>  MISC_FEATURE
```

<223> P-959: pcDNA3.4-mouse light chain kappa-hIgG1-LALA-PG-TY (knob)-20*GGS+G-IFNa2_R149A

<400> 1438

```
Met Lys Leu Pro Val Arg Leu Leu Val Leu Met Phe Trp Ile Pro Ala
1               5                  10                  15


Ser Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
            20                  25                  30


Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
        35                  40                  45


Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
    50                  55                  60


Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
65                  70                  75                  80


Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
                85                  90                  95


Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
            100                 105                 110


Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly
        115                 120                 125


Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
    130                 135                 140


Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
145                 150                 155                 160


Gln Val Ser Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
                165                 170                 175
```

```
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
            180                 185                 190

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
        195                 200                 205

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
    210                 215                 220

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
225                 230                 235                 240

Ser Leu Ser Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                245                 250                 255

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            260                 265                 270

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        275                 280                 285

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    290                 295                 300

Gly Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg
305                 310                 315                 320

Thr Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys
                325                 330                 335

Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn
            340                 345                 350

Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln
        355                 360                 365
```

```
Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp
    370                 375                 380


Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn
385                 390                 395                 400


Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro
                405                 410                 415


Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg
            420                 425                 430


Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu
        435                 440                 445


Val Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu
    450                 455                 460


Gln Glu Ser Leu Arg Ser Lys Glu
465                 470


<210>  1439
<211>  647
<212>  PRT
<213>  Mus musculus


<220>
<221>  MISC_FEATURE
<223>  P-960: pcDNA3.4-mouse light chain kappa-hIgG1-LALA-PG-YT
       (hole)-20*GGS-3LEC89-20*GGS+G-IFNa2_R149A

<400>  1439

Met Lys Leu Pro Val Arg Leu Leu Val Leu Met Phe Trp Ile Pro Ala
1               5                   10                  15


Ser Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
            20                  25                  30
```

```
Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
        35                  40                  45

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
    50                  55                  60

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
65                  70                  75                  80

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
                85                  90                  95

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
            100                 105                 110

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly
        115                 120                 125

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
    130                 135                 140

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
145                 150                 155                 160

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
                165                 170                 175

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
            180                 185                 190

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys
        195                 200                 205

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
    210                 215                 220
```

```
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
225                 230                 235                 240

Ser Leu Ser Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                245                 250                 255

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            260                 265                 270

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        275                 280                 285

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    290                 295                 300

Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro
305                 310                 315                 320

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser
                325                 330                 335

Val Asn Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu
            340                 345                 350

Leu Val Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser
        355                 360                 365

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr Val
    370                 375                 380

Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr
385                 390                 395                 400

Cys Lys Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Gln
                405                 410                 415
```

```
Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            420                 425                 430

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        435                 440                 445

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    450                 455                 460

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
465                 470                 475                 480

Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
                485                 490                 495

Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu
            500                 505                 510

Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
        515                 520                 525

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
    530                 535                 540

Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
545                 550                 555                 560

Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
                565                 570                 575

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu
            580                 585                 590

Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
        595                 600                 605
```

```
Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
    610                 615                 620


Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
625                 630                 635                 640


Glu Ser Leu Arg Ser Lys Glu
                645


<210>  1440
<211>  647
<212>  PRT
<213>  Mus musculus


<220>
<221>  MISC_FEATURE
<223>  P-961: pcDNA3.4-mouse Ig heavy
       chain-3LEC89-20*GGS-hIgG1-LALA-PG-YT (hole)-20*GGS+G-IFNa2_R149A

<400>  1440

Met Gly Trp Ser Cys Ile Ile Phe Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15


Val His Ser Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30


Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe
        35                  40                  45


Ser Val Asn Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg
    50                  55                  60


Glu Leu Val Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp
65                  70                  75                  80


Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr
```

```
                85                  90                  95

Val Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr
            100                 105                 110

Tyr Cys Lys Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr
        115                 120                 125

Gln Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    130                 135                 140

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
145                 150                 155                 160

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
                165                 170                 175

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
            180                 185                 190

Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
        195                 200                 205

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    210                 215                 220

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
225                 230                 235                 240

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
                245                 250                 255

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
            260                 265                 270

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
```

```
        275                 280                 285

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala
    290                 295                 300

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
305                 310                 315                 320

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
                325                 330                 335

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            340                 345                 350

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        355                 360                 365

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu
    370                 375                 380

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
385                 390                 395                 400

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
                405                 410                 415

Leu Ser Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            420                 425                 430

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        435                 440                 445

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    450                 455                 460

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
```

```
465                 470                 475                 480

Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
                485                 490                 495

Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu
            500                 505                 510

Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
        515                 520                 525

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
    530                 535                 540

Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
545                 550                 555                 560

Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
                565                 570                 575

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu
            580                 585                 590

Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
        595                 600                 605

Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
    610                 615                 620

Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
625                 630                 635                 640

Glu Ser Leu Arg Ser Lys Glu
                645
```

<210> 1441

<211> 246
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> P-962: pcDNA3.4-mouse light chain kappa-hIgG1-LALA-PG-TY (knob)

<400> 1441

Met Lys Leu Pro Val Arg Leu Leu Val Leu Met Phe Trp Ile Pro Ala
1 5 10 15

Ser Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
20 25 30

Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
35 40 45

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
50 55 60

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
65 70 75 80

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
85 90 95

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
100 105 110

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly
115 120 125

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
130 135 140

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn

```
145                 150                 155                 160

Gln Val Ser Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
                165                 170                 175

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
            180                 185                 190

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
        195                 200                 205

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
    210                 215                 220

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
225                 230                 235                 240

Ser Leu Ser Pro Gly Lys
                245
```

<210> 1442
<211> 357
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1442

```
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30

Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45
```

```
Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95

Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala
225                 230                 235                 240
```

```
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255


Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu
305                 310                 315                 320


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350


Leu Ser Pro Gly Lys
        355


<210>  1443
<211>  351
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1443

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
```

```
            20                  25                  30

Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45

Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95

Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His
        115                 120                 125

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
    130                 135                 140

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
145                 150                 155                 160

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
                165                 170                 175

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
            180                 185                 190

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
        195                 200                 205

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
```

```
    210                 215                 220

Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile
225                 230                 235                 240

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
                245                 250                 255

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
            260                 265                 270

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
        275                 280                 285

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
    290                 295                 300

Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val Asp Lys Ser Arg
305                 310                 315                 320

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
                325                 330                 335

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            340                 345                 350


<210>  1444
<211>  357
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1444

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
            20                  25                  30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45

Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
                85                  90                  95

Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205
```

```
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220


Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala
225                 230                 235                 240


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255


Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu
305                 310                 315                 320


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350


Leu Ser Pro Gly Lys
        355


<210>  1445
<211>  351
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence
```

<400> 1445

```
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
                85                  90                  95


Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His
        115                 120                 125


Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
    130                 135                 140


Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
145                 150                 155                 160


Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
                165                 170                 175


Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
```

```
            180                 185                 190

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
        195                 200                 205

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
    210                 215                 220

Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile
225                 230                 235                 240

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
                245                 250                 255

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
            260                 265                 270

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
        275                 280                 285

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
    290                 295                 300

Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val Asp Lys Ser Arg
305                 310                 315                 320

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
                325                 330                 335

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            340                 345                 350
```

<210> 1446
<211> 423
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1446

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175
```

```
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
            260                 265                 270


Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu
        275                 280                 285


Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
    290                 295                 300


Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
305                 310                 315                 320


Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
                325                 330                 335


Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
            340                 345                 350


Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu
        355                 360                 365
```

```
Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
    370                 375                 380


Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
385                 390                 395                 400


Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
                405                 410                 415


Glu Ser Leu Arg Ser Lys Glu
            420


<210>  1447
<211>  408
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1447

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
```

```
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg
                245                 250                 255

Thr Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys
            260                 265                 270

Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn
```

```
        275                 280                 285

Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln
    290                 295                 300

Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp
305                 310                 315                 320

Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn
                325                 330                 335

Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro
            340                 345                 350

Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg
        355                 360                 365

Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu
    370                 375                 380

Val Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu
385                 390                 395                 400

Gln Glu Ser Leu Arg Ser Lys Glu
                405
```

<210> 1448
<211> 402
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1448

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15
```

```
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205
```

```
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Cys Asp Leu
225                 230                 235                 240

Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala
                245                 250                 255

Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp
            260                 265                 270

Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu
        275                 280                 285

Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe
    290                 295                 300

Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys
305                 310                 315                 320

Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val
                325                 330                 335

Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys Glu Asp Ser
            340                 345                 350

Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys
        355                 360                 365

Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile
    370                 375                 380

Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser
385                 390                 395                 400
```

Lys Glu

<210> 1449
<211> 568
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1449

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
85 90 95

Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
115 120 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly

```
    130                 135                 140

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
145                 150                 155                 160

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                165                 170                 175

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            180                 185                 190

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        195                 200                 205

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    210                 215                 220

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
225                 230                 235                 240

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro
                245                 250                 255

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            260                 265                 270

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        275                 280                 285

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    290                 295                 300

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
305                 310                 315                 320

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
```

```
                325                 330                 335

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            340                 345                 350

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        355                 360                 365

Ser Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
    370                 375                 380

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
385                 390                 395                 400

Gly Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg
                405                 410                 415

Thr Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys
            420                 425                 430

Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn
        435                 440                 445

Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln
    450                 455                 460

Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp
465                 470                 475                 480

Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn
                485                 490                 495

Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro
            500                 505                 510

Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg
```

515 520 525

Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu
530 535 540

Val Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu
545 550 555 560

Gln Glu Ser Leu Arg Ser Lys Glu
565

<210> 1450
<211> 538
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1450

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
85 90 95

```
Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala
225                 230                 235                 240

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
```

```
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350

Leu Ser Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
        355                 360                 365

Ser Gly Gly Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser
    370                 375                 380

Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe
385                 390                 395                 400

Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe
                405                 410                 415

Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met
            420                 425                 430

Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala
        435                 440                 445

Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln
    450                 455                 460

Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu
465                 470                 475                 480
```

```
Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe
                485                 490                 495


Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala
            500                 505                 510


Trp Glu Val Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr
        515                 520                 525


Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu
    530                 535


<210>  1451
<211>  526
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1451

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
```

```
                85                  90                  95

Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His
        115                 120                 125

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
    130                 135                 140

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
145                 150                 155                 160

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
                165                 170                 175

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
            180                 185                 190

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
        195                 200                 205

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
    210                 215                 220

Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile
225                 230                 235                 240

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
                245                 250                 255

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
            260                 265                 270

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
```

```
        275                 280                 285

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
    290                 295                 300

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
305                 310                 315                 320

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
                325                 330                 335

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
            340                 345                 350

Gly Ser Gly Gly Ser Gly Gly Ser Gly Cys Asp Leu Pro Gln Thr His
        355                 360                 365

Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Lys
    370                 375                 380

Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro
385                 390                 395                 400

Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val
                405                 410                 415

Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp
            420                 425                 430

Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu
        435                 440                 445

Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val
    450                 455                 460

Gly Val Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val
```

465 470 475 480

Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr
485 490 495

Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Ala Ser Phe
500 505 510

Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu
515 520 525

<210> 1452
<211> 514
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1452

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
85 90 95

```
Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser Ala Ala Ala Asp Lys Thr His Thr Cys Pro Pro Cys Pro
        115                 120                 125


Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
    130                 135                 140


Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
145                 150                 155                 160


Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
                165                 170                 175


Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
            180                 185                 190


Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
        195                 200                 205


Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
    210                 215                 220


Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
225                 230                 235                 240


Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
                245                 250                 255


Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
            260                 265                 270


Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
        275                 280                 285
```

```
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
    290                 295                 300

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
305                 310                 315                 320

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
                325                 330                 335

Lys Ser Leu Ser Leu Ser Pro Gly Lys Ala Ala Ala Gly Cys Asp Leu
            340                 345                 350

Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala
        355                 360                 365

Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp
    370                 375                 380

Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu
385                 390                 395                 400

Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe
                405                 410                 415

Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys
            420                 425                 430

Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val
        435                 440                 445

Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys Glu Asp Ser
    450                 455                 460

Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys
465                 470                 475                 480
```

```
Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile
                485                 490                 495


Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser
            500                 505                 510


Lys Glu



<210>  1453
<211>  402
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1453

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
                85                  90                  95


Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
```

```
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
```

290 295 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305 310 315 320

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
325 330 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys

<210> 1454
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1454

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

```
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220
```

```
Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        275                 280                 285


Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
    290                 295                 300


Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp
305                 310                 315                 320


Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
                325                 330                 335


Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
            340                 345                 350


Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
        355                 360                 365


Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
    370                 375                 380


Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
385                 390                 395                 400


Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
                405                 410                 415
```

```
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
            420                 425                 430


Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
        435                 440                 445


Leu Arg Ser Lys Glu
    450


<210>  1455
<211>  402
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1455

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
                85                  90                  95


Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
```

```
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
```

290 295 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305 310 315 320

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
325 330 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys

<210> 1456
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1456

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

```
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Gln Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220
```

```
Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        275                 280                 285


Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
    290                 295                 300


Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp
305                 310                 315                 320


Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
                325                 330                 335


Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
            340                 345                 350


Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
        355                 360                 365


Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
    370                 375                 380


Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
385                 390                 395                 400


Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
                405                 410                 415
```

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
420 425 430

Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
435 440 445

Leu Arg Ser Lys Glu
450

<210> 1457
<211> 402
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1457

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
85 90 95

Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr

```
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
```

290 295 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305 310 315 320

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
325 330 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys

<210> 1458
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1458

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

```
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220
```

```
Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        275                 280                 285


Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
    290                 295                 300


Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp
305                 310                 315                 320


Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
                325                 330                 335


Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
            340                 345                 350


Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
        355                 360                 365


Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
    370                 375                 380


Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
385                 390                 395                 400


Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
                405                 410                 415
```

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
420 425 430

Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
435 440 445

Leu Arg Ser Lys Glu
450

<210> 1459
<211> 402
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1459

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
85 90 95

Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr

```
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
```

290 295 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305 310 315 320

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
325 330 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys

<210> 1460
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1460

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

```
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220
```

```
Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        275                 280                 285


Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
    290                 295                 300


Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp
305                 310                 315                 320


Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
                325                 330                 335


Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
            340                 345                 350


Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
        355                 360                 365


Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
    370                 375                 380


Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
385                 390                 395                 400


Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
                405                 410                 415
```

```
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
            420                 425                 430


Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
        435                 440                 445


Leu Arg Ser Lys Glu
    450


<210>  1461
<211>  357
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1461

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95


Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Leu Val Thr
```

```
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala
225                 230                 235                 240

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
```

290 295 300

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu
305 310 315 320

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
325 330 335

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
340 345 350

Leu Ser Pro Gly Lys
355

<210> 1462
<211> 357
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1462

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65 70 75 80

```
Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
                85                  90                  95

Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala
225                 230                 235                 240

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270
```

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275   280   285

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290   295   300

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu
305   310   315   320

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325   330   335

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340   345   350

Leu Ser Pro Gly Lys
        355

<210> 1463
<211> 423
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1463

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1   5   10   15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20   25   30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35   40   45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val

```
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
```

```
                245                 250                 255

Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
            260                 265                 270

Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu
        275                 280                 285

Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
    290                 295                 300

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
305                 310                 315                 320

Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
                325                 330                 335

Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
            340                 345                 350

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu
        355                 360                 365

Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
    370                 375                 380

Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
385                 390                 395                 400

Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
                405                 410                 415

Glu Ser Leu Arg Ser Lys Glu
            420
```

<210> 1464

<211> 423
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1464

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160
```

```
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
            260                 265                 270

Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu
        275                 280                 285

Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
    290                 295                 300

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
305                 310                 315                 320

Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
                325                 330                 335

Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
            340                 345                 350
```

```
Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu
        355                 360                 365


Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
    370                 375                 380


Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
385                 390                 395                 400


Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
                405                 410                 415


Glu Ser Leu Arg Ser Lys Glu
            420


<210>  1465
<211>  423
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1465

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
```

```
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
```

```
            260                 265                 270

Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu
        275                 280                 285

Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
    290                 295                 300

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
305                 310                 315                 320

Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
                325                 330                 335

Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
            340                 345                 350

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu
        355                 360                 365

Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
    370                 375                 380

Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
385                 390                 395                 400

Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
                405                 410                 415

Glu Ser Leu Arg Ser Lys Glu
            420
```

<210> 1466
<211> 423
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1466

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175
```

```
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
            260                 265                 270


Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu
        275                 280                 285


Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
    290                 295                 300


Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
305                 310                 315                 320


Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
                325                 330                 335


Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
            340                 345                 350


Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu
        355                 360                 365
```

```
Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
    370                 375                 380


Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
385                 390                 395                 400


Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
                405                 410                 415


Glu Ser Leu Arg Ser Lys Glu
            420


<210>  1467
<211>  423
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1467

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
```

```
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
            260                 265                 270

Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu
```

```
        275                 280                 285

Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
    290                 295                 300

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
305                 310                 315                 320

Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
                325                 330                 335

Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
            340                 345                 350

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu
        355                 360                 365

Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
    370                 375                 380

Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
385                 390                 395                 400

Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
                405                 410                 415

Glu Ser Leu Arg Ser Lys Glu
            420


<210>  1468
<211>  423
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1468
```

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190
```

```
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
            260                 265                 270

Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu
        275                 280                 285

Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
    290                 295                 300

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
305                 310                 315                 320

Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
                325                 330                 335

Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
            340                 345                 350

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu
        355                 360                 365

Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
    370                 375                 380
```

```
Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
385                 390                 395                 400


Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
                405                 410                 415


Glu Ser Leu Arg Ser Lys Glu
            420


<210>  1469
<211>  402
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1469

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
                85                  90                  95


Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
```

```
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
```

290 295 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305 310 315 320

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
325 330 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys

<210> 1470
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1470

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

```
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220
```

```
Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        275                 280                 285


Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
    290                 295                 300


Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp
305                 310                 315                 320


Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
                325                 330                 335


Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
            340                 345                 350


Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
        355                 360                 365


Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
    370                 375                 380


Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
385                 390                 395                 400


Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
                405                 410                 415
```

```
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
            420                 425                 430


Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
        435                 440                 445


Leu Arg Ser Lys Glu
    450


<210>  1471
<211>  402
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1471

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95


Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Leu Val Thr
```

```
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
```

290 295 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305 310 315 320

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
325 330 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys

<210> 1472
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1472

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

```
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                165                 170                 175

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            180                 185                 190

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        195                 200                 205

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    210                 215                 220
```

```
Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225                 230                 235                 240


Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255


Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270


His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285


Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300


Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320


Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro
                325                 330                 335


Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350


Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365


Ser Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380


Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400


Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415
```

```
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430


Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445


Ser Pro Gly Lys
    450


<210>  1473
<211>  402
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1473

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
```

```
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
        275                 280                 285

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
```

290 295 300

Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn Val
305 310 315 320

Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val Ala
325 330 335

Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Lys Gly
340 345 350

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu Gln
355 360 365

Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr Leu
370 375 380

Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
385 390 395 400

Ser Ser

<210> 1474
<211> 402
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1474

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

```
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220
```

```
Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
        275                 280                 285


Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
    290                 295                 300


Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn Ala
305                 310                 315                 320


Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val Ala
                325                 330                 335


Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys Gly
            340                 345                 350


Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu Gln
        355                 360                 365


Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys Ala
    370                 375                 380


Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
385                 390                 395                 400


Ser Ser
```

<210> 1475
<211> 402
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1475

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
                85                  90                  95


Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
```

```
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    290                 295                 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305                 310                 315                 320

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                325                 330                 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
```

340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys

<210> 1476
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1476

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

```
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270
```

```
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        275                 280                 285


Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
    290                 295                 300


Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp
305                 310                 315                 320


Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
                325                 330                 335


Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
            340                 345                 350


Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
        355                 360                 365


Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
    370                 375                 380


Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
385                 390                 395                 400


Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
                405                 410                 415


Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
            420                 425                 430


Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
        435                 440                 445


Leu Arg Ser Lys Glu
    450
```

<210> 1477
<211> 357
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1477

```
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95


Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140


Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
```

```
145                 150                 155                 160

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala
225                 230                 235                 240

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu
305                 310                 315                 320

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
```

340 345 350

Leu Ser Pro Gly Lys
355

<210> 1478
<211> 400
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1478

Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
1 5 10 15

Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn Ala Met
20 25 30

Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val Ala Ala
35 40 45

Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys Gly Arg
50 55 60

Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr Val Tyr Leu Gln Met
65 70 75 80

Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys Ala Phe
85 90 95

Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser
100 105 110

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
115 120 125

```
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    130                 135                 140

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
145                 150                 155                 160

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr
                165                 170                 175

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
            180                 185                 190

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
        195                 200                 205

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
    210                 215                 220

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
225                 230                 235                 240

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
                245                 250                 255

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
            260                 265                 270

Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
        275                 280                 285

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu
    290                 295                 300

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys
305                 310                 315                 320
```

```
Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
                325                 330                 335


Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
            340                 345                 350


Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser
        355                 360                 365


Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
    370                 375                 380


Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
385                 390                 395                 400


<210>  1479
<211>  452
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1479

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
```

```
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
```

```
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300

Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380

Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430

Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
        435                 440                 445

Arg Ser Lys Glu
```

450

<210> 1480
<211> 402
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1480

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
20 25 30

Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr
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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
85 90 95

Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
115 120 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
130 135 140

```
Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
    290                 295                 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305                 310                 315                 320

Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                325                 330                 335
```

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys

<210> 1481
<211> 402
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1481

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
20 25 30

Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr
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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95

Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
```

```
            260                 265                 270

Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
    290                 295                 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305                 310                 315                 320

Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                325                 330                 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
            340                 345                 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp
        355                 360                 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    370                 375                 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385                 390                 395                 400

Gly Lys
```

<210> 1482
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1482

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190
```

```
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285


Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300


Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320


His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335


Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350


Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365


Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380
```

```
Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400


Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415


Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430


Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
        435                 440                 445


Arg Ser Lys Glu
    450


<210>  1483
<211>  627
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1483

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr
    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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95

Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
```

260 265 270

Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
275 280 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
290 295 300

Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305 310 315 320

Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
325 330 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
405 410 415

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
420 425 430

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
435 440 445

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys Asp

```
    450                 455                 460

Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu
465                 470                 475                 480

Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His
                485                 490                 495

Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala
            500                 505                 510

Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu
        515                 520                 525

Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp
    530                 535                 540

Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys
545                 550                 555                 560

Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu Asp
                565                 570                 575

Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu
            580                 585                 590

Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu
        595                 600                 605

Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg
    610                 615                 620

Ser Lys Glu
625
```

<210> 1484

<211> 577
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1484

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr
    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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95


Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160
```

```
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gln
                165                 170                 175

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly Ser
            180                 185                 190

Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn Val
        195                 200                 205

Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val Ala
    210                 215                 220

Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr Gly
225                 230                 235                 240

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln
                245                 250                 255

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr Leu
            260                 265                 270

Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
        275                 280                 285

Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    290                 295                 300

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
305                 310                 315                 320

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                325                 330                 335

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys
            340                 345                 350
```

```
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
        355                 360                 365

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    370                 375                 380

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
385                 390                 395                 400

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
                405                 410                 415

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
            420                 425                 430

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
        435                 440                 445

Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
    450                 455                 460

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr
465                 470                 475                 480

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser
                485                 490                 495

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            500                 505                 510

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
        515                 520                 525

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
    530                 535                 540
```

```
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
545                 550                 555                 560


Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                565                 570                 575


Lys
```

<210> 1485
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1485

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
```

```
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
```

```
    290                 295                 300

Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380

Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430

Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
        435                 440                 445

Arg Ser Lys Glu
    450


<210>  1486
<211>  357
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> Synthetic Sequence

<400> 1486

```
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95


Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140


Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175
```

```
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220


Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala
225                 230                 235                 240


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255


Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu
305                 310                 315                 320


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350


Leu Ser Pro Gly Lys
        355
```

<210> 1487
<211> 423
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1487

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
```

```
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
            260                 265                 270

Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu
        275                 280                 285

Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
    290                 295                 300

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
305                 310                 315                 320

Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
                325                 330                 335

Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
```

340 345 350

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu
355 360 365

Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
370 375 380

Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
385 390 395 400

Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
405 410 415

Glu Ser Leu Arg Ser Lys Glu
420

<210> 1488
<211> 423
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1488

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

```
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255
```

```
Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
            260                 265                 270


Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu
        275                 280                 285


Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
    290                 295                 300


Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
305                 310                 315                 320


Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
                325                 330                 335


Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
            340                 345                 350


Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu
        355                 360                 365


Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
    370                 375                 380


Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
385                 390                 395                 400


Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
                405                 410                 415


Glu Ser Leu Arg Ser Lys Glu
            420


<210>  1489
<211>  357
<212>  PRT
```

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1489

```
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95


Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140


Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
```

```
                165                 170                 175

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220

Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala
225                 230                 235                 240

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255

Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270

Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu
305                 310                 315                 320

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350

Leu Ser Pro Gly Lys
```

355

<210> 1490
<211> 423
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1490

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
130 135 140

```
Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
            260                 265                 270


Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu
        275                 280                 285


Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
    290                 295                 300


Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
305                 310                 315                 320


Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
                325                 330                 335
```

Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
340 345 350

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu
355 360 365

Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
370 375 380

Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
385 390 395 400

Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
405 410 415

Glu Ser Leu Arg Ser Lys Glu
420

<210> 1491
<211> 423
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1491

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val

```
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
```

```
                245                 250                 255

Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
            260                 265                 270

Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu
        275                 280                 285

Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
    290                 295                 300

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
305                 310                 315                 320

Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
                325                 330                 335

Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
            340                 345                 350

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu
        355                 360                 365

Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
    370                 375                 380

Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
385                 390                 395                 400

Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
                405                 410                 415

Glu Ser Leu Arg Ser Lys Glu
            420
```

<210> 1492

<211> 647
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1492

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn
20 25 30

Arg Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Leu Ile Thr Ser Asp Gly Thr Pro Ala Tyr Ala Asp Ser Ala Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His
85 90 95

Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser Ala Ala Ala Tyr Pro Tyr Asp Val Pro Asp Tyr Gly Ser
115 120 125

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
130 135 140

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
145 150 155 160

```
Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
                165                 170                 175

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His
            180                 185                 190

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
        195                 200                 205

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
    210                 215                 220

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
225                 230                 235                 240

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
                245                 250                 255

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
            260                 265                 270

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
        275                 280                 285

Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile
    290                 295                 300

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
305                 310                 315                 320

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
                325                 330                 335

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
            340                 345                 350
```

```
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
        355                 360                 365

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
    370                 375                 380

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
385                 390                 395                 400

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
                405                 410                 415

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            420                 425                 430

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        435                 440                 445

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    450                 455                 460

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Cys Asp Leu Pro
465                 470                 475                 480

Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln
                485                 490                 495

Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe
            500                 505                 510

Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr
        515                 520                 525

Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser
    530                 535                 540
```

```
Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe
545                 550                 555                 560


Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile
                565                 570                 575


Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile
            580                 585                 590


Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu
        595                 600                 605


Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met
    610                 615                 620


Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys
625                 630                 635                 640


Glu His His His His His His
                645


<210>  1493
<211>  402
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1493

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn
            20                  25                  30


Arg Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
```

```
        35                  40                  45

Ala Leu Ile Thr Ser Asp Gly Thr Pro Ala Tyr Ala Asp Ser Ala Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His
                85                  90                  95

Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
```

225 230 235 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
245 250 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
260 265 270

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
275 280 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
290 295 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305 310 315 320

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
325 330 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys

<210> 1494

<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1494

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160
```

```
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        275                 280                 285


Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
    290                 295                 300


Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp
305                 310                 315                 320


Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
                325                 330                 335


Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
            340                 345                 350
```

```
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
        355                 360                 365


Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
    370                 375                 380


Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
385                 390                 395                 400


Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
                405                 410                 415


Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
            420                 425                 430


Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
        435                 440                 445


Leu Arg Ser Lys Glu
    450


<210>  1495
<211>  402
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1495

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn
            20                  25                  30


Arg Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
```

```
        35                  40                  45

Ala Leu Ile Thr Ser Asp Gly Thr Pro Ala Tyr Ala Asp Ser Ala Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His
                85                  90                  95

Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
```

```
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
    290                 295                 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305                 310                 315                 320

Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                325                 330                 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
            340                 345                 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp
        355                 360                 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    370                 375                 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385                 390                 395                 400

Gly Lys
```

<210> 1496

<211> 627
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1496

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn
            20                  25                  30


Arg Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Leu Ile Thr Ser Asp Gly Thr Pro Ala Tyr Ala Asp Ser Ala Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His
                85                  90                  95


Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160
```

```
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    290                 295                 300

Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305                 310                 315                 320

Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                325                 330                 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
            340                 345                 350
```

```
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        355                 360                 365


Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    370                 375                 380


Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385                 390                 395                 400


Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                405                 410                 415


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            420                 425                 430


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        435                 440                 445


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys Asp
    450                 455                 460


Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu
465                 470                 475                 480


Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His
                485                 490                 495


Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala
            500                 505                 510


Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu
        515                 520                 525


Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp
    530                 535                 540
```

```
Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys
545                 550                 555                 560


Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu Asp
                565                 570                 575


Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu
            580                 585                 590


Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu
        595                 600                 605


Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg
    610                 615                 620


Ser Lys Glu
625


<210>  1497
<211>  414
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1497

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Asp
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Gly Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Thr Ile Ser Thr Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
```

```
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80

Leu Gln Ile Asn Ser Leu Lys Thr Glu Asp Ala Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Ala Arg Leu Ser Phe Asp Asn Thr Ala Phe Tyr Thr Ser Ala Ile
            100                 105                 110

Arg Tyr Ser Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                165                 170                 175

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His Thr
            180                 185                 190

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
        195                 200                 205

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
    210                 215                 220

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
225                 230                 235                 240

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
```

```
                245                 250                 255

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
            260                 265                 270

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
        275                 280                 285

Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
    290                 295                 300

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro
305                 310                 315                 320

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val
                325                 330                 335

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
            340                 345                 350

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
        355                 360                 365

Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
    370                 375                 380

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
385                 390                 395                 400

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                405                 410
```

<210> 1498
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1498

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175
```

```
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285


Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300


Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320


His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335


Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350


Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365
```

```
Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380


Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400


Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415


Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430


Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
        435                 440                 445


Arg Ser Lys Glu
    450


<210>  1499
<211>  405
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1499

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Ala Gln Ala Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Met Gly
            20                  25                  30


Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val Ala Ala Ile
        35                  40                  45


Thr Tyr Ser Gly Gly Ser Pro Tyr Tyr Ala Ser Ser Val Arg Gly Arg
```

```
    50                  55                  60

Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln Met
65                  70                  75                  80

Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala Asn
                85                  90                  95

Pro Thr Tyr Gly Ser Asp Trp Asn Ala Glu Asn Trp Gly Gln Gly Thr
            100                 105                 110

Gln Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                165                 170                 175

Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
            180                 185                 190

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        195                 200                 205

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    210                 215                 220

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
225                 230                 235                 240

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
```

245 250 255

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
260 265 270

Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala
275 280 285

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
290 295 300

Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
305 310 315 320

Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
325 330 335

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
340 345 350

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu
355 360 365

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
370 375 380

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
385 390 395 400

Leu Ser Pro Gly Lys
405

<210> 1500
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1500

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175
```

```
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285


Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300


Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320


His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335


Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350


Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365
```

```
Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380


Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400


Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415


Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430


Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
        435                 440                 445


Arg Ser Lys Glu
    450


<210>  1501
<211>  452
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1501

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
```

```
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
```

```
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300

Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380

Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430

Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
```

435 440 445

Arg Ser Lys Glu
450

<210> 1502
<211> 407
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1502

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Ile Asn
20 25 30

Ala Val Ala Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Leu Val
35 40 45

Ala Gly Ile Ser Gly Gly Gly Val Thr Asn Tyr Pro 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 Ser Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Leu Trp Pro Pro Arg Ala Ser Pro Gly Gly Arg Val Tyr Trp Gly Gln
100 105 110

Gly Thr Gln Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly
115 120 125

```
Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
    130                 135                 140

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
145                 150                 155                 160

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                165                 170                 175

Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
            180                 185                 190

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        195                 200                 205

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    210                 215                 220

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
225                 230                 235                 240

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
                245                 250                 255

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            260                 265                 270

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu
        275                 280                 285

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    290                 295                 300

Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
305                 310                 315                 320
```

```
Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp
                325                 330                 335


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            340                 345                 350


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser
        355                 360                 365


Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
    370                 375                 380


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
385                 390                 395                 400


Leu Ser Leu Ser Pro Gly Lys
                405


<210>  1503
<211>  407
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1503

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Gly Asn
            20                  25                  30


Ala Met Ala Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Leu Val
        35                  40                  45


Ala Gly Ile Ser Gly Gly Gly Val Thr Asn Tyr Pro 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 Ser Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Leu Trp Pro Pro Arg Val Ser Pro Gly Gly Gly Val Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Gln Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly
        115                 120                 125

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
    130                 135                 140

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
145                 150                 155                 160

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                165                 170                 175

Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
            180                 185                 190

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        195                 200                 205

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    210                 215                 220

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
225                 230                 235                 240

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
```

245 250 255

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
260 265 270

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu
275 280 285

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
290 295 300

Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
305 310 315 320

Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp
325 330 335

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
340 345 350

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser
355 360 365

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
370 375 380

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
385 390 395 400

Leu Ser Leu Ser Pro Gly Lys
405

<210> 1504
<211> 407
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1504

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Glu
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ser Thr Ser Ser Met Asn
            20                  25                  30


Ala Met Ala Trp Tyr Arg Gln Ala Pro Gly Lys Arg Arg Glu Leu Val
        35                  40                  45


Ala Gly Ile Ser Gly Gly Gly Ala Thr Asn Tyr Pro 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 Ser Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95


Leu Trp Pro Pro Arg Ala Ser Pro Gly Gly Gly Val Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Gln Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly
        115                 120                 125


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
    130                 135                 140


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
145                 150                 155                 160


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                165                 170                 175
```

```
Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
            180                 185                 190

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        195                 200                 205

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    210                 215                 220

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
225                 230                 235                 240

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
                245                 250                 255

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            260                 265                 270

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu
        275                 280                 285

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    290                 295                 300

Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
305                 310                 315                 320

Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp
                325                 330                 335

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            340                 345                 350

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser
        355                 360                 365
```

```
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
    370                 375                 380


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
385                 390                 395                 400


Leu Ser Leu Ser Pro Gly Lys
                405


<210>  1505
<211>  452
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1505

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
```

```
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
```

```
    290                 295                 300

Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380

Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430

Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
        435                 440                 445

Arg Ser Lys Glu
    450


<210>  1506
<211>  411
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> Synthetic Sequence

<400> 1506

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ser Phe Ser Ser Tyr
            20                  25                  30


Phe Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Gly Ile Gly Trp Asn Asp Gly Ser Ile Asn Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Gly Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Ala Ser Val Ser Leu Tyr Gly Leu Glu Lys Ser Ser Ala Tyr Thr
            100                 105                 110


Ser Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                165                 170                 175
```

```
Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro
            180                 185                 190


Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
        195                 200                 205


Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    210                 215                 220


Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
225                 230                 235                 240


Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                245                 250                 255


Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
            260                 265                 270


Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser
        275                 280                 285


Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    290                 295                 300


Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Asp
305                 310                 315                 320


Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe
                325                 330                 335


Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            340                 345                 350


Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        355                 360                 365
```

```
Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    370                 375                 380


Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
385                 390                 395                 400


Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                405                 410


<210>  1507
<211>  452
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1507

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
```

```
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
```

```
    290                 295                 300

Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380

Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430

Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
        435                 440                 445

Arg Ser Lys Glu
    450


<210>  1508
<211>  452
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> Synthetic Sequence

<400> 1508

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175
```

```
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285


Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300


Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320


His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335


Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350


Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365
```

```
Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380


Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400


Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415


Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430


Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
        435                 440                 445


Arg Ser Lys Glu
    450


<210>  1509
<211>  577
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1509

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr
```

```
    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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95

Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gln
                165                 170                 175

Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly Ser
            180                 185                 190

Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn Arg
        195                 200                 205

Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val Ala
    210                 215                 220

Leu Ile Thr Ser Asp Gly Thr Pro Ala Tyr Ala Asp Ser Ala Lys Gly
225                 230                 235                 240

Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu Gln
```

```
                245                 250                 255

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His Val
            260                 265                 270

Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
        275                 280                 285

Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    290                 295                 300

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
305                 310                 315                 320

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                325                 330                 335

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys
            340                 345                 350

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
        355                 360                 365

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    370                 375                 380

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
385                 390                 395                 400

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
                405                 410                 415

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
            420                 425                 430

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
```

```
        435                 440                 445

Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
    450                 455                 460

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr
465                 470                 475                 480

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser
                485                 490                 495

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            500                 505                 510

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
        515                 520                 525

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
    530                 535                 540

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
545                 550                 555                 560

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                565                 570                 575

Lys
```

<210> 1510
<211> 577
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1510

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn
            20                  25                  30


Arg Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Leu Ile Thr Ser Asp Gly Thr Pro Ala Tyr Ala Asp Ser Ala Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His
                85                  90                  95


Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gln
                165                 170                 175


Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly Ser
            180                 185                 190
```

```
Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn Val
        195                 200                 205

Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val Ala
    210                 215                 220

Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr Gly
225                 230                 235                 240

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln
                245                 250                 255

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr Leu
            260                 265                 270

Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
        275                 280                 285

Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    290                 295                 300

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
305                 310                 315                 320

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                325                 330                 335

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys
            340                 345                 350

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
        355                 360                 365

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    370                 375                 380
```

```
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
385                 390                 395                 400


Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
                405                 410                 415


Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
            420                 425                 430


Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
        435                 440                 445


Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
    450                 455                 460


Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
465                 470                 475                 480


Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp
                485                 490                 495


Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            500                 505                 510


Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
        515                 520                 525


Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
    530                 535                 540


Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
545                 550                 555                 560


Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                565                 570                 575
```

Lys

<210> 1511
<211> 402
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1511

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr
    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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95


Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
```

```
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
    290                 295                 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305                 310                 315                 320

Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
```

325 330 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys

<210> 1512
<211> 402
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1512

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn
20 25 30

Arg Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Leu Ile Thr Ser Asp Gly Thr Pro Ala Tyr Ala Asp Ser Ala Lys
50 55 60

```
Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His
                85                  90                  95

Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255
```

```
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270


Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        275                 280                 285


Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
    290                 295                 300


Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305                 310                 315                 320


Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                325                 330                 335


Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
            340                 345                 350


Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp
        355                 360                 365


Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    370                 375                 380


Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385                 390                 395                 400


Gly Lys
```

<210> 1513
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1513

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
```

```
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300

Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
```

370 375 380

Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385 390 395 400

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
405 410 415

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
420 425 430

Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
435 440 445

Arg Ser Lys Glu
450

<210> 1514
<211> 627
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1514

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn
20 25 30

Arg Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Leu Ile Thr Ser Asp Gly Thr Pro Ala Tyr Ala Asp Ser Ala Lys
50 55 60

```
Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His
                85                  90                  95


Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175


Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190


Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205


Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220


Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240


Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255
```

```
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    290                 295                 300

Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305                 310                 315                 320

Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                325                 330                 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
            340                 345                 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        355                 360                 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    370                 375                 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385                 390                 395                 400

Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                405                 410                 415

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            420                 425                 430

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        435                 440                 445
```

```
Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys Asp
    450                 455                 460

Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu
465                 470                 475                 480

Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His
                485                 490                 495

Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala
            500                 505                 510

Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu
        515                 520                 525

Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp
    530                 535                 540

Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys
545                 550                 555                 560

Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu Asp
                565                 570                 575

Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu
            580                 585                 590

Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu
        595                 600                 605

Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg
    610                 615                 620

Ser Lys Glu
625
```

<210> 1515
<211> 577
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1515

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45


Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
                85                  90                  95


Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
```

```
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
    290                 295                 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305                 310                 315                 320

Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                325                 330                 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
```

```
            340                 345                 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp
        355                 360                 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    370                 375                 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385                 390                 395                 400

Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                405                 410                 415

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            420                 425                 430

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        435                 440                 445

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gln Val
    450                 455                 460

Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly Ser Leu
465                 470                 475                 480

Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn Arg Met
                485                 490                 495

Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val Ala Leu
            500                 505                 510

Ile Thr Ser Asp Gly Thr Pro Ala Tyr Ala Asp Ser Ala Lys Gly Arg
        515                 520                 525

Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu Gln Met
```

530 535 540

Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His Val Ser
545 550 555 560

Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser
565 570 575

Ser

<210> 1516
<211> 577
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1516

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
20 25 30

Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr
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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
85 90 95

```
Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gln
                165                 170                 175


Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly Ser
            180                 185                 190


Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn Arg
        195                 200                 205


Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val Ala
    210                 215                 220


Leu Ile Thr Ser Asp Gly Thr Pro Ala Tyr Ala Asp Ser Ala Lys Gly
225                 230                 235                 240


Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu Gln
                245                 250                 255


Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His Val
            260                 265                 270


Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
        275                 280                 285
```

```
Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    290                 295                 300

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
305                 310                 315                 320

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                325                 330                 335

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys
            340                 345                 350

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
        355                 360                 365

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    370                 375                 380

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
385                 390                 395                 400

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
                405                 410                 415

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
            420                 425                 430

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
        435                 440                 445

Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
    450                 455                 460

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr
465                 470                 475                 480
```

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser
485 490 495

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
500 505 510

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
515 520 525

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
530 535 540

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
545 550 555 560

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
565 570 575

Lys

<210> 1517
<211> 802
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1517

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
20 25 30

Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val

```
        35                  40                  45

Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr
    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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95

Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gln
                165                 170                 175

Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly Ser
            180                 185                 190

Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile Phe Ser Ile Asn Arg
        195                 200                 205

Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val Ala
    210                 215                 220

Leu Ile Thr Ser Asp Gly Thr Pro Ala Tyr Ala Asp Ser Ala Lys Gly
```

```
225                 230                 235                 240

Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys Thr Val Ser Leu Gln
                245                 250                 255

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys His Val
            260                 265                 270

Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly Thr Gln Val Thr Val
        275                 280                 285

Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    290                 295                 300

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
305                 310                 315                 320

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                325                 330                 335

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys
            340                 345                 350

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
        355                 360                 365

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    370                 375                 380

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
385                 390                 395                 400

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
                405                 410                 415

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
```

```
            420                 425                 430

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
        435                 440                 445

Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
    450                 455                 460

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
465                 470                 475                 480

Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp
                485                 490                 495

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            500                 505                 510

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
        515                 520                 525

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
    530                 535                 540

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
545                 550                 555                 560

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                565                 570                 575

Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            580                 585                 590

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        595                 600                 605

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
```

```
    610                 615                 620

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys Asp Leu
625                 630                 635                 640

Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala
                645                 650                 655

Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp
            660                 665                 670

Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu
        675                 680                 685

Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe
    690                 695                 700

Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys
705                 710                 715                 720

Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val
                725                 730                 735

Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu Asp Ser
            740                 745                 750

Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys
        755                 760                 765

Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile
    770                 775                 780

Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser
785                 790                 795                 800

Lys Glu
```

<210> 1518
<211> 414
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1518

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Asp
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Gly Tyr
            20                  25                  30


Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Thr Ile Ser Thr Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80


Leu Gln Ile Asn Ser Leu Lys Thr Glu Asp Ala Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Ala Arg Leu Ser Phe Asp Asn Thr Ala Phe Tyr Thr Ser Ala Ile
            100                 105                 110


Arg Tyr Ser Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140
```

```
Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                165                 170                 175

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His Thr
            180                 185                 190

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
        195                 200                 205

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
    210                 215                 220

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
225                 230                 235                 240

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
                245                 250                 255

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
            260                 265                 270

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
        275                 280                 285

Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
    290                 295                 300

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro
305                 310                 315                 320

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val
                325                 330                 335
```

```
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
            340                 345                 350


Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
        355                 360                 365


Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
    370                 375                 380


Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
385                 390                 395                 400


Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                405                 410


<210>  1519
<211>  411
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1519

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ser Phe Ser Ser Tyr
            20                  25                  30


Phe Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Gly Ile Gly Trp Asn Asp Gly Ser Ile Asn Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Gly Tyr
```

```
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Ala Ser Val Ser Leu Tyr Gly Leu Glu Lys Ser Ser Ala Tyr Thr
            100                 105                 110

Ser Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                165                 170                 175

Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro
            180                 185                 190

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
        195                 200                 205

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    210                 215                 220

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
225                 230                 235                 240

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                245                 250                 255

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
```

```
            260                 265                 270

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser
        275                 280                 285

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    290                 295                 300

Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Asp
305                 310                 315                 320

Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe
                325                 330                 335

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            340                 345                 350

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        355                 360                 365

Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    370                 375                 380

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
385                 390                 395                 400

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                405                 410


<210>  1520
<211>  452
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1520
```

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190
```

```
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285


Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300


Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320


His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335


Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350


Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365


Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380
```

```
Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400


Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415


Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430


Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
        435                 440                 445


Arg Ser Lys Glu
    450


<210>  1521
<211>  632
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1521

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Thr Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Lys Ile Thr Asn Phe Gly Ile Thr Ser Tyr Ala Asp Ser Ala Gln
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Gly Asn Ala Lys Asn Thr Val Tyr Leu
```

```
65                  70                  75                  80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
                85                  90                  95

Leu Asp Thr Thr Gly Trp Gly Pro Pro Pro Tyr Gln Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Gln Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly
        115                 120                 125

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
    130                 135                 140

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
145                 150                 155                 160

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                165                 170                 175

Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
            180                 185                 190

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        195                 200                 205

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    210                 215                 220

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
225                 230                 235                 240

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
                245                 250                 255

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
```

```
            260                 265                 270

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu
        275                 280                 285

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    290                 295                 300

Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys
305                 310                 315                 320

Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                325                 330                 335

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            340                 345                 350

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        355                 360                 365

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
    370                 375                 380

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
385                 390                 395                 400

Leu Ser Leu Ser Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser
                405                 410                 415

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
            420                 425                 430

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
        435                 440                 445

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
```

```
    450                 455                 460

Gly Gly Ser Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg
465                 470                 475                 480

Thr Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys
                485                 490                 495

Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn
            500                 505                 510

Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln
        515                 520                 525

Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp
    530                 535                 540

Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn
545                 550                 555                 560

Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro
                565                 570                 575

Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg
            580                 585                 590

Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu
        595                 600                 605

Val Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu
    610                 615                 620

Gln Glu Ser Leu Arg Ser Lys Glu
625                 630
```

<210> 1522

<211> 541
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1522

```
Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Leu Gly
1               5                  10                  15


Asn Gln Ala Ser Ile Phe Cys Arg Ser Ser Leu Gly Leu Val His Arg
            20                  25                  30


Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Lys Leu Leu Ile Tyr Lys Val Ser His Arg Phe Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
                85                  90                  95


Thr His Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Gln Ala Tyr Leu Gln Gln Ser Gly Ala Glu Leu Val
    130                 135                 140


Arg Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
145                 150                 155                 160
```

```
Phe Thr Ser His Asn Leu His Trp Val Lys Gln Thr Pro Arg Gln Gly
                165                 170                 175

Leu Gln Trp Ile Gly Ala Ile Tyr Pro Gly Asn Gly Asn Thr Ala Tyr
            180                 185                 190

Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser
        195                 200                 205

Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Asp Asp Ser Ala
    210                 215                 220

Val Tyr Phe Cys Ala Arg Trp Gly Ser Val Val Gly Asp Trp Tyr Phe
225                 230                 235                 240

Asp Val Trp Gly Thr Gly Thr Thr Val Thr Val Ser Ser Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        275                 280                 285

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    290                 295                 300

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His Thr Cys
305                 310                 315                 320

Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
                325                 330                 335

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            340                 345                 350
```

```
Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
        355                 360                 365

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    370                 375                 380

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
385                 390                 395                 400

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln
                405                 410                 415

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            420                 425                 430

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser
        435                 440                 445

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys
    450                 455                 460

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
465                 470                 475                 480

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
                485                 490                 495

Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
            500                 505                 510

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        515                 520                 525

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    530                 535                 540
```

<210> 1523
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1523

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
```

```
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300

Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
```

340 345 350

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
355 360 365

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
370 375 380

Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385 390 395 400

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
405 410 415

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
420 425 430

Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
435 440 445

Arg Ser Lys Glu
450

<210> 1524
<211> 533
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1524

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
20 25 30

```
His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
        35                  40                  45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Gly Ser Thr Gly Gly
            100                 105                 110

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln
        115                 120                 125

Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys
    130                 135                 140

Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn Met His
145                 150                 155                 160

Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile Gly Ala Ile
                165                 170                 175

Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys
            180                 185                 190

Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu
        195                 200                 205

Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser
    210                 215                 220
```

```
Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly Ala Gly Thr
225                 230                 235                 240


Thr Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                245                 250                 255


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            260                 265                 270


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        275                 280                 285


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    290                 295                 300


Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
305                 310                 315                 320


Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                325                 330                 335


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            340                 345                 350


Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        355                 360                 365


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    370                 375                 380


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
385                 390                 395                 400


Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala
                405                 410                 415
```

```
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            420                 425                 430


Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
        435                 440                 445


Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    450                 455                 460


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
465                 470                 475                 480


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu
                485                 490                 495


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            500                 505                 510


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        515                 520                 525


Leu Ser Pro Gly Lys
    530


<210>  1525
<211>  452
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1525

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
```

```
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
```

```
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300

Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380

Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
```

405 410 415

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
420 425 430

Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
435 440 445

Arg Ser Lys Glu
450

<210> 1526
<211> 533
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1526

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
85 90 95

```
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Gly Ser Thr Gly Gly
            100                 105                 110

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln
        115                 120                 125

Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys
    130                 135                 140

Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn Met His
145                 150                 155                 160

Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile Gly Ala Ile
                165                 170                 175

Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys
            180                 185                 190

Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu
        195                 200                 205

Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser
    210                 215                 220

Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly Ala Gly Thr
225                 230                 235                 240

Thr Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                245                 250                 255

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            260                 265                 270

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        275                 280                 285
```

```
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    290                 295                 300


Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
305                 310                 315                 320


Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                325                 330                 335


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            340                 345                 350


Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        355                 360                 365


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    370                 375                 380


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
385                 390                 395                 400


Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala
                405                 410                 415


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            420                 425                 430


Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
        435                 440                 445


Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    450                 455                 460


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
465                 470                 475                 480
```

```
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu
                485                 490                 495


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            500                 505                 510


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        515                 520                 525


Leu Ser Pro Gly Lys
    530


<210>  1527
<211>  759
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1527

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
```

85 90 95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
130 135 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210 215 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225 230 235 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
245 250 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
260 265 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Ser

```
        275                 280                 285

Ser Arg Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro
    290                 295                 300

Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu
305                 310                 315                 320

Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser
                325                 330                 335

Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe Lys Gly Gln Gly
            340                 345                 350

Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile Ser Arg Ile Ala
        355                 360                 365

Val Ser Phe Gln Thr Lys Val Asn Leu Leu Ser Ala Ile Lys Ser Pro
    370                 375                 380

Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu
385                 390                 395                 400

Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu
                405                 410                 415

Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe Ala Glu Ser Gly
            420                 425                 430

Gln Val Tyr Phe Gly Ile Ile Ala Leu Gly Gly Gly Gly Ser Ser Ser
        435                 440                 445

Arg Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro Gln
    450                 455                 460

Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu Leu
```

```
465                 470                 475                 480

Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser Glu
                485                 490                 495

Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe Lys Gly Gln Gly Cys
            500                 505                 510

Pro Ser Thr His Val Leu Leu Thr His Thr Ile Ser Arg Ile Ala Val
        515                 520                 525

Ser Phe Gln Thr Lys Val Asn Leu Leu Ser Ala Ile Lys Ser Pro Cys
    530                 535                 540

Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu Pro
545                 550                 555                 560

Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu Ser
                565                 570                 575

Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe Ala Glu Ser Gly Gln
            580                 585                 590

Val Tyr Phe Gly Ile Ile Ala Leu Gly Gly Gly Gly Ser Ser Ser Arg
        595                 600                 605

Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro Gln Ala
    610                 615                 620

Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu Leu Ala
625                 630                 635                 640

Asn Gly Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser Glu Gly
                645                 650                 655

Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe Lys Gly Gln Gly Cys Pro
```

660 665 670

Ser Thr His Val Leu Leu Thr His Thr Ile Ser Arg Ile Ala Val Ser
675 680 685

Phe Gln Thr Lys Val Asn Leu Leu Ser Ala Ile Lys Ser Pro Cys Gln
690 695 700

Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu Pro Ile
705 710 715 720

Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu Ser Ala
725 730 735

Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe Ala Glu Ser Gly Gln Val
740 745 750

Tyr Phe Gly Ile Ile Ala Leu
755

<210> 1528
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1528

Thr Gln Asp Cys Ser Phe Gln His Ser Pro Ile Ser Ser Asp Phe Ala
1 5 10 15

Val Lys Ile Arg Glu Leu Ser Asp Tyr Leu Leu Gln Asp Tyr Pro Val
20 25 30

Thr Val Ala Ser Asn Leu Gln Asp Glu Glu Leu Cys Gly Gly Leu Trp
35 40 45

```
Arg Leu Val Leu Ala Gln Arg Trp Met Glu Arg Leu Lys Thr Val Ala
    50                  55                  60

Gly Ser Lys Met Gln Gly Leu Leu Glu Arg Val Asn Thr Glu Ile His
65                  70                  75                  80

Phe Val Thr Lys Cys Ala Phe Gln Pro Pro Pro Ser Cys Leu Arg Phe
                85                  90                  95

Val Gln Thr Asn Ile Ser Arg Leu Leu Gln Glu Thr Ser Glu Gln Leu
            100                 105                 110

Val Ala Leu Lys Pro Trp Ile Thr Arg Gln Asn Phe Ser Arg Cys Leu
        115                 120                 125

Glu Leu Gln Cys Gln Pro Asp Ser Ser Thr Leu Pro Pro Pro Trp Ser
    130                 135                 140

Pro Arg Pro Leu Glu Ala Thr Ala Pro Thr Ala Pro Gln Pro Ser Gly
145                 150                 155                 160

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                165                 170                 175

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            180                 185                 190

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        195                 200                 205

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His Thr
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225                 230                 235                 240
```

```
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255


Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            260                 265                 270


Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285


Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300


Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320


Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335


Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro
            340                 345                 350


Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val
        355                 360                 365


Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380


Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400


Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415


Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430
```

```
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210>  1529
<211>  452
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1529

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
```

```
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300

Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
```

325 330 335

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
340 345 350

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
355 360 365

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
370 375 380

Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385 390 395 400

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
405 410 415

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
420 425 430

Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
435 440 445

Arg Ser Lys Glu
450

<210> 1530
<211> 438
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1530

Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr
1 5 10 15

```
Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe
            20                  25                  30

Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr
        35                  40                  45

Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu
    50                  55                  60

Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu
65                  70                  75                  80

Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn
                85                  90                  95

Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala
            100                 105                 110

Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg
        115                 120                 125

Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly
    130                 135                 140

Gln Phe Gln Thr Leu Val Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                165                 170                 175

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            180                 185                 190

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        195                 200                 205
```

```
Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
    210                 215                 220

Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
225                 230                 235                 240

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
                245                 250                 255

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
            260                 265                 270

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
        275                 280                 285

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
    290                 295                 300

Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro
305                 310                 315                 320

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
                325                 330                 335

Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
            340                 345                 350

Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile
        355                 360                 365

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
    370                 375                 380

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys
385                 390                 395                 400
```

```
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
                405                 410                 415


Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
            420                 425                 430


Ser Leu Ser Pro Gly Lys
        435


<210>  1531
<211>  452
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1531

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
```

```
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
```

```
    290                 295                 300

Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380

Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430

Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
        435                 440                 445

Arg Ser Lys Glu
    450


<210>  1532
<211>  508
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> Synthetic Sequence

<400> 1532

```
Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr Gly Ser
1               5                   10                  15


Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu Asp Leu
            20                  25                  30


Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile Ile Gln
        35                  40                  45


Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser Tyr Arg
    50                  55                  60


Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn Ala Ala
65                  70                  75                  80


Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr Arg Cys
                85                  90                  95


Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val Lys Val
            100                 105                 110


Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val Asp Pro
        115                 120                 125


Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr Pro Lys
    130                 135                 140


Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser Gly Lys
145                 150                 155                 160


Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn Val Thr
                165                 170                 175
```

```
Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr Cys Thr
            180                 185                 190


Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu Val Ile
        195                 200                 205


Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Ser Gly Gly Ser
    210                 215                 220


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro
        275                 280                 285


Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
    290                 295                 300


Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
305                 310                 315                 320


Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                325                 330                 335


Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            340                 345                 350


Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
        355                 360                 365
```

```
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val
    370                 375                 380

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
385                 390                 395                 400

Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg
                405                 410                 415

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly
            420                 425                 430

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        435                 440                 445

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
    450                 455                 460

Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
465                 470                 475                 480

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                485                 490                 495

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            500                 505


<210>  1533
<211>  452
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1533

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
```

```
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
```

```
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300

Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380

Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
```

385 390 395 400

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
405 410 415

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
420 425 430

Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
435 440 445

Arg Ser Lys Glu
450

<210> 1534
<211> 438
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1534

Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr
1 5 10 15

Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe
20 25 30

Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr
35 40 45

Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu
50 55 60

Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu
65 70 75 80

```
Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn
                85                  90                  95

Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala
            100                 105                 110

Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg
        115                 120                 125

Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly
    130                 135                 140

Gln Phe Gln Thr Leu Val Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                165                 170                 175

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            180                 185                 190

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        195                 200                 205

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
    210                 215                 220

Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
225                 230                 235                 240

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
                245                 250                 255

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
            260                 265                 270
```

```
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
        275                 280                 285

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
    290                 295                 300

Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro
305                 310                 315                 320

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
                325                 330                 335

Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
            340                 345                 350

Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile
        355                 360                 365

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
    370                 375                 380

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys
385                 390                 395                 400

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
                405                 410                 415

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
            420                 425                 430

Ser Leu Ser Pro Gly Lys
        435


<210>  1535
<211>  663
<212>  PRT
```

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1535

```
Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr
1               5                  10                  15


Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe
            20                  25                  30


Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr
        35                  40                  45


Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu
    50                  55                  60


Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu
65                  70                  75                  80


Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn
                85                  90                  95


Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala
            100                 105                 110


Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg
        115                 120                 125


Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly
    130                 135                 140


Gln Phe Gln Thr Leu Val Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
```

```
                165                 170                 175

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            180                 185                 190

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        195                 200                 205

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
    210                 215                 220

Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
225                 230                 235                 240

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
                245                 250                 255

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
            260                 265                 270

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
        275                 280                 285

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
    290                 295                 300

Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro
305                 310                 315                 320

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
                325                 330                 335

Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn
            340                 345                 350

Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
```

```
        355                 360                 365

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
    370                 375                 380

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
385                 390                 395                 400

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
                405                 410                 415

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
            420                 425                 430

Ser Leu Ser Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        435                 440                 445

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    450                 455                 460

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
465                 470                 475                 480

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                485                 490                 495

Gly Ser Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
            500                 505                 510

Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu
        515                 520                 525

Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
    530                 535                 540

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
```

545 550 555 560

Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
565 570 575

Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
580 585 590

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu
595 600 605

Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
610 615 620

Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
625 630 635 640

Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln
645 650 655

Glu Ser Leu Arg Ser Lys Glu
660

<210> 1536
<211> 508
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1536

Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr Gly Ser
1 5 10 15

Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu Asp Leu
20 25 30

```
Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile Ile Gln
        35                  40                  45

Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser Tyr Arg
    50                  55                  60

Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn Ala Ala
65                  70                  75                  80

Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr Arg Cys
                85                  90                  95

Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val Lys Val
            100                 105                 110

Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val Asp Pro
        115                 120                 125

Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr Pro Lys
    130                 135                 140

Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser Gly Lys
145                 150                 155                 160

Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn Val Thr
                165                 170                 175

Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr Cys Thr
            180                 185                 190

Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu Val Ile
        195                 200                 205

Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Ser Gly Gly Ser
    210                 215                 220
```

```
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro
        275                 280                 285


Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
    290                 295                 300


Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
305                 310                 315                 320


Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                325                 330                 335


Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            340                 345                 350


Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
        355                 360                 365


Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val
    370                 375                 380


Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
385                 390                 395                 400


Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg
                405                 410                 415
```

```
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly
            420                 425                 430


Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        435                 440                 445


Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
    450                 455                 460


Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
465                 470                 475                 480


Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                485                 490                 495


Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            500                 505


<210>  1537
<211>  733
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1537

Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr Gly Ser
1               5                   10                  15


Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu Asp Leu
            20                  25                  30


Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile Ile Gln
        35                  40                  45


Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser Tyr Arg
```

```
    50                  55                  60

Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn Ala Ala
65                  70                  75                  80

Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr Arg Cys
                85                  90                  95

Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val Lys Val
            100                 105                 110

Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val Asp Pro
        115                 120                 125

Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr Pro Lys
    130                 135                 140

Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser Gly Lys
145                 150                 155                 160

Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn Val Thr
                165                 170                 175

Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr Cys Thr
            180                 185                 190

Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu Val Ile
        195                 200                 205

Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Ser Gly Gly Ser
    210                 215                 220

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
```

```
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro
        275                 280                 285

Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
    290                 295                 300

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
305                 310                 315                 320

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                325                 330                 335

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            340                 345                 350

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
        355                 360                 365

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val
    370                 375                 380

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
385                 390                 395                 400

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg
                405                 410                 415

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
            420                 425                 430

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
```

```
        435                 440                 445

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
    450                 455                 460

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
465                 470                 475                 480

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                485                 490                 495

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Ser Gly
            500                 505                 510

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
        515                 520                 525

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
    530                 535                 540

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
545                 550                 555                 560

Gly Ser Gly Gly Ser Gly Gly Ser Cys Asp Leu Pro Gln Thr His Ser
                565                 570                 575

Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Lys Ile
            580                 585                 590

Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln
        595                 600                 605

Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu
    610                 615                 620

His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser
```

625 630 635 640

Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu
645 650 655

Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly
660 665 670

Val Glu Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg
675 680 685

Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser
690 695 700

Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Ala Ser Phe Ser
705 710 715 720

Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu
725 730

<210> 1538
<211> 402
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1538

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

```
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240
```

```
Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
        275                 280                 285

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
    290                 295                 300

Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn Val
305                 310                 315                 320

Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val Ala
                325                 330                 335

Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Lys Gly
            340                 345                 350

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu Gln
        355                 360                 365

Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr Leu
    370                 375                 380

Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
385                 390                 395                 400

Ser Ser
```

<210> 1539
<211> 452
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1539

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                  10                  15


Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30


Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45


Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60


Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80


Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95


Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110


Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125


Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140


Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160


Leu Arg Ser Lys Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
```

```
                165                 170                 175

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            180                 185                 190

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        195                 200                 205

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    210                 215                 220

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
```

355 360 365

Ser Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385 390 395 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Gly Lys
450

<210> 1540
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1540

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

```
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Ser Gly Cys Asn Gly Arg Cys
225                 230
```

<210> 1541
<211> 459
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1541

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                   10                  15


Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30


Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45


Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60


Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80


Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95


Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110


Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125


Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140


Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
```

```
145                 150                 155                 160

Leu Arg Ser Lys Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                165                 170                 175

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            180                 185                 190

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        195                 200                 205

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    210                 215                 220

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
```

```
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly Lys Ser Gly Cys Asn Gly Arg Cys
    450                 455


<210>  1542
<211>  405
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1542

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Ala Gln Ala Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Met Gly
            20                  25                  30
```

```
Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val Ala Ala Ile
        35                  40                  45

Thr Tyr Ser Gly Gly Ser Pro Tyr Tyr Ala Ser Ser Val Arg Gly Arg
    50                  55                  60

Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln Met
65                  70                  75                  80

Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala Asn
                85                  90                  95

Pro Thr Tyr Gly Ser Asp Trp Asn Ala Glu Asn Trp Gly Gln Gly Thr
            100                 105                 110

Gln Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                165                 170                 175

Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
            180                 185                 190

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        195                 200                 205

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    210                 215                 220
```

```
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
225                 230                 235                 240


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
                245                 250                 255


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            260                 265                 270


Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala
        275                 280                 285


Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    290                 295                 300


Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
305                 310                 315                 320


Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                325                 330                 335


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            340                 345                 350


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu
        355                 360                 365


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    370                 375                 380


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
385                 390                 395                 400


Leu Ser Pro Gly Lys
                405
```

<210> 1543
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1543

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ser Phe Ser Ser Tyr
            20                  25                  30


Phe Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Gly Ile Gly Trp Asn Asp Gly Ser Ile Asn Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Gly Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Ala Ser Val Ser Leu Tyr Gly Leu Glu Lys Ser Ser Ala Tyr Thr
            100                 105                 110


Ser Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
```

```
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                165                 170                 175

Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro
            180                 185                 190

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
        195                 200                 205

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    210                 215                 220

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
225                 230                 235                 240

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                245                 250                 255

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
            260                 265                 270

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser
        275                 280                 285

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    290                 295                 300

Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Asp
305                 310                 315                 320

Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe
                325                 330                 335

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
```

```
            340                 345                 350

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        355                 360                 365

Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    370                 375                 380

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
385                 390                 395                 400

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                405                 410
```

<210> 1544
<211> 414
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1544

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Asp
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Gly Tyr
            20                  25                  30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45

Ala Thr Ile Ser Thr Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser Val Tyr
65                  70                  75                  80
```

```
Leu Gln Ile Asn Ser Leu Lys Thr Glu Asp Ala Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Ala Arg Leu Ser Phe Asp Asn Thr Ala Phe Tyr Thr Ser Ala Ile
            100                 105                 110


Arg Tyr Ser Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                165                 170                 175


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His Thr
            180                 185                 190


Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
        195                 200                 205


Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
    210                 215                 220


Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
225                 230                 235                 240


Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
                245                 250                 255


Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
            260                 265                 270
```

```
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
        275                 280                 285


Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
    290                 295                 300


Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro
305                 310                 315                 320


Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val
                325                 330                 335


Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
            340                 345                 350


Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
        355                 360                 365


Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
    370                 375                 380


Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
385                 390                 395                 400


Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                405                 410


<210>  1545
<211>  452
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1545

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
```

```
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
```

```
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300

Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380

Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
```

385 390 395 400

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
405 410 415

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
420 425 430

Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
435 440 445

Arg Ser Lys Glu
450

<210> 1546
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1546

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

```
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270
```

```
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285


Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300


Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320


His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335


Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350


Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365


Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380


Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400


Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415


Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430


Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
        435                 440                 445


Arg Ser Lys Glu
    450
```

<210> 1547
<211> 402
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1547

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr
    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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95


Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
```

```
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
    290                 295                 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305                 310                 315                 320

Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                325                 330                 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
```

340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys

<210> 1548
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1548

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

```
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270
```

```
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285


Asp Leu Pro Glu Thr His Ser Leu Asp Asn Arg Arg Thr Leu Met Leu
    290                 295                 300


Leu Ala Gln Met Ser Arg Ile Ser Pro Ser Ser Cys Leu Met Asp Arg
305                 310                 315                 320


His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln Phe Gln
                325                 330                 335


Lys Ala Pro Ala Ile Ser Val Leu His Glu Leu Ile Gln Gln Ile Phe
            340                 345                 350


Asn Leu Phe Thr Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Asp Leu
        355                 360                 365


Leu Asp Lys Phe Cys Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
    370                 375                 380


Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met Asn
385                 390                 395                 400


Ala Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr Leu
                405                 410                 415


Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
            420                 425                 430


Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu Arg
        435                 440                 445


Leu Arg Arg Lys Glu
    450
```

<210> 1549
<211> 402
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1549

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr
    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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95


Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
```

```
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
225                 230                 235                 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                245                 250                 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            260                 265                 270

Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        275                 280                 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
    290                 295                 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305                 310                 315                 320

Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                325                 330                 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
```

340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys

<210> 1550
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1550

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

```
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270
```

```
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Met
        275                 280                 285


Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln Cys
    290                 295                 300


Gln Lys Leu Leu Gly Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu Lys
305                 310                 315                 320


Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln Gln
                325                 330                 335


Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln Asn
            340                 345                 350


Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn Glu
        355                 360                 365


Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn His
    370                 375                 380


Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr Arg
385                 390                 395                 400


Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg Ile
                405                 410                 415


Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr Ile
            420                 425                 430


Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu Thr
        435                 440                 445


Gly Tyr Leu Arg Asn
    450
```

<210> 1551
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1551

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ser Phe Ser Ser Tyr
            20                  25                  30


Phe Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45


Ala Gly Ile Gly Trp Asn Asp Gly Ser Ile Asn Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Gly Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Ala Ser Val Ser Leu Tyr Gly Leu Glu Lys Ser Ser Ala Tyr Thr
            100                 105                 110


Ser Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
```

```
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
                165                 170                 175

Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro
            180                 185                 190

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
        195                 200                 205

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    210                 215                 220

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
225                 230                 235                 240

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                245                 250                 255

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
            260                 265                 270

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser
        275                 280                 285

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    290                 295                 300

Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Asp
305                 310                 315                 320

Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe
                325                 330                 335

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
```

```
            340                 345                 350

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        355                 360                 365

Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    370                 375                 380

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
385                 390                 395                 400

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                405                 410
```

<210> 1552
<211> 440
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1552

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80
```

```
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270
```

```
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Ala
        275                 280                 285


Pro Val Arg Ser Leu Asn Cys Thr Leu Arg Asp Ser Gln Gln Lys Ser
    290                 295                 300


Leu Val Met Ser Gly Pro Tyr Glu Leu Lys Ala Leu His Leu Gly Gly
305                 310                 315                 320


Gln Asp Met Glu Gln Gln Val Val Phe Ser Met Ser Phe Val Gln Gly
                325                 330                 335


Glu Glu Ser Asn Asp Lys Ile Pro Val Ala Leu Gly Leu Lys Glu Lys
            340                 345                 350


Asn Leu Tyr Leu Ser Cys Val Leu Lys Asp Asp Lys Pro Thr Leu Gln
        355                 360                 365


Leu Glu Ser Val Asp Pro Lys Asn Tyr Pro Lys Lys Lys Met Glu Lys
    370                 375                 380


Arg Phe Val Phe Asn Lys Ile Glu Ile Asn Asn Lys Leu Glu Phe Glu
385                 390                 395                 400


Ser Ala Gln Phe Pro Asn Trp Tyr Ile Ser Thr Ser Gln Ala Glu Asn
                405                 410                 415


Met Pro Val Phe Leu Gly Gly Thr Lys Gly Gly Gln Asp Ile Thr Asp
            420                 425                 430


Phe Thr Met Gln Phe Val Ser Ser
        435                 440


<210>  1553
<211>  405
<212>  PRT
```

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1553

```
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Ala Gln Ala Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Met Gly
            20                  25                  30


Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val Ala Ala Ile
        35                  40                  45


Thr Tyr Ser Gly Gly Ser Pro Tyr Tyr Ala Ser Ser Val Arg Gly Arg
    50                  55                  60


Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu Gln Met
65                  70                  75                  80


Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ala Asn
                85                  90                  95


Pro Thr Tyr Gly Ser Asp Trp Asn Ala Glu Asn Trp Gly Gln Gly Thr
            100                 105                 110


Gln Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
```

```
                165                 170                 175

Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
            180                 185                 190

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        195                 200                 205

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    210                 215                 220

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
225                 230                 235                 240

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
                245                 250                 255

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            260                 265                 270

Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala
        275                 280                 285

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    290                 295                 300

Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
305                 310                 315                 320

Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                325                 330                 335

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            340                 345                 350

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu
```

355 360 365

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
370 375 380

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
385 390 395 400

Leu Ser Pro Gly Lys
405

<210> 1554
<211> 759
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1554

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

```
Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Ser
        275                 280                 285
```

```
Ser Arg Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro
    290                 295                 300

Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu
305                 310                 315                 320

Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser
                325                 330                 335

Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe Lys Gly Gln Gly
            340                 345                 350

Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile Ser Arg Ile Ala
        355                 360                 365

Val Ser Phe Gln Thr Lys Val Asn Leu Leu Ser Ala Ile Lys Ser Pro
    370                 375                 380

Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu
385                 390                 395                 400

Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu
                405                 410                 415

Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe Ala Glu Ser Gly
            420                 425                 430

Gln Val Tyr Phe Gly Ile Ile Ala Leu Gly Gly Gly Gly Ser Ser Ser
        435                 440                 445

Arg Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro Gln
    450                 455                 460

Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu Leu
465                 470                 475                 480
```

```
Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser Glu
                485                 490                 495


Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe Lys Gly Gln Gly Cys
            500                 505                 510


Pro Ser Thr His Val Leu Leu Thr His Thr Ile Ser Arg Ile Ala Val
        515                 520                 525


Ser Phe Gln Thr Lys Val Asn Leu Leu Ser Ala Ile Lys Ser Pro Cys
    530                 535                 540


Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu Pro
545                 550                 555                 560


Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu Ser
                565                 570                 575


Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe Ala Glu Ser Gly Gln
            580                 585                 590


Val Tyr Phe Gly Ile Ile Ala Leu Gly Gly Gly Gly Ser Ser Ser Arg
        595                 600                 605


Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro Gln Ala
    610                 615                 620


Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu Leu Ala
625                 630                 635                 640


Asn Gly Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser Glu Gly
                645                 650                 655


Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe Lys Gly Gln Gly Cys Pro
            660                 665                 670
```

```
Ser Thr His Val Leu Leu Thr His Thr Ile Ser Arg Ile Ala Val Ser
        675                 680                 685


Phe Gln Thr Lys Val Asn Leu Leu Ser Ala Ile Lys Ser Pro Cys Gln
    690                 695                 700


Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu Pro Ile
705                 710                 715                 720


Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu Ser Ala
                725                 730                 735


Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe Ala Glu Ser Gly Gln Val
            740                 745                 750


Tyr Phe Gly Ile Ile Ala Leu
        755


<210>  1555
<211>  440
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1555

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
```

```
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
```

```
                245                 250                 255

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Ala
        275                 280                 285

Pro Val Arg Ser Leu Asn Cys Thr Leu Arg Asp Ser Gln Gln Lys Ser
    290                 295                 300

Leu Val Met Ser Gly Pro Tyr Glu Leu Lys Ala Leu His Leu Gly Gly
305                 310                 315                 320

Gln Asp Met Glu Gln Gln Val Val Phe Ser Met Ser Phe Val Gln Gly
                325                 330                 335

Glu Glu Ser Asn Asp Lys Ile Pro Val Ala Leu Gly Leu Lys Glu Lys
            340                 345                 350

Asn Leu Tyr Leu Ser Cys Val Leu Lys Asp Asp Lys Pro Thr Leu Gln
        355                 360                 365

Leu Glu Ser Val Asp Pro Lys Asn Tyr Pro Lys Lys Lys Met Glu Lys
    370                 375                 380

Arg Phe Val Phe Asn Lys Ile Glu Ile Asn Asn Lys Leu Glu Phe Glu
385                 390                 395                 400

Ser Ala Gln Phe Pro Asn Trp Tyr Ile Ser Thr Ser Gln Ala Glu Asn
                405                 410                 415

Met Pro Val Phe Leu Gly Gly Thr Lys Gly Gly Gln Asp Ile Thr Asp
            420                 425                 430

Phe Thr Met Gln Phe Val Ser Ser
```

435 440

<210> 1556
<211> 632
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1556

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Ile Asn
20 25 30

Val Met Gly Trp Tyr Arg Gln Thr Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Lys Ile Thr Asn Phe Gly Ile Thr Ser Tyr Ala Asp Ser Ala Gln
50 55 60

Gly Arg Phe Thr Ile Ser Arg Gly Asn Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Leu Asp Thr Thr Gly Trp Gly Pro Pro Pro Tyr Gln Tyr Trp Gly Gln
100 105 110

Gly Thr Gln Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly
115 120 125

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
130 135 140

```
Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
145                 150                 155                 160

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                165                 170                 175

Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
            180                 185                 190

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        195                 200                 205

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    210                 215                 220

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
225                 230                 235                 240

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
                245                 250                 255

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            260                 265                 270

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu
        275                 280                 285

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    290                 295                 300

Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys
305                 310                 315                 320

Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                325                 330                 335
```

```
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            340                 345                 350


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        355                 360                 365


Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
    370                 375                 380


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
385                 390                 395                 400


Leu Ser Leu Ser Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser
                405                 410                 415


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
            420                 425                 430


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
        435                 440                 445


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
    450                 455                 460


Gly Gly Ser Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg
465                 470                 475                 480


Thr Leu Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys
                485                 490                 495


Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn
            500                 505                 510


Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln
        515                 520                 525
```

```
Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp
    530                 535                 540


Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn
545                 550                 555                 560


Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro
                565                 570                 575


Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg
            580                 585                 590


Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu
        595                 600                 605


Val Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu
    610                 615                 620


Gln Glu Ser Leu Arg Ser Lys Glu
625                 630


<210>  1557
<211>  402
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1557

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
```

```
        35                  40                  45

Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr
    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 Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95

Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
        115                 120                 125

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
    130                 135                 140

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
145                 150                 155                 160

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp
                165                 170                 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
            180                 185                 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        195                 200                 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    210                 215                 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
```

225 230 235 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
245 250 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
260 265 270

Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
275 280 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
290 295 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
305 310 315 320

Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
325 330 335

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp
355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
385 390 395 400

Gly Lys

<210> 1558

<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1558

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160
```

```
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285


Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300


Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320


His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335


Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350
```

```
Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365


Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380


Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400


Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415


Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430


Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
        435                 440                 445


Arg Ser Lys Glu
    450


<210>  1559
<211>  403
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1559

Ser Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly
1               5                   10                  15


Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile
            20                  25                  30


Asn Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu
```

```
        35                  40                  45

Val Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val
    50                  55                  60

Thr Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys 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

Tyr Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val
            100                 105                 110

Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
        115                 120                 125

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
    130                 135                 140

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
145                 150                 155                 160

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
                165                 170                 175

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
            180                 185                 190

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
        195                 200                 205

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
    210                 215                 220

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
```

225 230 235 240

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
245 250 255

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
260 265 270

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
275 280 285

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
290 295 300

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
305 310 315 320

Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
325 330 335

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
340 345 350

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Arg Leu Thr Val
355 360 365

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
370 375 380

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
385 390 395 400

Leu Gly Lys

<210> 1560

<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 1560

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
        35                  40                  45


Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160
```

```
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Leu Gly Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
225                 230                 235                 240


Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
                245                 250                 255


Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
            260                 265                 270


Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Cys
        275                 280                 285


Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
    290                 295                 300


Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
305                 310                 315                 320


His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
                325                 330                 335


Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
            340                 345                 350
```

```
Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
        355                 360                 365


Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
    370                 375                 380


Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met Lys Glu
385                 390                 395                 400


Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
                405                 410                 415


Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
            420                 425                 430


Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
        435                 440                 445


Arg Ser Lys Glu
    450


<210>  1561
<211>  353
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence

<400>  1561

Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
```

```
        35                  40                  45

Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gly Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
                85                  90                  95

Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr
            100                 105                 110

Val Ser Ser Val Asp Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
        115                 120                 125

Ser Gly Gly Ser Gly Gly Ser Arg Ser Gly Gly Ser Gly Gly Ser Gly
    130                 135                 140

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
145                 150                 155                 160

Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
                165                 170                 175

Ala Ala Ala Met Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg
            180                 185                 190

Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser
        195                 200                 205

Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly
    210                 215                 220

Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile
```

225 230 235 240

Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp
245 250 255

Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu
260 265 270

Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr
275 280 285

Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln
290 295 300

Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp
305 310 315 320

Glu Val Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn
325 330 335

Leu Gln Glu Ser Leu Arg Ser Lys Glu Leu Glu His His His His His
340 345 350

His

<210> 1562
<211> 166
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (wild-type IFNalpha1)

<400> 1562

Cys Asp Leu Pro Glu Thr His Ser Leu Asp Asn Arg Arg Thr Leu Met
1 5 10 15

```
Leu Leu Ala Gln Met Ser Arg Ile Ser Pro Ser Ser Cys Leu Met Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln Phe
        35                  40                  45

Gln Lys Ala Pro Ala Ile Ser Val Leu His Glu Leu Ile Gln Gln Ile
    50                  55                  60

Phe Asn Leu Phe Thr Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Asp
65                  70                  75                  80

Leu Leu Asp Lys Phe Cys Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
                85                  90                  95

Glu Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met
            100                 105                 110

Asn Ala Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr
        115                 120                 125

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu
145                 150                 155                 160

Arg Leu Arg Arg Lys Glu
                165
```

<210> 1563
<211> 166
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (IFN-gamma)

<400> 1563

```
Met Lys Tyr Thr Ser Tyr Ile Leu Ala Phe Gln Leu Cys Ile Val Leu
1               5                  10                  15

Gly Ser Leu Gly Cys Tyr Cys Gln Asp Pro Tyr Val Lys Glu Ala Glu
            20                  25                  30

Asn Leu Lys Lys Tyr Phe Asn Ala Gly His Ser Asp Val Ala Asp Asn
        35                  40                  45

Gly Thr Leu Phe Leu Gly Ile Leu Lys Asn Trp Lys Glu Glu Ser Asp
    50                  55                  60

Arg Lys Ile Met Gln Ser Gln Ile Val Ser Phe Tyr Phe Lys Leu Phe
65                  70                  75                  80

Lys Asn Phe Lys Asp Asp Gln Ser Ile Gln Lys Ser Val Glu Thr Ile
                85                  90                  95

Lys Glu Asp Met Asn Val Lys Phe Phe Asn Ser Asn Lys Lys Lys Arg
            100                 105                 110

Asp Asp Phe Glu Lys Leu Thr Asn Tyr Ser Val Thr Asp Leu Asn Val
        115                 120                 125

Gln Arg Lys Ala Ile His Glu Leu Ile Gln Val Met Ala Glu Leu Ser
    130                 135                 140

Pro Ala Ala Lys Thr Gly Lys Arg Lys Arg Ser Gln Met Leu Phe Arg
145                 150                 155                 160

Gly Arg Arg Ala Ser Gln
                165
```

<210> 1564

<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (wild type IL-15)

<400> 1564

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1 5 10 15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr Ser

<210> 1565
<211> 227
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (hIgG1 Fc_L234A_L235A_P329G_Y407T)

<400> 1565

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Thr Ser Lys Leu Thr Val
```

180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210 215 220

Pro Gly Lys
225

<210> 1566
<211> 227
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (hIgG1 Fc_L234A_L235A_P329G_T366Y)

<400> 1566

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

```
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Tyr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys
225


<210>  1567
<211>  227
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (hIgG1
       Fc_L234A_L235A_K322Q_Y349C_T366S_L368A_Y407V)

<400>  1567
```

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1               5                  10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val
            180                 185                 190
```

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210 215 220

Pro Gly Lys
225

<210> 1568
<211> 227
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence (hIgG1 Fc_L234A_L235A_K322Q_S354C_T366W)

<400> 1568

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

```
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys
225


<210>  1569
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (R1CHCL50_opt4)

<400>  1569

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser Ile Asn
            20                  25                  30


Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
        35                  40                  45


Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
                85                  90                  95


Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  1570
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic Sequence (3LEC89_opt4)

<400>  1570

Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Ile Phe Ser Val Asn
            20                  25                  30


Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
        35                  40                  45
```

```
Ala Ala Ile Thr Asn Gln Gly Ala Pro Thr Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
                85                  90                  95

Ala Phe Thr Arg Gly Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser
        115
```