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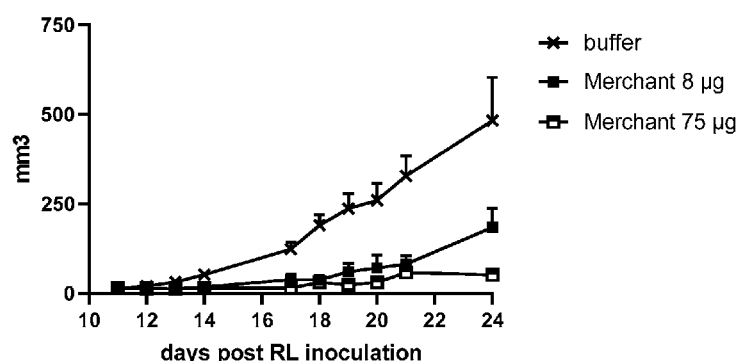
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(54) Title: CLEC9A-BASED CHIMERIC PROTEIN COMPLEXES

Figure 6:



(57) **Abstract:** The present invention relates, in part, to chimeric protein complexes including an anti-Clec9A targeting moiety, a modified Fc domain, and a modified human IFN α and their use as therapeutic agents. The present invention further relates to pharmaceutical compositions comprising the chimeric protein complexes and their use in the treatment of various diseases.

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CLEC9A-BASED CHIMERIC PROTEIN COMPLEXES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Provisional Patent Application No. 62/906,442, filed September 26, 2019, and to U.S. Provisional Patent Application No. 62/825,584, filed March 28, 2019, the content of which are hereby incorporated by reference in their entirety.

FIELD

The present invention relates, in part to, chimeric protein complexes that include a fragment crystallizable domain (Fc), a Clec9A VHH as a targeting moiety, and a modified interferon $\alpha 2$ (IFN $\alpha 2$) as a signaling agent. Use of these chimeric protein complexes as therapeutic agents is also disclosed.

SEQUENCE LISTING

The instant application contains a Sequence Listing that has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on March 26, 2020, is named ORN-063PC_ST25.txt and is 139,264 bytes in size.

BACKGROUND

Biologics with an effector function are a class of biologics that have many potential therapeutic applications. In some instances, these biologics, *e.g.*, cytokines, encode an effector functions that can be systemically toxic if administered to humans. Accordingly, maximizing tolerability and therapeutic index of these biologics in humans is important so that systemic toxicity in humans or subjects can be reduced.

Often, these biologics need be delivered to their target(s) inside a subject with high precision and in a regulated manner in order for them to be effective. Thus, there is a need for engineering biological molecules that have high inherent safety profile, have the ability to reach their target inside the subject with high precision, and are able to function in a regulated fashion.

One example of such biologics, is a chimeric protein having a signaling agent (having an effector function, *e.g.*, a cytokine), connected to a targeting element (having the ability to seek its target with high precision). In these biologics, the signaling agent can be a wild type signaling agent or a modified signaling agent (*e.g.* by mutation). The modified signaling agent is, generally, modified 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 the signaling agent's 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.

SUMMARY

The present technology provides chimeric protein complexes that comprise biological therapeutic agents whose effector function can be delivered in a highly precise fashion to a target of choice, with limited or no cross-reactivities, and with limited or no systemic 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, stability and storage properties).

In one aspect, the present invention relates to a heterodimeric protein complex and its individual polypeptide chain subunits (components), and where the protein complex includes a targeting moiety that specifically binds to C-type lectin domain family 9 member A (Clec9A), a modified human IFN α 2, and a modified Fc domain.

In an aspect, the present invention is related to a chimeric protein complex comprising: (i) a targeting moiety that specifically binds to C-type lectin domain family 9 member A (Clec9A), (ii) a modified human IFN α 2, and (iii) a modified Fc domain.

In one aspect, the present invention relates to a chimeric protein complex where the chimeric protein complex includes a targeting moiety that specifically binds to C-type lectin domain family 9 member A (Clec9A), a modified human IFN α 2, and a modified Fc domain.

In some embodiments, the chimeric protein complex comprises a polypeptide having at least 95% identity with any one of SEQ ID NOs: 1-4 and 43 or at least 98% identity with any one of SEQ ID NOs: 1-4 and 43 or at least 99% identity with any one of SEQ ID NOs: 1-4 and 43. In some embodiments, the chimeric protein complex comprises a polypeptide of any one of SEQ ID NOs: 1-4 and 43, optionally with 0, or 1, or 2, or 3, or 4, or 5 mutations. In some embodiments, the chimeric protein complex comprises a polypeptide of any one of SEQ ID NOs: 1-4 and 43.

In some embodiments, the chimeric protein complex comprises a polypeptide incorporating a contiguous amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 1-4 and 43 or at least 98% identity with any one of SEQ ID NOs: 1-4 and 43.

In another aspect, the present invention relates to a method of treating or preventing a cancer, comprising administering an effective amount of the chimeric protein complex, as disclosed herein, to a patient in need thereof.

Another aspect of the present invention relates to a pharmaceutical composition comprising a chimeric protein complex, as disclosed herein, and a pharmaceutically acceptable carrier. In another aspect, the present invention

relates to a method for treating or preventing a cancer, comprising administering an effective amount of the pharmaceutical composition as disclosed herein to a patient in need thereof. In another aspect, the present invention relates to a recombinant nucleic acid composition encoding one or more of the polypeptide chain subunits of chimeric protein complexes disclosed herein. In another aspect, the present invention relates to a host cell including a nucleic acid composition encoding one or more chimeric protein complexes disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows various non-limiting illustrative schematics of the chimeric protein complexes of the present invention. In embodiments, each schematic is a composition of the present invention. Here “IFN” refers IFN α 2, as described herein; “VHH” refers to anti-Clec9A VHH, as described herein; “” is an optional “linker” as described herein; and the two long parallel rectangles with one having a protrusion and the other having an indentation are human Fc domains from IgG1, with knob-in-hole mutations as described herein and, optionally, with effector knock-out and/or stabilization mutations as also described herein. Although SEQ ID Nos are shown, these are illustrative only, e.g. they will change if alternative mutations besides R149A, as described herein, are used.

Figure 2 shows plasma concentrations of Fc-AFNs after intravenous administration in mouse. Average values of 3 individual samples per time point time (+SEM) are plotted.

Figure 3 shows the plasma concentrations of a CLEC9A AFN (construct lacking Fc) after intravenous administration in mouse. Average values of 3 individual samples per time point time (+SEM) are plotted.

Figure 4A-D show specific binding of CLEC9A-AFN Fc-construct to cells expressing human CLEC9A (HL116-hCLEC9a) compared to control cells (HL116 and HEK293T).

Figure 5 shows tumor growth curves in humanized mice after treatment with buffer or four different CLEC9A-AFN Fc-constructs. Average values (in mm³) of 5 animals per time point time (+SEM) are plotted.

Figure 6 shows tumor growth curves in humanized mice after treatment with buffer or increasing doses of a single CLEC9A-AFN Fc-construct. Average values (in mm³) of 5 animals per time point time (+SEM) are plotted.

Figure 7 shows various bivalent orientations and/or configurations that are encompassed by the present invention. The second VHH moiety to achieve bivalency is shaded and forms together with the attached linker a N- or C-terminal extension of the SEQ ID mentioned in the figure. Although SEQ ID Nos are shown, these are illustrative only, e.g. they will change if alternative mutations besides R149A, as described herein, are used. Further, the VHHs may be identical. See **Figure 1** description for clarification.

Figure 8A shows results of pSTAT1 phosphorylation in Clec9A-/CD141- and Clec9A+/CD141+ PBMC's by IFN α 2.

Figure 8B shows results of pSTAT1 phosphorylation in Clec9A-/CD141- and Clec9A+/CD141+ PBMC's by AFNs with the A145G or M148A mutations.

Figure 9 shows tumor growth curves in humanized mice after treatment with buffer or a 7.5 μ g dose of two different CLEC9A-AFN Fc-constructs. Average values (+SEM) of tumor sizes (in mm³) of 6 animals per time point time were plotted.

Figures 10A-C show pSTAT1 activity in CLEC9A-/CD141- and CLEC9A+/CD141+ PBMC's after treatment with Clec9A targeted AFNs with (Figure 10A) and without T106 O-glycosylation in IFN α 2 (Figure 10B), and an untargeted variant (Figure 10C).

Figure 11 shows anti-tumor activity of Clec9A targeted-AFN Fc with the A145G mutation of IFN α 2.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the present invention relates to a chimeric protein complex where the chimeric protein complex includes a targeting moiety that specifically binds to C-type lectin domain family 9 member A (Clec9A), a modified human IFN α 2, and a modified Fc domain. In embodiments, the chimeric protein complex comprises a polypeptide having at least 95% identity with any one of SEQ ID NOs: 1-4 and 43. In embodiments, the chimeric protein complex comprises a polypeptide having at least 98% identity with any one of SEQ ID NOs: 1-4 and 43 or at least 99% identity with any one of SEQ ID Nos: 1-4 and 43. In embodiments, the chimeric protein complex comprises a polypeptide of SEQ ID NOs: 1-4 and 43 wherein the sequence has less than 10 mutations as compared to the selected sequence. In embodiments, the chimeric protein complex comprises a polypeptide of SEQ ID NOs: 1-4 and 43 wherein the sequence has less than 5 mutations as compared to the selected sequence.

In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence of SEQ ID NO: 1. This sequence includes a single domain antibody (VHH) against Clec9A (i.e., R1CHCL50(opt4)), a linker (i.e., 5*GGS), and a Fc hole Ridgway sequence with LALA-KQ mutation (i.e., Fc hole Ridgway (LALA-KQ), see Ridgway *et al.*, *Protein Engineering* 1996;9:617-621, which is incorporated by reference in its entirety). This construct of sequence of SEQ ID NO: 1 is denoted as follows: Variation 1 VHH-Fc R1CHCL50(opt4)-5*GGS-Fc hole Ridgway (LALA-KQ).

In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence of SEQ ID NO: 2. This sequence includes a single domain antibody (VHH) against Clec9A (i.e., R1CHCL50(opt4)), a linker (i.e., 5*GGS), and a Fc hole Merchant sequence with LALA-KQ mutation (i.e., Fc hole Merchant (LALA-KQ), see Merchant *et al.*, *Nature Biotechnology* 1998;16:677-681, which is incorporated by reference in its entirety). This construct of SEQ ID NO: 2 is denoted as follows: VHH-Fc: R1CHCL50(opt4)-5*GGS-Fc hole Merchant (LALA-KQ).

In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence of SEQ ID NO: 3. This sequence includes a single domain antibody (VHH) against Clec9A (i.e., 3LEC89(opt4)), a linker (i.e., 5*GGS), and a Fc hole Ridgway sequence with LALA-KQ mutation (i.e., Fc hole Ridgway (LALA-KQ), see Ridgway *et al.*, *Protein Engineering* 1996;9:617-621, which is incorporated by reference in its entirety). This construct of SEQ ID NO: 3 is denoted as follows: VHH-Fc: 3LEC89(opt4)-5*GGS-Fc hole Ridgway (LALA-KQ)

In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence of SEQ ID NO: 4. This sequence includes a single domain antibody (VHH) against Clec9A (i.e., 3LEC89(opt4)), a linker (i.e., 5*GGS), and a Fc hole Merchant sequence with LALA-KQ mutation (i.e., Fc hole Merchant (LALA-KQ), see

Merchant *et al.*, *Nature Biotechnology* 1998;16:677-681, which is incorporated by reference in its entirety). This construct of SEQ ID NO: 4 is denoted as follows: VHH-Fc: 3LEC89(opt4)-5*GGG-Fc hole Merchant (LALA-KQ).

In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence of SEQ ID NO: 43. This sequence includes a single domain antibody (VHH) against Clec9A (i.e., R1CHCL50(opt4)), a linker (i.e., 5*GGG), and a Fc hole Merchant sequence with LALA-KQ mutation and without C terminal lysine (i.e., Fc hole Merchant (LALA-KQ), see Merchant *et al.*, *Nature Biotechnology* 1998;16:677-681, which is incorporated by reference in its entirety).

The chimeric protein complex of the present invention may further include an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 5-8, 29-36, or 41-42. In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence of at least 98% identity with any one of SEQ ID NOs: 5-8, 29-36, or 41-42 or at least 99% identity with any one of SEQ ID Nos: 5-8, 29-36, or 41-42. In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence selected from SEQ ID NOs: 5-8, 29-36, or 41-42 wherein the sequence has less than 10 mutations as compared to the selected sequence. In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence selected from SEQ ID NOs: 5-8, 29-36, or 41-42 wherein the sequence has less than 5 mutations as compared to the selected sequence.

In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence of SEQ ID NO: 5. This sequence includes a modified human interferon $\alpha 2b$ having a R149A mutations (i.e., hulFNa2B_R149A), a linker (i.e., 10*GGG-G), and a Fc knob Ridgway sequence with LALA-KQ mutation (i.e., Fc knob Ridgway (LALA-KQ), see Ridgway *et al.*, *Protein Engineering* 1996;9:617-621, which is incorporated by reference in its entirety). This construct of sequence of SEQ ID NO: 5 is denoted as follows: Variation 1 Fc-AFN: Fc knob Ridgway (LALA-KQ)-10*GGG-G-hulFNa2B_R149A.

In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence of SEQ ID NO: 6. This sequence includes a modified human interferon $\alpha 2b$ having R149A and T106E mutations (i.e., hulFNa2B_R149A_T106E), a linker (i.e., 10*GGG-G), and a Fc knob Ridgway sequence with LALA-KQ mutation (i.e., Fc knob Ridgway (LALA-KQ), see Ridgway *et al.*, *Protein Engineering* 1996;9:617-621, which is incorporated by reference in its entirety). This construct of sequence of SEQ ID NO: 6 is denoted as follows: Variation 2 Fc-AFN: Fc knob Ridgway (LALA-KQ)-10*GGG-G-hulFNa2B_R149A_T106E.

In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence of SEQ ID NO: 7. This sequence includes a modified human interferon $\alpha 2b$ having a R149A mutations (i.e., hulFNa2B_R149A), a linker (i.e., 10*GGG-G), and a Fc knob Merchant sequence with LALA-KQ mutation (i.e., Fc knob Merchant (LALA-KQ), see Merchant *et al.*, *Nature Biotechnology* 1998;16:677-681, which is incorporated by reference in its entirety). This construct of sequence of SEQ ID NO: 7 is denoted as follows: Variation 3 Fc-AFN: Fc knob Merchant (LALA-KQ)-10*GGG-G-hulFNa2B_R149A.

In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence of SEQ ID NO: 8. This sequence includes a modified human interferon α 2b having R149A and T106E mutations (i.e., hIFNa2B_R149A_T106E), a linker (i.e., 10*GGG-G), and a Fc knob Merchant sequence with LALA-KQ mutation (i.e., Fc knob Merchant (LALA-KQ), see Merchant *et al.*, *Nature Biotechnology* 1998;16:677-681, which is incorporated by reference in its entirety). This construct of sequence of SEQ ID NO: 8 is denoted as follows: Variation 4 Fc-AFN: Fc knob Merchant (LALA-KQ)-10*GGG-G-hIFNa2B_R149A_T106E.

In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence of SEQ ID NO: 41. This sequence includes a modified interferon α 2b having A145G mutation, a linker (i.e., 10*GGG-G), and a Fc knob Merchant sequence with LALA-KQ mutation (i.e., Fc knob Merchant (LALA-KQ), see Merchant *et al.*, *Nature Biotechnology* 1998;16:677-681, which is incorporated by reference in its entirety). This construct of sequence of SEQ ID NO: 41 is denoted as follows: Fc4'-IFNa2b_A145G.

In embodiments, the chimeric protein complex comprises a polypeptide that has an amino acid sequence of SEQ ID NO: 42. This sequence includes a modified interferon α 2b having T106A and A145G mutations, a linker (i.e., 10*GGG-G), and a Fc knob Merchant sequence with LALA-KQ mutation (i.e., Fc knob Merchant (LALA-KQ), see Merchant *et al.*, *Nature Biotechnology* 1998;16:677-681, which is incorporated by reference in its entirety). This construct of sequence of SEQ ID NO: 42 is denoted as follows: Fc4'-IFNa2a_T106E_A145G.

In one embodiment, the chimeric protein complex includes (i) an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 1 or 3 and (ii) an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 5 or 6. In another embodiment, the chimeric protein complex includes (i) an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 1 or 3 and (ii) an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 5 or 6. In another embodiment, the chimeric protein complex includes (i) an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 1 or 3 and (ii) an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 5 or 6. In an embodiment, the chimeric protein complex includes (i) an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 2 or 4 and (ii) an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 7 or 8. In an embodiment, the chimeric protein complex includes (i) an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 2 or 4 and (ii) an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 7 or 8. In another embodiment, the chimeric protein complex includes (i) an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 2 or 4 and (ii) an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 7 or 8.

In some embodiments, the chimeric protein complex comprises (i) a polypeptide having an amino acid sequence having at least 95% identity with SEQ ID NO: 2 and (ii) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 31 or 32. In some embodiments, the chimeric protein complex comprises (i) a polypeptide having an amino acid sequence having at least 98% identity with SEQ ID NO: 2 and (ii) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 31 or

32. In embodiments, the chimeric protein complex comprises (i) a polypeptide having an amino acid sequence having at least 99% identity with SEQ ID NO: 2 and (ii) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 31 or 32. In some embodiments, the chimeric protein complex comprises (i) a polypeptide having an amino acid sequence having at least 95% identity with SEQ ID NO: 43 and (ii) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 41 or 42. In some embodiments, the chimeric protein complex comprises (i) a polypeptide having an amino acid sequence having at least 98% identity with SEQ ID NO: 43 and (ii) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 41 or 42. In embodiments, the chimeric protein complex comprises (i) a polypeptide having an amino acid sequence having at least 99% identity with SEQ ID NO: 43 and (ii) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 41 or 42.

In some embodiments, the chimeric protein complex comprises: (i) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 1 or 3 and (ii) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 5 or 6.

In some embodiments, the chimeric protein complex comprises: (i) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 1 or 3 and (ii) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 5 or 6.

In some embodiments, the chimeric protein complex comprises: (i) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 1 or 3 and (ii) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 5 or 6.

In some embodiments, the chimeric protein complex comprises: (i) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 2 or 4 and (ii) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 7 or 8.

In embodiments, the chimeric protein complex comprises: (i) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 2 or 4 and (ii) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 7 or 8.

In embodiments, the chimeric protein complex comprises: (i) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 2 or 4 and (ii) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 7 or 8.

In embodiments, the chimeric protein complex comprises: (i) a polypeptide having an amino acid sequence having at least 95% identity with SEQ ID NO: 2 and (ii) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 31 or 32.

In embodiments, the chimeric protein complex comprises: (i) a polypeptide having an amino acid sequence having at least 98% identity with SEQ ID NO: 2 and (ii) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 31 or 32.

In embodiments, the chimeric protein complex comprises: (i) a polypeptide having an amino acid sequence having at least 99% identity with SEQ ID NO: 2 and (ii) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 31 or 32.

In embodiments, the chimeric protein complex comprises: (i) a polypeptide having an amino acid sequence having at least 95% identity with SEQ ID NO: 43 and (ii) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 41 or 42.

In embodiments, the chimeric protein complex comprises: (i) a polypeptide having an amino acid sequence having at least 98% identity with SEQ ID NO: 43 and (ii) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 41 or 42.

In some embodiments, the chimeric protein complex comprises: (i) a polypeptide having an amino acid sequence having at least 99% identity with SEQ ID NO: 43 and (ii) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 41 or 42.

In some embodiments, the present invention is related to a multivalent or bivalent chimeric protein complex comprising: a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 17 and a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 7; a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 2 and a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 19; a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 18 and a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 7; a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 20 and a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 7; a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 2 and a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 22; or a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 21 and a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 7. In some embodiments, the present invention is related to a method for treating or preventing a cancer, comprising administering an effective amount of the multivalent or bivalent chimeric protein complex described herein to a patient in need thereof.

In some embodiments, the present invention is related to a chimeric protein complex comprising at least two polypeptides having a sequence at least 95%, or 97%, or 98%, or 99%, or 100% identical to the amino acid

sequence of any one of SEQ ID Nos: 1-43. In embodiments, the present invention is related to a method for treating or preventing a cancer, comprising administering an effective amount of the chimeric protein complex comprising at least two polypeptides having a sequence at least 95%, or 97%, or 98%, or 99%, or 100% identical to the amino acid sequence of any one of SEQ ID Nos: 1-43 to a patient in need thereof.

In some embodiments, the chimeric protein complex includes a modified human interferon $\alpha 2$. In embodiments, the modified IFN- $\alpha 2$ 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- $\alpha 2$ 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 some embodiments, the modified human interferon $\alpha 2$, as disclosed herein, has an amino acid sequence having at least 95% identity with of SEQ ID NOs: 9 or 10. In other embodiments, the modified human IFN $\alpha 2$ has an amino acid sequence having at least 98% identity or at least 99% identity with of SEQ ID NOs: 9 or 10. In some embodiments, the modified human IFN $\alpha 2$ has 1-3 mutations relative to the amino acid sequence of SEQ ID NOs: 9 or 10. In one embodiment, the modified human IFN $\alpha 2$ comprises a R149A mutation with respect to SEQ ID NOs: 9 or 10. In one embodiment, the modified human IFN $\alpha 2$ comprises a A145G mutation with respect to SEQ ID NOs: 9 or 10.

In some embodiments, the targeting moiety of the chimeric protein complex disclosed herein comprises a recombinant heavy-chain-only antibody (VHH). In some embodiments, the VHH has an amino acid sequence of at least 95% identity with of one of SEQ ID NOs: 11 or 12. In other embodiments, the VHH has an amino acid sequence of at least 98% identity with of one of SEQ ID NOs: 11 or 12 or at least 99% identity with of one of SEQ ID NOs: 11 or 12. In some embodiments, the VHH has an amino acid sequence of any one of SEQ ID NOs: 11 and 12.

In some embodiments, the chimeric protein complex disclosed herein comprises two targeting moieties. In some embodiments, the chimeric protein complex disclosed herein comprises two identical targeting moieties. In embodiments, these bivalent modes are oriented as shown in **Figure 7**.

In some embodiments, the chimeric protein complex disclosed herein comprises two targeting moieties. In some embodiments, the chimeric protein complex disclosed herein comprises two non-identical targeting moieties. In embodiments, these bivalent modes are oriented as shown in **Figure 7**. For example, in some embodiments, the chimeric protein complex disclosed herein comprises targeting moieties (without limitation, VHHs) against Clec9A and PD-L1.

In embodiments, the R149A mutation is present in the IFN- $\alpha 2$.

In embodiments, the R149A mutation is not present in the IFN- $\alpha 2$ and instead, another mutation is present. For instance, this alternative mutation could be at one of positions R33, R144, A145, M148, and L153. In embodiments, the alternative mutation is one of R33A, R144A, R144I, R144L, R144S, R144T, R144Y, A145D, A145G, A145H, A145K, A145Y, M148A, and L153A. For clarity, in embodiments, any reference to R149A herein may be replaced with one of R33A, R144A, R144I, R144L, R144S, R144T, R144Y, A145D, A145G, A145H, A145K, A145Y, M148A and L153A. In embodiments, any reference to R149A herein may be replaced with A145G.

In some embodiments, the chimeric protein complex disclosed herein include at least one Fc domain. In some embodiments, the chimeric protein complex includes a modified Fc domain where the modified Fc domain includes one or more of the following mutations: P329G, K322Q, K322A, or P331S relative to any of one of SEQ ID NO: 13-16. In other embodiments, the modified Fc domain includes one or more of the following mutations: P329G, K322Q, K322A, or P331S relative to human IgG1 Fc.

In some embodiments, the chimeric protein complex includes a modified Fc domain that has an amino acid sequence having at least 90% identity with SEQ ID NO: 13-16. In other embodiments, the modified Fc domain has an amino acid sequence having at least 93% identity with SEQ ID NO: 13-16. In other embodiments, the modified Fc domain has an amino acid sequence having at least 95% identity with SEQ ID NO: 13-16.

In another aspect, the present invention relates to a method of treating or preventing a cancer, comprising administering an effective amount of the chimeric protein complex, as disclosed herein, to a patient in need thereof. The method can be used to treat or prevent cancers selected from 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 (e.g., Kaposi's 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.

Another aspect of the present invention relates to a pharmaceutical composition comprising a chimeric protein complex, as disclosed herein, and a pharmaceutically acceptable carrier. In some embodiments, the present invention pertains to pharmaceutical compositions comprising the present chimeric protein complex.

Another aspect of the present invention relates to a method for treating or preventing a cancer, comprising administering an effective amount of the pharmaceutical composition as disclosed herein to a patient in need

thereof. The pharmaceutical composition can be used for the treatment or prevention of a cancer selected from 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 (e.g., Kaposi's 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.

In another aspect, the present invention relates to a recombinant nucleic acid composition encoding one or more chimeric protein complexes disclosed herein, e.g. encoding the entire chimeric protein complex or constituent polypeptides thereof. In another aspect, the present invention relates to a host cell including the recombinant nucleic acid composition complexes disclosed herein.

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.

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.”

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.

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.

As used herein, Fc domain mutations are numbered according to EU convention (Edelman *et al.*, *PNAS* 1969; 63 (1) 78-85, incorporated by reference in its entirety). As used herein, the term “LALA” mutation refers to a double

mutant Fc domain having L234A mutation and a L235A mutation. As used herein, the term "KQ" mutation refers to a mutant Fc domain having a K322Q mutation.

Knob in hole mutants are those described in Ridgway *et al.*, *Protein Engineering* 1996;9:617-621, which is hereby incorporated by reference in its entirety, i.e. Y407T / T366Y.

Alternatively, knob in hole mutants are those described in Merchant *et al.*, *Nature Biotechnology* 1998;16:677-681, which is incorporated by reference in its entirety, i.e. S354C:T366W / Y349C:T366S:L368A:Y407V.

Unless noted, the Fc is from human IgG1.

SEQUENCES

SEQ ID NO: 1 Variation 1 VHH-Fc R1CHCL50(opt4)-**5*GGS**-Fc hole Ridgway (LALA-KQ)

DVQLVESGGGLVQPGGSLRLSCAASGFSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTISRDN
KNTVYLQMNSLRPEDTAVYYCYLVALKAIEYWGQGLTVTVSS**GGSGGSGGSGGSGGSGG**SKTHTCPPCPAPEAAG
GPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTTPVLDSGFSFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 2 Variation 2 VHH-Fc: R1CHCL50(opt4)-**5*GGS**-Fc hole Merchant (LALA-KQ)

DVQLVESGGGLVQPGGSLRLSCAASGFSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTISRDN
KNTVYLQMNSLRPEDTAVYYCYLVALKAIEYWGQGLTVTVSS**GGSGGSGGSGGSGGSGG**SKTHTCPPCPAPEAAG
GPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESN
GQPENNYKTTTPVLDSGFSFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 3 Variation 3 VHH-Fc: 3LEC89(opt4)-**5*GGS**-Fc hole Ridgway (LALA-KQ)

DVQLVESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAITNQGAPTYADSVKGRFTISRDN
SKNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGLTVTVSS**GGSGGSGGSGGSGGSGG**SKTHTCPPCPAPEAA
GGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTTPVLDSGFSFLTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 4 Variation 4 VHH-Fc: 3LEC89(opt4)-**5*GGS**-Fc hole Merchant (LALA-KQ)

DVQLVESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAITNQGAPTYADSVKGRFTISRDN
SKNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGLTVTVSS**GGSGGSGGSGGSGGSGG**SKTHTCPPCPAPEAA
GGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWES
NGQPENNYKTTTPVLDSGFSFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 5 Variation 1 Fc-AFN: Fc knob Ridgway (LALA-KQ)-**10*GGS-G**-hulFNa2B_R149A

CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAA
 WDETLLDKFYTELYQQNDLEACVIQGVGTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEWRAEIMRSF
 SLSTNLQESLSRKE

SEQ ID NO: 11 R1CHCL50_opt4 (anti-human Clec9a VHH)

DVQLVESGGGLVQPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTISRDN
 KNTVYLQMNSLRPEDTAVYYCYLVALKAEYWGGGTLTVSS

SEQ ID NO: 12 3LEC89_opt4 (anti-human Clec9a VHH)

DVQLVESGGGLVQPGGSLRLSCAASGRIFSVNAMGWYRQAPGKQRELVAITNQGAPTYADSVKGRFTISRDN
 SKNTVYLQMNSLRPEDTAVYYCKAFTRGDDYWGQGTLLTVSS

SEQ ID NO: 13 Amino acid sequence of the Fc (human IgG1)– with LALA mutations and Ridgway hole

DKHTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
 QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
 KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLTSLKTVDKSRWQQGNVFSCSVMEALHNHYTQKSLS
 LSPGK

SEQ ID NO: 14 Amino acid sequence of the Fc (human IgG1)– with LALA mutations and Ridgway knob

DKHTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
 QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLYCLV
 KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLS
 LSPGK

SEQ ID NO: 15 Amino acid sequence of the Fc (human IgG1) – with LALA mutations and Merchant hole

DKHTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
 QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPSPSRDELTKNQVSLSCAV
 KGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLS
 LSPGK

SEQ ID NO: 16 Amino acid sequence of the Fc (human IgG1) – with LALA mutations and Merchant knob

DKHTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
 QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCL
 VKGFYPDSIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSL
 SLSPGK

Other sequences are identified elsewhere in the text.

EXAMPLES

rProtein A Sepharose Fast Flow resin (GE Healthcare) according to the manufacturer's guidelines. Unexpectedly the proteins although expressed at 70-170 mg/L showed severe solubility problems and even at concentrations below 1 mg/ml they tended to aggregate and precipitate when stored at 4°C or after a single freeze-thaw cycle. When the VHH 3LEC89 was replaced by the unrelated VHH 2LIG99 specific for human PD-L1 similar observations were made indicating that an Fc-based AcTakine format has manufacturability liabilities.

Surprisingly the solubility problem was solved by designing a different type of Fc-construct. In this new format a heterodimeric Fc complex is generated by combining a VHH-Fc fusion with a Fc-IFN fusion using either the knob into hole mutations Y407T / T366Y or S354C:T366W / Y349C:T366S:L368A:Y407V. Additional variants include an optional knock-out of the O-glycosylation site in the hLFNa2 by the T106E mutation. In total 8 constructs were designed based on 2 different humanized human CLEC9A specific VHH. To reduce effector functions of the IgG1-Fc protein the mutation LALA-K322Q was used. The sequences of the mature proteins are represented by SEQ ID NO: 1- 8. This result in total in 8 different Fc-complexes that can be generated by combining knob and hole constructs as shown in **Figure 1**.

For expression in mammalian cells the sequences are linked to a leader sequence and constructs were made by GeneArt (Thermo Fisher). 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. Proteins showed to remain soluble at 4°C or after repeated freeze/thaw cycles at concentrations of at least 10 mg/mL.

Example 2: PK Effects of Chimera With or Without Fc

PK (pharmacokinetics) study in mouse with the 4 different variants of the R1CHCL50 based Fc-proteins.

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 CLEC9A-AFN Fc-construct 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 **Figure 2** 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

show the tumor growth until 6 days after the second treatment. **Figure 5** demonstrates that all constructs induced a similar level of tumor growth inhibition at the lower dose of 8 µg. **Figure 6** 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 4: Bivalent and bispecific variants

In order to further increase the targeting capacity of the molecules, additional VHH moieties are added resulting in constructs of which non-limiting examples of configurations are shown in **Figure 7**. These novel constructs target CLEC9A in a bivalent mode or co-target e.g. both CLEC9A and PD-L1. By way of example constructs below are based on the R1CHCL50(opt4) VHH directed against CLEC9A and/or the 2LIG99 VHH directed against PD-L1 and the hulfNa2B_R149A. By replacing R1CHCL50(opt4) with 3LEC89(opt4) a similar series can be generated. Alternatively the hulfNa2B_R149A can be replaced with hulfNa2B_R149A_T106E. Finally examples below are based on Fc moieties containing Merchant based knob-into-hole mutations which can be exchanged for Fc moieties with Ridgway based knob-into-hole mutations.

Novel constructs

A. Hole chain for bivalent CLEC9A targeting by additional VHH at N-terminus of Fc (Merchant)

VHH-VHH-Fc: R1CHCL50(opt4)-**5*GGS**-R1CHCL50(opt4)-**5*GGS**-Fc (LALA-KQ)

DVQLVESGGGLVQPGGSLRLSCAASGFSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTISR
DNSKNTVYLQMNSLRPEDTAVYYCYLVALKAIEYWGQGLTVTVSS**GGSGGSGGSGGSGGSD**VQLVESGGG
LVQPGGSLRLSCAASGFSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTISRDNKNTVYLQ
MNSLRPEDTAVYYCYLVALKAIEYWGQGLTVTVSS**GGSGGSGGSGGSGGSD**KTHTCPPCPAPEAAGGPSV
FLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWES
NGQPENNYKTTTPVLDSGDSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID
NO: 17)

B. Hole chain for bivalent CLEC9A targeting by additional VHH on C-terminus of Fc (Merchant)

VHH-Fc-VHH: R1CHCL50(opt4)- **5*GGS**-Fc (LALA-KQ)-**5*GGS**-R1CHCL50(opt4)

DVQLVESGGGLVQPGGSLRLSCAASGFSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTISR
DNSKNTVYLQMNSLRPEDTAVYYCYLVALKAIEYWGQGLTVTVSS**GGSGGSGGSGGSGGSD**KTHTCPPCP
APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGK**GGSGGSGGSGGSGGSD**VQLVESGGGLVQPGGSLRLSCAASGFSINVMGWYRQAPGKERELVA

VHH-Fc-AFN: 2LIG99-5***GGG**-Fc(LALA-KQ)-10***GGG-G**-hIFNa2B_R149A

QVQLQESGGGLVQAGGSLRLSCTASGTIFSINRMDWFRQAPGKQRELVALITSDGTPAYADSAKGRFTISR
DNTKKTVSLQMNSLKPEDTAVYYCHVSSGVVNYWGQGTQVTVSS**GGSGGGSGGGSGGGSGG**SKTHTCPPC
PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKG
FYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSL
SLSPGK**GGSGGGSGGGSGGGSGGGSGGGSGGGSGG**CDLPQTHSLGSRRTLMLLAQMRRLSFSLCK
DRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNLEACVIQGV
GVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMASFSLSLTNLQESLSKE (SEQ ID NO: 22)

For expression in mammalian cells the sequences are linked to a leader sequence and expression constructs were made by GeneArt (Thermo Fisher). Production is performed in ExpiCHO cells as described above. Recombinant proteins are purified from the supernatant on a HiTrap Protein A HP (GE Healthcare) and eluted proteins are, after neutralization, desalted on a G25 column (GE Healthcare) followed by final and 0.22 µm filtration. More specifically the following expressions constructs are combined to generate the Fc-based AcTaférons

- Construct containing SEQ ID NO: 17 + construct containing SEQ ID NO: 7
- Construct containing SEQ ID NO: 2 + construct containing SEQ ID NO: 19
- Construct containing SEQ ID NO: 18 + construct containing SEQ ID NO: 7
- Construct containing SEQ ID NO: 20 + construct containing SEQ ID NO: 7
- Construct containing SEQ ID NO: 2 + construct containing SEQ ID NO: 22
- Construct containing SEQ ID NO: 21 + construct containing SEQ ID NO: 7

Example 5: A145G and M148A AFN mutations

In this example, the potential of the IFN variations A145G and M148A as AFN mutation (i.e. the warhead mutation that results in a loss in biological activity, which can be restored upon targeting of the warhead) was evaluated.

Mutations were evaluated in the heterodimeric, 'knob-in-hole' Fc AFN context. Here, the Clec9A VHH R1CHCL50 sequence was, via the flexible 20*GGG-linker and in the pcDNA3.4 expression vector, fused to the human IgG1 Fc sequence containing the L234A_L235A_K322Q effector mutations and the 'hole' modifications Y349C_T366S_L368A_Y407V (see sequence R1CHCL50-Fc3 below). Second AFN partner, also cloned in the pcDNA3.4 vector, consisted of the fusion between the human IgG1 Fc sequence containing the L234A_L235A_K322Q effector mutations and the 'knob' modifications S354C_T366W and the hIFNa2 sequence with the AFN mutation A145G or M148A and the O-glycosylation mutation T106E (see sequences below).

To produce these 'knob-in-hole' Fc AFNs, a combination of both 'hole' and 'knob' plasmids was transfected in ExpiCHO™ cells (ThermoFisher) according to the manufacturer's instructions. Seven days post transfection, recombinant proteins were purified using protein A spin plates (ThermoFisher), quantified and purity tested using SDS-PAGE.

Resulting A145G and M148 AFN's were tested for STAT1 phosphorylation in primary cDC1 cells (expressing Clec9A, the target of the AFN's) compared to other PBMC populations. In brief, PBMCs from buffy coats of healthy donors were isolated using density gradient centrifugation using Lymphoprep™ (StemCell technologies). Cells were washed twice with FACS buffer (2% FBS, 1 mM EDTA in PBS) and stained with anti-Clec9A and anti-CD141 Abs (both Miltenyi) to identify the cDC1 population for 20 minutes at 4 °C. After two washes, cells were stimulated with a serial dilution wild type IFN α 2 or both AFN's 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 analyzed using the FlowLogic™ software (Miltenyi Biotec). Data in **Figure 8A-B** clearly illustrate that (i) Clec9A-/CD141- and Clec9A+/CD141+ cells are comparable sensitive to wild type IFN α 2, and that (ii) both A145G and M148A mutations abolishes most of the signaling in non-cDC1 PBMC's (Clec9A-/CD141-) but that targeting to Clec9A positive cells (Clec9A+/CD141+) to a great extent restores this signaling. This results in an AFN effect of at least 100-fold for both the A145G or M148A mutations and illustrates the potential of these mutations for the design of AFNs.

Sequences:

P-1451: R1CHCL50-20*GGs-hlgG1 Fc_L234A_L235A_K322Q_Y349C_T366S_L368A_Y407V (short: R1CHCL50-Fc3)

QVQLQESGGGLVHPGGSRLSCAASGSFSSINVMGWYRQAPGKERELVARITNLGLPNYADSVTGRFTISR
DNAKNTVYLQMNSLKPEDTAVYYCYLVALKA EYWQGQTQVT VSSGGSGSGSGSGSGSGSGSGSGS
GGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSDKTHTCPPCPAPEAAGGPSVFLFPKP KDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
QVS NKALPAPIEKTI SKAKGQPREPVCTLP SRDEL TKNQVSLSCAVKG FYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 26)

P-1846: *hlgG1 Fc_L234A_L235A_K322Q_S354C_T366W-20*GGs-hIFNa2_T106E* **A145G**

(short: Fc4-hlFNa2_A145G)

[illegible]

[illegible]

C. hlgG1 Fc_L234A_L235A_K322Q_S354C_T366W-10***GGG-G**-hIFNa2_T106E_A145G

[illegible]

D. hlgG1 Fc_L234A_L235A_K322Q_S354C_T366W-10*GGG-G-hlFNa2_A145G

[illegible]

E. hlgG1 Fc_L234A_L235A_K322Q_T366Y-10***GGG-G**-hIFNa2_T106E_M148A

[illegible]

F. hlgG1 Fc_L234A_L235A_K322Q_T366Y-**10*GGG-G**-hIFNa2_M148A

[illegible]

G. hlgG1 Fc_L234A_L235A_K322Q_T366Y-**10*GGG-G**-hIFNa2_T106E_A145G

H. hlgG1 Fc_L234A_L235A_K322Q_T366Y-10***GGG-G**-hIFNa2_A145G

Example 8: A145G mutation with or without O-glycosylation on T106

To evaluate the potency the constructs were tested for STAT1 phosphorylation in primary cDC1 (CLEC9A+/CD141+) and non-cDC1 (CLEC9A-/CD141-) populations in human PBMC as described in Example 5. Figure 10 shows the specificity of the CLEC9A targeted construct with or without O-glycosylation on T106 as this construct is much more potent in activating IFN signaling in cDC1 cells compared to non-cDC1 cells and is much more potent on cDC1 cells compared to cDC1 cells treated with the untargeted variant.

To evaluate the *in vivo* efficacy of the aforementioned heterodimeric, 'knob-in-hole' Fc AFN construct, they were tested in a tumor model in a humanized mouse. In brief, new-born NSG mice (1-2 days of age) were sublethal irradiated with 100 cGy prior to intrahepatic delivery of 1×10^5 CD34+ human stem cells (from HLA-A2 positive cord bloods). At week 13 after stem cell transfer mice were subcutaneously inoculated with 25×10^5 human RL follicular lymphoma cells (ATCC CRL-2261; not sensitive to the direct anti-proliferative effect of IFN). Mice were treated intraperitoneally with 30 μ g of human Flt3L protein, from day 7 to day 17 after tumor inoculation. Weekly intravenous injection with buffer or Fc-AFN (2.5 μ g) constructs was initiated at day 9 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 Figure 11 show the tumor growth until one week after the third treatment and demonstrates that both targeted AFNs induced a strong level of tumor growth, while no significant effect was observed with the untargeted variant. 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.

Sequences

1. **P-1479:** R1CHCL50-Fc3

DVQLVESGGGLVQPGGSLRLSCAASGFSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTIS
RDNSKNTVYLQMNSLRPEDTAVYYCYLVALKAHEYWGQGTLLTVSSGGSGSGSGSGSGSGSDKTHTCPP
CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPSSRDELTKNQVSLSCAV
KGFYPDSIAVEWESNGQPENNYKTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 2)

2. **P-1542:** Fc3

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPSSRDELTKN
QVSLSCAVKGFYPDSIAVEWESNGQPENNYKTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCVMHE
ALHNHYTQKSLSLSPGK (SEQ ID NO: 38)

3. **P-2157:** Fc4-IFNa2_145G

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPS
DIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCVMHEALHNHYTQKSLSLSPGKGSGG
GSGSGSGSGSGSGSGSGSGSGSGSGSGCDLPQTHSLGSRRTLMLLAQMRRLSFLSCLKDRHDFGFPQEEFGNQFQ
KAETIPVLHEMIQIFNLFSKDSAAWDETLLDKFYTELYQQNDLEACVIQGVGTETPLMKEDSILAVRKYFQRITLY
LKEKKYSPCAWEVVRGEIMRSFSLSTNLQESLSRKE (SEQ ID NO: 32)

4. **P-2158:** Fc4-IFNa2_T106E_145G

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTK
 PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKN
 QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHE
 ALHNHYTQKSLSLSPGKGGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGCDLPQTHSLGSRRTLMLLA
 QMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQ
 LNDLEACVIQGVGVETETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRGEIMRSFSLSTNLQESLRS
 KE (SEQ ID NO: 31)

Example 9: Fc-AFN constructs

Mass spectrometry analysis illustrated that the C-terminal lysine K residue in the R1CHCL50-Fc3 chain is cleaved off in almost all mature proteins. Therefore, variants are constructed in which this lysine residue in both Fc-chains was removed. Resulting proteins will be referred to as Fc' proteins. By way of example, the sequences for the chimeric protein combination of R1CHCL50-Fc3' with Fc4'-AFN fusions in which residue A145 was mutated to G in IFNa2b, or in which the residues T106 and A145 were mutated to respectively E and G in IFNa2a, are shown below.

Sequences:

P-2379: Fc4'-IFNa2b_A145G

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
 REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQ
 VSLWCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEAL
 HNHYTQKSLSLSPGKGGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGCDLPQTHSLGSRRTLMLLAQMR
 RISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQNLNDL
 EACVIQGVGVETETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRGEIMRSFSLSTNLQESLRSKE
 (SEQ ID NO: 41)

P-2380: Fc4'-IFNa2a_T106E_A145G

DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
 REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKQVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQ
 VSLWCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEAL
 HNHYTQKSLSLSPGKGGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGCDLPQTHSLGSRRTLMLLAQMR
 KISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQNLNDL
 EACVIQGVGVETETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRGEIMRSFSLSTNLQESLRSKE
 (SEQ ID NO: 42)

P-1479b: R1CHCL50-Fc3'

DVQLVESGGGLVQPGGSLRLSCAASGFSINVMGWYRQAPGKERELVARITNLGLPNYADSVKGRFTISR
 DNSKNTVYLMNSLRPEDTAVYYCYLVALKAIEYWGQGLTVTVSSGGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGSGDKTHTCPPCP

APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCQVSNKALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFY
PSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPG (SEQ ID NO: 43)

CLAIMS

What is claimed is:

1. A chimeric protein complex comprising:
 - (i) a targeting moiety that specifically binds to C-type lectin domain family 9 member A (Clec9A),
 - (ii) a modified human IFN α 2, and
 - (iii) a modified Fc domain.
2. The chimeric protein complex of claim 1, wherein the chimeric protein complex is a heterodimer.
3. The chimeric protein complex of claim 2, wherein the chimeric protein complex comprises a polypeptide having an amino acid sequence having at least 95%, or at least 98%, or at least 99% identity with any one of SEQ ID NOs: 1-4 and 43.
4. The chimeric protein complex of claim 1, wherein the chimeric protein complex comprises a polypeptide having an amino acid sequence selected from SEQ ID NOs: 1-4 and 43 and less than 10 mutations to the amino acid sequence.
5. The chimeric protein complex of claim 4, wherein the chimeric protein complex comprises a polypeptide having an amino acid sequence selected from SEQ ID NOs: 1-4 and 43, and less than 5 mutations to the amino acid sequence.
6. The chimeric protein complex of claim 1, wherein the chimeric protein complex comprises a polypeptide having an amino acid sequence selected from SEQ ID NOs: 1-4 and 43.
7. The chimeric protein complex of any one of claims 1 to 6, wherein the chimeric protein complex further comprises a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 5-8, 29-36, or 41-42.
8. The chimeric protein complex of claim 7, wherein the chimeric protein complex further comprises a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 5-8, 29-36, or 41-42.
9. The chimeric protein complex of claim 8, wherein chimeric protein complex further comprises a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 5-8, 29-36, or 41-42.
10. The chimeric protein complex of any one of claims 7-9, wherein the chimeric protein complex comprises:
 - (i) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 1 or 3 and
 - (ii) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 5 or 6.

11. The chimeric protein complex of claim 10, wherein the chimeric protein complex comprises:
 - (i) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 1 or 3 and
 - (ii) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 5 or 6.
12. The chimeric protein complex of claim 11, wherein the chimeric protein complex comprises:
 - (i) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 1 or 3 and
 - (ii) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 5 or 6.
13. The chimeric protein complex of any one of claims 7-9, wherein the chimeric protein complex comprises:
 - (i) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 2 or 4 and
 - (ii) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 7 or 8.
14. The chimeric protein complex of claim 13, wherein the chimeric protein complex comprises:
 - (i) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 2 or 4 and
 - (ii) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 7 or 8.
15. The chimeric protein complex of claim 14, wherein the chimeric protein complex comprises:
 - (i) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 2 or 4 and
 - (ii) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 7 or 8.
16. The chimeric protein complex of any one of claims 7-9, wherein the chimeric protein complex comprises:
 - (i) a polypeptide having an amino acid sequence having at least 95% identity with SEQ ID NO: 2 and
 - (ii) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 31 or 32.
17. The chimeric protein complex of claim 16, wherein the chimeric protein complex comprises:
 - (i) a polypeptide having an amino acid sequence having at least 98% identity with SEQ ID NO: 2 and

- (ii) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 31 or 32.
18. The chimeric protein complex of claim 17, wherein the chimeric protein complex comprises:
- (i) a polypeptide having an amino acid sequence having at least 99% identity with SEQ ID NO: 2 and
- (ii) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 31 or 32.
19. The chimeric protein complex of any one of claims 7-9, wherein the chimeric protein complex comprises:
- (i) a polypeptide having an amino acid sequence having at least 95% identity with SEQ ID NO: 43 and
- (ii) a polypeptide having an amino acid sequence having at least 95% identity with any one of SEQ ID NOs: 41 or 42.
20. The chimeric protein complex of claim 16, wherein the chimeric protein complex comprises:
- (i) a polypeptide having an amino acid sequence having at least 98% identity with SEQ ID NO: 43 and
- (ii) a polypeptide having an amino acid sequence having at least 98% identity with any one of SEQ ID NOs: 41 or 42.
21. The chimeric protein complex of claim 17, wherein the chimeric protein complex comprises:
- (i) a polypeptide having an amino acid sequence having at least 99% identity with SEQ ID NO: 43 and
- (ii) a polypeptide having an amino acid sequence having at least 99% identity with any one of SEQ ID NOs: 41 or 42.
22. The chimeric protein complex of any one of claims 1-21, wherein the modified human IFN α 2 has an amino acid sequence having at least 95% identity with of SEQ ID NOs: 9 or 10.
23. The chimeric protein complex of claim 22, wherein the modified human IFN α 2 has an amino acid sequence having at least 98% identity with of SEQ ID NOs: 9 or 10.
24. The chimeric protein complex of claim 23, wherein the modified human IFN α 2 has an amino acid sequence having at least 99% identity with of SEQ ID NOs: 9 or 10.
25. The chimeric protein complex of any one of claims 1-24, wherein the modified human IFN α 2 has 1-3 mutations relative to the amino acid sequence of SEQ ID NOs: 9 or 10.
26. The chimeric protein complex of claim 25, wherein the modified human IFN α 2 comprises a R149A mutation with respect to SEQ ID NOs: 9 or 10 or one of a R33A, R144A, R144I, R144L, R144S, R144T, R144Y, A145D, A145G, A145H, A145K, A145Y, M148A and L153A mutation with respect to SEQ ID NOs: 9 or 10, optionally A145G .

27. The chimeric protein complex of any one of claims 1-26, wherein the chimeric protein complex comprises a recombinant heavy-chain-only antibody (VHH).
28. The chimeric protein complex of claim 27, wherein VHH has an amino acid sequence of at least 95% identity with one of SEQ ID NOs: 11 or 12.
29. The chimeric protein complex of claim 28, wherein VHH has an amino acid sequence of at least 98% identity with one of SEQ ID NOs: 11 or 12.
30. The chimeric protein complex of claim 29, wherein VHH has an amino acid sequence of at least 99% identity with one of SEQ ID NOs: 11 or 12.
31. The chimeric protein complex of claim 30, wherein the VHH has an amino acid sequence of any one of SEQ ID NOs: 11, and 12.
32. The chimeric protein complex of any one of claims 1-31, wherein the modified Fc domain comprises one or more of the following mutations: P329G, K322Q, K322A, or P331S relative to any one of SEQ ID NO: 13-16.
33. The chimeric protein complex of claim 32, wherein the modified Fc domain comprises one or more of the following mutations: P329G, K322Q, K322A, or P331S relative to human IgG1 Fc.
34. The chimeric protein complex of claim 32 or 33, wherein the modified Fc domain has an amino acid sequence of at least 90% identity with SEQ ID NO: 13-16.
35. The chimeric protein complex of claim 32 or 33, wherein the modified Fc domain has an amino acid sequence of at least 93% identity with SEQ ID NO: 13-16.
36. The chimeric protein complex of claim 32 or 33, wherein the modified Fc domain has an amino acid sequence of at least 95% identity with SEQ ID NO: 13-16.
37. A method for treating or preventing a cancer, comprising administering an effective amount of the chimeric protein complex of any one of the above claims to a patient in need thereof.
38. The method of claim 37, wherein the cancer is selected from 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 (e.g., Kaposi's 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.

39. A pharmaceutical composition comprising the chimeric protein complex of any one of claims 1-36 and a pharmaceutically acceptable carrier.

40. A method for treating or preventing a cancer, comprising administering an effective amount of the pharmaceutical composition of claim 39 to a patient in need thereof.

41. The method of claim 40, wherein the cancer is selected from 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 (e.g., Kaposi's 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.

42. A recombinant nucleic acid composition encoding one or more chimeric protein complexes of any one of claims 1-36, or constituents thereof.

43. A host cell comprising a nucleic acid of claim 42.

44. The chimeric protein complex of any one of claims 1-36, wherein the chimeric protein complex has an orientation and/or configuration as set forth in either **Figure 1** or **Figure 7**.
45. A multivalent or bivalent chimeric protein complex comprising:
- a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 17 and a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 7;
 - a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 2 and a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 19;
 - a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 18 and a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 7;
 - a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 20 and a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 7;
 - a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 2 and a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 22; or
 - a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 21 and a polypeptide having a sequence at least 95%, or 97%, or 98%, or 99% identical to the amino acid sequence of SEQ ID NO: 7.
46. A method for treating or preventing a cancer, comprising administering an effective amount of the multivalent or bivalent chimeric protein complex of claim 45 to a patient in need thereof.
47. A chimeric protein complex comprising at least two polypeptides having a sequence at least 95%, or 97%, or 98%, or 99%, or 100% identical to the amino acid sequence of any one of SEQ ID Nos: 1-43.
48. A method for treating or preventing a cancer, comprising administering an effective amount of the chimeric protein complex of claim 47 to a patient in need thereof.

Figure 1:

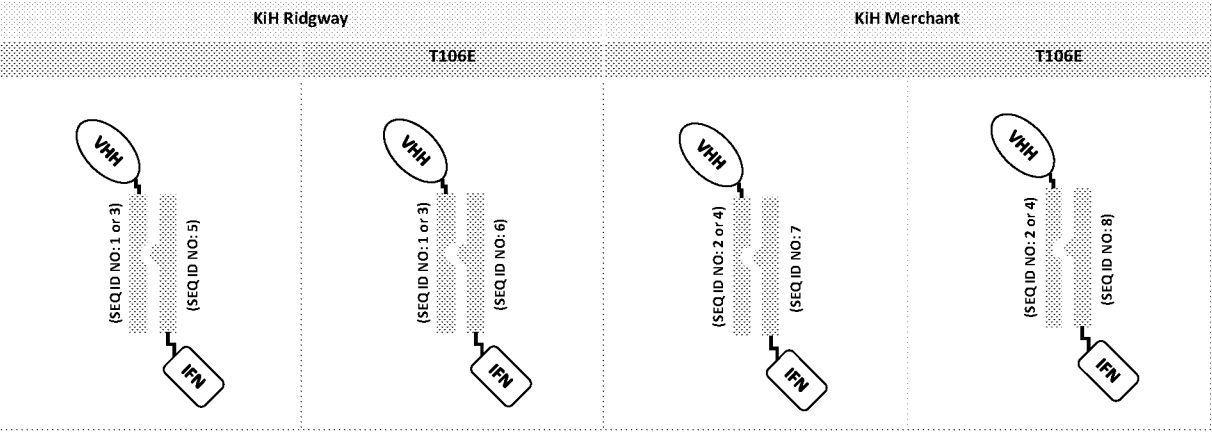


Figure 2:

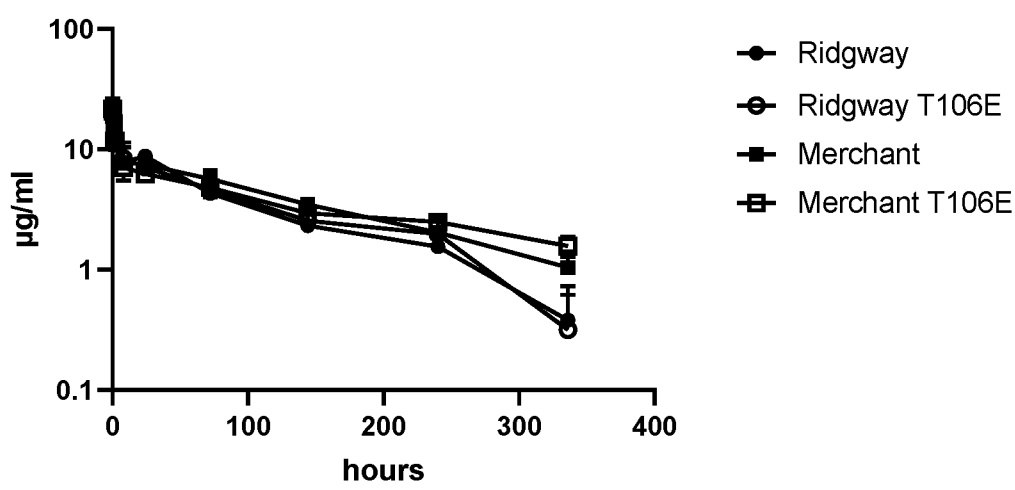


Figure 3:

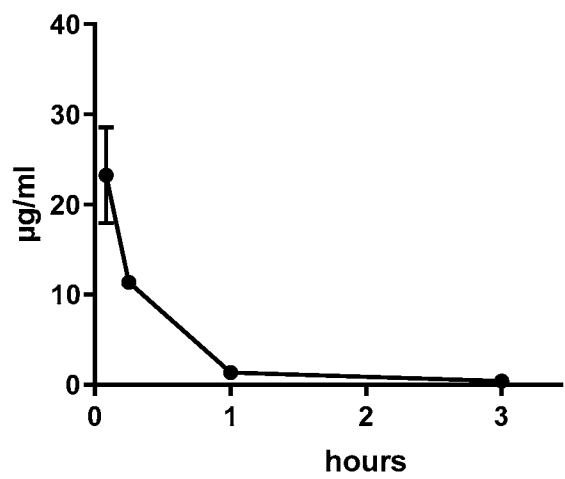


Figure 4A:

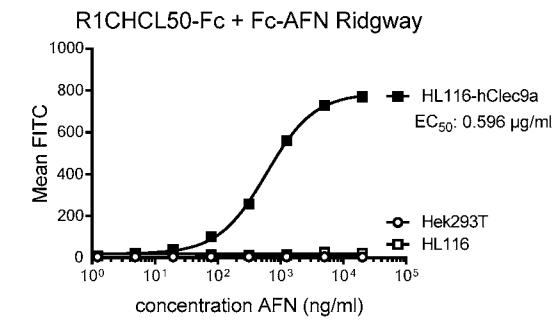


Figure 4B:

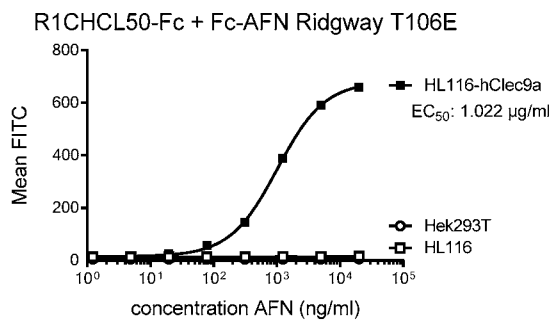


Figure 4C:

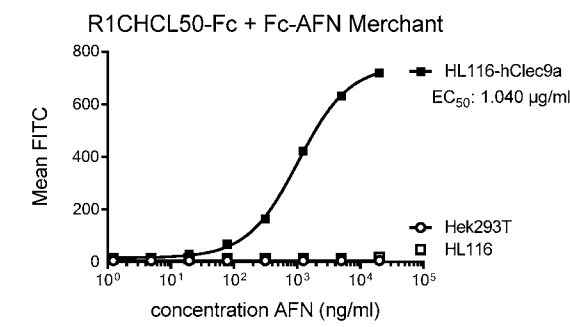


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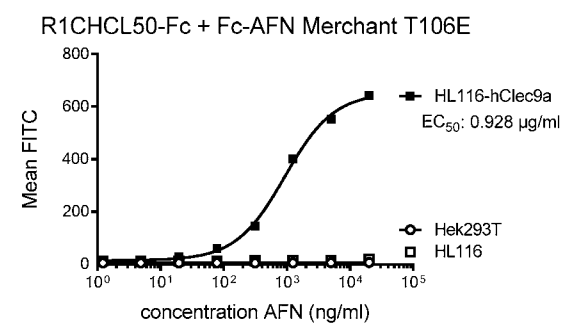


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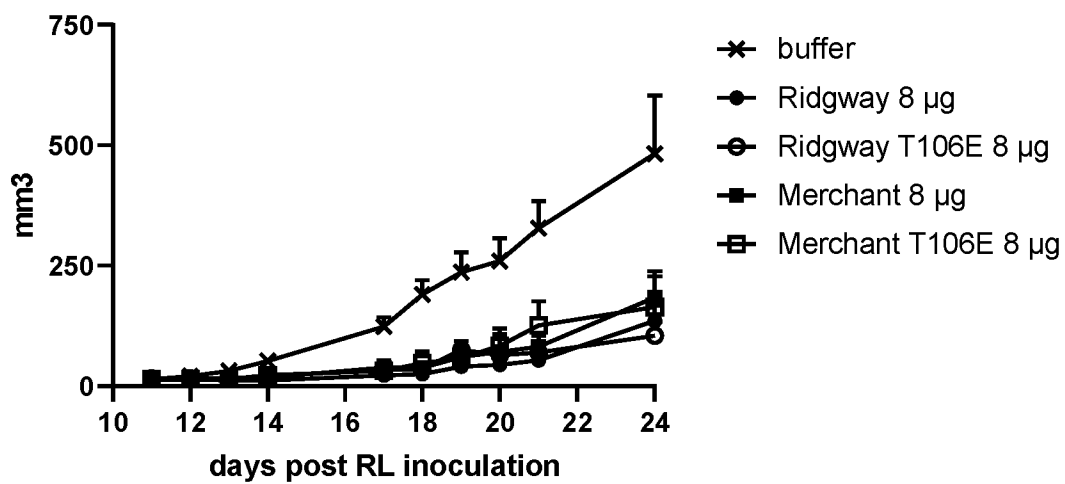


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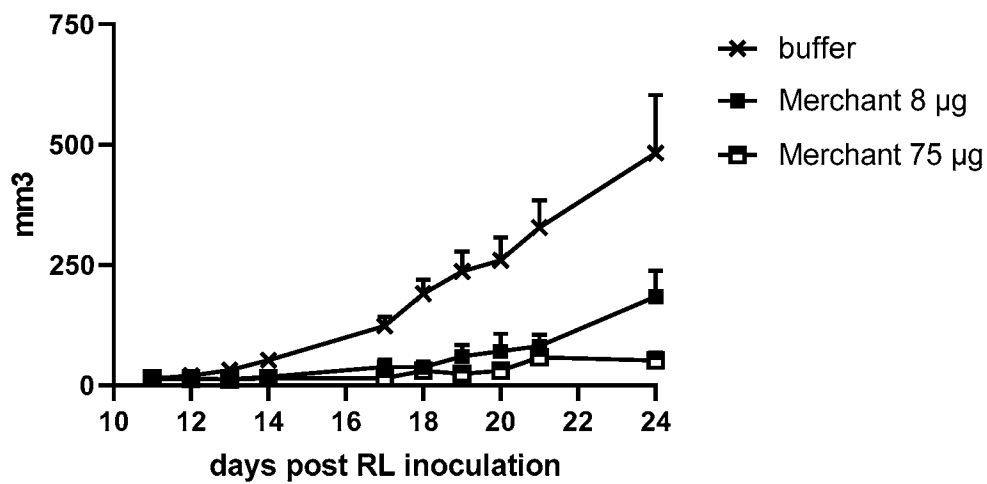


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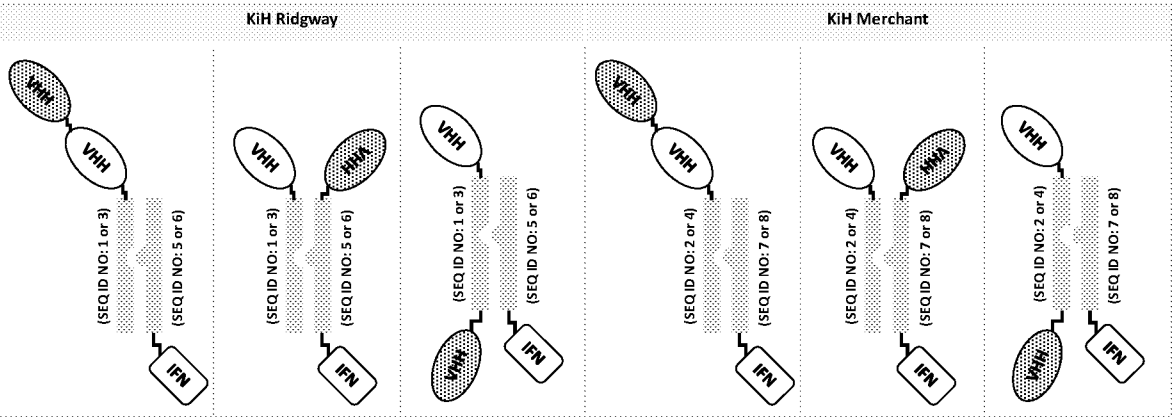


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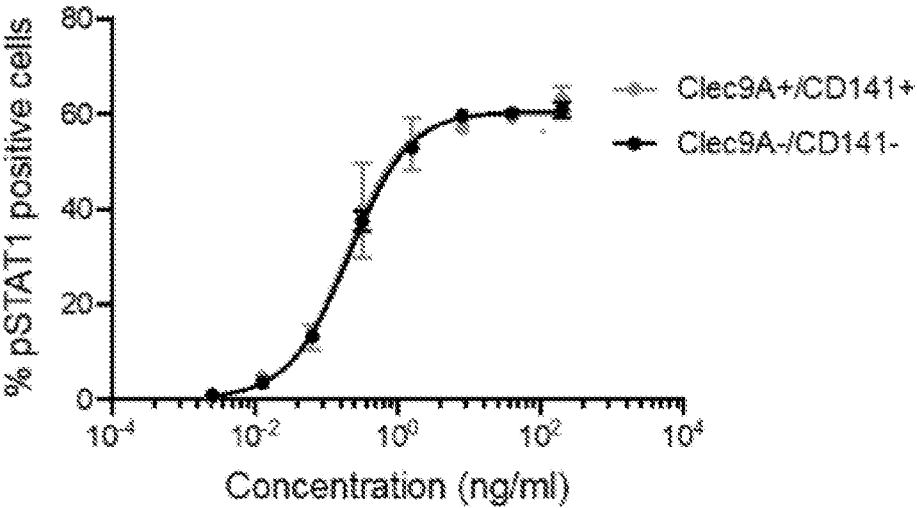


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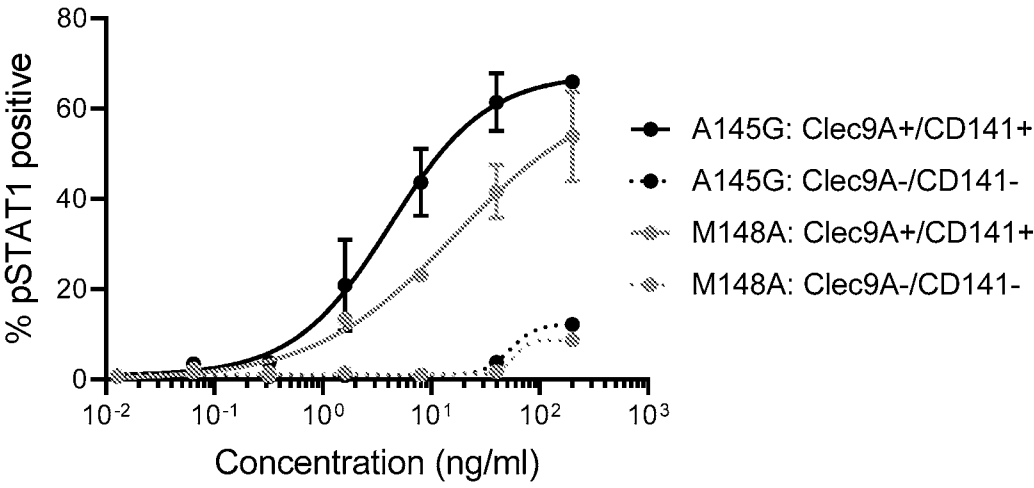


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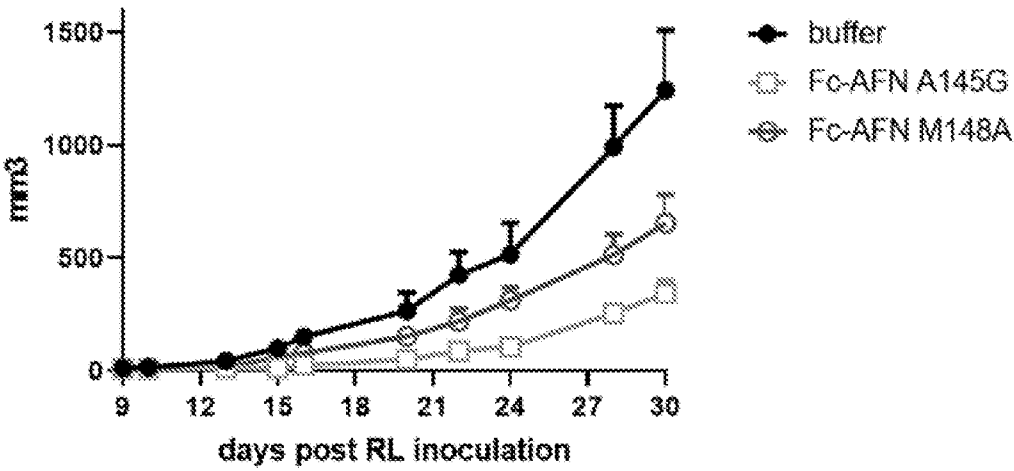


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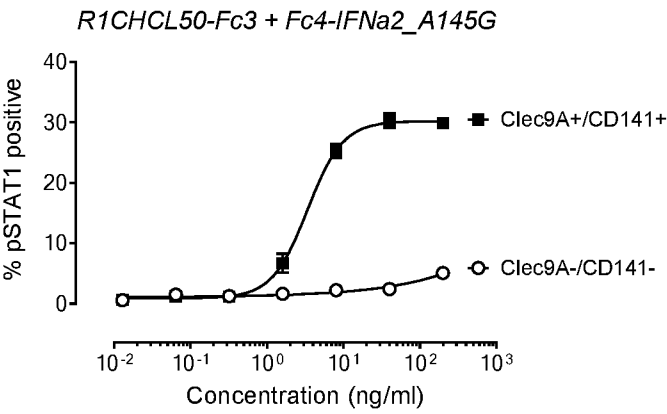


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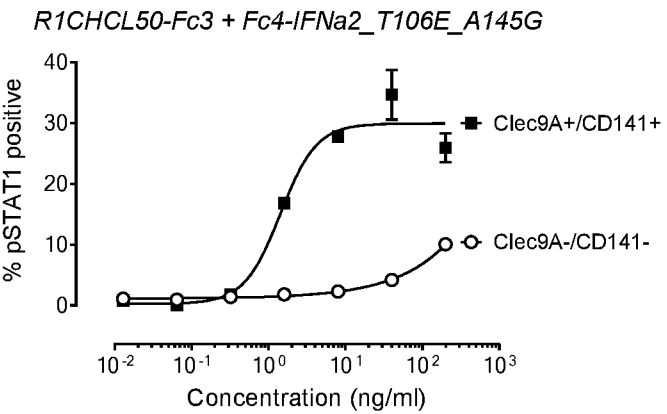


Figure 10C:

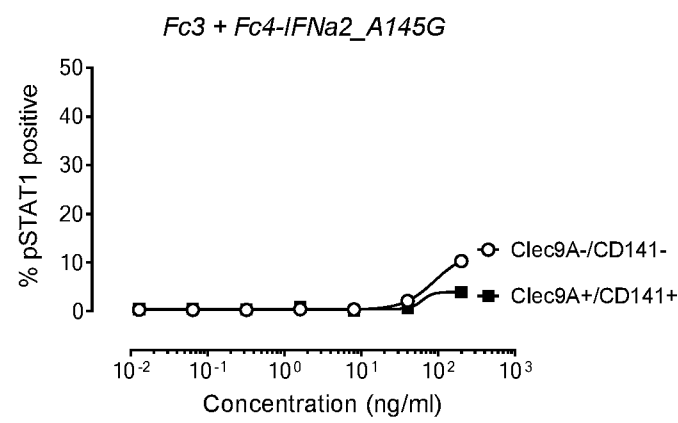
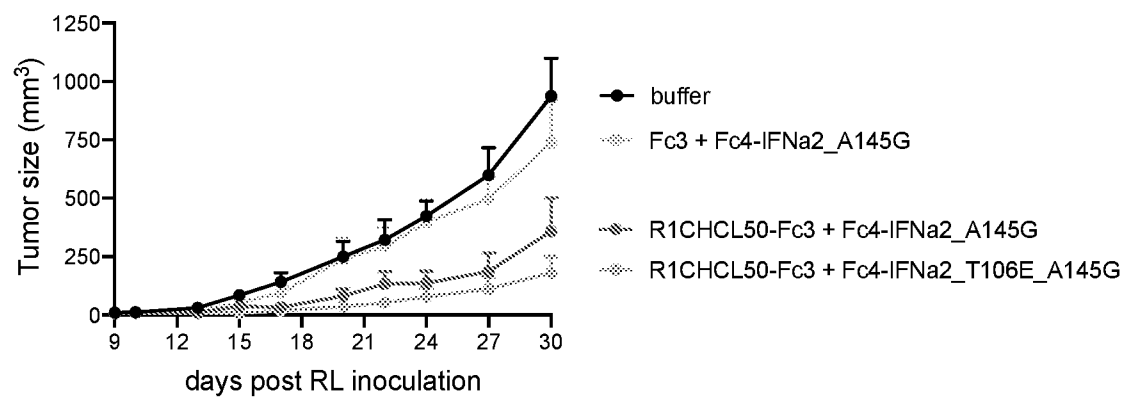


Figure 11:



SEQUENCE LISTING

<110> Orionis Biosciences, Inc.
 Orionis Biosciences BV
 Kley, Nikolai
 Depla, Erik
 Zabeau, Lennart
 Tavernier, Jan

<120> CLEC9A-BASED CHIMERIC PROTEIN COMPLEXES

<130> ORN-063PC/114384-5063

<150> US 62/906,442

<151> 2019-09-26

<150> US 62/825,584

<151> 2019-03-28

<160> 43

<170> PatentIn version 3.5

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 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
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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

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 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 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
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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 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

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<212> PRT
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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
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Glu Ser Leu Arg Ser Lys Glu
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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

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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

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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

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410

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Glu Ser Leu Arg Ser Lys Glu
420

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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> 10
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<212> PRT
<213> Artificial Sequence

<220>
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<400> 10

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 Trp Arg Ala
130 135 140

Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
145 150 155 160

Arg Ser Lys Glu

<210> 11

<211> 115

<212> PRT

<213> Artificial Sequence

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<400> 11

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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> 12
<211> 115
<212> PRT
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<223> Synthetic Sequence

<400> 12

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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

<210> 13
<211> 227
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 13

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> 14

<211> 227

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 14

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> 15

<211> 227

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 15

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> 16

<211> 227

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 16

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> 17

<211> 487

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 17

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

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser
145 150 155 160

Ile Asn Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu
165 170 175

Leu Val Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser
180 185 190

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val
195 200 205

Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr
210 215 220

Cys Tyr Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Leu
225 230 235 240

Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
245 250 255

Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
260 265 270

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
275 280 285

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
290 295 300

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
305 310 315 320

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
325 330 335

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
340 345 350

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu
355 360 365

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
370 375 380

Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
385 390 395 400

Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp
405 410 415

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
420 425 430

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser
435 440 445

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
450 455 460

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
465 470 475 480

Leu Ser Leu Ser Pro Gly Lys
485

<210> 18

<211> 487

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 18

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 Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
355 360 365

Ser Gly Gly Ser Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
370 375 380

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

Ser Ser Ile Asn Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu
405 410 415

Arg Glu Leu Val Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala
420 425 430

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
435 440 445

Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val
450 455 460

Tyr Tyr Cys Tyr Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly
465 470 475 480

Thr Leu Val Thr Val Ser Ser
485

<210> 19
<211> 553
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 19

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 Cys Arg Asp Glu Leu Thr Lys Asn Gln
260 265 270

Val Ser Leu Trp 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 Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
370 375 380

Gly Gly Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg
385 390 395 400

Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser
405 410 415

Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly
420 425 430

Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile
435 440 445

Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp
450 455 460

Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu
465 470 475 480

Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr
485 490 495

Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln
500 505 510

Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp
515 520 525

Glu Val Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn
530 535 540

Leu Gln Glu Ser Leu Arg Ser Lys Glu
545 550

<210> 20
<211> 487
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 20

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

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Phe Ser Ser
145 150 155 160

Ile Asn Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu
165 170 175

Leu Val Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser
180 185 190

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val
195 200 205

Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr
210 215 220

Cys Tyr Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Leu
225 230 235 240

Val Thr Val Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
245 250 255

Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
260 265 270

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
275 280 285

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
290 295 300

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
305 310 315 320

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
325 330 335

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
340 345 350

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Gln Val Ser Asn Lys Ala Leu
355 360 365

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
370 375 380

Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
385 390 395 400

Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp
405 410 415

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
420 425 430

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser
435 440 445

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
450 455 460

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
465 470 475 480

Leu Ser Leu Ser Pro Gly Lys
485

<210> 21

<211> 487

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 21

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 Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
355 360 365

Ser Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val
370 375 380

Gln Ala Gly Gly Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Thr Ile
385 390 395 400

Phe Ser Ile Asn Arg Met Asp Trp Phe Arg Gln Ala Pro Gly Lys Gln
405 410 415

Arg Glu Leu Val Ala Leu Ile Thr Ser Asp Gly Thr Pro Ala Tyr Ala
420 425 430

Asp Ser Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Thr Lys Lys
435 440 445

Thr Val Ser Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val
450 455 460

Tyr Tyr Cys His Val Ser Ser Gly Val Tyr Asn Tyr Trp Gly Gln Gly
465 470 475 480

Thr Gln Val Thr Val Ser Ser
485

<210> 22
<211> 553
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 22

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 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 Cys Arg Asp Glu Leu Thr Lys Asn Gln
260 265 270

Val Ser Leu Trp 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 Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
370 375 380

Gly Gly Ser Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg
385 390 395 400

Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser
405 410 415

Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly
420 425 430

Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile
435 440 445

Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp
450 455 460

Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu
465 470 475 480

Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr
485 490 495

Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln
500 505 510

Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp
515 520 525

Glu Val Val Arg Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn
530 535 540

Leu Gln Glu Ser Leu Arg Ser Lys Glu
545 550

<210> 23
<211> 647
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 23

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> 24
<211> 647
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 24

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> 25

<211> 353

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 25

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> 26
<211> 402
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 26

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 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> 27
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 27

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 Gly
 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> 28
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 28

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 Ala Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
 435 440 445

Arg Ser Lys Glu
 450

<210> 29
 <211> 423
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Sequence

<400> 29

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 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 Ala Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln
 405 410 415

Glu Ser Leu Arg Ser Lys Glu
 420

<210> 30
 <211> 423
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Sequence

<400> 30

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 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 Ala Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln
 405 410 415

Glu Ser Leu Arg Ser Lys Glu
 420

<210> 31
 <211> 423
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Sequence

<400> 31

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 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 Gly Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln
405 410 415

Glu Ser Leu Arg Ser Lys Glu
420

<210> 32
 <211> 423
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Sequence

<400> 32

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 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 Gly Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln
 405 410 415

Glu Ser Leu Arg Ser Lys Glu
 420

<210> 33
 <211> 423
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Sequence

<400> 33

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 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 Ala Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln
405 410 415

Glu Ser Leu Arg Ser Lys Glu
420

<210> 34
<211> 423
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 34

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 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 Ala Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln
 405 410 415

Glu Ser Leu Arg Ser Lys Glu
 420

<210> 35
 <211> 423
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Sequence

<400> 35

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 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 Gly Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln
 405 410 415

Glu Ser Leu Arg Ser Lys Glu
 420

<210> 36
 <211> 423
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Sequence

<400> 36

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 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 Gly Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln
405 410 415

Glu Ser Leu Arg Ser Lys Glu
420

<210> 37

<400> 37
000

<210> 38

<211> 227

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 38

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
225

<210> 39

<400> 39
000

<210> 40

<400> 40
000

<210> 41
<211> 422
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 41

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 Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
225 230 235 240

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

Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
260 265 270

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
275 280 285

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe

290

295

300

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
 305 310 315 320

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
 325 330 335

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
 340 345 350

Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
 355 360 365

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
 370 375 380

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
 385 390 395 400

Arg Gly Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
 405 410 415

Ser Leu Arg Ser Lys Glu
 420

<210> 42
 <211> 422
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Sequence

<400> 42

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 Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
 225 230 235 240

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

Gly Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
 260 265 270

Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys
 275 280 285

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
 290 295 300

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
 305 310 315 320

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
 325 330 335

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
 340 345 350

Glu Ala Cys Val Ile Gln Gly Val Gly Val Glu Glu Thr Pro Leu Met
 355 360 365

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr

370

375

380

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
385 390 395 400

Arg Gly Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
405 410 415

Ser Leu Arg Ser Lys Glu
420

<210> 43
<211> 356
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 43

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
355