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N-acetylated and non-acetylated dipeptides containing arginine to reduce the viscosity of viscous compositions of therapeutic polypeptides

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(54) Title: N-ACETYLATED AND NON-ACETYLATED DIPEPTIDES CONTAINING ARGININE TO REDUCE THE VISCOSITY OF VISCOUS COMPOSITIONS OF THERAPEUTIC POLYPEPTIDES

FIG. 2A

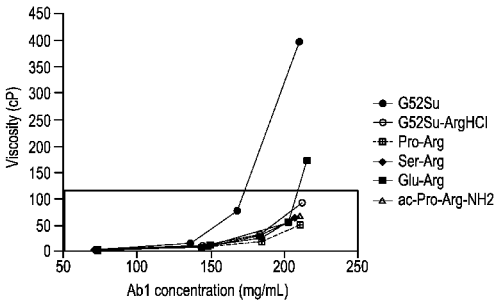
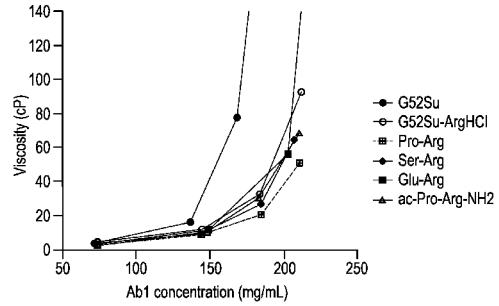


FIG. 2B



(57) Abstract: Provided herein are excipients capable of effectively reducing the viscosity of polypeptide (e.g., therapeutic polypeptide) formulations. The viscosity reducing excipients are dipeptides containing arginine at the carboxy terminus and N-acetylated serine or N-acetylated proline at the N-terminus. Glutamate-arginine is also disclosed as a viscosity-reducing dipeptide. Among the disclosed methods, methods of reducing the viscosities of such formulations are also provided.

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[Continued on next page]

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N-ACETYLATED AND NON-ACETYLATED DIPEPTIDES CONTAINING ARGININE TO REDUCE THE VISCOSITY OF VISCOUS COMPOSITIONS OF THERAPEUTIC POLYPEPTIDES

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 62/492,020, filed April 28, 2017, the contents of which are incorporated herein by reference.

SEQUENCE LISTING

The present application is being filed with a sequence listing in electronic format. The sequence listing provided as a file titled, "A-2142-WO-PCT_sequence listing_ST25.txt," created April 27, 2018, and is 258 KB in size. The information in the electronic format of the sequence listing is incorporated herein by reference in its entirety.

FIELD

The presented subject matter relates to the field of pharmaceutical compositions of antigen binding polypeptides and methods of reducing viscosity of such compositions. Specifically, disclosed herein are excipients that reduce viscosity of pharmaceutical compositions. Furthermore, the disclosed subject matter presents methods related to making such pharmaceutical compositions.

BACKGROUND

Certain therapeutic polypeptides can be difficult to formulate such that an optimal viscosity is attained, whether because of the nature of the therapeutic polypeptide itself, or because of the concentration (high) of the therapeutic polypeptide, or even both. High viscosity formulations are difficult to handle during formulation and packaging. Furthermore, such preparations can be difficult to administer optimally to a patient, and such administration can be uncomfortable for the patient. The need to identify compounds that are useful for reducing viscosity of highly concentrated protein formulations, to develop methods of reducing the viscosity of such formulations, and to provide pharmaceutical formulations with reduced viscosity are well known in the pharmaceutical arts.

SUMMARY

In a first form, provided herein is a liquid pharmaceutical composition comprising a therapeutic polypeptide, a buffer, and at least one N-acetyl-dipeptide, wherein the N-acetyl-dipeptide is N-acetyl-serine-arginine, N-acetyl-proline-arginine, or N-acetyl-proline-arginine-NH2.

In a second form, provided herein is a method of reducing viscosity in a pharmaceutical composition comprising a therapeutic polypeptide, wherein the method comprises:

a. providing a solution comprising (i) the therapeutic polypeptide, (ii) at least one N-acetyl-dipeptide, wherein the N-acetyl-dipeptide is N-acetyl-serine-arginine, N-acetyl-proline-arginine, or N-acetyl-proline-arginine-NH2, and is present at a viscosity-reducing concentration, and (iii) a buffer; and

b. adjusting the pH of the solution to about 4 to about 8.

In a first aspect, provided herein are liquid pharmaceutical compositions comprising a therapeutic polypeptide, such as an antibody or an antigen-binding fragment thereof; a buffer, and at least one N-acetyl-dipeptide, wherein the N-acetyl-dipeptide is N-acetyl-serine-arginine, N-acetyl-proline-arginine, or N-acetyl-proline-arginine-NH_2, wherein the pH of the composition is about 4 to about 8. The therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof, can be present in a concentration of at least about 70 mg/ml, at least about 85 mg/ml, at least about 100 mg/ml, at least about 100 mg/ml, at least 140 mg/ml, at least about 160 mg/ml, at least about 180 mg/ml, at least about 200 mg/ml, and at least about 210 mg/ml. In the case wherein the therapeutic polypeptide is an antibody, the antibody can be selected from the group consisting of adalimumab, bevacizumab, blinatumomab, cetuximab, conatumumab, denosumab, eculizumab, erenumab, evolocumab, infliximab, natalizumab, panitumumab, rilotumumab, rituximab, romosozumab, and trastuzumab, or an antigen binding fragment thereof, or is an antibody selected from those presented in Table 1, or an antigen binding fragment thereof. In some sub-aspects, the antibody is evolocumab. The N-acetyl-dipeptide can have a concentration from about 10 mM to about 500 mM, such as from about 100 mM to about 200 mM, 100 mM, 150 mM, and about 200 mM. The N-acetylated dipeptide can be N-acetyl-serine-arginine. The N-acetylated dipeptide can be N-acetyl-proline-arginine. The N-acetylated dipeptide can be N-acetyl-proline-arginine-NH_2. The buffer can be selected from the group consisting of acetate, glutamate, histidine, and phosphate buffers, or a combination thereof, such as acetate. The buffer can be present at a concentration of about 5 mM to about 30 mM, such as about 10 mM. The pH of the compositions can have a pH of about 4 to 8, such as a pH of about 4.8 to about 6.9, and such as a pH of about 5.2. The compositions can further comprise a surfactant, such as a surfactant selected from the group consisting of polyoxyethylenesorbitan monooleate (polysorbate 80 or polysorbate 20),

polyoxyethylene-polyoxypropylene block copolymer (Poloxamers such as Pluronic® F-68 and other Pluronics®), Sorbitan alkyl esters (Spans®) Polyethylene glycol octylphenyl ethers (Triton X-100), Polyethylene glycol alkyl ethers (Brij), Polypropylene glycol alkyl ethers, Glucoside alkyl ethers, and D-α-tocopherol polyethylene glycol succinate (vitamin E TPGS). In some aspects, the surfactant is polysorbate 80, such as at a concentration of about 0.01% (w/v) polysorbate 80 or 0.004% polysorbate 20. The compositions can further comprise an amino acid, N-acetyl-arginine, N-acetyl-lysine, N-acetyl-histidine, N-acetyl-proline or mixtures of any thereof. The amino acid can be arginine or proline.

In a second aspect, disclosed herein are methods of reducing viscosity in a pharmaceutical composition comprising a therapeutic polypeptide, such as an antibody or an antigen-binding fragment thereof, wherein the method comprises:

a. providing a solution comprising (i) the therapeutic polypeptide, (ii) an N-acetyl-dipeptide, wherein the N-acetyl-dipeptide is N-acetyl-serine-arginine, N-acetyl-proline-arginine, or N-acetyl-proline-arginine-NH_2 and is present in a viscosity-reducing concentration, and (iii) a buffer; and

b. adjusting the pH of the solution to about 4 to about 8.

The therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof, can be present in a concentration of at least about 70 mg/ml, at least about 85 mg/ml, at least about 100 mg/ml, at least about 100 mg/ml, at least 140 mg/ml, at least about 160 mg/ml, at least about 180 mg/ml, at least about 200 mg/ml, and at least about 210 mg/ml. In cases where the therapeutic polypeptide is an antibody, the antibody can be selected from the group consisting of adalimumab, bevacizumab, blinatumomab, cetuximab, conatumumab, denosumab, eculizumab, erenumab, evolocumab, infliximab, natalizumab, panitumumab, rilotumumab, rituximab, romosozumab, and trastuzumab, or an antigen binding fragment thereof, or is an antibody selected from those presented in Table 1, or an antigen binding fragment thereof. In some sub-aspects, the antibody is evolocumab. The N-acetyl-dipeptide can have a concentration from about 10 mM to about 500 mM, such as from about 100 mM to about 200 mM, 100 mM, 150 mM, and about 200 mM. The N-acetyl-dipeptide can be N-acetyl-serine-arginine. The N-acetyl-dipeptide can be N-acetyl-proline-arginine. The N-acetyl-dipeptide can be N-acetyl-proline-arginine-NH_2. The N-acetyl-dipeptide can be a lyophilized powder prior to being placed in solution. The buffer can be selected from the group consisting of acetate, glutamate, histidine, and phosphate buffers, or a combination thereof, such as acetate. The buffer can be present at a concentration of about 5 mM to about 30 mM, such as about 10 mM. The pH of the compositions can have a pH of about 4 to about 8, such as a pH of about 4.8 to about 6.9, and such as a pH of about 5.2. The compositions can further comprise a surfactant, such as a surfactant selected from the group consisting of polyoxyethylenesorbitan monooleate (polysorbate 80 or polysorbate 20), polyoxyethylene-polyoxypropylene block copolymer (Poloxamers such as Pluronic® F-68 and other Pluronics®), Sorbitan alkyl esters (Spans®) Polyethylene glycol octylphenyl ethers (Triton X-100), Polyethylene glycol alkyl ethers (Brij), Polypropylene glycol alkyl ethers, Glucoside alkyl ethers, and D-α-tocopherol polyethylene glycol succinate (vitamin E TPGS), such as polysorbate 20 or polysorbate 80. In some aspects, the surfactant is polysorbate 80, such as at a concentration of about 0.1% (w/v) polysorbate 80 or 0.004%

(w/v) polysorbate 20. The compositions can further comprise an amino acid, N-acetyl-arginine, N-acetyl-lysine, N-acetyl-histidine, N-acetyl-proline or mixtures of any thereof. The amino acid can be arginine or proline. In some sub-aspects, the viscosity of the composition is reduced by at least about 30% when compared to a control solution lacking the N-acetyl-dipeptide. In other sub-aspects, the viscosity of the composition is reduced by at least about 50% when compared to a control solution lacking the N-acetyl-dipeptide.

In a third aspect, disclosed herein are lyophilized powders comprising a therapeutic polypeptide, such as an antibody or an antigen-binding fragment thereof, and an N-acetyl-dipeptide, wherein the N-acetyl-dipeptide is N-acetyl-serine-arginine, N-acetyl-proline-arginine, or N-acetyl-proline-arginine-NH_2. The N-acetyl-dipeptide can be N-acetyl-proline-arginine-NH_2, and the N-acetyl-dipeptide is present at a weight:weight concentration effective to reduce viscosity upon reconstitution with a diluent. The N-acetyl-dipeptide can be present at about 10 μg/mg to about 500 μg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof, from about 50 μg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof to about 500 μg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof, from about 100 μg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof to about 500 μg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof, from about 200 μg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof to about 500 μg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof, and from about 150 μg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof to about 250 μg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof. In some sub-aspects, the N-acetyl-dipeptide is present about 100 μg/mg antibody to about 500 μg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof.

In a fourth aspect, disclosed herein are methods of reconstituting a lyophilized powder of the third aspect, comprising the step of adding a sterile aqueous diluent comprising a buffer in sufficient concentration so that the reconstituted solution has a pH of about 4 to about 8, such as wherein the reconstituted solution has a pH of about 4.8 to about 6.9, such as a pH of about 5.2.

In a fifth aspect, provided herein are liquid pharmaceutical compositions comprising a therapeutic polypeptide, such as an antibody or an antigen-binding fragment thereof; a buffer, and at least one glutamate-arginine dipeptide, wherein the pH of the composition is about 4 to about 8. The therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof, can be present in a

concentration of at least about 70 mg/ml, at least about 85 mg/ml, at least about 100 mg/ml, at least about 100 mg/ml, at least 140 mg/ml, at least about 160 mg/ml, at least about 180 mg/ml, at least about 200 mg/ml, and at least about 210 mg/ml. In the case wherein the therapeutic polypeptide is an antibody, the antibody can be selected from the group consisting of adalimumab, bevacizumab, blinatumomab, cetuximab, conatumumab, denosumab, eculizumab, erenumab, evolocumab, infliximab, natalizumab, panitumumab, rilotumumab, rituximab, romosozumab, and trastuzumab, or an antigen binding fragment thereof, or is an antibody selected from those presented in Table 1, or an antigen binding fragment thereof. In some sub-aspects, the antibody is evolocumab. The glutamate-arginine dipeptide can have a concentration from about 1 mM to about 25 mM, such as from about 10 mM to about 25 mM, and about 25 mM. The buffer can be selected from the group consisting of acetate, glutamate, histidine, and phosphate buffers, or a combination thereof, such as acetate. The buffer can be present at a concentration of about 5 mM to about 30 mM, such as about 10 mM. The pH of the compositions can have a pH of about 4 to 8, such as a pH of about 4.8 to about 6.9, and such as a pH of about 5.2. The compositions can further comprise a surfactant, such as a surfactant selected from the group consisting of polyoxyethylenesorbitan monooleate (polysorbate 80 or polysorbate 20), polyoxyethylene-polyoxypropylene block copolymer (Poloxamers such as Pluronic® F-68 and other Pluronics®), Sorbitan alkyl esters (Spans®) Polyethylene glycol octylphenyl ethers (Triton X-100), Polyethylene glycol alkyl ethers (Brij), Polypropylene glycol alkyl ethers, Glucoside alkyl ethers, and D-α-tocopherol polyethylene glycol succinate (vitamin E TPGS). In some aspects, the surfactant is polysorbate 80, such as at a concentration of about 0.01% (w/v) polysorbate 80 or 0.004% polysorbate 20. The compositions can further comprise an amino acid, N-acetyl-arginine, N-acetyl-lysine, N-acetyl-histidine, N-acetyl-proline or mixtures of any thereof. The amino acid can be arginine or proline.

In a sixth aspect, disclosed herein are methods of reducing viscosity in a pharmaceutical composition comprising a therapeutic polypeptide, such as an antibody or an antigen-binding fragment thereof, wherein the method comprises:

a. providing a solution comprising (i) the therapeutic polypeptide, (ii) a glutamate-arginine dipeptide and is present in a viscosity-reducing concentration, and (iii) a buffer; and

b. adjusting the pH of the solution to about 4 to about 8.

The therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof, can be present in a concentration of at least about 70 mg/ml, at least about 85 mg/ml, at least about 100 mg/ml, at least about 100 mg/ml, at least 140 mg/ml, at least about 160 mg/ml, at least about 180

mg/ml, at least about 200 mg/ml, and at least about 210 mg/ml. In cases where the therapeutic polypeptide is an antibody, the antibody can be selected from the group consisting of adalimumab, bevacizumab, blinatumomab, cetuximab, conatumumab, denosumab, eculizumab, erenumab, evolocumab, infliximab, natalizumab, panitumumab, rilotumumab, rituximab, romosozumab, and trastuzumab, or an antigen binding fragment thereof, or is an antibody selected from those presented in Table 1, or an antigen binding fragment thereof. In some sub-aspects, the antibody is evolocumab. The glutamate-arginine dipeptide can have a concentration from about 1 mM to about 25 mM, such as from about 10 mM to about 25 mM, and about 25 mM. The glutame-arginine dipeptide can be a lyophilized powder prior to being placed in solution. The buffer can be selected from the group consisting of acetate, glutamate, histidine, and phosphate buffers, or a combination thereof, such as acetate. The buffer can be present at a concentration of about 5 mM to about 30 mM, such as about 10 mM. The pH of the compositions can have a pH of about 4 to about 8, such as a pH of about 4.8 to about 6.9, and such as a pH of about 5.2. The compositions can further comprise a surfactant, such as a surfactant selected from the group consisting of polyoxyethylenesorbitan monooleate (polysorbate 80 or polysorbate 20), polyoxyethylene-polyoxypropylene block copolymer (Poloxamers such as Pluronic® F-68 and other Pluronics®), Sorbitan alkyl esters (Spans®) Polyethylene glycol octylphenyl ethers (Triton X-100), Polyethylene glycol alkyl ethers (Brij), Polypropylene glycol alkyl ethers, Glucoside alkyl ethers, and D-α-tocopherol polyethylene glycol succinate (vitamin E TPGS), such as polysorbate 20 or polysorbate 80. In some aspects, the surfactant is polysorbate 80, such as at a concentration of about 0.1% (w/v) polysorbate 80 or 0.004% (w/v) polysorbate 20. The compositions can further comprise an amino acid, N-acetyl-arginine, N-acetyl-lysine, N-acetyl-histidine, N-acetyl-proline or mixtures of any thereof. The amino acid can be arginine or proline. In some sub-aspects, the viscosity of the composition is reduced by at least about 30% when compared to a control solution lacking the N-acetyl-dipeptide. In other sub-aspects, the viscosity of the composition is reduced by at least about 50% when compared to a control solution lacking the N-acetyl-dipeptide.

In a seventh aspect, disclosed herein are lyophilized powders comprising a therapeutic polypeptide, such as an antibody or an antigen-binding fragment thereof, and at least one glutamate-arginine dipeptide that is present at a weight:weight concentration effective to reduce viscosity upon reconstitution with a diluent. The dipeptide can be present at about 10 µg/mg to about 500 µg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof, from about 50 µg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof to about 500 µg/mg

therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof, from about 100 µg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof to about 500 µg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof, from about 200 µg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof to about 500 µg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof, and from about 150 µg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof to about 250 µg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof. In some sub-aspects, the glutamate-arginine dipeptide is present about 100 µg/mg antibody to about 500 µg/mg therapeutic polypeptide, such as an antibody or antigen-binding fragment thereof.

In a eighth aspect, disclosed herein are methods of reconstituting a lyophilized powder of the seventh aspect, comprising the step of adding a sterile aqueous diluent comprising a buffer in sufficient concentration so that the reconstituted solution has a pH of about 4 to about 8, such as wherein the reconstituted solution has a pH of about 4.8 to about 6.9, such as a pH of about 5.2.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a line graph representation of the viscosity of various pharmaceutical formulations comprising the indicated amounts of a therapeutic antibody (Antibody 1, "Ab1"; concentration is shown as mg/mL) and various excipients at the indicated pH values.

Figures 2A and 2B show a line graph of observed viscosity of pharmaceutical formulations comprising 10 mM glutamic acid buffer pH 5.2 with 4% w/v sucrose vs the concentration of a therapeutic antibody (Antibody 1, "Ab1")) with and without the indicated excipients in the formulations. **Fig. 2A** shows the graph so that all values of the samples are shown for each point along the x-axis; and **Fig. 2B** shows the detail of the viscosity of the formulations wherein the viscosity was observed at 100 cP or less. G52Su, buffer, sucrose and Ab1 (no excipient); G52Su-ArgHCl, 150 mM ArgHCl as excipient; Pro-Arg, 150 mM N-acetyl-Pro-Arg dipeptide as excipient; Ser-Arg, 150 mM N-acetyl-Ser-Arg dipeptide as excipient; Glu-Arg, 25 mM Glu-Arg as excipient; ac-Pro-Arg-NH_2, 150 mM N-acetyl-Pro-Arg-NH_2 as excipient.

Figures 3A and 3B show a line graph of observed viscosity of pharmaceutical formulations comprising 10 mM glutamic acid buffer pH 5.2 with 4% w/v sucrose vs the concentration of a therapeutic antibody (Antibody 2, "Ab2")) with and without the indicated excipients in the formulations. **Fig. 3A** shows the graph so that all values of the samples are shown for each point along the x-axis; and

Fig. 3B shows the detail of the viscosity of the formulations wherein the viscosity was observed at 80 cP or less. G52Su, buffer, sucrose and Ab1 (no excipient); G52Su-ArgHCl, 150 mM ArgHCl as excipient; ac-Pro-Arg, 150 mM N-acetyl-Pro-Arg dipeptide as excipient; ac-Ser-Arg, 150 mM N-acetyl-Ser-Arg dipeptide as excipient; Glu-Arg, 25 mM Glu-Arg as excipient; ac-Pro-Arg-NH_2, 150 mM N-acetyl-Pro-Arg-NH_2 as excipient.

Figure 4 show a line graph of the observed viscosity of pharmaceutical formulations comprising 10 mM glutamic acid buffer pH 5.2 with 4% w/v sucrose vs the concentration of a therapeutic antibody (Antibody 3, "Ab3")) with and without the indicated excipients. G52Su, buffer, sucrose and Ab1 (no excipient); G52Su-ArgHCl, 150 mM ArgHCl as excipient; ac-Pro-Arg, 150 mM N-acetyl-Pro-Arg dipeptide as excipient; ac-Ser-Arg, 150 mM N-acetyl-Ser-Arg dipeptide as excipient; Glu-Arg, 25 mM Glu-Arg as excipient; ac-Pro-Arg-NH_2, 150 mM N-acetyl-Pro-Arg-NH_2 as excipient.

Figures 5(A)-5(D) show comparative line graphs of the viscosities for the three antibodies, Ab1, Ab2, and Ab3 at the indicated concentrations (mg/mL) and excipients. **Fig. 5(A)** shows the results for the three antibodies in the presence of 150 mM of N-acetyl-Pro-Arg and the observed viscosities. **Fig. 5(B)** shows the results for the three antibodies in the presence of 150 mM of N-acetyl-Ser-Arg and the observed viscosities. **Fig. 5(C)** shows the results for the three antibodies in the presence of 150 mM of N-acetyl-Pro-Arg-NH_2 and the observed viscosities. **Fig. 5(D)** shows the results for the three antibodies in the presence of 150 Glu-Arg and the observed viscosities. G52Su, buffer, sucrose and Ab1 (no excipient); ac-Pro-Arg, 150 mM N-acetyl-Pro-Arg dipeptide as excipient; ac-Ser-Arg, 150 mM N-acetyl-Ser-Arg dipeptide as excipient; ac-Pro-Arg-NH_2, 150 mM N-acetyl-Pro-Arg-NH_2 as excipient; Glu-Arg, 25 mM Glu-Arg as excipient.

DETAILED DESCRIPTION

N-acetyl-serine-arginine, N-acetyl-proline-arginine, N-acetyl-proline-arginine-NH_2, and glutamate-arginine dipeptides were found to reduce the viscosity of therapeutic polypeptide formulations, such as those containing antibodies. Surprisingly, while the N-acetyl-dipeptides reduced viscosity to a similar extent as N-acetyl-arginine (NAR), they are significantly more soluble than NAR. Because of their increased solubility, these N-acetyl dipeptides are able to reduce the viscosity of therapeutic proteins even more than NAR because they can be formulated at much higher concentrations.

Definitions

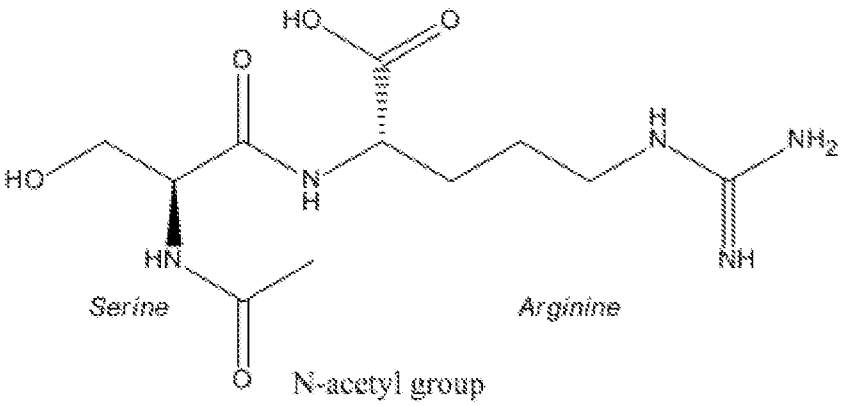
Both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive. The use of the singular includes the plural unless specifically stated otherwise. The use of "or" means "and/or" unless stated otherwise. The use of the term "including", as well as other forms, such as "includes" and "included", is not limiting. Terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit unless specifically stated otherwise. The use of the term "portion" can include part of a moiety or the entire moiety. When a numerical range is mentioned, *e.g.*, 1-5, all intervening values are explicitly included, such as 1, 2, 3, 4, and 5, as well as fractions thereof, such as 1.5, 2.2, 3.4, and 4.1.

"About" or "~" mean, when modifying a quantity (*e.g.*, "about" 3 mM), that variation around the modified quantity can occur. These variations can occur by a variety of means, such as typical measuring and handling procedures, inadvertent errors, ingredient purity, and the like.

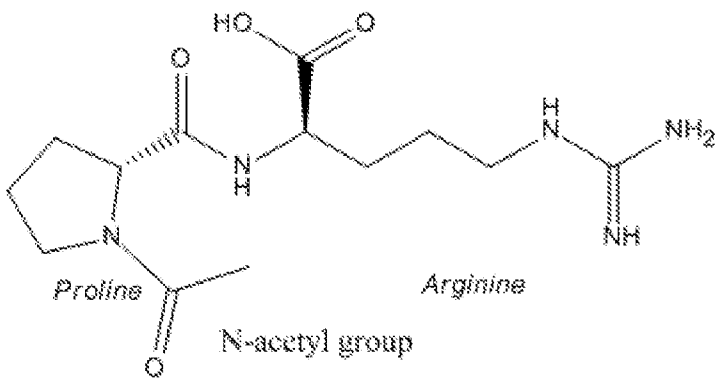
"Comprising" and "comprises" are intended to mean that the formulations and methods include the listed elements but do not exclude other unlisted elements. The terms "consisting essentially of" and "consists essentially of," when used to define formulations and methods include the listed elements, exclude unlisted elements that alter the basic nature of the formulation and/or method, but do not exclude other unlisted elements. So a formulation consisting essentially of elements defined herein would not exclude trace amounts of other elements, such as contaminants from any isolation and purification methods or pharmaceutically acceptable carriers (*e.g.*, phosphate buffered saline), preservatives, and the like, but would exclude, for example, additional unspecified amino acids. The terms "consisting of" and "consists of" when used to define formulations and methods exclude more than trace elements of other ingredients and substantial method steps for administering the compositions described herein. Embodiments defined by each of these transition terms are within the scope of this disclosure.

N-acetyl-Serine and N-acetyl-proline are modified versions of a naturally-occurring amino acids Serine and proline, respectively. N-acetyl-serine and N-acetyl-proline include both D and L forms of the amino acids, such as N-acetyl-L-serine, N-acetyl-D-serine, N-acetyl-L-proline, N-acetyl-D-proline. These N-acetyl-amino acids can be made part of arginine-containing dipeptides. The structure of N-acetyl-serine-arginine dipeptide is shown as structure **1**; the structure of N-acetyl-proline-arginine dipeptide is

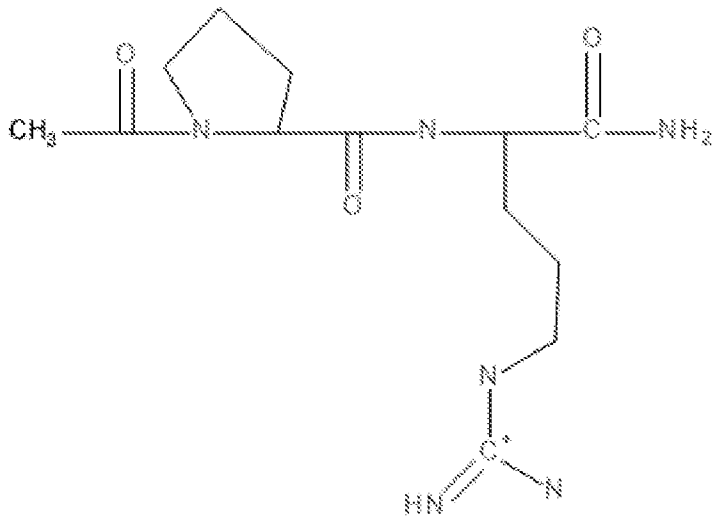
shown as formula **2**; the structure of N-actyl-proline-arginine-NH2 is shown as formula **3**. Also shown is a glutamate-arginine dipeptide as formula **4**.



(**1**)

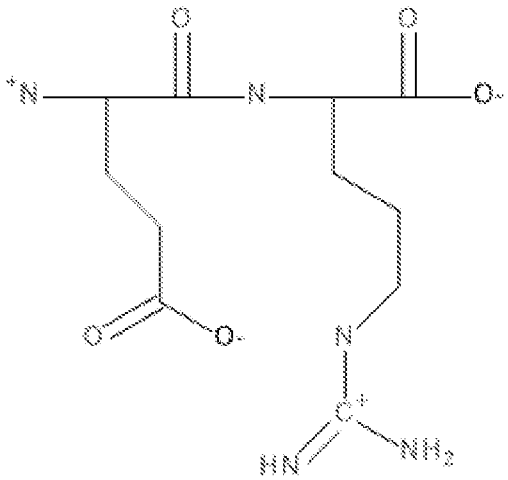


(**2**)



n-ac-Pro-Arg-NH2

(3)



Glu-Arg

(4)

A “pharmaceutical composition” or a “pharmaceutical formulation” is a sterile composition of (i) a pharmaceutically active drug, such as a biologically active polypeptide, that is suitable for parenteral administration (including intravenous, intramuscular, subcutaneous, aerosolized, intrapulmonary, intranasal and intrathecal administration) to a patient in need thereof and (ii) one or more pharmaceutically acceptable excipients, diluents, and other additives deemed safe by the Federal Drug

Administration or other foreign national authorities. Pharmaceutical formulations include liquid (*e.g.*, aqueous) solutions that can be directly administered, and lyophilized powders that can be reconstituted into solutions by adding a diluent before administration. The term "pharmaceutical formulation" specifically excludes, however, compositions for topical administration to patients, compositions for oral ingestion, and compositions for parenteral feeding.

"Viscosity" means a fluid's resistance to flow and can be measured in units of centipoise (cP) or milliPascal-second (mPa-s), where 1 cP=l mPa-s, at a given shear rate. Viscosity can be measured by using a rotational viscometer, such as a Brookfield Engineering Dial Reading Viscometer, model LVT, such as a Gemini 200 Rheometer (Malvern Instruments) or an AR-G2 Rheometer (TA Instruments). Viscosity can be measured using any other methods and in any other units known in the art (*e.g.*, absolute, kinematic or dynamic viscosity. Regardless of the method used to determine viscosity, the percent reduction in viscosity in excipient formulations versus control formulations remain approximately the same at a given shear rate.

A formulation containing an amount of an excipient effective to "reduce viscosity" (or a "viscosity-reducing" amount or concentration of such excipient) means that the viscosity of the formulation in its final form for administration is at least 5% less than the viscosity of an appropriate control formulation, such as water, buffer, other known viscosity-reducing agents such as salt and the like. Excipient-free control formulations might also be used even if they cannot be implementable as a therapeutic formulation, for example due to hypotonicity.

Likewise, a "reduced viscosity" formulation is a formulation that exhibits lower viscosity compared to a control formulation.

"Stable" formulations of biologically active polypeptides are formulations that exhibit either (i) reduced aggregation and/or reduced loss of biological activity of at least 20% upon storage at 2-8 °C for at least two years compared with a control formula sample, or (ii) reduced aggregation and/or reduced loss of biological activity under conditions of thermal stress (*e.g.* 25 °C for one week to 12 weeks; 40 °C for one to 12 weeks; 52 °C for seven-eight days, *etc.*). A formulation is considered stable when the polypeptide in the formulation retains physical stability, chemical stability and/or a biological activity.

A polypeptide can be said to "retain its physical stability" in a formulation if, for example, it shows no signs of aggregation, precipitation and/or denaturation upon visual examination of color and/or clarity, or as measured by UV light scattering or by size exclusion chromatography (SEC) or electrophoresis, such as with reference to turbidity or aggregate formation.

A polypeptide can be said to "retain its chemical stability" in a formulation if, for example, the chemical stability at a given time is such that no new chemical entity results from modification of the polypeptide by bond formation or cleavage. Chemical stability can be assessed by detecting and quantifying chemically-altered forms of the polypeptide. Chemical alteration can involve, for example, size modification (*e.g.*, clipping), which can be evaluated using size exclusion chromatography, SDS-PAGE and/or matrix-assisted laser desorption ionization/time-of-flight mass spectrometry (MALDI/TOF MS). Other types of chemical alteration include, for example, charge alteration (*e.g.*, resulting from deamidation), which can be evaluated by ion-exchange chromatography. Oxidation is another commonly observed chemical modification.

A polypeptide can be said to "retain its biological activity" in a pharmaceutical formulation relative to unmodified polypeptide if, for example, the percentage of biological activity of the formulated polypeptide (*e.g.*, an antibody) as determined by an assay (*e.g.*, an antigen binding assay) compared to the control polypeptide is between either about 50% to about 200%, about 60% to about 170%, about 70% to about 150%, about 80% to about 125%, or about 90% to about 110%. In some cases, a polypeptide can be said to "retain its biological activity" in a pharmaceutical formulation, if, for example, the biological activity of the polypeptide at a given time is at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100%.

"Antibodies" (Abs) and the synonym "immunoglobulins" (Igs) are glycopolypeptides having the same structural characteristics. While antibodies exhibit binding specificity to a specific antigen, immunoglobulins include both antibodies and other antibody-like molecules that lack antigen specificity. Polypeptides of the latter kind are, for example, produced at low levels by the lymph system and at increased levels by myelomas. Thus, the term "antibody" or "antibody peptide(s)" refers to an intact antibody, an antibody derivative, an antibody analog, a genetically altered antibody, an antibody having a detectable label, an antibody that competes for specific binding with a specified antibody, or an antigen-binding fragment (*e.g.*, Fab, Fab', F(ab')2, Fv, single domain antibody) thereof that competes with the intact antibody for specific binding and includes chimeric, humanized, fully human, and bispecific antibodies. In some cases, antigen-binding fragments are produced, for example, by recombinant DNA techniques. In other cases, antigen-binding fragments are produced by enzymatic or chemical cleavage of intact antibodies. Antigen-binding fragments include Fab, Fab', F(ab)2, F(ab')2, Fv, and single-chain antibodies.

Monoclonal antibodies and antibody constructs include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity. Chimeric antibodies include "primitized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (*e.g.*, Old World Monkey, Ape, *etc.*) and human constant region sequences.

Monoclonal antibodies and antibody constructs include antibodies referred to as "human" or "fully human." The terms "human antibody" and "fully human antibody" each refer to an antibody that has an amino acid sequence of a human immunoglobulin, including antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulins and that do not express endogenous immunoglobulins; for example, Xenomouse® antibodies and antibodies as described by Kucherlapati *et al.* in U.S. Pat. No. 5,939,598.

"Genetically altered antibodies" means antibodies wherein the amino acid sequence has been varied from that of a native antibody. Because of the relevance of recombinant DNA techniques in the generation of antibodies, one need not be confined to the sequences of amino acids found in natural antibodies; antibodies can be redesigned to obtain desired characteristics. The possible variations are many and range from changes to just one or a few amino acids to complete redesign of, for example, the variable and/or constant region. Changes in the constant region, in general, are made in order to improve or alter characteristics, such as complement fixation, interaction with membranes and other effector functions, as well as manufacturability and viscosity. Changes in the variable region can be made to improve antigen binding characteristics.

A "Fab fragment" is comprised of one light chain and the CH1 and variable regions of one heavy chain. The heavy chain of a Fab molecule cannot form a disulfide bond with another heavy chain molecule.

A "Fab' fragment" contains one light chain and one heavy chain that contains more of the constant region, between the CH1 and CH2 domains, such that an interchain disulfide bond can be formed between two heavy chains to form a F(ab')2 molecule.

A "F(ab')2 fragment" contains two light chains and two heavy chains containing a portion of the constant region between the CH1 and CH2 domains, such that an interchain disulfide bond is formed between two heavy chains.

"Fv fragment" and "single chain antibody" refer to polypeptides containing antibody variable regions from both heavy and light chains but lacking constant regions. Like an intact antibody, an Fv fragment or single chain antibody are able to bind selectively to a specific antigen. With a molecular weight of only about 25 kDa, Fv fragments are much smaller than common antibodies (150-160 kD), and even smaller than Fab fragments (about 50 kDa, one light chain and half a heavy chain).

A "single domain antibody" is an antibody fragment consisting of a single domain Fv unit, *e.g.*, VH or VL. Like an intact antibody, a single domain antibody is able to bind selectively to a specific antigen. With a molecular weight of only 12-15 kDa, single-domain antibodies are much smaller than common antibodies (150-160 kDa) which are composed of two heavy polypeptide chains and two light chains, and even smaller than Fab fragments (about 50 kDa, one light chain and half a heavy chain) and single-chain variable fragments (about 25 kDa, two variable domains, one from a light and one from a heavy chain). Nanobodies derived from light chains have also been shown to bind specifically to target epitopes.

"Amino acid" refers to either natural and/or unnatural or synthetic amino acids, including glycine and both the D and L optical isomers, amino acid analogs and peptidomimetics. In some aspects, the term amino acid refers to monomeric amino acids.

"Additive" means, in the context of a pharmaceutical composition, a substance not naturally part of a material (*e.g.*, drug substance) but deliberately added to fulfill some specific purpose (*e.g.,* preservation, viscosity reduction, stabilization).

"Surfactant" means surface-active agents, including substances commonly referred to as wetting agents, surface tension depressants, detergents, dispersing agents, emulsifiers, and quaternary ammonium antiseptics. Surfactants are further discussed below.

Components of the compositions and methods

Therapeutic polypeptides

Proteins, including those that bind to one or more of the following, can be useful in the disclosed compositions and methods. These include CD proteins, including CD3, CD4, CD8, CD19, CD20, CD22, CD30, and CD34; including those that interfere with receptor binding. HER receptor family

proteins, including HER2, HER3, HER4, and the EGF receptor. Cell adhesion molecules, for example, LFA-I, MoI, pl50, 95, VLA-4, ICAM-I, VCAM, and alpha v/beta 3 integrin. Growth factors, such as vascular endothelial growth factor ("VEGF"), growth hormone, thyroid stimulating hormone, follicle stimulating hormone, luteinizing hormone, growth hormone releasing factor, parathyroid hormone, Mullerian-inhibiting substance, human macrophage inflammatory protein (MIP-I -alpha), erythropoietin (EPO), nerve growth factor, such as NGF-beta, platelet-derived growth factor (PDGF), fibroblast growth factors, including, for instance, aFGF and bFGF, epidermal growth factor (EGF), transforming growth factors (TGF), including, among others, TGF- α and TGF-β, including TGF-βl, TGF-β2, TGF-β3, TGF- β4, or TGF- β 5, insulin-like growth factors-I and -II (IGF-I and IGF-II), des(l-3)-IGF-I (brain IGF-I), and osteoinductive factors. Insulins and insulin-related proteins, including insulin, insulin A-chain, insulin B-chain, proinsulin, and insulin-like growth factor binding proteins. Coagulation and coagulation-related proteins, such as, among others, factor VIII, tissue factor, von Willebrands factor, protein C, alpha-1-antitrypsin, plasminogen activators, such as urokinase and tissue plasminogen activator ("t-PA"), bombazine, thrombin, and thrombopoietin; (vii) other blood and serum proteins, including but not limited to albumin, IgE, and blood group antigens. Colony stimulating factors and receptors thereof, including the following, among others, M-CSF, GM-CSF, and G-CSF, and receptors thereof, such as CSF-1 receptor (c-fms). Receptors and receptor-associated proteins, including, for example, flk2/flt3 receptor, obesity (OB) receptor, LDL receptor, growth hormone receptors, thrombopoietin receptors ("TPO-R," "c-mpl"), glucagon receptors, interleukin receptors, interferon receptors, T-cell receptors, stem cell factor receptors, such as c-Kit, and other receptors. Receptor ligands, including, for example, OX40L, the ligand for the OX40 receptor. Neurotrophic factors, including bone-derived neurotrophic factor (BDNF) and neurotrophin-3, -4, -5, or -6 (NT-3, NT-4, NT-5, or NT-6). Relaxin A-chain, relaxin B-chain, and prorelaxin; interferons and interferon receptors, including for example, interferon-α, -β, and -γ, and their receptors. Interleukins and interleukin receptors, including IL-I to IL-33 and IL-I to IL-33 receptors, such as the IL-8 receptor, among others. Viral antigens, including an AIDS envelope viral antigen. Lipoproteins, calcitonin, glucagon, atrial natriuretic factor, lung surfactant, tumor necrosis factor-alpha and -beta, enkephalinase, RANTES (regulated on activation normally T-cell expressed and secreted), mouse gonadotropin-associated peptide, DNAse, inhibin, and activin. Integrin, protein A or D, rheumatoid factors, immunotoxins, bone morphogenetic protein (BMP), superoxide dismutase, surface membrane proteins, decay accelerating factor (DAF), AIDS envelope, transport proteins, homing receptors, addressins, regulatory proteins, immunoadhesins, antibodies. Myostatins, TALL proteins, including TALL-

I, amyloid proteins, including but not limited to amyloid-beta proteins, thymic stromal lymphopoietins ("TSLP"), RANK ligand ("OPGL"), c-kit, TNF receptors, including TNF Receptor Type 1, TRAIL-R2, angiopoietins, and biologically active fragments or analogs or variants of any of the foregoing.

Exemplary polypeptides and antibodies include Activase® (Alteplase); alirocumab, Aranesp® (Darbepoetin-alfa), Epogen® (Epoetin alfa, or erythropoietin); Avonex® (Interferon β-Ia); Bexxar® (Tositumomab); Betaseron® (Interferon-β); bococizumab (anti-PCSK9 monoclonal antibody designated as L1L3, see U.S.P.N. 8,080,243); Campath® (Alemtuzumab); Dynepo® (Epoetin delta); Velcade® (bortezomib); MLN0002 (anti-α4β7 Ab); MLN1202 (anti-CCR2 chemokine receptor Ab); Enbrel® (etanercept); Eprex® (Epoetin alfa); Erbitux® (Cetuximab); evolocumab; Genotropin® (Somatropin); Herceptin® (Trastuzumab); Humatrope® (somatropin [rDNA origin] for injection); Humira® (Adalimumab); Infergen® (Interferon Alfacon-1); Natrecor® (nesiritide); Kineret® (Anakinra), Leukine® (Sargamostim); LymphoCide® (Epratuzumab); BenlystaTM (Belimumab); Metalyse® (Tenecteplase); Mircera® (methoxy polyethylene glycol-epoetin beta); Mylotarg® (Gemtuzumab ozogamicin); Raptiva® (efalizumab); Cimzia® (certolizumab pegol); SolirisTM (Eculizumab); Pexelizumab (Anti-C5 Complement); MEDI-524 (Numax®); Lucentis® (Ranibizumab); Edrecolomab (,Panorex®); Trabio® (lerdelimumab); TheraCim hR3 (Nimotuzumab); Omnitarg (Pertuzumab, 2C4); Osidem® (IDM-I); OvaRex® (B43.13); Nuvion® (visilizumab); Cantuzumab mertansine (huC242-DMl); NeoRecormon® (Epoetin beta); Neumega® (Oprelvekin); Neulasta® (Pegylated filgastrim, pegylated G-CSF, pegylated hu-Met-G-CSF); Neupogen® (Filgrastim); Orthoclone OKT3® (Muromonab-CD3), Procrit® (Epoetin alfa); Remicade® (Infliximab), Reopro® (Abciximab), Actemra® (anti-IL6 Receptor Ab), Avastin® (Bevacizumab), HuMax-CD4 (zanolimumab), Rituxan® (Rituximab); Tarceva® (Erlotinib); Roferon-A®-(Interferon alfa-2a); Simulect® (Basiliximab); StelaraTM (Ustekinumab); Prexige® (lumiracoxib); Synagis® (Palivizumab); 146B7-CHO (anti-IL15 antibody, see U.S.P.N. 7.153,507), Tysabri® (Natalizumab); Valortim® (MDX-1303, anti-B. anthracis Protective Antigen Ab); ABthraxTM; Vectibix® (Panitumumab); Xolair® (Omalizumab), ETI211 (anti-MRSA Ab), IL-I Trap (the Fc portion of human IgGl and the extracellular domains of both IL-I receptor components (the Type I receptor and receptor accessory protein)), VEGF Trap (Ig domains of VEGFRl fused to IgGl Fc), Zenapax® (Daclizumab); Zenapax® (Daclizumab), Zevalin® (Ibritumomab tiuxetan), Zetia (ezetimibe), Atacicept (TACI-Ig), anti-α4β7 Ab (vedolizumab); galiximab (anti-CD80 monoclonal antibody), anti-CD23 Ab (lumiliximab); BR2-Fc (huBR3 / huFc fusion protein, soluble BAFF antagonist); SimponiTM (Golimumab); Mapatumumab (human anti-TRAIL Receptor-1 Ab); Ocrelizumab (anti-CD20 human Ab); HuMax-EGFR (zalutumumab); M200 (Volociximab, anti-α5β1 integrin Ab); MDX-

010 (Ipilimumab, anti-CTLA-4 Ab and VEGFR-I (IMC-18F1); anti-BR3 Ab; anti-C. difficile Toxin A and Toxin B C Abs MDX-066 (CDA-I) and MDX-1388); anti-CD22 dsFv-PE38 conjugates (CAT-3888 and CAT-8015); anti-CD25 Ab (HuMax-TAC); anti-TSLP antibodies; anti-TSLP receptor antibody (see U.S.P.N. 8,101,182); anti-TSLP antibody designated as A5 (see U.S.P.N. 7,982,016); (see anti-CD3 Ab (NI-0401); Adecatumumab (MT201, anti-EpCAM-CD326 Ab); MDX-060, SGN-30, SGN-35 (anti-CD30 Abs); MDX-1333 (anti- IFNAR); HuMax CD38 (anti-CD38 Ab); anti-CD40L Ab; anti-Cripto Ab; anti-CTGF Idiopathic Pulmonary Fibrosis Phase I Fibrogen (FG-3019); anti-CTLA4 Ab; anti-eotaxinl Ab (CAT-213); anti-FGF8 Ab; anti-ganglioside GD2 Ab; anti-sclerostin antibodies (see, U.S.P.N. 8,715,663 or U.S.P.N.7,592,429) anti-sclerostin antibody designated as Ab-5 (see U.S.P.N. 8,715,663 or U.S.P.N. 7,592,429); anti-ganglioside GM2 Ab; anti-GDF-8 human Ab (MYO-029); anti-GM-CSF Receptor Ab (CAM-3001); anti-HepC Ab (HuMax HepC); MEDI-545, MDX-1103 (anti-IFNα Ab); anti-IGFIR Ab; anti-IGF-IR Ab (HuMax-Inflam); anti-IL12/IL23p40 Ab (Briakinumab); anti-IL-23p19 Ab (LY2525623); anti-IL13 Ab (CAT-354); anti-IL-17 Ab (AIN457); anti-IL2Ra Ab (HuMax-TAC); anti-IL5 Receptor Ab; anti-integrin receptors Ab (MDX-Ol8, CNTO 95); anti-IPIO Ulcerative Colitis Ab (MDX- 1100); anti-LLY antibody; BMS-66513; anti-Mannose Receptor/hCGβ Ab (MDX-1307); anti-mesothelin dsFv-PE38 conjugate (CAT-5001); anti-PDlAb (MDX-1 106 (ONO- 4538)); anti-PDGFRα antibody (IMC-3G3); anti-TGFβ Ab (GC-1008); anti-TRAIL Receptor-2 human Ab (HGS-ETR2); anti-TWEAK Ab; anti-VEGFR/Flt-1 Ab; anti- ZP3 Ab (HuMax-ZP3); NVS Antibody #1; NVS Antibody #2; and an amyloid-beta monoclonal antibody comprising sequences, SEQ ID NO:8 and SEQ ID NO:6 (see U.S.P.N. 7,906,625).

Examples of antibodies suitable for the methods and pharmaceutical formulations include the antibodies shown in Table 1. Other examples of suitable antibodies include infliximab, bevacizumab, ranibizumab, cetuximab, ranibizumab, palivizumab, abagovomab, abciximab, actoxumab, adalimumab, afelimomab, afutuzumab, alacizumab, alacizumab pegol, ald518, alemtuzumab, alirocumab, alemtuzumab, altumomab, amatuximab, anatumomab mafenatox, anrukinzumab, apolizumab, arcitumomab, aselizumab, altinumab, atlizumab, atorolimiumab, tocilizumab, bapineuzumab, basiliximab, bavituximab, bectumomab, belimumab, benralizumab, bertilimumab, besilesomab, bevacizumab, bezlotoxumab, biciromab, bivatuzumab, bivatuzumab mertansine, blinatumomab, blosozumab, brentuximab vedotin, briakinumab, brodalumab, canakinumab, cantuzumab mertansine, cantuzumab mertansine, caplacizumab, capromab pendetide, carlumab, catumaxomab, cc49, cedelizumab,

certolizumab pegol, cetuximab, citatuzumab bogatox, cixutumumab, clazakizumab, clenoliximab, clivatuzumab tetraxetan, conatumumab, crenezumab, cr6261, dacetuzumab, daclizumab, dalotuzumab, daratumumab, demcizumab, denosumab, detumomab, dorlimomab aritox, drozitumab, duligotumab, dupilumab, ecromeximab, eculizumab, edobacomab, edrecolomab, efalizumab, efungumab, elotuzumab, elsilimomab, enavatuzumab, enlimomab pegol, enokizumab, enokizumab, enoticumab, enoticumab, ensituximab, epitumomab cituxetan, epratuzumab, erlizumab, ertumaxomab, etaracizumab, etrolizumab, exbivirumab, exbivirumab, fanolesomab, faralimomab, farletuzumab, fasinumab, fbta05, felvizumab, fezakinumab, ficlatuzumab, figitumumab, flanvotumab, fontolizumab, foralumab, foravirumab, fresolimumab, fulranumab, futuximab, galiximab, ganitumab, gantenerumab, gavilimomab, gemtuzumab ozogamicin, gevokizumab, girentuximab, glembatumumab vedotin, golimumab, gomiliximab, gs6624, ibalizumab, ibritumomab tiuxetan, icrucumab, igovomab, imciromab, imgatuzumab, inclacumab, indatuximab ravtansine, infliximab, intetumumab, inolimomab, inotuzumab ozogamicin, ipilimumab, iratumumab, itolizumab, ixekizumab, keliximab, labetuzumab, lebrikizumab, lemalesomab, lerdelimumab, lexatumumab, libivirumab, ligelizumab, lintuzumab, lirilumab, lorvotuzumab mertansine, lucatumumab, lumiliximab, mapatumumab, maslimomab, mavrilimumab, matuzumab, mepolizumab, metelimumab, milatuzumab, minretumomab, mitumomab, mogamulizumab, morolimumab, motavizumab, moxetumomab pasudotox, muromonab-cd3, nacolomab tafenatox, namilumab, naptumomab estafenatox, narnatumab, natalizumab, nebacumab, necitumumab, nerelimomab, nesvacumab, nimotuzumab, nivolumab, nofetumomab merpentan, ocaratuzumab, ocrelizumab, odulimomab, ofatumumab, olaratumab, olokizumab, omalizumab, onartuzumab, oportuzumab monatox, oregovomab, orticumab, otelixizumab, oxelumab, ozanezumab, ozoralizumab, pagibaximab, palivizumab, panitumumab, panobacumab, parsatuzumab, pascolizumab, pateclizumab, patritumab, pemtumomab, perakizumab, pertuzumab, pexelizumab, pidilizumab, pintumomab, placulumab, ponezumab, priliximab, pritumumab, PRO 140, quilizumab, racotumomab, radretumab, rafivirumab, ramucirumab, ranibizumab, raxibacumab, regavirumab, reslizumab, rilotumumab, rituximab, robatumumab, roledumab, romosozumab, rontalizumab, rovelizumab, ruplizumab, samalizumab, sarilumab, satumomab pendetide,

secukinumab, sevirumab, sibrotuzumab, sifalimumab, siltuximab, simtuzumab, siplizumab, sirukumab, solanezumab, solitomab, sonepcizumab, sontuzumab, stamulumab, sulesomab, suvizumab, tabalumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tanezumab, taplitumomab paptox, tefibazumab, telimomab aritox, tenatumomab, tefibazumab, telimomab aritox, tenatumomab, teneliximab, teplizumab, teprotumumab, TGN1412, tremelimumab, ticilimumab, tildrakizumab, tigatuzumab, TNX-650, tocilizumab, toralizumab, tositumomab, tralokinumab, trastuzumab, TRBS07, tregalizumab, tremelimumab, tucotuzumab celmoleukin, tuvirumab, ublituximab, urelumab, urtoxazumab, ustekinumab, vapaliximab, vatelizumab, vedolizumab, veltuzumab, vepalimomab, vesencumab, visilizumab, volociximab, vorsetuzumab mafodotin, votumumab, zalutumumab, zanolimumab, zatuximab, ziralimumab and zolimomab aritox.

Most preferred antibodies for use in the disclosed formulations and methods are adalimumab, bevacizumab, blinatumomab, cetuximab, conatumumab, denosumab, eculizumab, erenumab, evolocumab, infliximab, natalizumab, panitumumab, rilotumumab, rituximab, romosozumab, and trastuzumab, and antibodies selected from Table 1.

Table 1

Examples of therapeutic antibodies

Target (informal name)	**Conc. (mg/ml)**	**Viscosity (cP)**	**HC Type (including allotypes)**	**LC Type**	**pI**	**LC SEQ ID NO**	**HC SEQ ID NO**
anti-amyloid	142.2	5.0	IgG1 (f) (R;EM)	Kappa	9.0	1	2
GMCSF (247)	139.7	5.6	IgG2	Kappa	8.7	3	4
CGRPR	136.6	6.3	IgG2	Lambda	8.6	5	6
RANKL	152.7	6.6	IgG2	Kappa	8.6	7	8
Sclerostin (27H6)	145.0	6.7	IgG2	Kappa	6.6	9	10
IL-1R1	153.9	6.7	IgG2	Kappa	7.4	11	12

Target (informal name)	Conc. (mg/ml)	Viscosity (cP)	HC Type (including allotypes)	LC Type	pI	LC SEQ ID NO	HC SEQ ID NO
Myostatin	141.0	6.8	IgG1 (z) (K;EM)	Kappa	8.7	13	14
B7RP1	137.5	7.7	IgG2	Kappa	7.7	15	16
Amyloid	140.6	8.2	IgG1 (za) (K;DL)	Kappa	8.7	17	18
GMCSF (3.112)	156.0	8.2	IgG2	Kappa	8.8	19	20
CGRP (32H7)	159.5	8.3	IgG2	Kappa	8.7	21	22
CGRP (3B6.2)	161.1	8.4	IgG2	Lambda	8.6	23	24
PCSK9 (8A3.1)	150.0	9.1	IgG2	Kappa	6.7	25	26
PCSK9 (492)	150.0	9.2	IgG2	Kappa	6.9	27	28
CGRP	155.2	9.6	IgG2	Lambda	8.8	29	30
Hepcidin	147.1	9.9	IgG2	Lambda	7.3	31	32
TNFR p55)	157.0	10.0	IgG2	Kappa	8.2	33	34
OX40L	144.5	10.0	IgG2	Kappa	8.7	35	36
HGF	155.8	10.6	IgG2	Kappa	8.1	37	38
GMCSF	162.5	11.0	IgG2	Kappa	8.1	39	40
Glucagon R	146.0	12.1	IgG2	Kappa	8.4	41	42
GMCSF (4.381)	144.5	12.1	IgG2	Kappa	8.4	43	44
Sclerostin (13F3)	155.0	12.1	IgG2	Kappa	7.8	45	46
CD-22	143.7	12.2	IgG1 (f) (R;EM)	Kappa	8.8	47	48
INFgR	154.2	12.2	IgG1 (za) (K;DL)	Kappa	8.8	49	50
Ang2	151.5	12.4	IgG2	Kappa	7.4	51	52
TRAILR2	158.3	12.5	IgG1 (f) (R;EM)	Kappa	8.7	53	54
EGFR	141.7	14.0	IgG2	Kappa	6.8	55	56
IL-4R	145.8	15.2	IgG2	Kappa	8.6	57	58
IL-15	149.0	16.3	IgG1 (f) (R;EM)	Kappa	8.8	59	60

Target (informal name)	Conc. (mg/ml)	Viscosity (cP)	HC Type (including allotypes)	LC Type	pI	LC SEQ ID NO	HC SEQ ID NO
IGF1R	159.2	17.3	IgG1 (za) (K;DL)	Kappa	8.6	61	62
IL-17R	150.9	19.1	IgG2	Kappa	8.6	63	64
Dkk1 (6.37.5)	159.4	19.6	IgG2	Kappa	8.2	65	66
Sclerostin	134.8	20.9	IgG2	Kappa	7.4	67	68
TSLP	134.2	21.4	IgG2	Lambda	7.2	69	70
Dkk1 (11H10)	145.3	22.5	IgG2	Kappa	8.2	71	72
PCSK9	145.2	22.8	IgG2	Lambda	8.1	73	74
GIPR (2G10.006)	150.0	23.0	IgG1 (z) (K;EM)	Kappa	8.1	75	76
Activin	133.9	29.4	IgG2	Lambda	7.0	77	78
Sclerostin (2B8)	150.0	30.0	IgG2	Lambda	6.7	79	80
Sclerostin	141.4	30.4	IgG2	Kappa	6.8	81	82
c-fms	146.9	32.1	IgG2	Kappa	6.6	83	84
α4β7	154.9	32.7	IgG2	Kappa	6.5	85	86

* An exemplary concentration suitable for patient administration; ^HC – antibody heavy chain; LC – antibody light chain.

Exemplary polypeptide concentrations in the formulation may range from about 70 mg/ml to about 300 mg/ml (or more), about 120 mg/ml to about 270 mg/ml, from about 140 mg/ml to about 255 mg/ml, from about 140 mg/ml to about 240 mg/ml, or from about 140 mg/ml to about 220 mg/ml, or alternatively from about 190 mg/ml to about 210 mg/ml, such as 210 mg/ml. The concentration of protein will depend upon the end use of the pharmaceutical formulation and can be easily determined by a person of skill in the art. Particularly contemplated concentrations of protein are at least about 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295 and 300 mg/ml and including all values in between.

Pharmaceutical formulation components

Acceptable formulation components preferably are nontoxic to patients at the dosages and concentrations used. Pharmaceutical formulations can comprise agents for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition.

In general, excipients can be classified on the basis of the mechanisms by which they stabilize proteins against various chemical and physical stresses. Some excipients alleviate the effects of a specific stress or regulate a particular susceptibility of a specific polypeptide. Other excipients more generally affect the physical and covalent stabilities of proteins.

Common excipients of liquid and lyophilized protein formulations are shown in Table 2 (see also (Kamerzell, Esfandiary, Joshi, Middaugh, & Volkin, 2011)).

Table 2

Examples of excipient components for polypeptides formulations

Component	**Function**	**Examples**
Buffers	Maintaining solution pH Mediating buffer-ion specific interactions with polypeptides	Citrate Succinate Acetate glutamate Aspartate histidine Phosphate Tris Glycine
Sugars and carbohydrates	Stabilizing polypeptides Tonicifying agents Acting as carriers for inhaled drugs (*e.g.*, lactose)	Sucrose Trehalose Sorbitol Mannitol Glucose

Component	Function	Examples
	Providing dextrose solutions during IV administration	Lactose Cyclodextrin derivatives
Stabilizers and bulking agents	Enhancing product elegance and preventing blowout Providing structural strength to a lyo cake	Mannitol Glycine
Osmolytes	Stabilizing against environmental stress (temperature, dehydration)	Sucrose Trehalose Sorbitol Glycine proline glutamate Glycerol Urea
Amino acids	Mediating specific interactions with polypeptides Providing antioxidant activity (*e.g.*, His, Met) Buffering, tonicifying	histidine arginine Glycine proline lysine Methionine Aa mixtures (*e.g.*, Glu/Arg)
Polypeptides and polymers	Acting as competitive inhibitors of polypeptide adsorption Providing bulking agents for lyophilization Acting as drug delivery vehicles	HSA PVA PVP PLGA PEG Gelatin Dextran Hydroxyethyl starch HEC CMC

Component	Function	Examples
Anti-oxidants	Preventing oxidative polypeptides damage	Reducing agents
	Metal ion binders (if a metal is included as a co-factor or is required for protease activity)	Oxygen scavengers
		Free radical scavengers
		Chelating agents (*e.g.*, EDTA, EGTA, DTPA)
	Free radical scavengers	Ethanol
Metal ions	Polypeptides co-factors	Magnesium
	Coordination complexes (suspensions)	Zinc
Specific ligands	Stabilizers of native conformation against stress-induced unfolding	Metals
		Ligands
	Providing conformation flexibility	Amino acids
		Polyanions
Surfactants	Acting as competitive inhibitors of polypeptides adsorption	Polysorbate 20
		Polysorbate 80
	Acting as competitive inhibitor of polypeptides surface denaturation	Poloxamer 188
		Anionic surfactants (*e.g.*, sulfonates and sulfosuccinates)
	Providing liposomes as drug delivery vehicles	Cationic surfactants
	Inhibiting aggregation during lyophilization	Zwitterionic surfactants
	Acting as reducer of reconstitution times of lyophilized products	
Salts	Tonicifying agents	NaCl
	Stabilizing or destabilizing agents for polypeptidess, especially anions	KCl
		$NaSO_4$
Preservatives	Protecting against microbial growth	Benzyl alcohol
		M-cresol
		Phenol

Other excipients are known in the art (*e.g.*, see (Powell, Nguyen, & Baloian, 1998)).

Those skilled in the art can determine what amount or range of excipient can be included in any particular formulation to achieve a biopharmaceutical formulation that promotes retention in stability of the biopharmaceutical. For example, the amount and type of a salt to be included in a biopharmaceutical formulation can be selected based on to the desired osmolality (*i.e.*, isotonic, hypotonic or hypertonic) of the final solution as well as the amounts and osmolality of other components to be included in the formulation.

Buffers

Solution pH affects the chemical integrity of a polypeptide's amino acid residues (*e.g.*, Asn deamidation and Met oxidation) and maintenance of its higher order structure. Buffering agents are used to control solution pH and optimize protein stability. Maximal stability of a polypeptide drug is often within a narrow pH range. Several approaches (*e.g.*, accelerated stability studies and calorimetric screening studies) are useful for this purpose. Once a formulation is finalized, the drug product must be manufactured and maintained within a predefined specification throughout its shelf-life. Hence, buffering agents are almost always used to control pH in the formulation.

Organic acids, phosphates and Tris can be used as buffers in polypeptide formulations (see Table 3). The buffer capacity of the buffering species is maximal at a pH equal to the pKa and decreases as pH increases or decreases away from this value. Ninety percent of the buffering capacity exists within one pH unit of its pKa. Buffer capacity also increases proportionally with increasing buffer concentration.

Table 3

Commonly used buffering agents and their pKa values

Buffer	**pK_a**	**Example drug product**
Acetate	4.8	Neupogen®, Neulasta®
Succinate	pK_{a1} = 4.8, pK_{a2} = 5.5	Actimmune®
Citrate	pK_{a1} = 3.1, pK_{a2} = 4.8, pK_{a3} = 6.4	Humira®
histidine	6.0	Xolair®

Buffer	pK_a	Example drug product
(imidazole)		
phosphate	pK_{a1} = 2.15, pK_{a2} = 7.2, pK_{a3} = 12.3	Enbrel® (liquid formulation)
Tris	8.1	Leukine

In addition to the foregoing, some therapeutic polypeptides can be "self-buffering" at a pharmaceutically sufficient concentration. Formulations of such polypeptides can often dispense with a conventional buffer.

A pH buffering compound can be present in any amount suitable to maintain the pH of the formulation at a predetermined level. When the pH buffering agent is an amino acid, for example, the concentration of the amino acid is often between 0.1 mM and 1000 mM (1 M). The pH buffering agent can be at least 0.1, 0.5, 0.7, 0.8 0.9, 1.0, 1.2, 1.5, 1.7, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 500, 700, or 900 mM. In some cases, the concentration of the pH buffering agent is between 1, 1.2, 1.5, 1.7, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50, 60, 70, 80, or 90 mM and 100 mM. In other instances, the concentration of the pH buffering agent is between 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, or 40 mM and 50 mM. For example, the pH buffering agent is 10 mM. In some case, the buffer is 10 mM phosphate. In other examples, the buffer is 10 mM acetate.

Sugars and carbohydrates

Sugars are frequently used to stabilize polypeptides in both liquid and lyophilized formulations. Disaccharides, such as sucrose and trehalose, are thought to stabilize proteins by preferential hydration at high concentrations in the liquid state and by specific interactions with polypeptides and formation of viscous glassy matrices in the solid state. Sugar molecules can increase the viscosity of monoclonal antibody solutions, presumably due to a preferential hydration mechanism. Sugar alcohols, such as sorbitol, can stabilize polypeptides in solution and in the lyophilized state. Mannitol is often used as a bulking agent in lyophilized formulations. Lactose can be used as a carrier molecule for inhaled formulations of

polypeptides. Cyclodextrin derivatives can stabilize proteins in liquid formulations of antibodies, vaccine antigens, and such smaller proteins as growth factors, interleukin-2 and insulin.

Stabilizers and bulking agents

Bulking agents are typically used in lyophilized formulations to enhance product elegance and to prevent blowout. Conditions in the formulation are generally designed so that the bulking agent crystallizes out of the frozen amorphous phase (either during freezing or annealing above the glass transition temperature of maximally freeze-concentrated solutes (Tg')) giving the cake structure and bulk. Mannitol and glycine are examples of commonly used bulking agents.

Stabilizers include compounds that can serve as cryoprotectants, lyoprotectants, and glass-forming agents. Cryoprotectants act to stabilize polypeptides during freezing or in the frozen state at low temperatures. Lyoprotectants stabilize polypeptides in the freeze-dried solid dosage form by preserving the native-like conformational properties of the protein during dehydration stages of freeze-drying. Glassy state properties have been classified as "strong" or "fragile" depending on their relaxation properties as a function of temperature. It is important that cryoprotectants, lyoprotectants, and glass-forming agents remain in the same phase with the polypeptide in order to impart stability. Sugars, polymers, and polyols fall into this category and can sometimes serve all three roles of cryoprotectants, lyoprotectans, and glass-forming agents.

Polyols encompass a class of excipients that includes sugars, (*e.g.* mannitol, sucrose, sorbitol), and other polyhydric alcohols (*e.g.*, glycerol and propylene glycol). The polymer polyethylene glycol (PEG) is included in this category. Polyols are commonly used as stabilizing excipients and/or isotonicity agents in both liquid and lyophilized parenteral polypeptide formulations. With respect to the Hofmeister series, the polyols are kosmotropic and are preferentially excluded from the polypeptide surface. Polyols can protect polypeptides from both physical and chemical degradation. Preferentially excluded co-solvents increase the effective surface tension of solvent at the polypeptide interface whereby the most energetically favorable polypeptide conformations are those with the smallest surface areas.

Mannitol is often used as a bulking agent in lyophilized formulations because it crystallizes out of the amorphous protein phase during freeze-drying lending structural stability to the cake (*e.g.*, Leukine ®, Enbrel ® – Lyo, Betaseron®). It is generally used in combination with a cryo and/or lyoprotectant, like sucrose. Because of the propensity of mannitol to crystallize

under frozen conditions, sorbitol and sucrose are preferred tonicity agents/stabilizers in liquid formulations to protect the product against freeze-thaw stresses encountered during transport or when freezing bulk prior to manufacturing. Sorbitol and sucrose are far more resistant to crystallization and therefore less likely to phase separate from the polypeptide. The use of reducing sugars containing free aldehyde or ketone groups, such as glucose and lactose, is preferably avoided because they can react and glycate surface lysine and arginine residues of polypeptides via the Maillard reaction of aldehydes and primary amines. Sucrose can hydrolyze to fructose and glucose under acidic conditions, and consequently may cause glycation.

A stabilizer (or a combination of stabilizers) can be added to a lyophilization formulation to prevent or reduce lyophilization-induced or storage-induced aggregation and chemical degradation. A hazy or turbid solution upon reconstitution indicates that the polypeptide has precipitated. "Stabilizer" means an excipient capable of preventing aggregation or other physical degradation, as well as chemical degradation (for example, autolysis, deamidation, oxidation, *etc.*) in an aqueous and solid state. Stabilizers that are conventionally used in pharmaceutical compositions include sucrose, trehalose, mannose, maltose, lactose, glucose, raffinose, cellobiose, gentiobiose, isomaltose, arabinose, glucosamine, fructose, mannitol, sorbitol, glycine, arginine HCl, poly-hydroxy compounds, including polysaccharides such as dextran; starch, hydroxyethyl starch, cyclodextrins, N-methyl pyrollidene, cellulose and hyaluronic acid, sodium chloride.

Osmolytes

Examples of osmolytes are presented in Table A. Other osmolytes that can be useful as excipients include taurine, betaine, trimethylamine N-oxide (TMAO), choline-O-sulfate, and sarcosine.

Pharmaceutical formulation are preferably isotonic, with an osmolality ranging from between about 250 to about 400 mOsm/kg, *e.g.*, about 250 mOsm/kg, about 260 mOsm/kg, about 270 mOsm/kg, about 280 mOsm/kg, about 290 mOsm/kg, about 300 mOsm/kg, about 310 mOsm/kg, about 320 mOsm/kg, about 330 mOsm/kg, about 340 mOsm/kg, about 350 mOsm/kg, about 360 mOsm/kg, about 370 mOsm/kg, about 380 mOsm/kg, about 390

mOsm/kg, or about 400 mOsm/kg. Osmolality is the measure of the ratio of solutes to volume fluid. In other words, it is the number of molecules and ions (or molecules) per kilogram of a solution. In certain embodiments, the osmolality is 300 mOsm/kg. Osmolality can be measured by an osmometer, such as Advanced Instruments 2020 Multi-sample Osmometer, Norwood, MA. The Advanced Instruments 2020 Multi-sample Osmometer measures osmolality by using the Freezing Point Depression method. The higher the osmolytes in a solution, the temperature in which it will freeze drops. Osmolality can also be measured using any other methods and in any other units known in the art such as linear extrapolation. In other embodiments, the pharmaceutical formulation is isotonic to a human blood cell, such as a red blood cell.

Polypeptides and polymers

Polypeptide-based excipients add complexity to the formulation, especially in developing analytical methods to monitor the stability of the polypeptide-based drug or vaccine in the presence of a polypeptide-based excipient. Polymers have been evaluated as excipients (*e.g.*, as bulking agents) in lyophilized polypeptide formulations. Controlled release formulations of polypeptide drugs and vaccines in which polypeptides are formulated with polymers, such as PLGA (poly(lactic-co-glycolic acid) and PEG (polyethylene glycol), can also be made. Many additional water-soluble polymers (*e.g.*, HEC (hydroxyethylcellulose), CMC (carboxymethyl cellulose) can be used to formulate polypeptide drugs for topical application.

Anti-oxidants

Reducing agents, oxygen/free-radical scavengers, and chelating agents and be used as antioxidants in pharmaceutical formulations. Antioxidants in therapeutic polypeptide formulations must be water-soluble and remain active throughout the product shelf-life. Reducing agents and oxygen/free-radical scavengers work by ablating active oxygen species in solution. Chelating agents (*e.g.*, EDTA (ethylenediamine tetra-acetic acid)) can be effective by binding trace metal contaminants that promote free-radical formation. In the liquid formulation of acidic fibroblast growth factor, for example, EDTA inhibits metal ion-catalyzed oxidation of cysteine residues.

Metal ions

In general, transition metal ions are undesired in polypeptide formulations because they can catalyze physical and chemical degradation reactions in polypeptide drug products. Specific metal ions are included in formulations, however, when they act as co-factors to polypeptides. Metal ions can also be used in suspension formulations of polypeptides where they form coordination complexes (*e.g.*, zinc suspensions of insulin). Magnesium ions (10 –120 mM) can be usedto inhibit the isomerization of aspartic acid to isoaspartic acid.

Specific ligands

One approach to improve the conformational stability of polypeptide therapeutic drugs is to take advantage of the polypeptide's inherent ligand binding sites. For example, Pulmozyme® not only requires bivalent metal ions for its enzymatic activity, but it has improved conformational stability in the presence of calcium ions. Both acidic and basic fibroblast growth factors (aFGF and bFGF) naturally bind to the highly negatively charged proteoglycans on cell surfaces. A variety of other highly negatively charged compounds also bind and dramatically stabilize aFGF by interaction with the protein's polyanion binding site.

Surfactants

Polypeptide molecules have a high propensity to interact with surfaces, making them susceptible to adsorption and denaturation at air-liquid, vial-liquid, and liquid-liquid (silicone oil) interfaces. This phenomenon is inversely dependent on polypeptide concentration and results in soluble or insoluble polypeptide aggregates or the loss of polypeptide from solution through surface adsorption. In addition to container surface adsorption, surface-induced degradation is exacerbated with physical agitation, as can be experienced during shipping and handling.

Surfactants are commonly used in polypeptide formulations to prevent surface-induced degradation. Surfactants are amphipathic molecules with the capability of out-competing polypeptides for interfacial positions. Hydrophobic portions of surfactant molecules occupy interfacial positions (*e.g.*, air/liquid), while hydrophilic portions of surfactant molecules remain oriented towards the bulk solvent. At sufficient concentrations (typically around the detergent's

critical micellar concentration), a surface layer of surfactant molecules serve to prevent protein molecules from adsorbing at the interface, minimizing surface-induced degradation.

The most commonly used surfactants are the non-ionic fatty acid esters of sorbitan polyethoxylates--*i.e.*, polysorbate 20 and polysorbate 80 (*e.g.*, found in Avonex®, Neupogen®, Neulasta®). The two differ only in the length of the aliphatic chain that imparts hydrophobic character to the molecules, C-12 and C-18, respectively. Polysorbate 80 is more surface-active and has a lower critical micellar concentration than polysorbate 20. Both polysorbate 20 and polysorbate 80 have been shown to protect against agitation-induced aggregation. Polysorbate 20 and 80 also protect against stress induced by freezing, lyophilization and reconstitution. The surfactant poloxamer 188 has also been used in several marketed liquid products, such Gonal-F®, Norditropin®, and Ovidrel®. Non-ionic surfactants stabilize polypeptides primarily by outcompeting polypeptide molecules for hydrophobic surfaces (*e.g.*, air–water interfaces), thereby preventing polypeptides from unfolding at these hydrophobic interfaces. Non-ionic surfactants can also block polypeptide molecules from adsorbing to other hydrophobic surfaces present during processing. In addition, non-ionic surfactants can directly interact with hydrophobic regions in polypeptide molecules.

Other examples of surfactants include polyoxyethylene-polyoxypropylene block copolymer (Poloxamers such as Pluronic® F-68 and other Pluronics®), other sorbitan alkyl esters (Spans®), Polyethylene glycol alkyl ethers (Brij), Polypropylene glycol alkyl ethers, Glucoside alkyl ethers, and D-α-tocopherol polyethylene glycol succinate (vitamin E TPGS).

Surfactants can also affect the thermodynamic conformational stability of polypeptides. The effects of a given excipient are polypeptide-specific. For example, polysorbates can reduce the stability of some polypeptides and increase the stability of others. Surfactant destabilization of polypeptides can be rationalized in terms of the hydrophobic tails of the detergent molecules that can engage in specific binding with partially or wholly unfolded polypeptide states. These types of interactions can cause a shift in the conformational equilibrium towards the more expanded polypeptide states (*i.e.*, increasing the exposure of hydrophobic portions of the polypeptide molecule in complement to binding polysorbate). Alternatively, if the polypeptide

native state exhibits some hydrophobic surfaces, detergent binding to the native state can stabilize that conformation.

For surfactants, the effective concentration for a given polypeptide depends on the mechanism of stabilization.

Surfactants can also be added in appropriate amounts to prevent surface-related aggregation during freezing and drying. Exemplary surfactants include anionic, cationic, nonionic, zwitterionic, and amphoteric surfactants, including surfactants derived from naturally occurring amino acids. Anionic surfactants include sodium lauryl sulfate (SDS), dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate, chenodeoxycholic acid, N-lauroylsarcosine sodium salt, lithium dodecyl sulfate, 1-octanesulfonic acid sodium salt, sodium cholate hydrate, sodium deoxycholate, and glycodeoxycholic acid sodium salt. Cationic surfactants include benzalkonium chloride or benzethonium chloride, cetylpyridinium chloride monohydrate, and hexadecyltrimethylammonium bromide. Zwitterionic surfactants include CHAPS, CHAPSO, SB3-10, and SB3-12. Non-ionic surfactants include digitonin, TRITON™ X-100, TRITON™ X-114, TWEEN®-20, and TWEEN®-80. Surfactants also include lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 40, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, soy lecithin and other phospholipids, such as 1,2-Dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-Dimyristoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt (DMPG), 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), and 1,2-Dioleoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt (DOPG); sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. The surfactant can be in a concentration of about 0% to about 5% w/v, such as in a concentration of at least about 0.001, 0.002, 0.004, 0.005, 0.007, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, or 4.5% w/v. In another example, the surfactant is incorporated in a concentration of about 0.001% to about 0.5% w/v. In still another example, the surfactant is incorporated in a concentration of about 0.004, 0.005, 0.007, 0.01, 0.05, or 0.1% w/v to about 0.2% w/v. In yet another example, the surfactant is incorporated in a concentration of about 0.01% to about 0.1% w/v.

Salts

Salts are often added to increase the ionic strength of the formulation, which can be important for polypeptide solubility, physical stability, and isotonicity. Salts can affect the physical stability of polypeptides in a variety of ways. Ions can stabilize the native state of polypeptides by binding to charged residues on the polypeptide's surface. Alternatively, they can stabilize the denatured state by binding to the peptide groups along the polypeptide backbone. Salts can also stabilize the polypeptide native conformation by shielding repulsive electrostatic interactions between residues within a polypeptide. Electrolytes in polypeptide formulations can also shield attractive electrostatic interactions between polypeptide molecules that can lead to protein aggregation and insolubility.

The effect of salt on the stability and solubility of polypeptides varies significantly with the characteristics of the ionic species. The Hofmeister series originated in the 1880's as a way to rank order electrolytes based on their ability to precipitate polypeptides. The Hofmeister series can used to illustrate polypeptide stabilization effects by ionic and non-ionic co-solutes, as shown in Table 4 (Cacace, Landau, & Ramsden, 1997). In general, the differences in effects across the anions are far greater than that observed for the cations, and, for both types, the effects are most apparent at higher concentrations than are acceptable in parenteral formulations. High concentrations of kosmotropes (*e.g.*, >1 molar ammonium sulfate) are commonly used to precipitate polypeptides from solution (salting-out) where the kosmotrope is preferentially excluded from the polypeptide surface reducing the solubility of the polypeptide in its native conformation. Removal or dilution of the salt returns the polypeptide to solution. Salting in occurs when destabilizing ions are used to increase the solubility of polypeptides by solvating the peptide bonds of the polypeptide backbone. Increasing concentrations of the chaotrope favor the denatured state of the polypeptide as the solubility of the peptide chain increases. The relative effectiveness of ions to salt-in and salt-out defines their position in the Hofmeister series.

Table 4

The Hofmeister series of salts

Cosolute			Stabilization	
Anion	**Cation**	**Other**		
F^-	$(CH_3)_4N^+$	glycerol/sorbitol	Stabilizing (salting-out)	Kosmotropic
PO_4^{3-}	$(CH_3)_2NH_2^+$	sucrose/trehalose		
SO_4^{2-}	NH_4^+	trimethylamine N-oxide (TMAO)		
$CHCOO^-$	K^+			
Cl^-	Na^+			
Br^-	Cs^+			
I^-	Li^+			
	Mg^{2+}	guanidine		
	Ca^{2+}	arginine	Destabilizing (salting-in)	Chaotropic
	Ba^{2+}	urea		

In order to maintain isotonicity in a parenteral formulation, salt concentrations are generally limited to less than 150 mM for monovalent ion combinations. In this concentration range, the mechanism of salt stabilization is probably due to screening of electrostatic repulsive intramolecular forces or attractive intermolecular forces (Debye-Huckel screening). Interestingly, chaotropic salts can be more effective at stabilizing polypeptide structure than similar concentrations of kosmotropes by this mechanism. The chaotropic anions bind more strongly than the kosmotropic ions. With respect to covalent polypeptide degradation, differential effects of ionic strength on this mechanism are expected through Debye-Huckel

theory. The mechanisms by which salts affect polypeptide stability are polypeptide-specific and can vary significantly as a function of solution pH.

Preservatives

Preservatives can be necessary when developing multi-use parenteral formulations that involve more than one extraction from the same container. Their primary function is to inhibit microbial growth and ensure product sterility throughout the shelf-life or term of use of the drug product. Commonly used preservatives include benzyl alcohol, phenol and m-cresol. Development of polypeptide formulations that include preservatives can be challenging. Preservatives almost always have a destabilizing effect (aggregation) on polypeptides. Benzyl alcohol has also been shown to affect polypeptide structure and stability in a concentration-, temperature- and time-dependent manner. Due to these destabilizing effects, many lyophilized polypeptide formulations are reconstituted with diluent containing benzyl alcohol to minimize the contact time with the polypeptide prior to administration.

Several aspects need to be considered during the formulation development of preserved dosage forms. The effective preservative concentration in the drug product must be optimized. This requires testing a given preservative in the dosage form with concentration ranges that confer anti-microbial effectiveness without compromising polypeptide stability.

Development of liquid formulations containing preservatives are often more challenging than lyophilized formulations. Freeze-dried products can be lyophilized without a preservative and reconstituted with a preservative containing diluent at the time of use. With liquid formulations, preservative effectiveness and stability have to be maintained over the entire product shelf-life (usually about 18 –24 months). Preservative effectiveness often needs to be demonstrated in the final formulation containing the active drug and all excipient components.

Some preservatives can cause injection site reactions. For example, patient pain perception can be lower in formulations containing phenol and benzyl alcohol as compared to formulations containing m-cresol. Benzyl alcohol appears to possess anesthetic properties.

N-acetyl-serine-arginine, N-acetyl-proline-arginine, and N-acetyl-proline-arginine-NH_2 dipeptides to reduce viscosity of therapeutic polypeptide formulations

Reducing the viscosity of therapeutic polypeptide formulations is of interest in the pharmaceutical arts. The dipeptide excipients N-acetyl-serine-arginine N-acetyl-proline-arginine, and N-acetyl-proline-arginine-NH_2 were discovered to reduce the viscosity of therapeutic antibody formulations. Provided herein are viscosity-reducing excipients at selected concentrations for use in reducing the viscosity of therapeutic polypeptide (such as therapeutic antibodies) formulations. Provided herein are therapeutic polypeptide and antibody formulations and methods for reducing the viscosity of therapeutic polypeptide and antibody formulations by combining the therapeutic polypeptide or antibody with a viscosity-reducing concentration of a N-acetyl-serine-arginine, N-acetyl-proline-arginine and/or N-acetyl-proline-NH_2-arginine dipeptides.

N-acetyl-serine-arginine, N-acetyl-proline-arginine, and N-acetyl-proline-arginine-NH_2 dipeptides can be synthesized by understood methods in the art, such as by solid-state peptide synthesis. It is advantageous however, to use trifluoroacetic acid (TFA)-free methods, such as those that use, for example, HCl. In such methods, it can be advantageous to facilitate purification of the synthesized N-acetyl-dipeptides by purifying the protected dipeptides before deprotection.

The concentration of N-acetyl-serine-arginine, N-acetyl-proline-arginine, and N-acetyl-proline-arginine-NH_2 can be experimentally determined by one of ordinary skill. In some examples, the N-acetyl-dipeptide can have a concentration from about 10 mM to about 500 mM, such as from about 100 mM to about 200 mM, 100 mM, 150 mM, and about 200 mM. For example, the N-acetyl-dipeptide can be present from about (in mM) 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 1115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, and 200.

Glutamate-arginine dipeptides to reduce viscosity of therapeutic polypeptide formulations

The dipeptide excipient glutamate-arginine was discovered to reduce the viscosity of therapeutic polypeptide formulations. Provided herein are viscosity-reducing glutamate-arginine excipients at selected concentrations for use in reducing the viscosity of therapeutic polypeptide (such as therapeutic antibodies) formulations. Provided herein are therapeutic

polypeptide and antibody formulations and methods for reducing the viscosity of therapeutic polypeptide and antibody formulations by combining the therapeutic polypeptide or antibody with a viscosity-reducing concentration of a glutamate-arginine dipeptide.

Glutamate-arginine dipeptide can be synthesized by understood methods in the art, such as solid-state peptide synthesis.

The concentration of glutamate-arginine dipeptide to reduce viscosity can be experimentally determined by one of ordinary skill. In some examples, the glutamate-arginine dipeptide can have a concentration from about 1 mM to about 25 mM, such as from about 1 mM to about 25 mM, 10 mM, 15 mM, 20 mM and about 25 mM. For example, the glutamate-arginine dipeptide can be present from about (in mM) 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25.

Viscosity and other characteristics of the N-acetyl-serine-arginine, N-acetyl-proline-arginine, N-acetyl-proline-arginine-NH2, and glutamate-arginine-containing formulations

In one aspect, the disclosed pharmaceutical formulations have a viscosity level of less than about 80 centipoise (cP) as measured at room temperature (*i.e.*, 25 °C). In certain embodiments, the pharmaceutical formulation has a viscosity level of less than about 70 cP, about 60 cP, about 50 cP, about 40 cP, about 30 cP, about 25 cP, about 20 cP, about 18 cP, about 15 cP, about 12 cP, about 10 cP; about 8 cP, about 6 cP, about 4 cP; about 2 cP; or about 1 cP.

In one aspect, the pharmaceutical formulation is stable as measured by at least one stability assay, such as an assay that examines the biophysical or biochemical characteristics of the antibody over time. Pharmaceutical formulation stability can be measured using SEC-HPLC. SEC-HPLC separates proteins based on differences in their hydrodynamic volumes. Molecules with larger hydrodynamic proteins volumes elute earlier than molecules with smaller volumes. In the case of SEC-HPLC, a stable pharmaceutical formulation exhibits no more than about a 5% increase in HMW species as compared to a control sample, such as, for example no more than about a 4%, no more than about a 3%, no more than about a 2%, no more than about a 1%, no more than about a 0.5% increase in HMW species as compared to a control sample.

Alternatively, or in addition, stability can be measured using cation-exchange HPLC (CEX-HPLC). CEX-HPLC separates proteins based on differences in their surface charge. At a set pH, charged isoforms

of an antibody are separated on a cation-exchange column and eluted using a salt gradient. The eluent is monitored by ultraviolet light (UV) absorbance. The charged isoform distribution is evaluated by determining the peak area of each isoform as a percent of the total peak area. In the case of CEX-HPLC, a stable pharmaceutical formulation exhibits no more than about a 5% decrease in the main isoform peak as compared to a control sample, such as, for example, no more than about a 3% to about a 5% decrease in the main isoform peak as compared to a control sample; no more than about a 4% decrease, no more than about a 3% decrease, no more than about a 2% decrease, no more than about a 1% decrease, no more than about a 0.5% decrease in the main isoform peak as compared to a control sample.

Also alternatively, or in addition, formulation stability can be measured using Subvisible Particle Detection by Light Obscuration (HIAC). An electronic, liquid-borne particle-counting system (HIAC/Royco 9703 (Hach Company; Loveland, CO) or equivalent) containing a light-obscuration sensor (HIAC/Royco HRLD-150 or equivalent) with a liquid sampler quantifies the number of particles and their size range in a given test sample. When particles in a liquid pass between the light source and the detector they diminish or "obscure" the beam of light that falls on the detector. When the concentration of particles lies within the normal range of the sensor, these particles are detected one-by-one. The passage of each particle through the detection zone reduces the incident light on the photo-detector and the voltage output of the photo-detector is momentarily reduced. The changes in the voltage register as electrical pulses that are converted by the instrument into the number of particles present. The method is non-specific and measures particles regardless of their origin. Particle sizes monitored are generally 10 µm, and 25 µm. In the case of HIAC, a stable pharmaceutical formulation exhibits no more than 6000 10 µm particles per container (or unit), as compared to a control sample, such as, for example no more than 5000, no more than 4000, no more than 3000, no more than 2000, no more than 1000, 10µm particles per container (or unit) as compared to a control sample. In other cases, a stable pharmaceutical formulation exhibits no more than 600 25 µm particles per container (or unit) as compared to a control sample, such as, for example, no more than 500, no more than 400, no more than 300, no more than 200, no more than 100, no more than 50 25 µm particles per container (or unit) as compared to a control sample.

Pharmaceutical formulation stability can also be assessed using visual assessment. Visual assessment is a qualitative method used to describe the visible physical characteristics of a sample. The sample is viewed against a black and/or white background of an inspection booth, depending on the

characteristic being evaluated (*e.g.*, color, clarity, presence of particles or foreign matter). Samples are also viewed against an opalescent reference standard and color reference standards. In the case of visual assessment, a stable pharmaceutical formulation exhibits no significant change in color, clarity, presence of particles or foreign matter as compared to a control sample.

Polypeptide formulation preparation

Pharmaceutical formulations disclosed herein can be prepared by either of two processes designated processes 1 and 2. Process 1 comprises:

a. dialyzing or concentrating a solution of a therapeutic protein, such as a monoclonal Ab;

b. dialyzing or concentrating a solution of selected excipients or providing a dry mixture of selected excipients;

c. adding the excipient solution or the dry excipient mixture into the protein solution at a selected pH to achieve a desired final excipient concentration, a desired final protein concentration, and a desired final pH.

d. UF/DF ultra-filtration diafiltration process exchanges the buffer and concentrates the protein simultaneously. This process could also be used to introduce the dipeptides into the protein.

Process 2 comprises:

a. dialyzing a solution of therapeutic protein, such as a monoclonal antibody;

b. dialyzing a solution of selected excipients or providing a dry mixture of selected excipients;

c. adding the excipient solution or dry excipient mixture into the dialyzed protein solution at a selected pH and a desired excipient concentration, and

d. concentrating the solution resulting from step c to a desired final protein concentration and desired final pH

In process 1, the pH of the concentrated protein to achieve the desired final pH can range from about 4 to about 8. In process 2, the pH of the concentrated protein solution to achieve the desired final pH can range from about 4 to about 8. Where a particular excipient is reported in a formulation by, for example, percent (%) w/v, those skilled in the art recognize that the equivalent molar concentration of that excipient is also contemplated.

Storage and kits

Once the pharmaceutical formulation has been formulated, it can be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or as a dehydrated or lyophilized powder. Such formulations can be stored either in a ready-to-use form or in a form (*e.g.*, lyophilized) that is reconstituted prior to administration. In some cases, the therapeutic polypeptide formulations can be stored in containers, such as suitable storage bags (*e.g.*, as manufactured by Sartorius (Gottingen, DE)) or in polycarbonate carboys. Once the pharmaceutical formulation has been formulated, it can also be stored in pre-filled syringes (PFS; such as 2.25 ml PFS's) as a solution or suspension in a ready-to-use form, as well as in glass vials (such as 5 cc glass vials).

In certain embodiments, kits are provided for producing a single-dose administration unit. In certain embodiments, the kit can contain both a first container having a dried protein and a second container having an aqueous formulation. In certain embodiments, kits containing single and multi-chambered pre-filled syringes (*e.g.*, liquid syringes and lyosyringes) are included.

The following Examples section is given solely by way of example and are not set forth to limit the disclosure or claims in any way.

EXAMPLES

Example 1 – Materials and methods

N-acetyl-arginine and N-acetyl-arginine-NH_2 were purchased from BACHEM (Torrance, CA). arginine HCl was purchased from SAFC Ajinomoto (Sigma-Aldrich, St. Louis, MO; Itasca, IL). N-acetyl-proline-arginine dipeptide, N-acetyl-proline-arginine-NH_2, and N-acetyl-serine-arginine dipeptide were purchased from AnaSpec (Fremont, CA). The glutamate-arginine dipeptide was also sourced from from AnaSpec. A 0.1% wt polysorbate 80 stock solution at pH 5.2 was prepared using glacial acetic acid and 2N NaOH was used for titration. This stock solution also served as a control. The remaining five formulations were prepared to contain 200 mM of each excipient.

The protein concentration of each sample was measured using SoloVPE UV (C Technologies; Bridgewater, NJ) spectroscopy. The samples were stored at 2-8 °C until being brought to room temperature prior to sample loading on the viscometer. The samples were measured within 2 weeks of preparation (usually within 2-3 days).

The viscosity of the protein formulations was measured using a standard cone-and-plate rotational viscometer (AR-G2 TA Instruments (New Castle, DE) viscometer using a 25 mm diameter with 2 degree cone) at a temperature 25°C and a shear rate range of 100-1000 S^{-1}). Upon loading, each sample was equilibrated for 2 minutes at 25°C prior to the start of data collection. All formulation samples tested showed Newtonian rheological behavior. Therefore, the viscosity values reported herein were average values at a shear rate range of 100-1000 S^{-1}.

Example 2 – N-acetyl-proline-arginine and N-acetyl-serine-arginine dipeptides reduce the viscosity of a therapeutic human antibody formulated at high concentrations

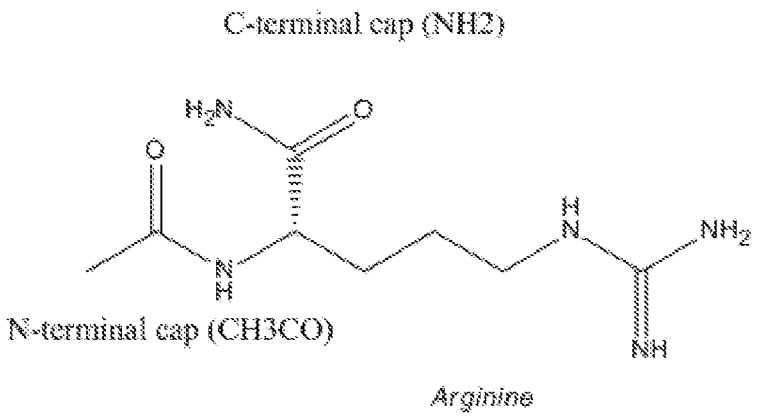
The objective of this example was to determine the ability of N-acetyl-proline-arginine and N-acetyl-serine-arginine dipeptides to reduce the viscosity of a high concentration therapeutic Ab. N-acetyl-arginine (NAR, see for example Sloey and Kanapuram (2016)) was used for comparison, as was arginine.

Ab1, a human monoclonal antibody, was formulated at various concentrations, and included samples that contained 200 mM of either N-acetyl-arginine (NAR), arginine, N-acetyl-serine-arginine and N-acetyl-proline-arginine, or N-acetyl-arginine-NH_2 (this structure is shown as formula **3**) The results are shown in Table 1.1 and in Fig. 1.

Table 1.1

Viscosity of 0.1% polysorbate 80-containing Ab1 solutions, pH 5.2

Excipient	Ab1 concentration (mg/ml)	Viscosity (cP)
arginine	208	38.2
N-acetyl-arginine	186	27.82
N-acetyl-proline-arginine	179	22.8
N-acetyl-serine-arginine	210	28.4
N-acetyl-arginine-NH_2 (amino capped)	255	166
Control (no excipient)	212	176



(3)

Fig. 1 is a line graph representation of the results shown in Table 1.1, plotted against the results of a previous experiment using Ab1 formulated into 10 mM acetate/165 mM N-acetyl-arginine/75 mM Arg HCl, pH 5.1 (plot labeled "pH5.1"); 10 mM phosphate/165 mM N-acetyl-arginine/75 mM Arg HCl, pH 6.6 (plot labeled "pH6.6"); or 10 mM phosphate/165 mM N-acetyl-arginine/75 mM Arg HCl, pH 6.9 (plot labeled "pH6.9").

As shown in Table 1.1 and Fig. 1, N-acetyl-proline-arginine dipeptide-containing sample ("PR") was observed to have a viscosity of 22.8 cP at 179 mg/ml of Ab1, and N-acetyl-serine-arginine dipeptide-containing sample ("SR") was observed to have a viscosity of 28.4 cP at 210 mg/ml of Ab1. The N-acetyl-arginine-containing sample ("NAR") had a viscosity of 27.82 cP at 186 mg/ml of Ab1, while the arginine-containing sample ("Arg") had a viscosity of 38.2 cP at 208 mg/ml of Ab1. In the case of the sample containing N-acetyl-arginine-NH_2 ("xRx"), viscosity was 166 cP at 255 mg/ml of Ab1, while the control containing no additional excipients (buffer and polysorbate 80; "A52 PS80"), viscosity was observed to be 176 cP at 212 mg/ml of Ab1.

Example 3 - N-acetyl-proline-arginine, N-acetyl-serine-arginine, glutamate-arginine, and N-acetyl-proline-arginine-NH_2 (dipeptide + amide cap) dipeptides reduce viscosities of high concentration therapeutic protein samples

The objective of this experiment was to extend the observations shown in Example 2 by assaying additional therapeutic proteins and additional Arg-containing dipeptides.

Using the methods described in Example 1 and sample preparation as described in Example 2, two additional therapeutic polypeptides, human antibodies Ab2 and Ab3, were tested at 210 mg/ml (+/-

20%), 180 mg/ml (+/-10%), 140 mg/ml (+/-10%), and 70 mg/ml (+/- 10%) (+/-10. The plan of the experiment is shown in Table 2.1.

Table 2.1

Excipient	Concentration
arginine HCl	150 mM
N-acetyl-proline-arginine (dipeptide)	150 mM
N-acetyl-serine-arginine (dipeptide)	150 mM
glutamate-arginine (dipeptide)	25 mM[1]
N-acetyl-proline-arginine-NH_2 (dipeptide + amide cap)	150 mM

[1]For the conditions used, this concentration is about the maximum solubility

Viscosities of the three therapeutic polypeptides (human Abs: Ab1, Ab2, and Ab3) at the indicated concentrations (see Tables 2.2-2.4) were measured in formulations containing the concentrations of the five excipients listed in Table 2.1, as well as the absence of an excipient. The results are presented in Tables 2.2 (Ab1), 2.3 (Ab2), and Ab3; as well as in the line graphs shown Figs. 2 (Ab1), 3 (Ab2), and 4 (Ab3). Figs. 2 and 3 include closer views (Figs. 2(B) and 3(B)) of the line graphs, as indicated by the boxes shown in Figs. 2(A) and 3(A).

Table 2.2

Observed concentrations and viscosities for compositions comprising Ab1

		[Target Ab] (mg/mL)			
Amino acid/dipeptide excipient	**Measured characteristics**	**210**	**180**	**140**	**70**
None	observed conc. (mg/mL)	209.98	168.21	136.52	70.93
	Viscosity (cP)	395.69	77.71	16.14	3.72
Arg-HCl	observed conc. (mg/mL)	212.08	183.45	144.46	73.30
	viscosity (cP)	92.87	32.56	11.72	4.11
N-acetyl-Pro-Arg	observed conc. (mg/mL)	210.57	184.86	144.07	73.60
	viscosity (cP)	50.98	20.46	8.90	3.47

		[Target Ab] (mg/mL)			
Amino acid/dipeptide excipient	**Measured characteristics**	**210**	**180**	**140**	**70**
N-acetyl-Ser-Arg	observed conc. (mg/mL)	207.04	184.52	142.98	72.08
	viscosity (cP)	64.39	26.75	9.13	3.74
Glu-Arg	observed conc. (mg/mL)	215.40	202.80	148.89	73.40
	viscosity (cP)	173.41	55.95	11.62	2.31
N-acetyl-Pro-Arg-NH_2	observed conc. (mg/mL)	210.35	182.81	147.67	73.58
	viscosity (cP)	68.90	30.65	9.99	2.44

As shown for Ab1 (referring to Figs. 2(A) and the inset of Fig. 2(A) shown in Fig. 2(B), the figure showing graphs of the data from Table 2.2), without any excipients, viscosity greatly increases as the concentration of Ab1 exceeds 140 mg/mL (small filled circles in Fig. 2). At 140 mg/mL, the viscosity is about 16 cP, but at about 200 mg/mL, the viscosity is almost 400 cP. The addition of Arg as Arg-HCl, N-acetyl-Pro-Arg, N-acetyl-Ser-Arg, and Glu-Arg decrease the viscosity of all tested samples at about 140 mg/mL Ab1 concentration, even at the highest Ab concentration of 200 mg/mL. However, Glu-Arg is less able to reduce the viscosity of the highest Ab1 concentration samples, having a viscosity of 173 cP at about 215 mg/mL of Ab1; interestingly, however, when the observed Ab1 concentration is decreased by about 13 mg/mL, the Glu-Arg dipeptide reduces the viscosity remarkably to about 56 cP (grey filled box in Figure 2). Surprisingly, N-acetyl-Pro-Arg-NH_2, which contains an amide cap that reduces the overall charge on the molecule, also appeared to decrease the viscosity of the Ab1 samples, even at high concentrations of Ab1, such as about 200 mg/mL (empty triangles in Fig. 2).

Table 2.3

Observed concentrations and viscosities for compositions comprising Ab2

		[Target Ab] (mg/mL)			
Amino acid/dipeptide excipient	**Measured characteristics**	**210**	**180**	**140**	**70**
None	observed conc. (mg/mL)	235.6	184.8	143.04	75.70
	Viscosity (cP)	179.49	56.96	15.94	2.60
Arg-HCl	observed conc. (mg/mL)	197.77	166.96	134.84	77.30
	viscosity (cP)	43.86	20.91	7.62	1.82
N-acetyl-Pro-Arg	observed conc. (mg/mL)	206.26	179.38	141.67	71.80
	viscosity (cP)	41.88	21.96	9.69	3.60
N-acetyl-Ser-Arg	observed conc. (mg/mL)	207.21	184.46	140.11	67.70
	viscosity (cP)	65.96	30.24	11.92	4.24
Glu-Arg	observed conc. (mg/mL)	216.55	173.68	138.83	67.90
	viscosity (cP)	85.10	40.21	14.31	3.41
N-acetyl-Pro-Arg-NH_2	observed conc. (mg/mL)	203.62	179.50	143.43	67.64
	viscosity (cP)	22.42	13.07	6.87	3.16

Likewise, as shown for Ab2, now referring to Figs. 3(A) and the inset of Fig. 3(A) as shown in Fig. 3(B) (the figure showing graphs of the data from Table 2.3), without any excipients, viscosity greatly increases as the concentration of Ab2 exceeds 140 mg/mL (small filled circles in Fig. 3). At 140 mg/mL, the viscosity is about 57 cP, but at about 200 mg/mL, the viscosity is about 180 cP. When formulated with the different excipients, viscosity was reduced for all samples, although less uniformly than was observed for Ab1. All of the N-acetylated dipeptides, including the amino capped dipeptide N-acetyl-Pro-Arg-NH_2, decreased the viscosities of all samples having an antibody concentration greater than about 140 mg/mL.

Table 2.4

Observed concentrations and viscosities for compositions comprising Ab3

		[Target Ab] (mg/mL)			
Amino acid/dipeptide excipient	**Measured characteristics**	**210**	**180**	**140**	**70**
None	observed conc. (mg/mL)	207.20	186.45	148.71	75.61
	Viscosity (cP)	41.34	19.69	8.26	2.23
Arg-HCl	observed conc. (mg/mL)	214.18	185.09	148.50	76.06
	viscosity (cP)	35.46	17.33	7.38	2.24
N-acetyl-Pro-Arg	observed conc. (mg/mL)	214.18	184.98	146.11	76.28
	viscosity (cP)	26.88	14.56	6.71	2.39
N-acetyl-Ser-Arg	observed conc. (mg/mL)	207.56	181.80	142.80	71.78
	viscosity (cP)	29.65	15.51	7.02	2.33
Glu-Arg	observed conc. (mg/mL)	211.35	177.38	135.68	73.29
	viscosity (cP)	35.08	16.93	7.28	2.15
N-acetyl-Pro-Arg-NH_2	observed conc. (mg/mL)	199.02	182.08	138.24	74.07
	viscosity (cP)	22.38	14.21	6.28	3.14

A third Ab, Ab3 was also tested. Referring to Fig. 4, which shows a line graph of the data shown in Table 2.4, this Ab does not show as high viscosity as Abs 1 and 2, with a viscosity of about 41 cP without any excipients. When viscosity was measured in these samples containing the indicated dipeptides and arginine, viscosity was reduced, but not as markedly as when the viscosity was greater. Even though the effect of the tested excipients is less notable, achieving a viscosity of, for example, about 30 cPs or less, can permit delivery by automated injection devices.

Figure 5 aggregates the results such that the three antibodies are compared to each other in the presence of an excipient. Fig. 5A shows the results of the three antibodies in the presence of N-acetyl-Pro-Arg; Fig. 5B shows the results of the three antibodies in the presence of N-acetyl-Ser-Arg, while Fig.

5C shows the results for N-acetyl-Pro-Arg-NH_2, and Fig. 5D shows the results for Glu-Arg. This figure clearly shows the viscosity-lowering effects of these four excipients particularly for therapeutic polypeptides that are viscous, such as at high therapeutic polypeptide concentrations, in the absence of these excipients.

EMBODIMENTS

1. A liquid pharmaceutical composition comprising a therapeutic polypeptide, a buffer, and at least one N-acetyl-dipeptide, wherein the N-acetyl-dipeptide is N-acetyl-serine-arginine, N-acetyl-proline-arginine, or N-acetyl-proline-arginine-NH_2.

2. The composition of embodiment 1, wherein the therapeutic polypeptide is an antibody or an antigen-binding fragment thereof.

3. The composition of embodiment 2, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 70 mg/ml.

4. The composition of embodiment 2, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 140 mg/ml.

5. The composition of embodiment 2, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 180 mg/ml.

6. The composition of embodiment 2, wherein the antibody or antigen-binding fragment thereof is present in a concentration of about 200 mg/ml.

7. The composition of embodiment 2, wherein the antibody or antigen-binding fragment thereof is present in a concentration of about 210 mg/ml.

8. The composition of embodiment 2, wherein the antibody is selected from the group consisting of adalimumab, bevacizumab, blinatumomab, cetuximab, conatumumab, denosumab, eculizumab, erenumab, evolocumab, infliximab, natalizumab, panitumumab, rilotumumab, rituximab, romosozumab, and trastuzumab, or antigen-binding fragment thereof; or is selected from those presented in Table 1, or an antigen-binding fragment thereof.

9. The composition of embodiment 8, wherein the antibody is evolocumab.

10. The composition of embodiment 1, wherein the N-acetyl-dipeptide has a concentration of about 10 mM to about 500 mM.

11. The composition of embodiment 1, wherein the N-acetyl-dipeptide has a concentration of about 100 mM to about 200 mM.

12. The composition of embodiment 1, wherein the N-acetyl-dipeptide has a concentration of about 150 mM.

13. The composition of embodiment 1, wherein the N-acetyl-dipeptide has a concentration of about 200 mM.

14. The composition of embodiment 1, wherein the N-acetyl-dipeptide is N-acetyl-serine-arginine.

15. The composition of embodiment 1, wherein the N-acetyl-dipeptide is N-acetyl-proline-arginine.

16. The composition of embodiment 1, wherein the N-acetyl-dipeptide is N-acetyl-proline-arginine-NH_2.

17. The composition of embodiment 1, wherein the buffer is selected from the group consisting of acetate, glutamate, histidine, and phosphate buffers, or a combination thereof.

18. The composition of embodiment 1, wherein the buffer is acetate.

19. The composition of embodiment 1, wherein the buffer is present at a concentration of about 5 mM to about 30 mM.

20. The composition of embodiment 1, wherein the buffer is acetate and is present at a concentration of about 10 mM.

21. The composition of embodiment 1, wherein the composition has a pH of about 4 to about 8.

22. The composition of embodiment 21, wherein the composition has a pH of about 4.8 to 6.9.

23. The composition of embodiment 21, wherein the composition has a pH of about 5.2.

24. The composition of embodiment 1, further comprising a surfactant.

25. The composition of embodiment 24, wherein the surfactant is selected from the group consisting of polyoxyethylenesorbitan monooleate (polysorbate 80 or polysorbate 20), polyoxyethylene-polyoxypropylene block copolymer (Poloxamers such as Pluronic® F-68 and other Pluronics®), Sorbitan alkyl esters (Spans®) Polyethylene glycol octylphenyl ethers (Triton X-100), Polyethylene glycol alkyl ethers (Brij), Polypropylene glycol alkyl ethers, Glucoside alkyl ethers, and D-α-tocopherol polyethylene glycol succinate (vitamin E TPGS).

26. The composition of embodiment 25, wherein the surfactant is polysorbate 20 or polysorbate 80.

27. The composition of embodiment 26, wherein the surfactant is 0.01% (w/v) polysorbate 80 or 0.004% polysorbate 20.

28. The composition of embodiment 1, further comprising a second oligopeptide comprising arginine and consisting of two to ten amino acid residues.

29. The composition of embodiment 1, further comprising an amino acid, N-acetyl-arginine, N-acetyl-lysine, N-acetyl-histidine, N-acetyl-proline or mixtures thereof.

30. The composition of embodiment 29, wherein the amino acid is arginine or proline.

31. A method of reducing viscosity in a pharmaceutical composition comprising a therapeutic polypeptide, wherein the method comprises:

a. providing a solution comprising (i) the therapeutic polypeptide, (ii) at least one N-acetyl-dipeptide, wherein the N-acetyl-dipeptide is N-acetyl-serine-arginine, N-acetyl-proline-arginine, or N-acetyl-proline-arginine-NH_2, and is present at a viscosity-reducing concentration, and (iii) a buffer; and

b. adjusting the pH of the solution to about 4 to about 8.

32. The method of embodiment 31, wherein the therapeutic polypeptide is an antibody or an antigen-binding fragment thereof.

33. The method of embodiment 32, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 70 mg/ml.

34. The method of embodiment 32, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 140 mg/ml.

35. The method of embodiment 32, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 180 mg/ml.

36. The method of embodiment 32, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 200 mg/ml.

37. The method of embodiment 32, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 210 mg/ml.

38. The method of embodiment 32, wherein the antibody is selected from the group consisting of adalimumab, bevacizumab, blinatumomab, cetuximab, conatumumab, denosumab, eculizumab, erenumab, evolocumab, infliximab, natalizumab, panitumumab, rilotumumab, rituximab, romosozumab, and trastuzumab, or antigen-binding fragment thereof; or is selected from those presented in Table 1, or an antigen-binding fragment thereof.

39. The method of embodiment 38, wherein the antibody or antigen-binding fragment thereof is evolocumab.

40. The method of embodiment 31, wherein the N-acetyl-dipeptide has a concentration of about 10 mM to about 500 mM.

41. The method of embodiment 31, wherein the N-acetyl-dipeptide has a concentration of about 100 mM to about 200 mM.

42. The method of embodiment 31, wherein the N-acetyl-dipeptide has a concentration of about 150 mM.

43. The method of embodiment 31, wherein the N-acetyl-dipeptide has a concentration of about 200 mM.

44. The method of embodiment 31, wherein the N-acetyl-dipeptide is a lyophilized powder prior to being placed in solution.

45. The method of embodiment 31, wherein the buffer is selected from the group consisting of acetate, glutamate, histidine, and phosphate buffers, or a combination thereof.

46. The method of embodiment 45, wherein the buffer is acetate.

47. The method of embodiment 31, wherein the buffer is present at a concentration of about 5 mM to about 30 mM.

48. The method of embodiment 31, wherein the buffer is acetate and is present at a concentration of about 10 mM.

49. The method of embodiment 31, wherein the pH is adjusted to about 4.8 to 6.9.

50. The method of embodiment 31, wherein the pH is adjusted to about 5.2.

51. The method of embodiment 31, further comprising a surfactant.

52. The method of embodiment 51, wherein the surfactant is selected from the group consisting of polyoxyethylenesorbitan monooleate (polysorbate 80 or polysorbate 20), polyoxyethylene-polyoxypropylene block copolymer (Poloxamers such as Pluronic® F-68 and other Pluronics®), Sorbitan alkyl esters (Spans®) Polyethylene glycol octylphenyl ethers (Triton X-100), Polyethylene glycol alkyl ethers (Brij), Polypropylene glycol alkyl ethers, Glucoside alkyl ethers, and D-α-tocopherol polyethylene glycol succinate (vitamin E TPGS).

53. The method of embodiment 52, wherein the surfactant is polysorbate 20 or polysorbate 80.

54. The method of embodiment 53, wherein the surfactant is 0.01% (w/v) polysorbate 80 or 0.004% polysorbate 20.

55. The method of embodiment 31, wherein the solution further comprises a second oligopeptide comprising arginine and consisting of two to ten amino acid residues.

56. The method of embodiment 31, wherein the solution further comprises an amino acid, N-acetyl-arginine, N-acetyl-lysine, N-acetyl-histidine, N-acetyl-proline or mixtures of any thereof.

57. The method of embodiment 55, wherein the amino acid is arginine or proline.

58. The method of embodiment 31, wherein viscosity of the composition is reduced by at least about 30% when compared to a control solution lacking the N-acetyl-dipeptide.

59. The method of embodiment 31, wherein viscosity of the composition is reduced by at least about 50% when compared to a control solution lacking the N-acetyl-dipeptide.

60. A lyophilized powder comprising a therapeutic polypeptide, and an N-acetyl-dipeptide, wherein the N-acetyl-dipeptide is N-acetyl-serine-arginine, N-acetyl-proline-arginine, or N-acetyl-proline-arginine-NH_2, wherein the N-acetyl-dipeptide is present at a weight:weight concentration effective to reduce viscosity upon reconstitution with a diluent.

61. The lyophilized powder of embodiment 60, wherein the therapeutic polypeptide is an antibody or an antigen-binding fragment thereof.

62. The lyophilized powder of embodiment 61, wherein the N-acetyl-dipeptide is about 10 µg/mg antibody or an antigen-binding fragment thereof to about 500 µg/mg antibody or an antigen-binding fragment thereof.

63. The lyophilized powder of embodiment 61, wherein the N-acetyl-dipeptide is about 50 µg/mg antibody or an antigen-binding fragment thereof to about 500 µg/mg antibody or an antigen-binding fragment thereof.

64. The lyophilized powder of embodiment 61, wherein the N-acetyl-dipeptide is about 100 µg/mg antibody or an antigen-binding fragment thereof to about 500 µg/mg antibody or an antigen-binding fragment thereof.

65. The lyophilized powder of embodiment 61, wherein the N-acetyl-dipeptide is about 200 µg to about 500 µg/mg antibody or an antigen-binding fragment thereof.

66. The lyophilized powder of embodiment 61, wherein the N-acetyl-dipeptide is about 150 µg to about 250 µg/mg antibody or an antigen-binding fragment thereof.

67. A method of reconstituting the lyophilized powder of any of embodiments 61 to 66, comprising the step of adding a sterile aqueous diluent comprising a buffer in sufficient concentration so that the reconstituted solution has a pH of about 4 to about 8.

68. The method of embodiment 67, wherein the buffer is in sufficient concentration so that the reconstituted solution has a pH of about 4.8 to about 6.9.

69. A liquid pharmaceutical composition comprising a therapeutic polypeptide, a buffer, and a glutamate-arginine dipeptide

70. The composition of embodiment 69, wherein the therapeutic polypeptide is an antibody or an antigen-binding fragment thereof.

71. The composition of embodiment 71, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 70 mg/ml.

72. The composition of embodiment 71, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 140 mg/ml.

73. The composition of embodiment 71, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 180 mg/ml.

74. The composition of embodiment 71, wherein the antibody or antigen-binding fragment thereof is present in a concentration of about 200 mg/ml.

75. The composition of embodiment 71, wherein the antibody or antigen-binding fragment thereof is present in a concentration of about 210 mg/ml.

76. The composition of embodiment 70, wherein the antibody is selected from the group consisting of adalimumab, bevacizumab, blinatumomab, cetuximab, conatumumab, denosumab, eculizumab, erenumab, evolocumab, infliximab, natalizumab, panitumumab, rilotumumab, rituximab, romosozumab, and trastuzumab, or antigen-binding fragment thereof; or is selected from those presented in Table 1, or an antigen-binding fragment thereof.

77. The composition of embodiment 76, wherein the antibody is evolocumab.

78. The composition of embodiment 69, wherein the dipeptide has a concentration of about 1 mM to about 25 mM.

79. The composition of embodiment 69, wherein the dipeptide has a concentration of about 25 mM.

80. The composition of embodiment 69, wherein the buffer is selected from the group consisting of acetate, glutamate, histidine, and phosphate buffers, or a combination thereof.

81. The composition of embodiment 69, wherein the buffer is acetate.

82. The composition of embodiment 69, wherein the buffer is present at a concentration of about 5 mM to about 30 mM.

83. The composition of embodiment 69, wherein the buffer is acetate and is present at a concentration of about 10 mM.

84. The composition of embodiment 69, wherein the composition has a pH of about 4 to about 8.

85. The composition of embodiment 84, wherein the composition has a pH of about 4.8 to 6.9.

86. The composition of embodiment 84, wherein the composition has a pH of about 5.2.

87. The composition of embodiment 69, further comprising a surfactant.

88. The composition of embodiment 87, wherein the surfactant is selected from the group consisting of polyoxyethylenesorbitan monooleate (polysorbate 80 or polysorbate 20), polyoxyethylene-polyoxypropylene block copolymer (Poloxamers such as Pluronic® F-68 and other Pluronics®), Sorbitan alkyl esters (Spans®) Polyethylene glycol octylphenyl ethers (Triton X-100), Polyethylene glycol alkyl ethers (Brij), Polypropylene glycol alkyl ethers, Glucoside alkyl ethers, and D-α-tocopherol polyethylene glycol succinate (vitamin E TPGS).

89. The composition of embodiment 88, wherein the surfactant is polysorbate 20 or polysorbate 80.

90. The composition of embodiment 88, wherein the surfactant is 0.01% (w/v) polysorbate 80 or 0.004% polysorbate 20.

91. The composition of embodiment 69, further comprising a second oligopeptide comprising arginine and consisting of two to ten amino acid residues.

92. The composition of embodiment 69, further comprising an amino acid, N-acetyl-arginine, N-acetyl-lysine, N-acetyl-histidine, N-acetyl-proline or mixtures thereof.

93. The composition of embodiment 92, wherein the amino acid is arginine or proline.

94. A method of reducing viscosity in a pharmaceutical composition comprising a therapeutic polypeptide, wherein the method comprises:

a. providing a solution comprising (i) the therapeutic polypeptide, (ii) a glutamate-arginine dipeptide present at a viscosity-reducing concentration, and (iii) a buffer; and

b. adjusting the pH of the solution to about 4 to about 8.

95. The method of embodiment 94, wherein the therapeutic polypeptide is an antibody or an antigen-binding fragment thereof.

96. The method of embodiment 95, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 70 mg/ml.

97. The method of embodiment 95, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 140 mg/ml.

98. The method of embodiment 95, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 180 mg/ml.

99. The method of embodiment 95, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 200 mg/ml.

100. The method of embodiment 95, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 210 mg/ml.

101. The method of embodiment 95, wherein the antibody is selected from the group consisting of adalimumab, bevacizumab, blinatumomab, cetuximab, conatumumab, denosumab, eculizumab, erenumab, evolocumab, infliximab, natalizumab, panitumumab, rilotumumab, rituximab, romosozumab, and trastuzumab, or antigen-binding fragment thereof; or is selected from those presented in Table 1, or an antigen-binding fragment thereof.

102. The method of embodiment 101, wherein the antibody or antigen-binding fragment thereof is evolocumab.

103. The method of embodiment 94, wherein the dipeptide has a concentration of about 1 mM to about 25 mM.

104. The method of embodiment 94, wherein the dipeptide has a concentration of about 25 mM.

105. The method of embodiment 94, wherein the dipeptide is a lyophilized powder prior to being placed in solution.

106. The method of embodiment 94, wherein the buffer is selected from the group consisting of acetate, glutamate, histidine, and phosphate buffers, or a combination thereof.

107. The method of embodiment 106, wherein the buffer is acetate.

108. The method of embodiment 94, wherein the buffer is present at a concentration of about 5 mM to about 30 mM.

109. The method of embodiment 94, wherein the buffer is acetate and is present at a concentration of about 10 mM.

110. The method of embodiment 94, wherein the pH is adjusted to about 4.8 to 6.9.

111. The method of embodiment 94, wherein the pH is adjusted to about 5.2.

112. The method of embodiment 94, further comprising a surfactant.

113. The method of embodiment 112, wherein the surfactant is selected from the group consisting of polyoxyethylenesorbitan monooleate (polysorbate 80 or polysorbate 20), polyoxyethylene-polyoxypropylene block copolymer (Poloxamers such as Pluronic® F-68 and other Pluronics®), Sorbitan alkyl esters (Spans®) Polyethylene glycol octylphenyl ethers (Triton X-100), Polyethylene glycol alkyl ethers (Brij), Polypropylene glycol alkyl ethers, Glucoside alkyl ethers, and D-α-tocopherol polyethylene glycol succinate (vitamin E TPGS).

114. The method of embodiment 113, wherein the surfactant is polysorbate 20 or polysorbate 80.

115. The method of embodiment 113, wherein the surfactant is 0.01% (w/v) polysorbate 80 or 0.004% polysorbate 20.

116. The method of embodiment 94, wherein the solution further comprises a second oligopeptide comprising arginine and consisting of two to ten amino acid residues.

117. The method of embodiment 94, wherein the solution further comprises an amino acid, N-acetyl-arginine, N-acetyl-lysine, N-acetyl-histidine, N-acetyl-proline or mixtures of any thereof.

118. The method of embodiment 117, wherein the amino acid is arginine or proline.

119. The method of embodiment 94, wherein viscosity of the composition is reduced by at least about 30% when compared to a control solution lacking the dipeptide.

120. The method of embodiment 94, wherein viscosity of the composition is reduced by at least about 50% when compared to a control solution lacking the dipeptide.

121. A lyophilized powder comprising a therapeutic polypeptide and a glutamate-arginine dipeptide, wherein the dipeptide is present at a weight:weight concentration effective to reduce viscosity upon reconstitution with a diluent.

122. The lyophilized powder of embodiment 121, wherein the therapeutic polypeptide is an antibody or an antigen-binding fragment thereof.

123. The lyophilized powder of embodiment 122, wherein the dipeptide is about 10 μg/mg antibody or an antigen-binding fragment thereof to about 500 μg/mg antibody or an antigen-binding fragment thereof.

124. The lyophilized powder of embodiment 122, wherein the dipeptide is about 50 μg/mg antibody or an antigen-binding fragment thereof to about 500 μg/mg antibody or an antigen-binding fragment thereof.

125. The lyophilized powder of embodiment 122, wherein the dipeptide is about 100 μg/mg antibody or an antigen-binding fragment thereof to about 500 μg/mg antibody or an antigen-binding fragment thereof.

126. The lyophilized powder of embodiment 122, wherein the dipeptide is about 200 μg to about 500 μg/mg antibody or an antigen-binding fragment thereof.

127. The lyophilized powder of embodiment 122, wherein the dipeptide is about 150 μg to about 250 μg/mg antibody or an antigen-binding fragment thereof.

128. A method of reconstituting the lyophilized powder of any of embodiments 121 to 127, comprising the step of adding a sterile aqueous diluent comprising a buffer in sufficient concentration so that the reconstituted solution has a pH of about 4 to about 8.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety for any purpose.

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CLAIMS

1. A liquid pharmaceutical composition comprising a therapeutic polypeptide, a buffer, and at least one N-acetyl-dipeptide, wherein the N-acetyl-dipeptide is N-acetyl-serine-arginine, N-acetyl-proline-arginine, or N-acetyl-proline-arginine-NH_2.

2. The composition of claim 1, wherein the therapeutic polypeptide is an antibody or an antigen-binding fragment thereof.

3. The composition of claim 2, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 70 mg/ml.

4. The composition of claim 2 or claim 3, wherein the antibody is selected from the group consisting of adalimumab, bevacizumab, blinatumomab, cetuximab, conatumumab, denosumab, eculizumab, erenumab, evolocumab, infliximab, natalizumab, panitumumab, rilotumumab, rituximab, romosozumab, and trastuzumab, or antigen-binding fragment thereof.

5. The composition of any one of claims 1 to 4, wherein the N-acetyl-dipeptide has a concentration of about 10 mM to about 500 mM.

6. The composition of any one of claims 1 to 5, wherein the N-acetyl-dipeptide is N-acetyl-serine-arginine or N-acetyl-proline-arginine.

7. The composition of any one of claims 1 to 6, wherein the buffer is selected from the group consisting of acetate, glutamate, histidine, and phosphate buffers, or a combination thereof.

8. The composition of any one of claims 1 to 7, wherein the composition has a pH of about 4 to about 8.

9. The composition of any one of claims 1 to 8, further comprising a surfactant, wherein the surfactant is selected from the group consisting of polyoxyethylenesorbitan monooleate (polysorbate 80 or polysorbate 20), polyoxyethylene-polyoxypropylene block copolymer (Poloxamers such as Pluronic® F-68 and other Pluronics®), Sorbitan alkyl esters (Spans®) Polyethylene glycol octylphenyl ethers (Triton X-100), Polyethylene glycol alkyl ethers (Brij), Polypropylene glycol alkyl ethers, Glucoside alkyl ethers, and D-α-tocopherol polyethylene glycol succinate (vitamin E TPGS).

10. The composition of claim 9, wherein the surfactant is 0.01% (w/v) polysorbate 80 or 0.004% polysorbate 20.

11. The composition of any one of claims 1 to 10, further comprising an amino acid, N-acetyl-arginine, N-acetyl-lysine, N-acetyl-histidine, N-acetyl-proline or mixtures thereof, wherein the amino acid is arginine or proline.

12. A method of reducing viscosity in a pharmaceutical composition comprising a therapeutic polypeptide, wherein the method comprises:

a. providing a solution comprising (i) the therapeutic polypeptide, (ii) at least one N-acetyl-dipeptide, wherein the N-acetyl-dipeptide is N-acetyl-serine-arginine, N-acetyl-proline-arginine, or N-acetyl-proline-arginine-NH_2, and is present at a viscosity-reducing concentration, and (iii) a buffer; and

b. adjusting the pH of the solution to about 4 to about 8.

13. The method of claim 12, wherein the therapeutic polypeptide is an antibody or an antigen-binding fragment thereof.

14. The method of claim 13, wherein the antibody or antigen-binding fragment thereof is present in a concentration of at least about 70 mg/ml.

15. The method of claim 13 or claim 14, wherein the antibody is selected from the group consisting of adalimumab, bevacizumab, blinatumomab, cetuximab, conatumumab, denosumab, eculizumab, erenumab, evolocumab, infliximab, natalizumab,

panitumumab, rilotumumab, rituximab, romosozumab, and trastuzumab, or antigen-binding fragment thereof.

16. The method of any one of claims 12 to 15, wherein the N-acetyl-dipeptide has a concentration of about 10 mM to about 500 mM.

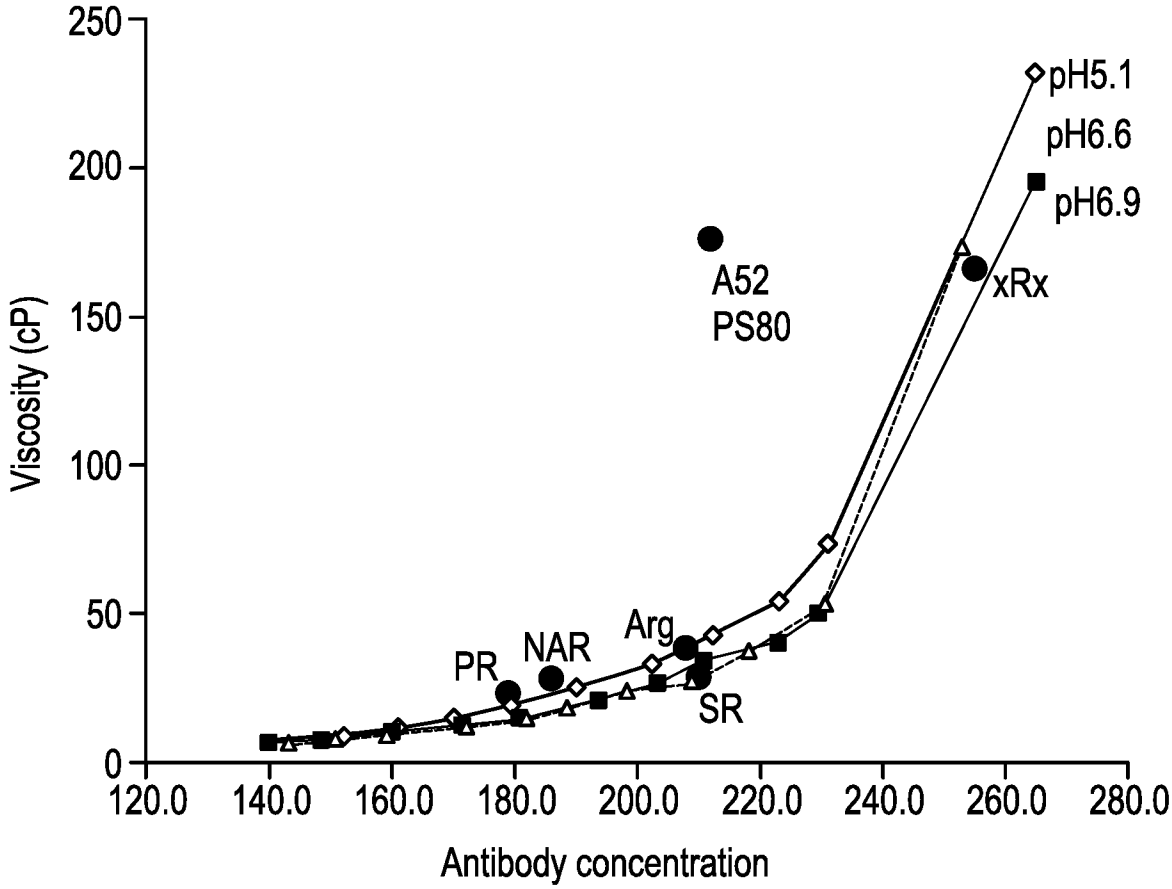
17. The method of any one of claims 12 to 16, wherein the buffer is selected from the group consisting of acetate, glutamate, histidine, and phosphate buffers, or a combination thereof.

18. The method of any one of claims 12 to 17, further comprising a surfactant, wherein the surfactant is selected from the group consisting of polyoxyethylenesorbitan monooleate (polysorbate 80 or polysorbate 20), polyoxyethylene-polyoxypropylene block copolymer (Poloxamers such as Pluronic® F-68 and other Pluronics®), Sorbitan alkyl esters (Spans®) Polyethylene glycol octylphenyl ethers (Triton X-100), Polyethylene glycol alkyl ethers (Brij), Polypropylene glycol alkyl ethers, Glucoside alkyl ethers, and D-α-tocopherol polyethylene glycol succinate (vitamin E TPGS).

19. The method of any one of claims 12 to 18, wherein the solution further comprises an amino acid, N-acetyl-arginine, N-acetyl-lysine, N-acetyl-histidine, N-acetyl-proline or mixtures of any thereof, wherein the amino acid is arginine or proline.

20. The method of any one of claims 12 to 19, wherein viscosity of the composition is reduced by at least about 30% when compared to a control solution lacking the N-acetyl-dipeptide.

FIG. 1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100
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Viscosity (cP)
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140.0
160.0
180.0
200.0
220.0
240.0
260.0
280.0
Antibody concentration
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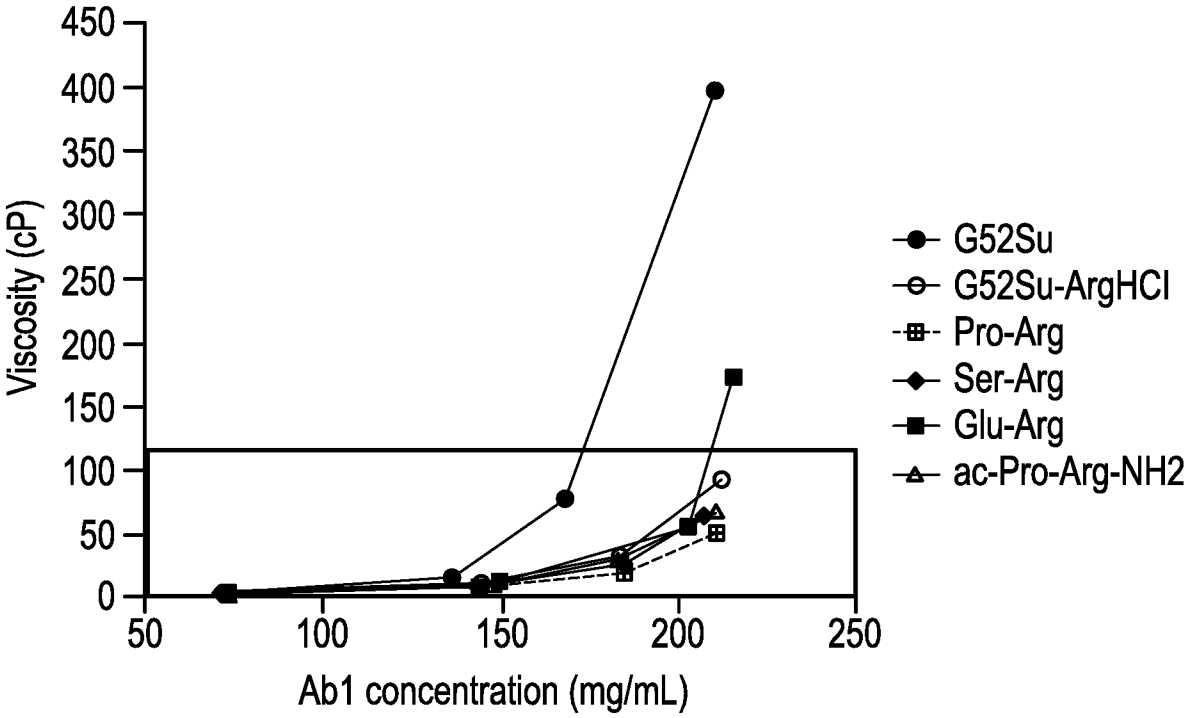
pH6.6
pH6.9
A52
PS80
xRx
PR
NAR
Arg
SR

FIG. 2A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300
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150
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Ab1 concentration (mg/mL)
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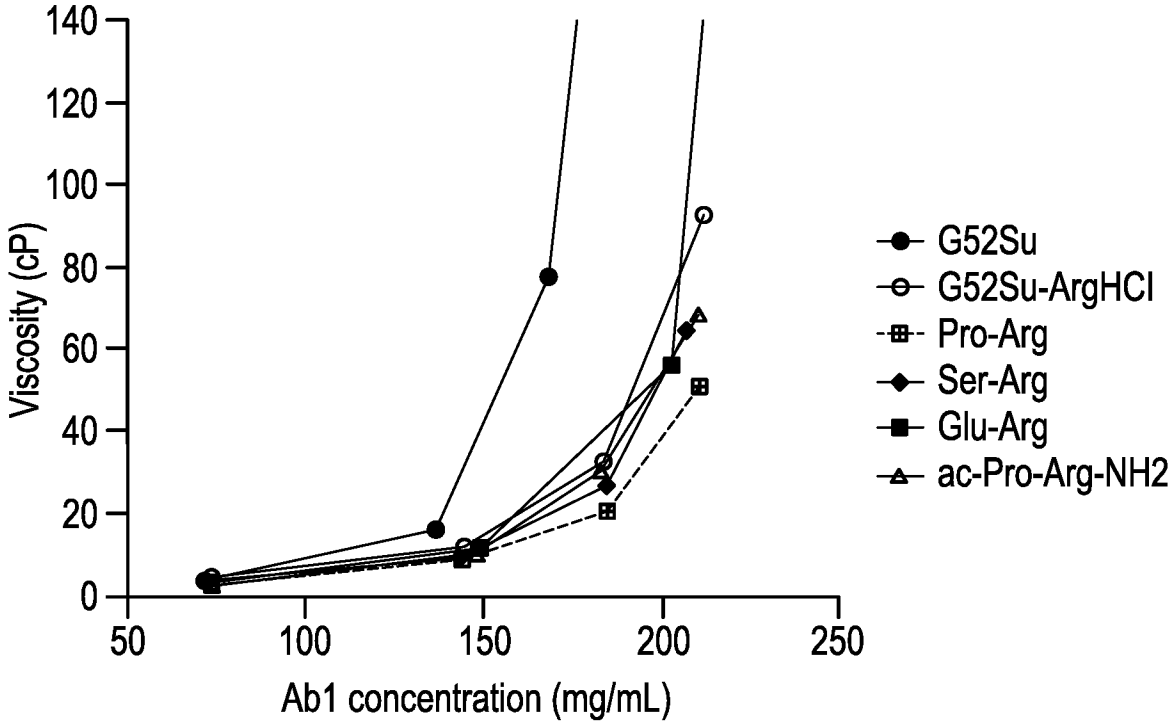
G52Su-ArgHCl
Pro-Arg
Ser-Arg
Glu-Arg
ac-Pro-Arg-NH2

FIG. 2B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120
100
80
60
40
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50
100
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Ab1 concentration (mg/mL)
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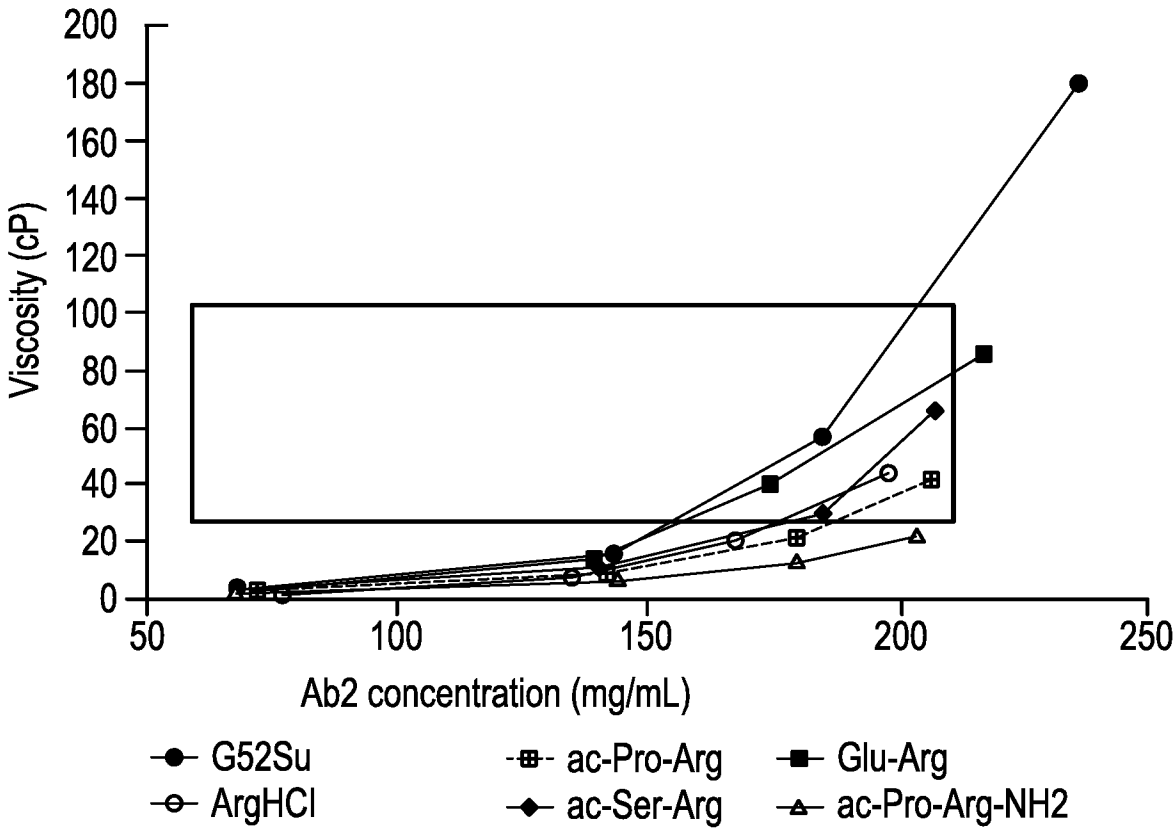
G52Su-ArgHCl
Pro-Arg
Ser-Arg
Glu-Arg
ac-Pro-Arg-NH2

FIG. 3A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Viscosity (cP)
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100
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Ab2 concentration (mg/mL)
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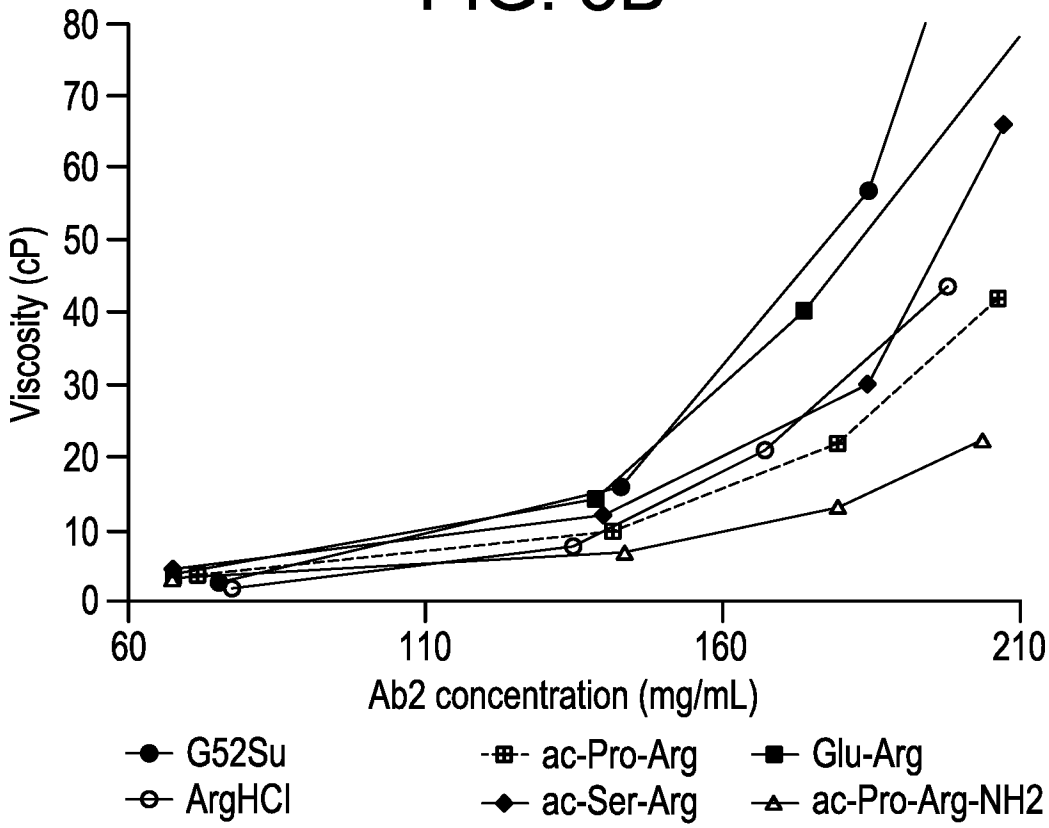
ac-Pro-Arg
ac-Ser-Arg
Glu-Arg
ac-Pro-Arg-NH2

FIG. 3B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Viscosity (cP)
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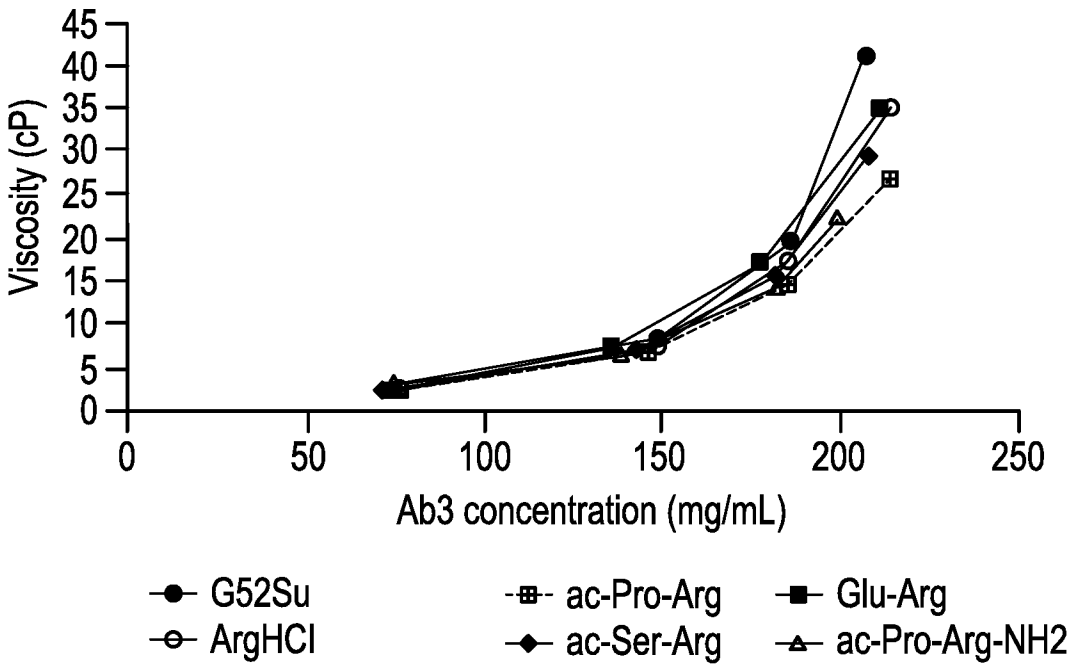
ArgHCl
ac-Pro-Arg
ac-Ser-Arg
Glu-Arg
ac-Pro-Arg-NH2

FIG. 4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30
25
20
15
10
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100
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200
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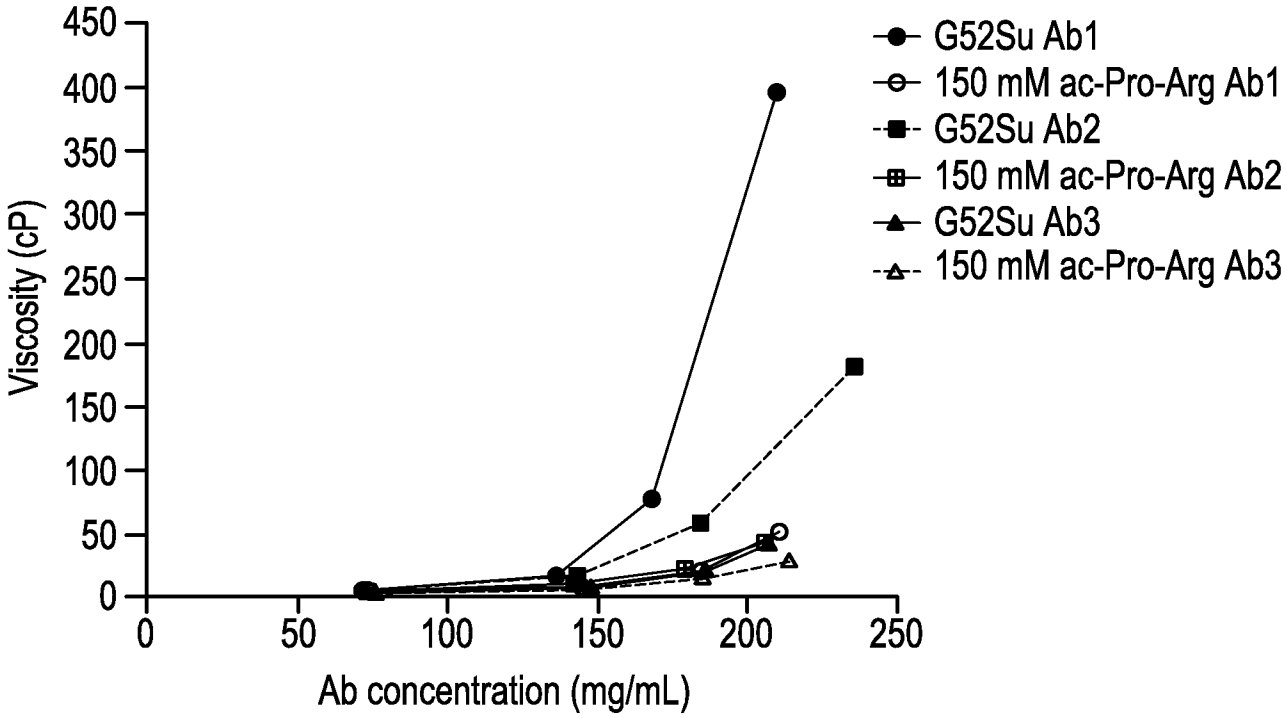
Ab3 concentration (mg/mL)
G52Su
ArgHCl
ac-Pro-Arg
ac-Ser-Arg
Glu-Arg
ac-Pro-Arg-NH2

FIG. 5A


Viscosity (cP)
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400
350
300
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100
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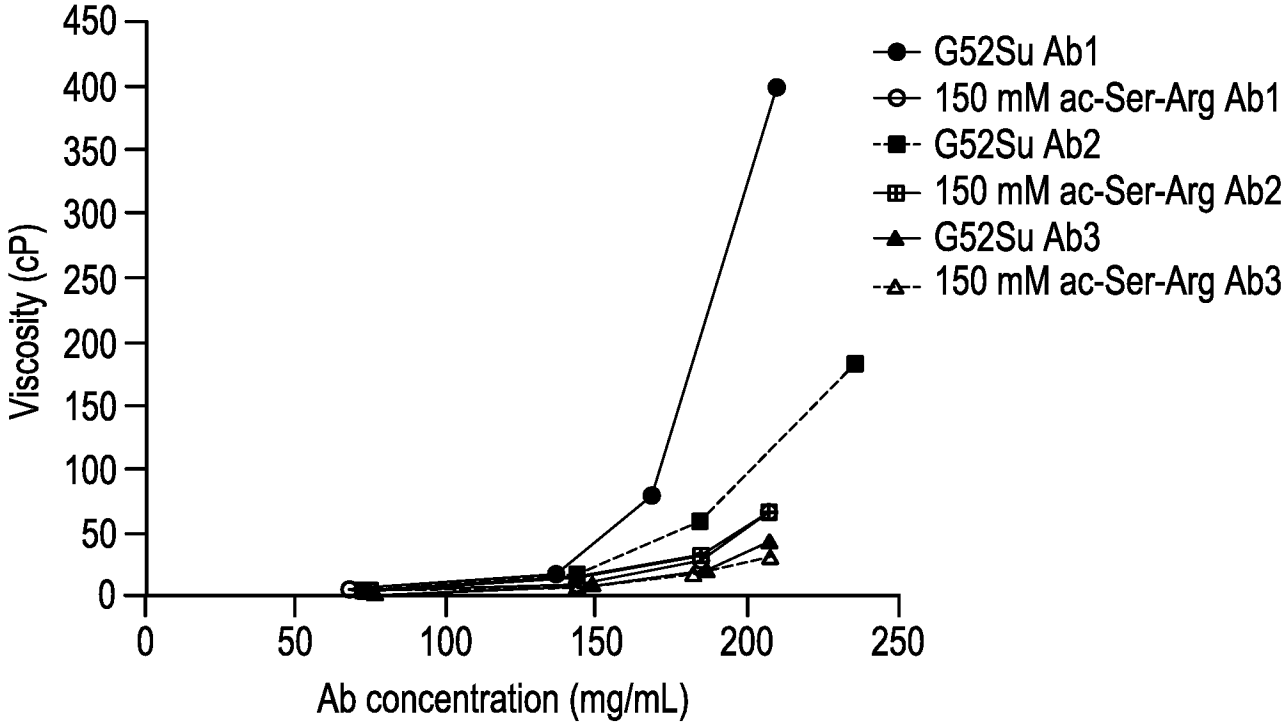
100
150
200
250
Ab concentration (mg/mL)
G52Su Ab1
150 mM ac-Pro-Arg Ab1
G52Su Ab2
150 mM ac-Pro-Arg Ab2
G52Su Ab3
150 mM ac-Pro-Arg Ab3

FIG. 5B


Viscosity (cP)
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350
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200
150
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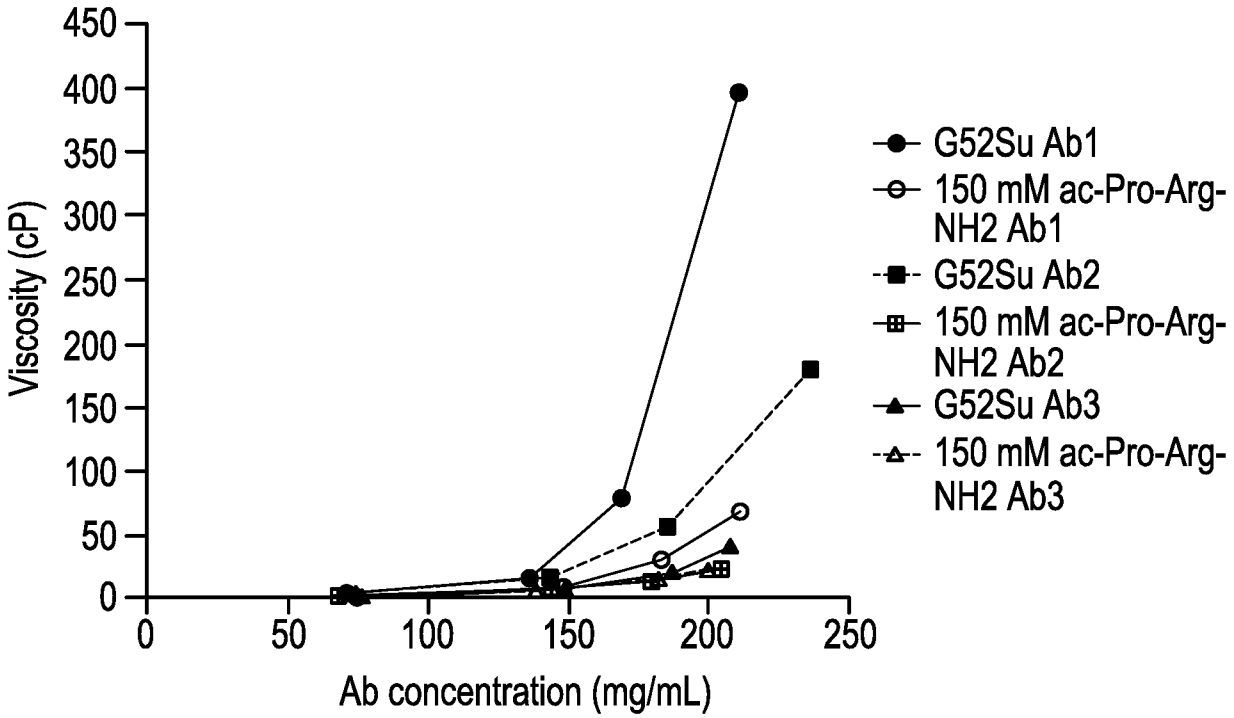
50
0
0
50
100
150
200
250
Ab concentration (mg/mL)
G52Su Ab1
150 mM ac-Ser-Arg Ab1
G52Su Ab2
150 mM ac-Ser-Arg Ab2
G52Su Ab3
150 mM ac-Ser-Arg Ab3

FIG. 5C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350
300
250
200
150
100
50
0
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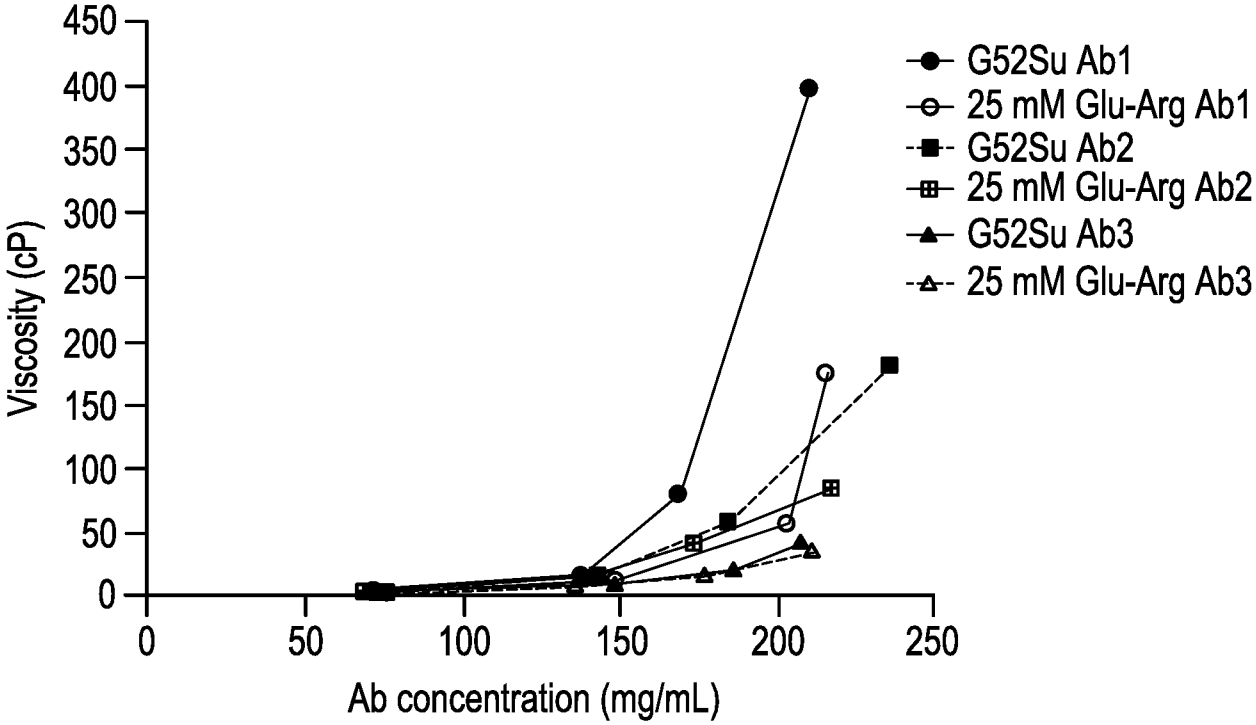
50
100
150
200
250
Ab concentration (mg/mL)
G52Su Ab1
150 mM ac-Pro-Arg-NH2 Ab1
G52Su Ab2
150 mM ac-Pro-Arg-NH2 Ab2
G52Su Ab3
150 mM ac-Pro-Arg-NH2 Ab3

FIG. 5D


Viscosity (cP)
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200
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100
50
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0
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100
150
200
250
Ab concentration (mg/mL)
G52Su Ab1
25 mM Glu-Arg Ab1
G52Su Ab2
25 mM Glu-Arg Ab2
G52Su Ab3
25 mM Glu-Arg Ab3

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AGRAWAL, Neeraj Jagdish
GHATTYVENKATAKRISHNA, Pavan
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SLOEY, Christopher James

<120> N-ACETYLATED AND NON-ACETYLATED DIPEPTIDES CONTAINING ARGININE TO REDUCE THE VISCOSITY OF VISCOUS COMPOSITIONS OF THERAPEUTIC POLYPEPTIDES

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

Ile Thr Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys
                85                  90                  95

Ser Gln Val Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala
            100                 105                 110

Thr Tyr Tyr Cys Ala Arg Ile Pro Leu Arg Ser Pro Gly Ala Phe Asp
        115                 120                 125

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys
    130                 135                 140

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
145                 150                 155                 160

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
        195                 200                 205

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
    210                 215                 220

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro
225                 230                 235                 240

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
```

```
                245                 250                 255

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
            260                 265                 270

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
        275                 280                 285

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
    290                 295                 300

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
305                 310                 315                 320

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
                325                 330                 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
            340                 345                 350

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
        355                 360                 365

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
    370                 375                 380

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
385                 390                 395                 400

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
                405                 410                 415

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
            420                 425                 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
        435                 440                 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
```

450 455 460

Ser Leu Ser Pro Gly Lys
465 470

<210> 3
<211> 235
<212> PRT
<213> Homo sapiens

<400> 3

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
20 25 30

Leu Ser Pro Gly Asp Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45

Val Ser Ser Ser Tyr Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro
65 70 75 80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
85 90 95

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
100 105 110

Asp Arg Ser Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
115 120 125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130 135 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145 150 155 160

```
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165                 170                 175


Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180                 185                 190


Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195                 200                 205


Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210                 215                 220


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  4
<211>  463
<212>  PRT
<213>  Homo sapiens

<400>  4

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15


Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30


Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ser Ser Gly Tyr Thr Phe
        35                  40                  45


Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60


Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala
65                  70                  75                  80


Gln Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser
                85                  90                  95
```

```
Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110


Tyr Tyr Cys Ala Arg Asp Lys Trp Leu Asp Gly Phe Asp Tyr Trp Gly
        115                 120                 125


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


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


Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                165                 170                 175


Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
            180                 185                 190


Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        195                 200                 205


Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
    210                 215                 220


Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
225                 230                 235                 240


Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
                245                 250                 255


Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            260                 265                 270


Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        275                 280                 285


Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    290                 295                 300
```

```
Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
305                 310                 315                 320


Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                325                 330                 335


Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
            340                 345                 350


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


Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    370                 375                 380


Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
385                 390                 395                 400


Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
                405                 410                 415


Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            420                 425                 430


Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        435                 440                 445


His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460


<210>  5
<211>  235
<212>  PRT
<213>  Homo sapiens

<400>  5

Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Asp Thr Gly
1               5                   10                  15
```

```
Ser Trp Ala Gln Ser Val Leu Thr Gln Ser Pro Ser Ala Ser Gly Thr
            20                  25                  30

Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile
        35                  40                  45

Gly Ser Asn Tyr Val Tyr Trp Tyr Gln Gln Leu Pro Gly Ala Ala Pro
    50                  55                  60

Lys Leu Leu Ile Leu Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp
65                  70                  75                  80

Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Thr Ile Ser
                85                  90                  95

Gly Leu Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp
            100                 105                 110

Asp Ser Leu Ser Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
        115                 120                 125

Leu Gly Gln Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser
    130                 135                 140

Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser
145                 150                 155                 160

Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser
                165                 170                 175

Pro Val Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn
            180                 185                 190

Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp
        195                 200                 205

Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr
    210                 215                 220
```

Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230 235

<210> 6
<211> 479
<212> PRT
<213> Homo sapiens

<400> 6

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly
20 25 30

Leu Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Phe Ser Asn Ala Trp Met Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly
65 70 75 80

Thr Thr Asp Tyr Thr Ala Pro Val Lys Gly Arg Phe Thr Ile Ser Arg
85 90 95

Asp Asp Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Lys Ala
100 105 110

Glu Asp Thr Ala Val Tyr Tyr Cys Thr Thr Asp Arg Thr Gly Tyr Ser
115 120 125

Ile Ser Trp Ser Ser Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly
130 135 140

Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
145 150 155 160

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala

```
                165                 170                 175

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
            180                 185                 190

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
        195                 200                 205

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
    210                 215                 220

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

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
                245                 250                 255

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
            260                 265                 270

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
        275                 280                 285

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
    290                 295                 300

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
305                 310                 315                 320

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
                325                 330                 335

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
            340                 345                 350

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
        355                 360                 365

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
```

```
    370                 375                 380

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

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
                405                 410                 415

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
            420                 425                 430

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
        435                 440                 445

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
    450                 455                 460

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475


<210>  7
<211>  235
<212>  PRT
<213>  Homo sapiens

<400>  7

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                   10                  15

Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
            20                  25                  30

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45

Val Arg Gly Arg Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro
65                  70                  75                  80
```

```
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Phe Tyr Cys Gln Gln Tyr
            100                 105                 110

Gly Ser Ser Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130                 135                 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145                 150                 155                 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165                 170                 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180                 185                 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195                 200                 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210                 215                 220

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  8
<211>  467
<212>  PRT
<213>  Homo sapiens

<400>  8

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15
```

```
Val Gln Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ser Gly Ile Thr Gly Ser Gly Gly Ser Thr Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Lys Asp Pro Gly Thr Thr Val Ile Met Ser Trp Phe
        115                 120                 125

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

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
145                 150                 155                 160

Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                165                 170                 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
            180                 185                 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
        195                 200                 205

Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys
    210                 215                 220
```

```
Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu
225                 230                 235                 240

Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala
                245                 250                 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            260                 265                 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        275                 280                 285

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe
305                 310                 315                 320

Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly
                325                 330                 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
            340                 345                 350

Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val
        355                 360                 365

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    370                 375                 380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385                 390                 395                 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                405                 410                 415

Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            420                 425                 430
```

```
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        435                 440                 445


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    450                 455                 460


Pro Gly Lys
465


<210>  9
<211>  242
<212>  PRT
<213>  Homo sapiens

<400>  9

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Arg Gly Ala Arg Cys Asp Ile Val Met Thr Gln Thr Pro Leu Ser
            20                  25                  30


Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser
        35                  40                  45


Gln Ser Leu Leu Asn Ser Val Asp Gly Ser Thr Asn Leu Asp Trp Tyr
    50                  55                  60


Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Thr Leu Ser
65                  70                  75                  80


Tyr Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
                85                  90                  95


Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly
            100                 105                 110


Val Tyr Tyr Cys Met Gln Arg Ile Glu Phe Pro Leu Thr Phe Gly Gly
        115                 120                 125
```

```
Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe
    130                 135                 140


Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
145                 150                 155                 160


Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
                165                 170                 175


Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
            180                 185                 190


Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
        195                 200                 205


Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
    210                 215                 220


Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
225                 230                 235                 240


Glu Cys



<210>  10
<211>  465
<212>  PRT
<213>  Homo sapiens

<400>  10

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


Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30


Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45


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

```
    50                  55                  60

Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Ser Ile Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Glu Arg Tyr Tyr Gly Asp Thr Pro Phe Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
    130                 135                 140

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

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
    210                 215                 220

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
225                 230                 235                 240

Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
                245                 250                 255

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
```

```
            260                 265                 270

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
        275                 280                 285

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
    290                 295                 300

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
305                 310                 315                 320

Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
                325                 330                 335

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
            340                 345                 350

Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
        355                 360                 365

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
    370                 375                 380

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
385                 390                 395                 400

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
                405                 410                 415

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
            420                 425                 430

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
        435                 440                 445

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
    450                 455                 460

Lys
```

465

<210> 11
<211> 233
<212> PRT
<213> Homo sapiens

<400> 11

Met Ser Pro Ser Gln Leu Ile Gly Phe Leu Leu Leu Trp Val Pro Ala
1 5 10 15

Ser Arg Gly Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val
20 25 30

Thr Pro Lys Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile
35 40 45

Gly Ser Ser Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys
50 55 60

Leu Leu Ile Lys Tyr Ala Ser Gln Ser Phe Ser Gly Val Pro Ser Arg
65 70 75 80

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser
85 90 95

Leu Glu Ala Glu Asp Ala Ala Ala Tyr Tyr Cys His Gln Ser Ser Ser
100 105 110

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

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
130 135 140

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
145 150 155 160

Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
165 170 175

```
Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
            180                 185                 190


Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
        195                 200                 205


Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
    210                 215                 220


Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230


<210>  12
<211>  463
<212>  PRT
<213>  Homo sapiens

<400>  12

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


Val Cys Ala Glu Val Gln Leu Met Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30


Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe
        35                  40                  45


Ser Phe His Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu
    50                  55                  60


Glu Trp Met Gly Ile Ile His Pro Gly Ala Ser Asp Thr Arg Tyr Ser
65                  70                  75                  80


Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Asn Ser Asn Ser
                85                  90                  95


Ala Thr Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met
            100                 105                 110
```

```
Tyr Phe Cys Ala Arg Gln Arg Glu Leu Asp Tyr Phe Asp Tyr Trp Gly
        115                 120                 125


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


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


Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                165                 170                 175


Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
            180                 185                 190


Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        195                 200                 205


Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
    210                 215                 220


Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
225                 230                 235                 240


Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
                245                 250                 255


Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            260                 265                 270


Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        275                 280                 285


Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    290                 295                 300


Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
305                 310                 315                 320
```

```
Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                325                 330                 335


Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
            340                 345                 350


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


Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    370                 375                 380


Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
385                 390                 395                 400


Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
                405                 410                 415


Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            420                 425                 430


Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        435                 440                 445


His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460


<210>  13
<211>  236
<212>  PRT
<213>  Homo sapiens

<400>  13

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30
```

```
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
        35                  40                  45

Gln Asp Ile Asn Lys Tyr Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser Trp Leu Gln Pro Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Leu Gln
            100                 105                 110

Tyr Asp Asn Leu Leu Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235
```

<210> 14
<211> 467
<212> PRT
<213> Homo sapiens

<400> 14

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15


Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly
            20                  25                  30


Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45


Phe Thr Phe Ser Arg Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly
    50                  55                  60


Lys Gly Leu Glu Trp Val Ala Gln Ile Arg Leu Lys Ser Asp Asn Tyr
65                  70                  75                  80


Ala Thr His Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
                85                  90                  95


Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala
            100                 105                 110


Glu Asp Thr Ala Val Tyr Tyr Cys Thr Glu Gly Leu Asp Tyr Trp Gly
        115                 120                 125


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


Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145                 150                 155                 160


Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                165                 170                 175


Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
```

```
            180                 185                 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        195                 200                 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
    210                 215                 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225                 230                 235                 240

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
                245                 250                 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            260                 265                 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        275                 280                 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305                 310                 315                 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                325                 330                 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            340                 345                 350

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        355                 360                 365

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    370                 375                 380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
```

385 390 395 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> 15
<211> 236
<212> PRT
<213> Homo sapiens

<400> 15

Met Asp Met Arg Val Leu Ala Gln Leu Leu Gly Leu Leu Leu Leu Cys
1 5 10 15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Gly Ile Ser Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys
50 55 60

Ala Pro Lys Ser Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

```
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

Tyr Asp Ser Tyr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  16
<211>  466
<212>  PRT
<213>  Homo sapiens

<400>  16

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

Val His Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30
```

```
Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Ser Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Tyr Ile Lys Gln Asp Gly Asn Glu Lys Tyr Tyr Val
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Glu Gly Ile Leu Trp Phe Gly Asp Leu Pro Thr
        115                 120                 125

Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
    130                 135                 140

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

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
        195                 200                 205

Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
    210                 215                 220

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
225                 230                 235                 240
```

```
Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445
```

```
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
    450                 455                 460


Gly Lys
465


<210>  17
<211>  241
<212>  PRT
<213>  Homo sapiens

<400>  17

Met Asp Met Arg Leu Pro Ala Gln Leu Leu Gly Leu Leu Met Leu Trp
1               5                   10                  15


Val Pro Gly Ser Ser Gly Asp Val Leu Met Thr Gln Ser Pro Leu Ser
            20                  25                  30


Leu Pro Val Thr Leu Gly Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser
        35                  40                  45


Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu
    50                  55                  60


Gln Arg Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn
65                  70                  75                  80


Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
                85                  90                  95


Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val
            100                 105                 110


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


Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile
    130                 135                 140
```

```
Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val
145                 150                 155                 160


Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys
                165                 170                 175


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


Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu
        195                 200                 205


Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr
    210                 215                 220


His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
225                 230                 235                 240


Cys



<210>  18
<211>  470
<212>  PRT
<213>  Homo sapiens

<400>  18

Met Asp Thr Leu Cys Ser Thr Leu Leu Leu Leu Thr Ile Pro Ser Trp
1               5                   10                  15


Val Leu Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Ala Leu Val Lys
            20                  25                  30


Pro Thr Gln Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu
        35                  40                  45


Arg Thr Ser Gly Met Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60


Ala Leu Glu Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Ser Tyr
```

```
65                  70                  75                  80

Asn Pro Ser Leu Lys Ser Gln Leu Thr Ile Ser Lys Asp Thr Ser Lys
                85                  90                  95

Asn Gln Val Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala
            100                 105                 110

Thr Tyr Tyr Cys Ala Arg Arg Asn Tyr Tyr Tyr Asp Asp Tyr Phe Ala
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
    130                 135                 140

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
145                 150                 155                 160

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
        195                 200                 205

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
    210                 215                 220

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
225                 230                 235                 240

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
                245                 250                 255

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
            260                 265                 270

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
```

```
        275                 280                 285

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
    290                 295                 300

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
305                 310                 315                 320

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
                325                 330                 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
            340                 345                 350

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
        355                 360                 365

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
    370                 375                 380

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
385                 390                 395                 400

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
                405                 410                 415

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
            420                 425                 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
        435                 440                 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
    450                 455                 460

Ser Leu Ser Pro Gly Lys
465                 470
```

<210> 19

<211> 235
<212> PRT
<213> Homo sapiens

<400> 19

```
Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                  10                  15


Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
            20                  25                  30


Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45


Val Ser Ser Ser Tyr Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60


Pro Arg Leu Leu Ile Tyr Gly Thr Ser Ser Arg Ala Thr Gly Ile Pro
65                  70                  75                  80


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Val
                85                  90                  95


Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
            100                 105                 110


Asp Arg Ser Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
        115                 120                 125


Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130                 135                 140


Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145                 150                 155                 160


Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165                 170                 175


Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180                 185                 190
```

```
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195                 200                 205


Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210                 215                 220


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  20
<211>  463
<212>  PRT
<213>  Homo sapiens

<400>  20

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15


Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Ala Val Lys Lys
            20                  25                  30


Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45


Thr Gly Tyr Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60


Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala
65                  70                  75                  80


Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser
                85                  90                  95


Thr Ala Ser Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110


Tyr Phe Cys Ala Arg Asp Arg Trp Leu Asp Ala Phe Asp Ile Trp Gly
        115                 120                 125
```

```
Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
    130                 135                 140

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

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                165                 170                 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
            180                 185                 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        195                 200                 205

Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
    210                 215                 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
225                 230                 235                 240

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
                245                 250                 255

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            260                 265                 270

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        275                 280                 285

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    290                 295                 300

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
305                 310                 315                 320

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                325                 330                 335
```

```
Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
            340                 345                 350


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


Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    370                 375                 380


Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
385                 390                 395                 400


Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
                405                 410                 415


Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            420                 425                 430


Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        435                 440                 445


His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460


<210>  21
<211>  235
<212>  PRT
<213>  Homo sapiens

<400>  21

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                   10                  15


Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
            20                  25                  30


Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45
```

```
Val Ser Ser Gly Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro
65                  70                  75                  80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
            100                 105                 110

Gly Asn Ser Leu Ser Arg Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130                 135                 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145                 150                 155                 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165                 170                 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180                 185                 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195                 200                 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210                 215                 220

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235
```

<210> 22
<211> 474
<212> PRT
<213> Homo sapiens

<400> 22

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Arg Gly Ala Arg Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly
            20                  25                  30

Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys
65                  70                  75                  80

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Lys
                85                  90                  95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg Ala Gly Gly Ile Ala Ala Ala Gly
        115                 120                 125

Leu Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val
    130                 135                 140

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
145                 150                 155                 160

Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
                165                 170                 175

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
            180                 185                 190

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
```

```
        195                 200                 205

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe
    210                 215                 220

Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
225                 230                 235                 240

Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
            260                 265                 270

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
        275                 280                 285

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
    290                 295                 300

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
305                 310                 315                 320

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
                325                 330                 335

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
            340                 345                 350

Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
        355                 360                 365

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
    370                 375                 380

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
385                 390                 395                 400

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
```

405 410 415

Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe
420 425 430

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
435 440 445

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
450 455 460

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 23
<211> 236
<212> PRT
<213> Homo sapiens

<400> 23

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Ser Ser Glu Leu Thr Gln Asp Pro Thr Val
20 25 30

Ser Val Ala Leu Gly Gln Thr Val Lys Ile Thr Cys Gln Gly Asp Ser
35 40 45

Leu Arg Ser Phe Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Val Leu Val Phe Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro
65 70 75 80

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

Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg
100 105 110

```
Asp Ser Ser Val Tyr His Leu Val Leu Gly Gly Gly Thr Lys Leu Thr
        115                 120                 125


Val Leu Gly Gln Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro
    130                 135                 140


Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile
145                 150                 155                 160


Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly
                165                 170                 175


Ser Pro Val Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser
            180                 185                 190


Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln
        195                 200                 205


Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser
    210                 215                 220


Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225                 230                 235


<210>  24
<211>  478
<212>  PRT
<213>  Homo sapiens

<400>  24

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Arg Gly Ala Arg Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu
            20                  25                  30


Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
        35                  40                  45
```

```
Tyr Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Gln Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr
65                  70                  75                  80

Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr
                85                  90                  95

Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp
            100                 105                 110

Thr Ala Val Tyr Phe Cys Ala Arg Asp Gln Met Ser Ile Ile Met Leu
        115                 120                 125

Arg Gly Val Phe Pro Pro Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln
    130                 135                 140

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
145                 150                 155                 160

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
                165                 170                 175

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
            180                 185                 190

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
        195                 200                 205

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
    210                 215                 220

Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
225                 230                 235                 240

Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
                245                 250                 255
```

```
Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
            260                 265                 270

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
        275                 280                 285

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
    290                 295                 300

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
305                 310                 315                 320

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
                325                 330                 335

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
            340                 345                 350

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
        355                 360                 365

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
    370                 375                 380

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
385                 390                 395                 400

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
                405                 410                 415

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
            420                 425                 430

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
        435                 440                 445

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
    450                 455                 460
```

```
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475


<210>  25
<211>  241
<212>  PRT
<213>  Homo sapiens

<400>  25

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Arg Gly Ala Arg Cys Asp Ile Val Met Thr Gln Ser Pro Leu Ser
            20                  25                  30


Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser
        35                  40                  45


Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu
    50                  55                  60


Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn
65                  70                  75                  80


Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
                85                  90                  95


Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val
            100                 105                 110


Tyr Tyr Cys Met Gln Ala Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly
        115                 120                 125


Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile
    130                 135                 140


Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val
145                 150                 155                 160
```

```
Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys
                165                 170                 175

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

Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu
        195                 200                 205

Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr
    210                 215                 220

His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
225                 230                 235                 240

Cys
```

<210> 26
<211> 475
<212> PRT
<213> Homo sapiens

<400> 26

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly
            20                  25                  30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Thr Phe Ser Ser Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Val Ala Ser Ile Lys Gln Asp Gly Ser Glu Lys
65                  70                  75                  80

Tyr Tyr Val Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
```

```
                85                  90                  95

Ala Arg Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg Asp Leu Val Leu Met Val Tyr Asp
        115                 120                 125

Ile Asp Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
    130                 135                 140

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
145                 150                 155                 160

Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
                165                 170                 175

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
            180                 185                 190

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
        195                 200                 205

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn
    210                 215                 220

Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
225                 230                 235                 240

Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro
                245                 250                 255

Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
```

```
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475


<210>  27
<211>  241
<212>  PRT
<213>  Homo sapiens
```

<400> 27

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Arg Gly Ala Arg Cys Asp Ile Val Met Thr Gln Ser Pro Leu Ser
            20                  25                  30

Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser
        35                  40                  45

Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu
    50                  55                  60

Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn
65                  70                  75                  80

Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
                85                  90                  95

His Leu Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val
            100                 105                 110

Tyr Tyr Cys Met Gln Thr Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly
        115                 120                 125

Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile
    130                 135                 140

Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val
145                 150                 155                 160

Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys
                165                 170                 175

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

Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu
        195                 200                 205
```

```
Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr
    210                 215                 220

His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
225                 230                 235                 240

Cys
```

<210> 28
<211> 475
<212> PRT
<213> Homo sapiens

<400> 28

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly
            20                  25                  30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Thr Phe Ser Asn Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Val Ala Ser Ile Lys Gln Asp Gly Ser Glu Lys
65                  70                  75                  80

Tyr Tyr Val Asp Ser Val Lys Gly Arg Phe Ala Ile Ser Arg Asp Asn
                85                  90                  95

Ala Lys Asn Ser Leu Phe Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg Asp Leu Val Leu Met Val Tyr Asp
        115                 120                 125
```

```
Ile Asp Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
    130                 135                 140

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
145                 150                 155                 160

Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
                165                 170                 175

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
            180                 185                 190

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
        195                 200                 205

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn
    210                 215                 220

Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
225                 230                 235                 240

Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro
                245                 250                 255

Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
                325                 330                 335
```

```
Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350


Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
        355                 360                 365


Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
    370                 375                 380


Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400


Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415


Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430


Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445


Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460


Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475


<210>  29
<211>  235
<212>  PRT
<213>  Homo sapiens

<400>  29

Met Thr Cys Ser Pro Leu Leu Leu Thr Leu Leu Ile His Cys Thr Gly
1               5                   10                  15


Ser Trp Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala
            20                  25                  30
```

```
Pro Gly Gln Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile
        35                  40                  45

Gly Asn Asn Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro
    50                  55                  60

Lys Leu Leu Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Ile Pro Asp
65                  70                  75                  80

Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Thr Thr Leu Gly Ile Thr
                85                  90                  95

Gly Leu Gln Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp
            100                 105                 110

Ser Arg Leu Ser Ala Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val
        115                 120                 125

Leu Gly Gln Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser
    130                 135                 140

Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser
145                 150                 155                 160

Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser
                165                 170                 175

Pro Val Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn
            180                 185                 190

Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp
        195                 200                 205

Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr
    210                 215                 220

Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225                 230                 235
```

<210> 30
<211> 475
<212> PRT
<213> Homo sapiens

<400> 30

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1 5 10 15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
20 25 30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Ser Phe Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ala Val Ile Ser Phe Asp Gly Ser Ile Lys Tyr Ser Val
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

Thr Leu Phe Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Asp Arg Leu Asn Tyr Tyr Asp Ser Ser Gly Tyr
115 120 125

Tyr His Tyr Lys Tyr Tyr Gly Met Ala Val Trp Gly Gln Gly Thr Thr
130 135 140

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
145 150 155 160

Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
165 170 175

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser

```
            180                 185                 190

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
        195                 200                 205

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn
    210                 215                 220

Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
225                 230                 235                 240

Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro
                245                 250                 255

Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
    370                 375                 380

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
```

385 390 395 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
405 410 415

Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
420 425 430

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
435 440 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
450 455 460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470 475

<210> 31
<211> 234
<212> PRT
<213> Homo sapiens

<400> 31

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser
20 25 30

Val Ser Pro Gly Gln Thr Ala Thr Ile Thr Cys Ser Gly Asp Lys Leu
35 40 45

Gly Glu Arg Tyr Ala Ser Trp Tyr Gln Gln Arg Pro Gly Gln Ser Pro
50 55 60

Val Leu Val Ile Tyr Gln Asp Ile Lys Arg Pro Ser Gly Ile Pro Glu
65 70 75 80

Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser
85 90 95

```
Gly Thr Gln Ala Met Asp Glu Ala Asp Tyr Phe Cys Gln Ala Trp Tyr
            100                 105                 110

Ser Ser Thr Asn Val Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
        115                 120                 125

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

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
145                 150                 155                 160

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
                165                 170                 175

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
            180                 185                 190

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
        195                 200                 205

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
    210                 215                 220

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225                 230


<210>  32
<211>  466
<212>  PRT
<213>  Homo sapiens

<400>  32

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30
```

```
Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Val Ile Trp Tyr Ala Glu Ser Asn Lys Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Ala Gln Glu Gly Ile Ala Pro Asp Ala Phe Asp
        115                 120                 125

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys
    130                 135                 140

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

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
        195                 200                 205

Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
    210                 215                 220

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
225                 230                 235                 240
```

```
Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445
```

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
450 455 460

Gly Lys
465

<210> 33
<211> 234
<212> PRT
<213> Homo sapiens

<400> 33

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

Gly Arg Ala Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu
20 25 30

Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val
35 40 45

Ser Ser Ser Tyr Leu Ala Trp His Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60

Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95

Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly
100 105 110

Ser Ser Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
115 120 125

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
130 135 140

```
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
145                 150                 155                 160


Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
                165                 170                 175


Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190


Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
        195                 200                 205


His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
    210                 215                 220


Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230


<210>  34
<211>  463
<212>  PRT
<213>  Homo sapiens

<400>  34

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


Gly Arg Ala Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30


Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45


Ser Thr Tyr Val Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60


Glu Trp Val Ser Ser Ile Ser Gly Ser Gly Leu Gly Ser Tyr Tyr Ala
65                  70                  75                  80


Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
```

```
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Lys Glu Ala His Arg Gly Pro Phe Asp Tyr Trp Gly
        115                 120                 125

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

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

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                165                 170                 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
            180                 185                 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        195                 200                 205

Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
    210                 215                 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
225                 230                 235                 240

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
                245                 250                 255

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            260                 265                 270

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        275                 280                 285

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
```

290 295 300

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
305 310 315 320

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
325 330 335

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
340 345 350

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

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
370 375 380

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
385 390 395 400

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
405 410 415

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
420 425 430

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
435 440 445

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 35
<211> 239
<212> PRT
<213> Homo sapiens

<400> 35

Met Arg Leu Leu Ala Gln Leu Leu Gly Leu Leu Met Leu Trp Val Pro
1 5 10 15

```
Gly Ser Ser Gly Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro
            20                  25                  30

Val Thr Leu Gly Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser
        35                  40                  45

Leu Val His Ser Asp Gly Asn Thr Tyr Leu Ser Trp Leu Gln Gln Arg
    50                  55                  60

Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Lys Lys Phe Asn Arg Phe
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe
                85                  90                  95

Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr
            100                 105                 110

Cys Met Gln Ala Thr Gln Ile Pro Leu Thr Phe Gly Pro Gly Thr Lys
        115                 120                 125

Val Asp Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
    130                 135                 140

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145                 150                 155                 160

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175

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

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220
```

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 36
<211> 472
<212> PRT
<213> Homo sapiens

<400> 36

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1 5 10 15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
20 25 30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Phe Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Gly Gly Tyr Asp Tyr Val Trp Gly Ser Tyr Arg
115 120 125

Arg Asn Ser Asp Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
130 135 140

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys
145 150 155 160

```
Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys
                165                 170                 175

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
            180                 185                 190

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
        195                 200                 205

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr
    210                 215                 220

Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val
225                 230                 235                 240

Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
                245                 250                 255

Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            260                 265                 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        275                 280                 285

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
    290                 295                 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305                 310                 315                 320

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
                325                 330                 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
            340                 345                 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
        355                 360                 365
```

```
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    370                 375                 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385                 390                 395                 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                405                 410                 415

Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            420                 425                 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        435                 440                 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    450                 455                 460

Ser Leu Ser Leu Ser Pro Gly Lys
465                 470
```

<210> 37
<211> 235
<212> PRT
<213> Homo sapiens

<400> 37

```
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                   10                  15

Asp Thr Thr Gly Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser
            20                  25                  30

Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45

Val Asp Ser Asn Leu Ala Trp Tyr Arg Gln Lys Pro Gly Gln Ala Pro
    50                  55                  60
```

```
Arg Leu Leu Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala
65                  70                  75                  80


Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser
                85                  90                  95


Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ile
            100                 105                 110


Asn Trp Pro Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
        115                 120                 125


Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130                 135                 140


Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145                 150                 155                 160


Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165                 170                 175


Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180                 185                 190


Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195                 200                 205


Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210                 215                 220


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  38
<211>  465
<212>  PRT
<213>  Homo sapiens

<400>  38

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
```

```
1               5                   10                  15

Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20                  25                  30

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
        35                  40                  45

Ser Ile Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Ile Gly Tyr Val Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro
65                  70                  75                  80

Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln
                85                  90                  95

Phe Ser Leu Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
            100                 105                 110

Tyr Cys Ala Arg Gly Gly Tyr Asp Phe Trp Ser Gly Tyr Phe Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
    130                 135                 140

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

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
```

```
    210                 215                 220

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
225                 230                 235                 240

Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
                245                 250                 255

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
            260                 265                 270

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
        275                 280                 285

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
    290                 295                 300

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
305                 310                 315                 320

Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
                325                 330                 335

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
            340                 345                 350

Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
        355                 360                 365

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
    370                 375                 380

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
385                 390                 395                 400

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
                405                 410                 415

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
```

420 425 430

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
435 440 445

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
450 455 460

Lys
465

<210> 39
<211> 240
<212> PRT
<213> Homo sapiens

<400> 39

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

Gly Ala Tyr Gly Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala
20 25 30

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser
35 40 45

Ile Leu Tyr Ser Ser Ser Asn Glu Asn Phe Leu Thr Trp Tyr Gln Gln
50 55 60

Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg
65 70 75 80

Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
85 90 95

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Val Tyr
100 105 110

Tyr Cys Gln Gln Tyr Phe Ser Val Phe Arg Thr Phe Gly Gln Gly Thr
115 120 125

```
Arg Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
    130                 135                 140

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
145                 150                 155                 160

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
                165                 170                 175

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

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
        195                 200                 205

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
    210                 215                 220

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235                 240
```

<210> 40
<211> 465
<212> PRT
<213> Homo sapiens

<400> 40

```
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Thr Gly Tyr Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60
```

```
Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Ser Ala
65                  70                  75                  80

Gln Lys Phe Arg Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Glu Gly Gly Tyr Ser Tyr Gly Tyr Phe Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
    130                 135                 140

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

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
    210                 215                 220

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
225                 230                 235                 240

Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
                245                 250                 255

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
            260                 265                 270
```

```
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
        275                 280                 285


Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
    290                 295                 300


Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
305                 310                 315                 320


Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
                325                 330                 335


Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
            340                 345                 350


Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
        355                 360                 365


Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
    370                 375                 380


Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
385                 390                 395                 400


Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
                405                 410                 415


Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
            420                 425                 430


Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
        435                 440                 445


Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
    450                 455                 460


Lys
465
```

<210> 41
<211> 236
<212> PRT
<213> Homo sapiens

<400> 41

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15


Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30


Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45


Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60


Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65                  70                  75                  80


Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
                85                  90                  95


Ile Ser Ser Val Gln Pro Glu Asp Phe Val Thr Tyr Tyr Cys Leu Gln
            100                 105                 110


His Asn Ser Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115                 120                 125


Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140


Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160


Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175
```

```
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190


Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205


Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220


Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  42
<211>  473
<212>  PRT
<213>  Homo sapiens

<400>  42

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1               5                   10                  15


Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30


Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45


Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60


Glu Trp Val Ala Val Met Trp Tyr Asp Gly Ser Asn Lys Asp Tyr Val
65                  70                  75                  80


Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95


Thr Leu Tyr Leu Gln Met Asn Arg Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110


Tyr Tyr Cys Ala Arg Glu Lys Asp His Tyr Asp Ile Leu Thr Gly Tyr
```

```
        115                 120                 125

Asn Tyr Tyr Tyr Gly Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr
    130                 135                 140

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
145                 150                 155                 160

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
                165                 170                 175

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
            180                 185                 190

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
        195                 200                 205

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
    210                 215                 220

Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
225                 230                 235                 240

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
                245                 250                 255

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            260                 265                 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        275                 280                 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
    290                 295                 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305                 310                 315                 320

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
```

325 330 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
355 360 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
370 375 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 43
<211> 235
<212> PRT
<213> Homo sapiens

<400> 43

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
20 25 30

```
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Tyr
        35                  40                  45

Ile Ser Asn Thr Tyr Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr Gly Ala Ala Thr Arg Ala Thr Gly Ile Pro
65                  70                  75                  80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
                85                  90                  95

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
            100                 105                 110

Gly Ser Ser Pro Trp Thr Phe Gly Gln Gly Thr Thr Val Glu Ile Lys
        115                 120                 125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130                 135                 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145                 150                 155                 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165                 170                 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180                 185                 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195                 200                 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210                 215                 220

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235
```

<210> 44
<211> 463
<212> PRT
<213> Homo sapiens

<400> 44

```
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                  10                  15


Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30


Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45


Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60


Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala
65                  70                  75                  80


Gln Arg Phe Arg Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser
                85                  90                  95


Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110


Tyr Tyr Cys Ala Arg Ala Pro Tyr Asp Trp Thr Phe Asp Tyr Trp Gly
        115                 120                 125


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


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


Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                165                 170                 175
```

```
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
            180                 185                 190


Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        195                 200                 205


Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
    210                 215                 220


Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
225                 230                 235                 240


Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
                245                 250                 255


Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            260                 265                 270


Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        275                 280                 285


Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    290                 295                 300


Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
305                 310                 315                 320


Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                325                 330                 335


Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
            340                 345                 350


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


Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    370                 375                 380
```

```
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
385                 390                 395                 400


Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
                405                 410                 415


Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            420                 425                 430


Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        435                 440                 445


His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460


<210>  45
<211>  236
<212>  PRT
<213>  Homo sapiens

<400>  45

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30


Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45


Gln Gly Ile Ser Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Thr
    50                  55                  60


Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65                  70                  75                  80


Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95
```

```
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110


Ala Asn Ser Phe Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
        115                 120                 125


Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140


Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160


Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175


Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190


Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205


Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220


Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  46
<211>  469
<212>  PRT
<213>  Homo sapiens

<400>  46

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Arg Gly Ala Arg Cys Gln Val Gln Leu Val Gln Ser Gly Thr Glu
            20                  25                  30


Val Lys Lys Pro Gly Ala Ser Met Lys Val Ser Cys Lys Ala Ser Gly
```

```
        35                  40                  45

Tyr Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Gln Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Asp Ser Thr
65                  70                  75                  80

Ser Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr
                85                  90                  95

Ser Thr Asn Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
            100                 105                 110

Thr Ala Met Tyr Tyr Cys Ala Arg Asp Val Glu Val Arg Gly Ile Ser
        115                 120                 125

His Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
    130                 135                 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser
145                 150                 155                 160

Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
                165                 170                 175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
            180                 185                 190

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
        195                 200                 205

Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr
    210                 215                 220

Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr
225                 230                 235                 240

Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro
```

```
                245                 250                 255

Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            260                 265                 270

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        275                 280                 285

Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    290                 295                 300

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
305                 310                 315                 320

Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu
                325                 330                 335

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala
            340                 345                 350

Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro
        355                 360                 365

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
    370                 375                 380

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
385                 390                 395                 400

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                405                 410                 415

Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
            420                 425                 430

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
        435                 440                 445

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
```

450 455 460

Leu Ser Pro Gly Lys
465

<210> 47
<211> 238
<212> PRT
<213> Homo sapiens

<400> 47

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

Val His Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala
20 25 30

Ser Val Gly Asp Arg Val Thr Met Ser Cys Lys Ser Ser Gln Ser Val
35 40 45

Leu Tyr Ser Ala Asn His Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
50 55 60

Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu
65 70 75 80

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr
100 105 110

Cys His Gln Tyr Leu Ser Ser Trp Thr Phe Gly Gly Gly Thr Lys Val
115 120 125

Gln Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
130 135 140

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
145 150 155 160

```
Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
                165                 170                 175

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

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
        195                 200                 205

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
    210                 215                 220

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  48
<211>  465
<212>  PRT
<213>  Homo sapiens

<400>  48

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

Val His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Thr Ser Tyr Trp Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Ile Gly Tyr Ile Asn Pro Arg Asn Asp Tyr Thr Glu Tyr Asn
65                  70                  75                  80

Gln Asn Phe Lys Asp Lys Ala Thr Ile Thr Ala Asp Glu Ser Thr Asn
                85                  90                  95
```

```
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Phe
            100                 105                 110

Tyr Phe Cys Ala Arg Arg Asp Ile Thr Thr Phe Tyr Trp Gly Gln Gly
        115                 120                 125

Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
    130                 135                 140

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
145                 150                 155                 160

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
                165                 170                 175

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
            180                 185                 190

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
        195                 200                 205

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
    210                 215                 220

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
225                 230                 235                 240

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
                245                 250                 255

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
            260                 265                 270

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
        275                 280                 285

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
    290                 295                 300
```

```
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
305                 310                 315                 320

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
                325                 330                 335

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
            340                 345                 350

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
        355                 360                 365

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
    370                 375                 380

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
385                 390                 395                 400

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
                405                 410                 415

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
            420                 425                 430

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
        435                 440                 445

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
    450                 455                 460

Lys
465
```

<210> 49
<211> 235
<212> PRT
<213> Homo sapiens

<400> 49

```
Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                  10                  15

Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
            20                  25                  30

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45

Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro
65                  70                  75                  80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Arg Ser
            100                 105                 110

Gly Gly Ser Ser Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
        115                 120                 125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130                 135                 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145                 150                 155                 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165                 170                 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180                 185                 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195                 200                 205
```

```
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210                 215                 220


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  50
<211>  466
<212>  PRT
<213>  Homo sapiens

<400>  50

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


Val Cys Ala Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30


Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Asn Phe
        35                  40                  45


Thr Ser Tyr Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu
    50                  55                  60


Glu Leu Met Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser
65                  70                  75                  80


Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser
                85                  90                  95


Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met
            100                 105                 110


Tyr Tyr Cys Gly Ser Gly Ser Tyr Phe Tyr Phe Asp Leu Trp Gly Arg
        115                 120                 125


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


Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
```

```
145                 150                 155                 160

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
                165                 170                 175

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
            180                 185                 190

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
        195                 200                 205

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
    210                 215                 220

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
225                 230                 235                 240

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
```

```
        355                 360                 365

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
    450                 455                 460

Gly Lys
465
```

<210> 51
<211> 241
<212> PRT
<213> Homo sapiens

<400> 51

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15

Leu Arg Gly Ala Arg Cys Asp Ile Val Met Thr Gln Ser Pro Leu Ser
            20                  25                  30

Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser
        35                  40                  45

Gln Ser Leu Leu His Ser His Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu
    50                  55                  60
```

```
Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn
65                  70                  75                  80

Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val
            100                 105                 110

Tyr Tyr Cys Met Gln Gly Thr His Trp Pro Pro Thr Phe Gly Gln Gly
        115                 120                 125

Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile
    130                 135                 140

Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val
145                 150                 155                 160

Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys
                165                 170                 175

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

Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu
        195                 200                 205

Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr
    210                 215                 220

His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
225                 230                 235                 240

Cys
```

<210> 52
<211> 470

<212> PRT
<213> Homo sapiens

<400> 52

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Val Gln Ser Gly Gly Gly
            20                  25                  30

Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile
65                  70                  75                  80

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
                85                  90                  95

Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg Asp Leu Leu Asp Tyr Asp Leu Leu
        115                 120                 125

Thr Gly Tyr Gly Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
145                 150                 155                 160

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
                165                 170                 175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
            180                 185                 190
```

```
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
        195                 200                 205

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
    210                 215                 220

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
225                 230                 235                 240

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
                245                 250                 255

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
            260                 265                 270

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
        275                 280                 285

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
    290                 295                 300

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
305                 310                 315                 320

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
                325                 330                 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
            340                 345                 350

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
        355                 360                 365

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
    370                 375                 380

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
385                 390                 395                 400
```

```
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
                405                 410                 415


Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
            420                 425                 430


Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
        435                 440                 445


Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
    450                 455                 460


Ser Leu Ser Pro Gly Lys
465                 470


<210>  53
<211>  235
<212>  PRT
<213>  Homo sapiens

<400>  53

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                   10                  15


Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
            20                  25                  30


Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Gly
        35                  40                  45


Ile Ser Arg Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60


Pro Ser Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro
65                  70                  75                  80


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95
```

```
Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Phe
            100                 105                 110


Gly Ser Ser Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
        115                 120                 125


Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130                 135                 140


Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145                 150                 155                 160


Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165                 170                 175


Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180                 185                 190


Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195                 200                 205


Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210                 215                 220


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  54
<211>  471
<212>  PRT
<213>  Homo sapiens

<400>  54

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1               5                   10                  15


Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20                  25                  30


Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
```

```
        35                  40                  45

Ser Ser Gly Asp Tyr Phe Trp Ser Trp Ile Arg Gln Leu Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly His Ile His Asn Ser Gly Thr Thr Tyr Tyr
65                  70                  75                  80

Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys
                85                  90                  95

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

Val Tyr Tyr Cys Ala Arg Asp Arg Gly Gly Asp Tyr Tyr Tyr Gly Met
        115                 120                 125

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
    130                 135                 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
145                 150                 155                 160

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                165                 170                 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
            180                 185                 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
        195                 200                 205

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
    210                 215                 220

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
225                 230                 235                 240

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
```

```
                245                 250                 255

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            260                 265                 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        275                 280                 285

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    290                 295                 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
305                 310                 315                 320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                325                 330                 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
            340                 345                 350

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        355                 360                 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
    370                 375                 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385                 390                 395                 400

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

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            420                 425                 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        435                 440                 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
```

```
    450                 455                 460


Leu Ser Leu Ser Pro Gly Lys
465                 470


<210>  55
<211>  236
<212>  PRT
<213>  Homo sapiens

<400>  55

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Ser Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30


Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser
        35                  40                  45


Gln Asp Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60


Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val
65                  70                  75                  80


Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
                85                  90                  95


Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Phe Cys Gln His
            100                 105                 110


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


Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140


Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160
```

```
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175


Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190


Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205


Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220


Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  56
<211>  464
<212>  PRT
<213>  Homo sapiens

<400>  56

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1               5                   10                  15


Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20                  25                  30


Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Val
        35                  40                  45


Ser Ser Gly Asp Tyr Tyr Trp Thr Trp Ile Arg Gln Ser Pro Gly Lys
    50                  55                  60


Gly Leu Glu Trp Ile Gly His Ile Tyr Tyr Ser Gly Asn Thr Asn Tyr
65                  70                  75                  80


Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Ile Asp Thr Ser Lys
                85                  90                  95
```

```
Thr Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110


Ile Tyr Tyr Cys Val Arg Asp Arg Val Thr Gly Ala Phe Asp Ile Trp
        115                 120                 125


Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
    130                 135                 140


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


Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
                165                 170                 175


Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
            180                 185                 190


Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
        195                 200                 205


Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
    210                 215                 220


His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys
225                 230                 235                 240


Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
                245                 250                 255


Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
            260                 265                 270


Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
        275                 280                 285


Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
    290                 295                 300
```

```
Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val
305                 310                 315                 320


Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
                325                 330                 335


Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr
            340                 345                 350


Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
        355                 360                 365


Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
    370                 375                 380


Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
385                 390                 395                 400


Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp
                405                 410                 415


Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
            420                 425                 430


Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
        435                 440                 445


Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460


<210>  57
<211>  236
<212>  PRT
<213>  Homo sapiens

<400>  57

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                   10                  15
```

```
Asp Thr Ala Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
            20                  25                  30

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45

Val Ser Asn Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Pro Gly Ile Pro
65                  70                  75                  80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
            100                 105                 110

Asp His Ser Ala Gly Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220
```

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 58
<211> 460
<212> PRT
<213> Homo sapiens

<400> 58

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

Val Ala Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Arg Asn Ala Met Phe Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Gly Ile Gly Thr Gly Gly Ala Thr Ser Tyr Ala Asp
65 70 75 80

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser
85 90 95

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
100 105 110

Tyr Cys Ala Arg Gly Arg Tyr Tyr Phe Pro Trp Trp Gly Gln Gly Thr
115 120 125

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
130 135 140

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

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn

```
                165                 170                 175

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
            180                 185                 190

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
        195                 200                 205

Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
    210                 215                 220

Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys
225                 230                 235                 240

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
                245                 250                 255

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
            260                 265                 270

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
        275                 280                 285

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
    290                 295                 300

Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr
305                 310                 315                 320

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
                325                 330                 335

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
            340                 345                 350

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

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
```

370 375 380

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
385 390 395 400

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
405 410 415

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
420 425 430

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
435 440 445

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 59
<211> 234
<212> PRT
<213> Homo sapiens

<400> 59

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
20 25 30

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45

Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr Gly Ala Ser Arg Arg Ala Thr Gly Ile Pro
65 70 75 80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
85 90 95

```
Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Arg Tyr
            100                 105                 110


Gly Ser Ser His Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Ser Arg
        115                 120                 125


Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
    130                 135                 140


Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
145                 150                 155                 160


Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
                165                 170                 175


Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190


Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
        195                 200                 205


His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
    210                 215                 220


Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230


<210>  60
<211>  467
<212>  PRT
<213>  Homo sapiens

<400>  60

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


Val Cys Ala Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30
```

```
Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Val Ser Gly Tyr Phe Phe
        35                  40                  45

Thr Thr Tyr Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu
    50                  55                  60

Glu Tyr Met Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser
65                  70                  75                  80

Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser
                85                  90                  95

Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met
            100                 105                 110

Tyr Tyr Cys Ala Arg Gly Gly Asn Trp Asn Cys Phe Asp Tyr Trp Gly
        115                 120                 125

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145                 150                 155                 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                165                 170                 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
            180                 185                 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        195                 200                 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
    210                 215                 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
225                 230                 235                 240
```

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
                245                 250                 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            260                 265                 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        275                 280                 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305                 310                 315                 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                325                 330                 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            340                 345                 350

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        355                 360                 365

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    370                 375                 380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385                 390                 395                 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                405                 410                 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            420                 425                 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        435                 440                 445
```

```
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    450                 455                 460


Pro Gly Lys
465


<210>  61
<211>  241
<212>  PRT
<213>  Homo sapiens

<400>  61

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Arg Gly Ala Arg Cys Asp Val Val Met Thr Gln Ser Pro Leu Ser
            20                  25                  30


Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser
        35                  40                  45


Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu
    50                  55                  60


Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn
65                  70                  75                  80


Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
                85                  90                  95


Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val
            100                 105                 110


Tyr Tyr Cys Met Gln Gly Thr His Trp Pro Leu Thr Phe Gly Gln Gly
        115                 120                 125


Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile
    130                 135                 140
```

```
Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val
145                 150                 155                 160


Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys
                165                 170                 175


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


Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu
        195                 200                 205


Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr
    210                 215                 220


His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
225                 230                 235                 240


Cys



<210>  62
<211>  471
<212>  PRT
<213>  Homo sapiens

<400>  62

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Arg Gly Ala Arg Cys Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
            20                  25                  30


Leu Val Lys Pro Ser Gly Thr Leu Ser Leu Thr Cys Ala Val Ser Gly
        35                  40                  45


Gly Ser Ile Ser Ser Ser Asn Trp Trp Ser Trp Val Arg Gln Pro Pro
    50                  55                  60


Gly Lys Gly Leu Glu Trp Ile Gly Glu Ile Tyr His Ser Gly Ser Thr
```

```
65                  70                  75                  80

Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Lys
                85                  90                  95

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

Thr Ala Val Tyr Tyr Cys Ala Arg Trp Thr Gly Arg Thr Asp Ala Phe
        115                 120                 125

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr
    130                 135                 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
145                 150                 155                 160

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                165                 170                 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
            180                 185                 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
        195                 200                 205

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
    210                 215                 220

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
225                 230                 235                 240

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
                245                 250                 255

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            260                 265                 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
```

275 280 285

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
290 295 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
305 310 315 320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
325 330 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
340 345 350

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
355 360 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
370 375 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385 390 395 400

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

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
420 425 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
435 440 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
450 455 460

Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 63

<211> 234
<212> PRT
<213> Homo sapiens

<400> 63

```
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                  10                  15


Asp Thr Thr Gly Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser
            20                  25                  30


Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45


Val Ser Ser Asn Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro
    50                  55                  60


Arg Pro Leu Ile Tyr Asp Ala Ser Thr Arg Ala Thr Gly Val Pro Ala
65                  70                  75                  80


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85                  90                  95


Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp
            100                 105                 110


Asn Trp Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
        115                 120                 125


Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
    130                 135                 140


Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
145                 150                 155                 160


Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
                165                 170                 175


Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190
```

```
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
        195                 200                 205


His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
    210                 215                 220


Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230


<210>  64
<211>  461
<212>  PRT
<213>  Homo sapiens

<400>  64

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


Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30


Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45


Thr Arg Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60


Glu Trp Met Gly Trp Ile Ser Thr Tyr Ser Gly Asn Thr Asn Tyr Ala
65                  70                  75                  80


Gln Lys Leu Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                85                  90                  95


Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110


Tyr Tyr Cys Ala Arg Arg Gln Leu Tyr Phe Asp Tyr Trp Gly Gln Gly
        115                 120                 125
```

```
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
    130                 135                 140

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
145                 150                 155                 160

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
                165                 170                 175

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
            180                 185                 190

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
        195                 200                 205

Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
    210                 215                 220

Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu
225                 230                 235                 240

Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu
                245                 250                 255

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            260                 265                 270

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln
        275                 280                 285

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    290                 295                 300

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu
305                 310                 315                 320

Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
                325                 330                 335
```

```
Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            340                 345                 350


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


Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    370                 375                 380


Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
385                 390                 395                 400


Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly
                405                 410                 415


Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
            420                 425                 430


Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        435                 440                 445


His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460


<210>  65
<211>  239
<212>  PRT
<213>  Homo sapiens

<400>  65

Met Arg Leu Pro Ala Gln Leu Leu Gly Leu Leu Met Leu Trp Ile Pro
1               5                   10                  15


Gly Ser Ser Ala Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser
            20                  25                  30


Val Thr Pro Gly Gln Pro Ala Ser Ile Ser Cys Lys Ser Gly Gln Ser
        35                  40                  45
```

```
Leu Leu His Ser Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Gln Phe Leu Ile Tyr Glu Val Ser Asn Arg Phe
65                  70                  75                  80

Ser Arg Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr
            100                 105                 110

Cys Met Gln Ser Ile Gln Leu Pro Trp Thr Phe Gly Gln Gly Thr Gln
        115                 120                 125

Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
    130                 135                 140

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145                 150                 155                 160

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175

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

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235
```

<210> 66
<211> 459
<212> PRT
<213> Homo sapiens

<400> 66

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

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Gly Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Val Ile Ser Tyr Asp Gly Asn Asp Lys Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Glu Leu Arg Val Leu Trp Gly Gln Gly Thr Leu
        115                 120                 125

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
    130                 135                 140

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

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
                165                 170                 175

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
            180                 185                 190

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn
```

```
        195                 200                 205

Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
    210                 215                 220

Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro
225                 230                 235                 240

Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
                245                 250                 255

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
            260                 265                 270

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
        275                 280                 285

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
    290                 295                 300

Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
305                 310                 315                 320

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
                325                 330                 335

Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
            340                 345                 350

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
        355                 360                 365

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
    370                 375                 380

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
385                 390                 395                 400

Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
```

405 410 415

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
420 425 430

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
435 440 445

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 67
<211> 235
<212> PRT
<213> Homo sapiens

<400> 67

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Asp Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

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

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Asp Ile Lys His Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
115 120 125

```
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
    130                 135                 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145                 150                 155                 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
                165                 170                 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
            180                 185                 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
        195                 200                 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
    210                 215                 220

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  68
<211>  465
<212>  PRT
<213>  Homo sapiens

<400>  68

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

Ala His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe
        35                  40                  45

Thr Asp Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60
```

```
Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Asp Thr Glu Tyr Asn
65                  70                  75                  80

Glu Lys Phe Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Ser Ile Tyr Tyr Tyr Asp Ala Pro Phe Ala Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
    130                 135                 140

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

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
    210                 215                 220

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
225                 230                 235                 240

Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
                245                 250                 255

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
            260                 265                 270
```

```
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
        275                 280                 285


Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
    290                 295                 300


Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
305                 310                 315                 320


Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
                325                 330                 335


Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
            340                 345                 350


Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
        355                 360                 365


Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
    370                 375                 380


Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
385                 390                 395                 400


Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
                405                 410                 415


Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
            420                 425                 430


Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
        435                 440                 445


Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
    450                 455                 460


Lys
465
```

<210> 69
<211> 233
<212> PRT
<213> Homo sapiens

<400> 69

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

Gly Arg Ala Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala
20 25 30

Pro Gly Gln Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Leu Gly Ser
35 40 45

Lys Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu
50 55 60

Val Val Tyr Asp Asp Ser Asp Arg Pro Ser Trp Ile Pro Glu Arg Phe
65 70 75 80

Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Gly
85 90 95

Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser
100 105 110

Ser Asp His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
115 120 125

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
130 135 140

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
145 150 155 160

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
165 170 175

```
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
            180                 185                 190


Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
        195                 200                 205


His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
    210                 215                 220


Lys Thr Val Ala Pro Thr Glu Cys Ser
225                 230


<210>  70
<211>  467
<212>  PRT
<213>  Homo sapiens

<400>  70

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


Gly Arg Ala Gln Met Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30


Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45


Arg Thr Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60


Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala
65                  70                  75                  80


Asp Ser Val Lys Gly Arg Phe Thr Ile Thr Arg Asp Asn Ser Lys Asn
                85                  90                  95


Thr Leu Asn Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110


Tyr Tyr Cys Ala Arg Ala Pro Gln Trp Glu Leu Val His Glu Ala Phe
```

```
        115                 120                 125

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr
    130                 135                 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
145                 150                 155                 160

Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                165                 170                 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
            180                 185                 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
        195                 200                 205

Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys
    210                 215                 220

Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu
225                 230                 235                 240

Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala
                245                 250                 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            260                 265                 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        275                 280                 285

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe
305                 310                 315                 320

Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly
```

325 330 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
340 345 350

Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val
355 360 365

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
370 375 380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385 390 395 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415

Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> 71
<211> 234
<212> PRT
<213> Homo sapiens

<400> 71

Met Gly Val Pro Thr His Leu Leu Gly Leu Leu Leu Leu Trp Ile Thr
1 5 10 15

His Ala Ile Cys Asp Ile Arg Met Thr Gln Ser Pro Ala Ser Leu Ser
20 25 30

```
Ala Ser Leu Gly Glu Thr Val Asn Ile Glu Cys Leu Ala Ser Glu Asp
        35                  40                  45

Ile Tyr Ser Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro
    50                  55                  60

Gln Leu Leu Ile Tyr Asn Ala Asn Ser Leu Gln Asn Gly Val Pro Ser
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn
                85                  90                  95

Ser Leu Gln Ser Glu Asp Val Ala Thr Tyr Phe Cys Gln Gln Tyr Asn
            100                 105                 110

Asn Tyr Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg
        115                 120                 125

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Thr Glu Gln
    130                 135                 140

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

Pro Arg Asp Ile Ser Val Lys Trp Lys Ile Asp Gly Thr Glu Arg Arg
                165                 170                 175

Asp Gly Val Leu Asp Ser Val Thr Asp Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190

Tyr Ser Met Ser Ser Thr Leu Ser Leu Thr Lys Ala Asp Tyr Glu Ser
        195                 200                 205

His Asn Leu Tyr Thr Cys Glu Val Val His Lys Thr Ser Ser Ser Pro
    210                 215                 220

Val Val Lys Ser Phe Asn Arg Asn Glu Cys
225                 230
```

<210> 72
<211> 465
<212> PRT
<213> Homo sapiens

<400> 72

Met Asp Ile Arg Leu Ser Leu Ala Phe Leu Val Leu Phe Ile Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Ala Asn Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Asp Tyr Ala Met Ala Trp Val Arg Gln Ser Pro Lys Lys Gly Leu
50 55 60

Glu Trp Val Ala Thr Ile Ile Tyr Asp Gly Ser Ser Thr Tyr Tyr Arg
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser
85 90 95

Thr Leu Tyr Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr
100 105 110

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

Trp Gly Gln Gly Val Leu Val Thr Val Ser Ser Ala Glu Thr Thr Ala
130 135 140

Pro Ser Val Tyr Pro Leu Ala Pro Gly Thr Ala Leu Lys Ser Asn Ser
145 150 155 160

Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val
165 170 175

```
Thr Val Thr Trp Asn Ser Gly Ala Leu Ser Ser Gly Val His Thr Phe
            180                 185                 190


Pro Ala Val Leu Gln Ser Gly Leu Tyr Thr Leu Thr Ser Ser Val Thr
        195                 200                 205


Val Pro Ser Ser Thr Trp Pro Ser Gln Thr Val Thr Cys Asn Val Ala
    210                 215                 220


His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asn
225                 230                 235                 240


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


Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr
            260                 265                 270


Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Gln Asp Asp
        275                 280                 285


Pro Glu Val His Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
    290                 295                 300


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


Val Ser Glu Leu Pro Ile Leu His Gln Asp Trp Leu Asn Gly Arg Thr
                325                 330                 335


Phe Arg Cys Lys Val Thr Ser Ala Ala Phe Pro Ser Pro Ile Glu Lys
            340                 345                 350


Thr Ile Ser Lys Pro Glu Gly Arg Thr Gln Val Pro His Val Tyr Thr
        355                 360                 365


Met Ser Pro Thr Lys Glu Glu Met Thr Gln Asn Glu Val Ser Ile Thr
    370                 375                 380
```

```
Cys Met Val Lys Gly Phe Tyr Pro Pro Asp Ile Tyr Val Glu Trp Gln
385                 390                 395                 400


Met Asn Gly Gln Pro Gln Glu Asn Tyr Lys Asn Thr Pro Pro Thr Met
                405                 410                 415


Asp Thr Asp Gly Ser Tyr Phe Leu Tyr Ser Lys Leu Asn Val Lys Lys
            420                 425                 430


Glu Lys Trp Gln Gln Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
        435                 440                 445


Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
    450                 455                 460


Lys
465


<210>  73
<211>  237
<212>  PRT
<213>  Homo sapiens

<400>  73

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Arg Gly Ala Arg Cys Glu Ser Ala Leu Thr Gln Pro Ala Ser Val
            20                  25                  30


Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser
        35                  40                  45


Ser Asp Val Gly Gly Tyr Asn Ser Val Ser Trp Tyr Gln Gln His Pro
    50                  55                  60


Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Val Ser Asn Arg Pro Ser
65                  70                  75                  80
```

```
Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser
                85                  90                  95


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


Asn Ser Tyr Thr Ser Thr Ser Met Val Phe Gly Gly Gly Thr Lys Leu
        115                 120                 125


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


Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu
145                 150                 155                 160


Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp
                165                 170                 175


Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln
            180                 185                 190


Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu
        195                 200                 205


Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly
    210                 215                 220


Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225                 230                 235


<210>  74
<211>  460
<212>  PRT
<213>  Homo sapiens

<400>  74

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15


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

```
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Leu
        35                  40                  45

Thr Ser Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Met Gly Trp Val Ser Phe Tyr Asn Gly Asn Thr Asn Tyr Ala
65                  70                  75                  80

Gln Lys Leu Gln Gly Arg Gly Thr Met Thr Thr Asp Pro Ser Thr Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Gly Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
        115                 120                 125

Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
    130                 135                 140

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

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
                165                 170                 175

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
            180                 185                 190

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
        195                 200                 205

Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
    210                 215                 220

Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys
```

225 230 235 240

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
245 250 255

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
260 265 270

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
275 280 285

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
290 295 300

Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr
305 310 315 320

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
325 330 335

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
340 345 350

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

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
370 375 380

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
385 390 395 400

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
405 410 415

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
420 425 430

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His

435 440 445

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 75
<211> 234
<212> PRT
<213> Homo sapiens

<400> 75

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30

Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45

Val Ser Ser Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60

Arg Leu Leu Ile Tyr Gly Ala Ala Thr Arg Ala Thr Gly Ile Pro Ala
65 70 75 80

Arg Val Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser
85 90 95

Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn
100 105 110

Asn Trp Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
115 120 125

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
130 135 140

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
145 150 155 160

```
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
                165                 170                 175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
        195                 200                 205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
    210                 215                 220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230


<210>  76
<211>  472
<212>  PRT
<213>  Homo sapiens

<400>  76

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15

Leu Arg Gly Ala Arg Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly
            20                  25                  30

Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Thr Phe Ser Asn Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Glu Gly Leu Glu Trp Val Ala Ala Ile Trp Phe Asp Ala Ser Asp Lys
65                  70                  75                  80

Tyr Tyr Ala Asp Ala Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
                85                  90                  95
```

```
Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            100                 105                 110


Thr Ala Val Tyr Tyr Cys Ala Arg Asp Gln Ala Ile Phe Gly Val Val
        115                 120                 125


Pro Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
    130                 135                 140


Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
145                 150                 155                 160


Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175


Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190


His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
        195                 200                 205


Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
    210                 215                 220


Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
225                 230                 235                 240


Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
                245                 250                 255


Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            260                 265                 270


Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        275                 280                 285


Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    290                 295                 300
```

```
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln
305                 310                 315                 320


Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln
                325                 330                 335


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


Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        355                 360                 365


Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    370                 375                 380


Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385                 390                 395                 400


Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                405                 410                 415


Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            420                 425                 430


Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        435                 440                 445


Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    450                 455                 460


Ser Leu Ser Leu Ser Pro Gly Lys
465                 470


<210>  77
<211>  231
<212>  PRT
<213>  Homo sapiens

<400>  77
```

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

Ser Val Ala Ser Tyr Glu Val Thr Gln Ala Pro Ser Val Ser Val Ser
            20                  25                  30

Pro Gly Gln Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp
        35                  40                  45

Lys Tyr Ala Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu
    50                  55                  60

Val Ile Tyr Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr
                85                  90                  95

Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser
            100                 105                 110

Thr Ala Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
        115                 120                 125

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
    130                 135                 140

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
145                 150                 155                 160

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
                165                 170                 175

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
            180                 185                 190

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
        195                 200                 205
```

```
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
    210                 215                 220


Val Ala Pro Thr Glu Cys Ser
225                 230


<210>  78
<211>  467
<212>  PRT
<213>  Homo sapiens

<400>  78

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


Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30


Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45


Thr Ser Tyr Gly Leu Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60


Glu Trp Met Gly Trp Ile Ile Pro Tyr Asn Gly Asn Thr Asn Ser Ala
65                  70                  75                  80


Gln Lys Leu Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                85                  90                  95


Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110


Tyr Phe Cys Ala Arg Asp Arg Asp Tyr Gly Val Asn Tyr Asp Ala Phe
        115                 120                 125


Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr
    130                 135                 140


Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
```

145 150 155 160

Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
165 170 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
180 185 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
195 200 205

Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys
210 215 220

Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu
225 230 235 240

Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala
245 250 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
260 265 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
275 280 285

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290 295 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe
305 310 315 320

Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly
325 330 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
340 345 350

Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val

355 360 365

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
370 375 380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385 390 395 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415

Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> 79
<211> 235
<212> PRT
<213> Homo sapiens

<400> 79

Met Ala Trp Ala Pro Leu Leu Leu Thr Leu Leu Ala His Cys Thr Gly
1 5 10 15

Ser Trp Ala Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser
20 25 30

Pro Gly Lys Thr Val Ala Ile Ser Cys Thr Arg Asn Ser Gly Ser Ile
35 40 45

Ala Ser Asn Ser Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro
50 55 60

```
Thr Thr Val Ile Phe Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp
65                  70                  75                  80

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

Ile Ser Gly Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser
            100                 105                 110

Tyr Asp Ser Asn Asn Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val
        115                 120                 125

Leu Gly Gln Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser
    130                 135                 140

Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser
145                 150                 155                 160

Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser
                165                 170                 175

Pro Val Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn
            180                 185                 190

Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp
        195                 200                 205

Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr
    210                 215                 220

Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225                 230                 235


<210>  80
<211>  470
<212>  PRT
<213>  Homo sapiens

<400>  80
```

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

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Ser Tyr Val Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Glu Gly Tyr Asp Tyr Gly Glu Asp Tyr Tyr Tyr
        115                 120                 125

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
    130                 135                 140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
145                 150                 155                 160

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
                165                 170                 175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
            180                 185                 190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
        195                 200                 205
```

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
    210                 215                 220

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
225                 230                 235                 240

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
                245                 250                 255

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
            260                 265                 270

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
        275                 280                 285

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
    290                 295                 300

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
305                 310                 315                 320

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
                325                 330                 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
            340                 345                 350

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
        355                 360                 365

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
    370                 375                 380

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
385                 390                 395                 400

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
                405                 410                 415
```

```
Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
            420                 425                 430


Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
        435                 440                 445


Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
    450                 455                 460


Ser Leu Ser Pro Gly Lys
465                 470


<210>  81
<211>  236
<212>  PRT
<213>  Homo sapiens

<400>  81

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30


Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45


Gln Asp Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60


Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser Arg Leu Leu Ser Gly Val
65                  70                  75                  80


Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95


Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110
```

```
Gly Asp Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115                 120                 125


Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140


Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160


Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175


Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190


Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205


Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220


Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  82
<211>  468
<212>  PRT
<213>  Homo sapiens

<400>  82

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15


Ala His Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30


Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45


Thr Asp Tyr Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
```

```
    50                  55                  60

Glu Trp Met Gly Glu Ile Asn Pro Asn Ser Gly Gly Ala Gly Tyr Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Leu Gly Tyr Asp Asp Ile Tyr Asp Asp Trp Tyr
        115                 120                 125

Phe Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
    130                 135                 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
145                 150                 155                 160

Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
        195                 200                 205

Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
    210                 215                 220

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
225                 230                 235                 240

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
                245                 250                 255

Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
```

```
            260                 265                 270

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        275                 280                 285

His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
    290                 295                 300

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
305                 310                 315                 320

Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
                325                 330                 335

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
            340                 345                 350

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln
        355                 360                 365

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
    370                 375                 380

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385                 390                 395                 400

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                405                 410                 415

Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            420                 425                 430

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        435                 440                 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    450                 455                 460

Ser Pro Gly Lys
```

465

<210> 83
<211> 240
<212> PRT
<213> Homo sapiens

<400> 83

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

Gly Ala Tyr Gly Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala
20 25 30

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser
35 40 45

Val Leu Asp Ser Ser Asp Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln
50 55 60

Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Asn Arg
65 70 75 80

Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
85 90 95

Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr
100 105 110

Tyr Cys Gln Gln Tyr Tyr Ser Asp Pro Phe Thr Phe Gly Pro Gly Thr
115 120 125

Lys Val Asp Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
130 135 140

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
145 150 155 160

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
165 170 175

```
Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
            180                 185                 190


Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
        195                 200                 205


Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
    210                 215                 220


Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235                 240


<210>  84
<211>  465
<212>  PRT
<213>  Homo sapiens

<400>  84

Met Asp Trp Thr Trp Ser Ile Leu Phe Leu Val Ala Ala Pro Thr Gly
1               5                   10                  15


Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30


Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45


Thr Ser Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60


Glu Trp Met Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala
65                  70                  75                  80


Gln Lys Leu Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                85                  90                  95


Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110
```

```
Tyr Tyr Cys Ala Arg Glu Ser Trp Phe Gly Glu Val Phe Phe Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
    130                 135                 140

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

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val
    210                 215                 220

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys
225                 230                 235                 240

Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
                245                 250                 255

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
            260                 265                 270

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
        275                 280                 285

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
    290                 295                 300

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
305                 310                 315                 320
```

```
Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
                325                 330                 335

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
            340                 345                 350

Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
        355                 360                 365

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
    370                 375                 380

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
385                 390                 395                 400

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
                405                 410                 415

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
            420                 425                 430

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
        435                 440                 445

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
    450                 455                 460

Lys
465
```

<210> 85
<211> 236
<212> PRT
<213> Homo sapiens

<400> 85

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15
```

```
Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Tyr Gly Ala Ser Asn Leu Glu Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Asn Tyr Tyr Cys Gln Gln
            100                 105                 110

Ala Asn Ser Phe Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220
```

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 86
<211> 466
<212> PRT
<213> Homo sapiens

<400> 86

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu
20 25 30

Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Val Ser Gly
35 40 45

Tyr Thr Leu Ser Asp Leu Ser Ile His Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Met Gly Gly Phe Asp Pro Gln Asp Gly Glu Thr
65 70 75 80

Ile Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Glu Asp Thr
85 90 95

Ser Thr Asp Thr Ala Tyr Met Glu Leu Ser Ser Leu Lys Ser Glu Asp
100 105 110

Thr Ala Val Tyr Tyr Cys Ala Thr Gly Ser Ser Ser Ser Trp Phe Asp
115 120 125

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

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

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro

```
                165                 170                 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
        195                 200                 205

Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
    210                 215                 220

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
225                 230                 235                 240

Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
```

```
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
    450                 455                 460

Gly Lys
465
```