

DESCRIPTION

PHARMACEUTICAL COMPOSITION FOR USE IN PREVENTION AND/OR TREATMENT
5 OF DISEASE THAT DEVELOPS OR PROGRESSES AS A RESULT OF DECREASE OR
LOSS OF ACTIVITY OF BLOOD COAGULATION FACTOR VIII AND/OR ACTIVATED
BLOOD COAGULATION FACTOR VIII

Technical Field

10 The present invention relates to a pharmaceutical composition or a dosage regimen used
for preventing and/or treating a disease that develops and/or progresses due to a decrease or
deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation
factor VIII. More specifically, the present invention relates to a dosage regimen or a
pharmaceutical composition comprising a bispecific antigen-binding molecule that recognizes
15 blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation
factor X and/or activated blood coagulation factor X, which are used for preventing and/or
treating hemophilia A, acquired hemophilia A, von Willebrand disease, and hemophilia A in
which an inhibitor against blood coagulation factor VIII and/or activated blood coagulation
factor VIII emerges. Furthermore, the present invention relates to a product that includes a
20 statement regarding administration of the pharmaceutical composition comprising the bispecific
antigen-binding molecule.

Background Art

Hemophilia is a hemorrhagic disease caused by a congenital deficiency or dysfunction
25 of coagulation factor VIII (FVIII) or coagulation factor IX (FIX). The former is called
hemophilia A and the latter is called hemophilia B. Genes for both factors are located on the X
chromosome, and since genetic defects take the X-chromosome-linked recessive hereditary form,
99% or more of the patients who develop the disease are men. It is known that the prevalence
rate is approximately one in 10,000 live male births, and the ratio between hemophilia A and
30 hemophilia B is approximately 5:1.

The severity of hemophilia A is defined by the FVIII activity in blood. Patients with
an activity of less than 1% are classified as severe, patients with an activity of 1% or more to less
than 5% are classified as moderate, and patients with an activity of 5% or more and less than
40% are classified as mild. Severe patients who account for approximately half of hemophilia
35 A patients exhibit bleeding symptoms several times a month, and this frequency is markedly high
as compared to those of moderate and mild patients.

For bleeding in hemophilia A patients, FVIII formulations are generally administered (on-demand therapy). In recent years, FVIII formulations are also administered prophylactically to prevent bleeding events (regular replacement therapy; Non-patent Documents 1 and 2). The half-life of FVIII formulations in blood is approximately 8 to 12 hours.

Therefore, for continuous prevention, FVIII formulations are administered to patients three times a week (Non-patent Documents 3 and 4). In on-demand therapy, FVIII formulations are also additionally administered at regular intervals as necessary to prevent rebleeding. In addition, FVIII formulations are mainly administered at home, but since they are administered intravenously, the difficulty of securing a blood vessel is a problem. Therefore, there has been a strong need for pharmaceutical agents with a lesser burden regarding their administration as compared to FVIII formulations.

Occasionally, antibodies against FVIII (inhibitors) develop in hemophilia A patients. Such inhibitors counteract the effects of the FVIII formulations. For bleeding in patients who have developed inhibitors (inhibitor patients), bypassing agents are administered. Their mechanisms of action are not dependent on FVIII function, that is, on the function of catalyzing the activation of blood coagulation factor X (FX) by activated blood coagulation factor IX (FIXa). Therefore, in some cases, bypassing agents cannot sufficiently stop the bleeding. Recently, results suggesting the effectiveness of regular administration therapy of bypassing agents have been obtained, but this has not yielded a sufficient effect to suppress bleeding as compared to FVIII formulations. Accordingly, there has been a strong need for therapeutic agents that can be administered subcutaneously, as well as long-acting therapeutic agents that can be administered less frequently, regardless of the presence of inhibitors.

Recently, as a means for solving the problem, antibodies that functionally substitute for FVIII and their use were disclosed (Patent Documents 1, 2, 3, and 4, and Non-patent Documents 5, 6, and 7).

Prior Art Documents

[Patent Documents]

[Patent Document 1] WO 2005/035754

[Patent Document 2] WO 2005/035756

[Patent Document 3] WO 2006/109592

[Patent Document 4] WO 2012/067176

[Non-patent Documents]

[Non-patent Document 1] Blood 58, 1-13 (1981)

[Non-patent Document 2] Nature 312, 330-337 (1984)

[Non-patent Document 3] Nature 312, 337-342 (1984)

[Non-patent Document 4] Biochim.Biophys.Acta 871, 268-278 (1986)

[Non-patent Document 5] Nature Medicine 18, 1570-1574(2012)

[Non-patent Document 6] PLOS ONE 8, 1-13(2013)

[Non-patent Document 7] J Thromb Haemost. 12, 206-213(2014)

5

Summary of the Invention

[Problems to be solved by the Invention]

An objective of the present invention is to provide a more effective pharmaceutical composition or a dosage regimen for preventing and/or treating a disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII.

10

[Means for Solving the Problems]

As a result of dedicated research, the present inventors succeeded in discovering a more effective dosage regimen for a pharmaceutical composition containing a bispecific antigen-binding molecule that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X for preventing and/or treating a disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII.

15

20

Specifically, the present invention relates to a pharmaceutical composition or a dosage regimen used for preventing and/or treating a disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII, and specifically relates to the following:

25

30

[1] a pharmaceutical composition for use in preventing and/or treating a disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII, wherein the composition comprises a bispecific antigen-binding molecule that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X, wherein the antigen-binding molecule is administered at an initial dose of approximately 0.001 to 100 mg/kg and is continually administered several times at continued doses that are nearly the same as or less than the initial dose, wherein the interval between individual administrations is at least one day or longer;

35

[2] the pharmaceutical composition of [1], wherein the continued dose is a dose selected from the group consisting of the same dose as the initial dose, and approximately one-half, approximately one-third, approximately 0.3-times, approximately one-fourth, approximately

one-fifth, and approximately one-tenth the initial dose;

[3] the pharmaceutical composition of [2], wherein the initial dose is 1 mg/kg and at least one of the continued doses is 0.3 mg/kg;

[4] the pharmaceutical composition of [2], wherein the initial dose is 3 mg/kg and at least one of the continued doses is 1 mg/kg;

[5] the pharmaceutical composition of [2], wherein the initial dose is 3 mg/kg and at least one of the continued doses is 3 mg/kg;

[6] the pharmaceutical composition of any one of [1] to [5], wherein at least one of the intervals between individual administrations is one week;

[7] the pharmaceutical composition of any one of [1] to [6], wherein the disease is selected from the group consisting of hemophilia A, acquired hemophilia A, von Willebrand disease, and hemophilia A with emergence of an inhibitor against blood coagulation factor VIII and/or activated blood coagulation factor VIII;

[8] the pharmaceutical composition of any one of [1] to [7], wherein the antigen-binding molecule is the bispecific antibody described below, wherein the first polypeptide and the third polypeptide are associated and the second polypeptide and the fourth polypeptide are associated:

a bispecific antibody comprising a first polypeptide which is an H chain comprising the amino acid sequence of SEQ ID NO: 20; a second polypeptide which is an H chain comprising the amino acid sequence of SEQ ID NO: 25; a third polypeptide and a fourth polypeptide which are a commonly shared L chain comprising the amino acid sequence of SEQ ID NO: 32;

[9] the pharmaceutical composition of any one of [1] to [8], wherein the antigen-binding molecule is administered subcutaneously;

[10] a product comprising (i) a container; (ii) a pharmaceutical composition in the container, wherein the composition comprises a bispecific antigen-binding molecule that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X; and (iii) a document instructing administration of the antigen-binding molecule at an initial dose of approximately 0.001 to 100 mg/kg and several continued administrations of continued doses that are nearly the same as or less than the initial dose, wherein the interval between individual administrations is at least one day or longer;

[11] the product of [10], wherein the initial dose is 1 mg/kg and at least one of the continued doses is 0.3 mg/kg;

[12] the product of [10] or [11], wherein at least one of the intervals between individual administrations is one week;

[13] the product of any one of [10] to [12], which further comprises a label attached to the container which indicates that the pharmaceutical composition can be used for preventing and/or treating a disease that develops and/or progresses due to a decrease or deficiency in the activity

of blood coagulation factor VIII and/or activated blood coagulation factor VIII;

[14] the product of [13], wherein the label indicates that the pharmaceutical composition can be used for the treatment of hemophilia A, acquired hemophilia A, von Willebrand disease, and hemophilia A with emergence of an inhibitor against blood coagulation factor VIII and/or

5 activated blood coagulation factor VIII; and

[15] the product of any one of [10] to [14], wherein the antigen-binding molecule is the bispecific antibody described below, wherein the first polypeptide and the third polypeptide are associated and the second polypeptide and the fourth polypeptide are associated:

10 a bispecific antibody comprising a first polypeptide which is an H chain comprising the amino acid sequence of SEQ ID NO: 20; a second polypeptide which is an H chain comprising the amino acid sequence of SEQ ID NO: 25; and a third polypeptide and a fourth polypeptide which are commonly shared L chain comprising the amino acid sequence of SEQ ID NO: 32.

Furthermore, the present invention relates to:

15 [16] a method for preventing and/or treating a disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII, which comprises administering a bispecific antigen-binding molecule which recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X at an initial dose of approximately 0.001 to 100 mg/kg and continually administering the antigen-binding molecule
20 several times at continued doses that are nearly the same as or less than the initial dose, wherein the interval between administrations is at least one day or longer;

[17] an antigen-binding molecule for use in preventing and/or treating a disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII, wherein the bispecific antigen-binding molecule
25 recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X and is administered at an initial dose of approximately 0.001 to 100 mg/kg and then continually administered several times at continued doses that are nearly the same as or less than the initial dose, wherein the interval between administrations is at least one day or longer; and

30 [18] use of an antigen-binding molecule in the manufacture of a pharmaceutical composition used for preventing and/or treating a disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII, wherein the bispecific antigen-binding molecule recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated
35 blood coagulation factor X and is administered at an initial dose of approximately 0.001 to 100 mg/kg and then continually administered several times at continued doses that are nearly the

same as or less than the initial dose, wherein the interval between administrations is at least one day or longer.

Brief Description of the Drawings

Fig. 1 shows a graph indicating the changes in bleeding frequency of inhibitor-possessing patients and inhibitor-non-possessing patients who received ACE910 administration for 12 weeks in Examination 1. The numbers on the horizontal axis indicate the numbering of the patients who participated in the examination.

Fig. 2 shows a graph indicating the changes in bleeding frequency of inhibitor-possessing patients and inhibitor-non-possessing patients who received ACE910 administration for 12 weeks in Examination 2. The numbers on the horizontal axis indicate the numbering of the patients who participated in the examination.

Fig. 3 shows a graph indicating the changes in bleeding frequency of inhibitor-possessing patients and inhibitor-non-possessing patients who received ACE910 administration for 12 weeks in Examination 3. The numbers on the horizontal axis indicate the numbering of the patients who participated in the examination.

Mode for Carrying Out the Invention

A bispecific antigen-binding molecule that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X preferably has an activity of functionally substituting for coagulation factor VIII.

In the present invention, the phrase “functionally substitute for coagulation factor VIII” means that coagulation factor IX (FIX) or coagulation factor IXa (FIXa), and coagulation factor X (FX) are recognized, and the activation of FX by FIXa is promoted (FXa generation by FIXa is promoted). FXa generation-promoting activity can be evaluated using, for example, a measurement system comprising FIXa, FX, the synthetic substrate S-2222 (a synthetic substrate of FXa), and phospholipids. Such a measurement system shows the correlation between the severity of the disease and the clinical symptoms in hemophilia A cases (Rosen S, Andersson M, Blomback M *et al.* Clinical applications of a chromogenic substrate method for determination of FVIII activity. *Thromb Haemost* 1985; 54: 811-23).

Such antigen-binding molecules can be obtained according to methods described, for example, in WO2005/035756, WO2006/109592, and WO2012/067176. Specifically, based on the sequences of antibodies against coagulation factor IX and/or activated coagulation factor IX and antibodies against coagulation factor X, antibodies can be generated using genetic recombination techniques known to those skilled in the art. A polynucleotide encoding an

antibody can be constructed based on the sequences of the antibodies against coagulation factor IX and/or activated coagulation factor IX and antibodies against coagulation factor X, and this can be inserted into an expression vector and subsequently expressed in appropriate host cells (see for example, Co, M. S. *et al.*, J. Immunol. (1994) 152, 2968-2976; Better, M. and Horwitz, A. H., Methods Enzymol. (1989) 178, 476-496; Pluckthun, A. and Skerra, A., Methods Enzymol. (1989) 178, 497-515; Lamoyi, E., Methods Enzymol. (1986) 121, 652-663; Rousseaux, J. *et al.*, Methods Enzymol. (1986) 121, 663-669; and Bird, R. E. and Walker, B. W., Trends Biotechnol. (1991) 9, 132-137).

Such bispecific antigen-binding molecules can be isolated from inside host cells or from outside the cells (such as from the medium), and purified as substantially pure and homogeneous antibodies. Isolation and purification of antibodies can be carried out using methods generally used for isolating and purifying antibodies, and are not limited. For example, antibodies can be isolated and purified by appropriately selecting and combining column chromatography columns, filters, ultrafiltration, salting-out, solvent precipitation, solvent extraction, distillation, immunoprecipitation, SDS-polyacrylamide gel electrophoresis, isoelectric focusing, dialysis, recrystallization, and such.

The bispecific antigen-binding molecules of the present invention include the antibodies described, for example, in WO2005/035756, WO2006/109592, and WO2012/067176.

A bispecific antigen-binding molecule comprises a first antigen-binding site and a second antigen-binding site which can specifically bind to at least two different types of antigens. While the first antigen-binding site and the second antigen-binding site of the bispecific antigen-binding molecule of the present invention are not particularly limited as long as they have an activity to bind to coagulation factor IX and/or activated coagulation factor IX, and coagulation factor X, respectively, examples include sites necessary for binding with antigens, such as antibodies, scaffold molecules (antibody-like molecules), and peptides, and fragments containing such sites. A scaffold molecule is a molecule that exhibits a function by binding to a target molecule, and any polypeptide may be used as long as it is a conformationally stable polypeptide that can bind to at least one target antigen. Examples of such polypeptides include antibody variable regions, fibronectin (WO 2002/032925), protein A domain (WO 1995/001937), LDL receptor A domain (WO 2004/044011, WO 2005/040229), ankyrin (WO 2002/020565), as well as the molecules described in Nygren *et al.* (Current Opinion in Structural Biology, 7: 463-469 (1997); and Journal of Immunol Methods, 290: 3-28 (2004)), Binz *et al.* (Nature Biotech 23: 1257-1266 (2005)), and Hosse *et al.* (Protein Science 15: 14-27(2006)). Furthermore, as described in Curr Opin Mol Ther. 2010 Aug; 12(4): 487-95 and Drugs. 2008; 68(7): 901-12, peptide molecules that can bind to the target antigens can also be used.

Bispecific antigen-binding molecules can be produced using, for example, genetic

recombination techniques (see, for example, Borrebaeck CAK and Larrick JW, THERAPEUTIC MONOCLONAL ANTIBODIES, Published in the United Kingdom by MACMILLAN PUBLISHERS LTD, 1990). Recombinant antibodies can be obtained by cloning DNAs encoding the antibodies from hybridomas or antibody-producing cells, such as sensitized lymphocytes that produce antibodies, inserting them into suitable vectors, and then introducing them into hosts (host cells) to produce the antibodies.

Furthermore, bispecific antigen-binding molecules may include not only whole antibodies but also antibody fragments and low-molecular-weight antibodies, and modified antibodies.

For example, antibody fragments and low-molecular-weight antibodies include diabodies (Dbs), linear antibodies, and single chain antibody (hereinafter, also denoted as scFv) molecules. Herein, an “Fv” fragment is a smallest antibody fragment and comprises a full antigen recognition site and binding site.

Bispecific antibodies include human antibodies, mouse antibodies, rat antibodies, and such, and their origins are not limited. They may also be genetically modified antibodies, such as chimeric antibodies and humanized antibodies.

Methods for obtaining human antibodies are already known. For example, a human antibody of interest can be obtained by immunizing a transgenic animal carrying the entire repertoire of human antibody genes with an antigen of interest (see International Publication No. WO 93/12227, WO 92/03918, WO 94/02602, WO 94/25585, WO 96/34096, and WO 96/33735).

Genetically modified antibodies can also be produced using known methods. Specifically, for example, a chimeric antibody is an antibody that comprises H chain and L chain variable regions of an immunized animal antibody, and H chain and L chain constant regions of a human antibody. Chimeric antibodies can be obtained by linking DNAs encoding the variable regions of an antibody derived from an immunized animal with DNAs encoding the constant regions of a human antibody, inserting this into an expression vector, and then introducing this into host cells to produce the antibodies.

A humanized antibody is a modified antibody which is also often referred to as a reshaped human antibody. A humanized antibody is constructed by transferring the CDRs of an antibody derived from an immunized animal to the complementarity determining regions of a human antibody. General genetic recombination techniques for producing them are also known (see European Patent Application Publication No. EP 239400; International Publication No. WO 96/02576; Sato K *et al.*, Cancer Research 1993, 53: 851-856; International Publication No. WO 99/51743).

More specifically, the bispecific antigen-binding molecule of the present invention is a bispecific antibody in which a first polypeptide and a third polypeptide are associated and a

second polypeptide and a fourth polypeptide are associated, and is preferably any one of the antibodies described below:

(a) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 1; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 4; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 9 (Q1-G4k/J268-G4h/L45-k);

(b) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 1; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 5; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 9 (Q1-G4k/J321-G4h/L45-k);

(c) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 2; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 6; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 8 (Q31-z7/J326-z107/L2-k);

(d) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 3; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 7; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 9 (Q64-z55/J344-z107/L45-k);

(e) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 10; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 6; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 30 (Q64-z7/J326-z107/L334-k);

(f) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 10; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 7; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 33 (Q64-z7/J344-z107/L406-k);

(g) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 11; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 4; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 33

(Q85-G4k/J268-G4h/L406-k);

(h) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 11; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 5; and a third and fourth polypeptide which are a

commonly shared L chain containing the amino acid sequence of SEQ ID NO: 30
(Q85-G4k/J321-G4h/L334-k);

(i) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 12; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 21; and a third and fourth polypeptide which are a

commonly shared L chain containing the amino acid sequence of SEQ ID NO: 33
(Q153-G4k/J232-G4h/L406-k);

(j) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 13; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 22; and a third and fourth polypeptide which are a

commonly shared L chain containing the amino acid sequence of SEQ ID NO: 29
(Q354-z106/J259-z107/L324-k);

(k) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 14; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 21; and a third and fourth polypeptide which are a

commonly shared L chain containing the amino acid sequence of SEQ ID NO: 33
(Q360-G4k/J232-G4h/L406-k);

(l) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 15; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 23; and a third and fourth polypeptide which are a

commonly shared L chain containing the amino acid sequence of SEQ ID NO: 30
(Q360-z118/J300-z107/L334-k);

(m) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 16; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 21; and a third and fourth polypeptide which are a

commonly shared L chain containing the amino acid sequence of SEQ ID NO: 28
(Q405-G4k/J232-G4h/L248-k);

(n) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 17; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 27; and a third and fourth polypeptide which are a

commonly shared L chain containing the amino acid sequence of SEQ ID NO: 34
(Q458-z106/J346-z107/L408-k);

(o) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 18; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 25; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 30

5 (Q460-z121/J327-z119/L334-k);

(p) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 19; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 24; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 30

10 (Q499-z118/J327-z107/L334-k);

(q) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 19; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 24; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 31

15 (Q499-z118/J327-z107/L377-k);

(r) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 19; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 27; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 28

20 (Q499-z118/J346-z107/L248-k);

(s) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 20; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 25; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 32

25 (Q499-z121/J327-z119/L404-k);

(t) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 20; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 26; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 31

30 (Q499-z121/J339-z119/L377-k); and

(u) a bispecific antibody comprising a first polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 12; a second polypeptide which is an H chain containing the amino acid sequence of SEQ ID NO: 35; and a third and fourth polypeptide which are a commonly shared L chain containing the amino acid sequence of SEQ ID NO: 36

35 (Q153-G4k/J142-G4h/L180-k).

The bispecific antibody of (s) is particularly preferred.

Pharmaceutical compositions of the present invention which are used for therapeutic or preventive purposes can be prepared by mixing, if necessary, with suitable pharmaceutically acceptable carriers, vehicles, and such and made into a freeze-dry formulation or a solution formulation. Examples of suitable pharmaceutically acceptable carriers and vehicles include
 5 sterilized water, physiological saline, stabilizers, excipients, antioxidants (such as ascorbic acid), buffers (such as phosphate, citrate, histidine, and other organic acids), antiseptics, surfactants (such as PEG and Tween), chelating agents (such as EDTA), and binders. They may also contain other low-molecular-weight polypeptides, proteins such as serum albumin, gelatin, and immunoglobulins, amino acids such as glycine, glutamine, asparagine, glutamic acid, aspartic
 10 acid, methionine, arginine, and lysine, sugars and carbohydrates such as polysaccharides and monosaccharides, and sugar alcohols such as mannitol and sorbitol. When preparing an aqueous solution for injection, for example, physiological saline and isotonic solutions containing glucose and other adjuvants such as D-sorbitol, D-mannose, D-mannitol, and sodium chloride may be used, and appropriate solubilizers such as alcohol (for example, ethanol),
 15 polyalcohols (such as propylene glycol and PEG), and nonionic surfactants (such as polysorbate 80, polysorbate 20, poloxamer 188, and HCO-50) may be used in combination. By mixing hyaluronidase into the formulation, a larger fluid volume can be administered subcutaneously (Expert Opin Drug Deliv. 2007 Jul; 4(4): 427-40). Further, the pharmaceutical compositions of the present invention may be preliminarily loaded in a syringe. Meanwhile, the solution
 20 formulation can be prepared according to the method described in WO 2011/090088.

If necessary, the antigen-binding molecules of the present invention can be encapsulated in microcapsules (e.g., those made of hydroxymethylcellulose, gelatin, and poly(methylmethacrylate)), or prepared as colloidal drug delivery systems (e.g., liposomes, albumin microspheres, microemulsion, nanoparticles, and nanocapsules) (see, for example,
 25 “Remington's Pharmaceutical Science 16th edition”, Oslo Ed. (1980)). Methods for preparing the pharmaceutical agents as controlled-release pharmaceutical agents are also well known, and such methods may be applied to the antigen-binding molecules of the present invention (Langer *et al.*, J. Biomed. Mater. Res. 15: 267-277 (1981); Langer, Chemtech. 12: 98-105 (1982); U.S. Patent No. 3,773,919; European Patent Application Publication No. EP 58,481; Sidman *et al.*,
 30 Biopolymers 22: 547-556 (1983); EP 133,988).

The pharmaceutical compositions of the present invention can be administered to a patient *via* any appropriate route, for example, intravenously by bolus injection or continuous infusion for a given period, intramuscularly, intraperitoneally, intracerebrospinally, transdermally, subcutaneously, intraarticularly, sublingually, intrasynovially, orally, by inhalation, locally, or
 35 externally. Intravenous administration or subcutaneous administration is preferred.

In the present invention, “initial dose” refers to, for example, the dose used when a

bispecific antigen-binding molecule of the present invention is administered to a patient for the first time. The initial dose is within the range of approximately 0.001 mg/kg to approximately 100 mg/kg, and is for example, approximately 0.001 mg/kg, approximately 0.002 mg/kg, approximately 0.0025 mg/kg, approximately 0.003 mg/kg, approximately 0.004 mg/kg, approximately 0.005 mg/kg, approximately 0.006 mg/kg, approximately 0.007 mg/kg, approximately 0.0075 mg/kg, approximately 0.008 mg/kg, approximately 0.009 mg/kg, approximately 0.01 mg/kg, approximately 0.02 mg/kg, approximately 0.025 mg/kg, approximately 0.03 mg/kg, approximately 0.04 mg/kg, approximately 0.05 mg/kg, approximately 0.06 mg/kg, approximately 0.07 mg/kg, approximately 0.075 mg/kg, approximately 0.08 mg/kg, approximately 0.09 mg/kg, approximately 0.1 mg/kg, approximately 0.2 mg/kg, approximately 0.25 mg/kg, approximately 0.3 mg/kg, approximately 0.4 mg/kg, approximately 0.5 mg/kg, approximately 0.6 mg/kg, approximately 0.7 mg/kg, approximately 0.75 mg/kg, approximately 0.8 mg/kg, approximately 0.9 mg/kg, approximately 1 mg/kg, approximately 2 mg/kg, approximately 2.5 mg/kg, approximately 3 mg/kg, approximately 4 mg/kg, approximately 5 mg/kg, approximately 6 mg/kg, approximately 7 mg/kg, approximately 7.5 mg/kg, approximately 8 mg/kg, approximately 9 mg/kg, approximately 10 mg/kg, approximately 11 mg/kg, approximately 12 mg/kg, approximately 12.5 mg/kg, approximately 13 mg/kg, approximately 14 mg/kg, approximately 15 mg/kg, approximately 16 mg/kg, approximately 17 mg/kg, approximately 17.5 mg/kg, approximately 18 mg/kg, approximately 19 mg/kg, approximately 20 mg/kg, approximately 21 mg/kg, approximately 22 mg/kg, approximately 22.5 mg/kg, approximately 23 mg/kg, approximately 24 mg/kg, approximately 25 mg/kg, approximately 26 mg/kg, approximately 27 mg/kg, approximately 27.5 mg/kg, approximately 28 mg/kg, approximately 29 mg/kg, approximately 30 mg/kg, approximately 35 mg/kg, approximately 40 mg/kg, approximately 45 mg/kg, approximately 50 mg/kg, approximately 60 mg/kg, approximately 70 mg/kg, approximately 75 mg/kg, approximately 80 mg/kg, approximately 90 mg/kg, or approximately 100 mg/kg.

“Continued dose” refers to, for example, the dose that is administered continually after administration of the initial dose. The continued dose is nearly the same as or less than the initial dose, and for example, it is nearly the same as the initial dose, or approximately 1/2, approximately 1/3, approximately 1/4, approximately 1/5, approximately 1/6, approximately 1/7, approximately 1/8, approximately 1/9, approximately 1/10, approximately 1/20, approximately 1/25, approximately 1/30, approximately 1/40, approximately 1/50, approximately 1/60, approximately 1/70, approximately 1/80, approximately 1/90, approximately 1/100 of the initial dose, approximately 0.01 times, approximately 0.02 times, approximately 0.03 times, approximately 0.04 times, approximately 0.05 times, approximately 0.06 times, approximately 0.07 times, approximately 0.08 times, approximately 0.09 times, approximately 0.1 times,

approximately 0.2 times, approximately 0.25 times, approximately 0.3 times, approximately 0.4 times, approximately 0.5 times, approximately 0.6 times, approximately 0.7 times, approximately 0.8 times, approximately 0.9 times, or approximately 1 time the initial dose.

As long as the continued dose is nearly the same or less than the initial dose, the dose may vary within that range, and the multiple doses during continued dosing do not have to be the same dose. For example, the dose may be decreased gradually, or various doses may arbitrarily be administered repeatedly.

Preferably, the initial dose is 10 mg/kg and at least one of the continued doses is 10 mg/kg, the initial dose is 10 mg/kg and at least one of the continued doses is 3 mg/kg, the initial dose is 10 mg/kg and at least one of the continued doses is 1 mg/kg, the initial dose is 10 mg/kg and at least one of the continued doses is 0.3 mg/kg, the initial dose is 10 mg/kg and at least one of the continued doses is 0.1 mg/kg, the initial dose is 3 mg/kg and at least one of the continued doses is 3 mg/kg, the initial dose is 3 mg/kg and at least one of the continued doses is 1 mg/kg, the initial dose is 3 mg/kg and at least one of the continued doses is 0.3 mg/kg, the initial dose is 3 mg/kg and at least one of the continued doses is 0.1 mg/kg, the initial dose is 1 mg/kg and at least one of the continued doses is 1 mg/kg, the initial dose is 1 mg/kg and at least one of the continued doses is 0.3 mg/kg, or the initial dose is 1 mg/kg and at least one of the continued doses is 0.1 mg/kg.

More preferably, the initial dose is 10 mg/kg and the continued dose is 10 mg/kg, the initial dose is 10 mg/kg and the continued dose is 3 mg/kg, the initial dose is 10 mg/kg and the continued dose is 1 mg/kg, the initial dose is 10 mg/kg and the continued dose is 0.3 mg/kg, the initial dose is 10 mg/kg and the continued dose is 0.1 mg/kg, the initial dose is 3 mg/kg and the continued dose is 3 mg/kg, the initial dose is 3 mg/kg and the continued dose is 1 mg/kg, the initial dose is 3 mg/kg and the continued dose is 0.3 mg/kg, the initial dose is 3 mg/kg and the continued dose is 0.1 mg/kg, the initial dose is 1 mg/kg and the continued dose is 1 mg/kg, the initial dose is 1 mg/kg and the continued dose is 0.3 mg/kg, or the initial dose is 1 mg/kg and the continued dose is 0.1 mg/kg.

Besides mg/kg, the dose may be denoted as a fixed dose (mg/body) and/or a body surface area-based dose (mg/m^2) corresponding to the aforementioned body weight-based dose.

The number of times the continued dose is continually administered is not particularly limited, and the number is for example once, twice, three times, four times, five times, six times, seven times, eight times, nine times, ten times, 15 times, 20 times, 25 times, 35 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, 100 times, 500 times, 1000 times, and 10000 times.

“Administration interval” (an interval between individual administrations) indicates the interval between administration of the initial dose and administration of the first continued dose,

and the interval between administration of the n^{th} continued dose (n is an integer of 1 or greater) and administration of the $(n+1)^{\text{th}}$ continued dose. The administration interval may be one or more days, for example, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 1 year. The administration interval can be expressed in different terms, such as once a day, once every 2 days, once every 3 days, once every 4 days, once every 5 days, once every 6 days, once a week, once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks, once every 8 weeks, once every 9 weeks, once every 10 weeks, once every 11 weeks, once every 12 weeks, once every 13 weeks, once every 14 weeks, once every 15 weeks, once every 16 weeks, once every 17 weeks, once every 18 weeks, once every 19 weeks, once every 20 weeks, once every 21 weeks, once every 22 weeks, once every 23 weeks, once every 24 weeks, once every 25 weeks, once a month, once every 2 months, once every 3 months, once every 4 months, once every 5 months, once every 6 months, once every 7 months, once every 8 months, once every 9 months, once every 10 months, once every 11 months, or once a year. Further, the administration interval can be expressed in other terms, such as every day, every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, every week, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, every 8 weeks, every 9 weeks, every 10 weeks, every 11 weeks, every 12 weeks, every 13 weeks, every 14 weeks, every 15 weeks, every 16 weeks, every 17 weeks, every 18 weeks, every 19 weeks, every 20 weeks, every 21 weeks, every 22 weeks, every 23 weeks, every 24 weeks, every 25 weeks, every month, every 2 months, every 3 months, every 4 months, every 5 months, every 6 months, every 7 months, every 8 months, every 9 months, every 10 months, every 11 months, or every year.

The interval between administration of the initial dose and administration of the first continued dose and the interval between administration of the n^{th} continued dose (n is an integer of 1 or greater) and administration of the $(n+1)^{\text{th}}$ continued dose may all be the same; however, they do not have to be all the same. For example, the interval between administration of the initial dose and administration of the first continued dose may be longer than the interval between administration of the n^{th} continued dose and administration of the $(n+1)^{\text{th}}$ continued dose; or the interval between administration of the initial dose and administration of the first continued dose may be shorter than the interval between administration of the n^{th} continued dose and administration of the $(n+1)^{\text{th}}$ continued dose. Furthermore, the interval between administration of the n^{th} continued dose and administration of the $(n+1)^{\text{th}}$ continued dose and the interval between administration of the m^{th} continued dose (m is an integer of 1 or greater) and

administration of the $(m+1)^{\text{th}}$ continued dose may be the same or different. For example, as the number of times the continued dose is administered increases, the administration interval may become longer or shorter.

Preferably, the initial dose is 10 mg/kg and at least one of the continued doses is 10 mg/kg and the administration interval is one week, the initial dose is 10 mg/kg and at least one of the continued doses is 3 mg/kg and the administration interval is one week, the initial dose is 10 mg/kg and at least one of the continued doses is 1 mg/kg and the administration interval is one week, the initial dose is 10 mg/kg and at least one of the continued doses is 0.3 mg/kg and the administration interval is one week, the initial dose is 10 mg/kg and at least one of the continued doses is 0.1 mg/kg and the administration interval is one week, the initial dose is 3 mg/kg and at least one of the continued doses is 3 mg/kg and the administration interval is one week, the initial dose is 3 mg/kg and at least one of the continued doses is 1 mg/kg and the administration interval is one week, the initial dose is 3 mg/kg and at least one of the continued doses is 0.3 mg/kg and the administration interval is one week, the initial dose is 3 mg/kg and at least one of the continued doses is 0.1 mg/kg and the administration interval is one week, the initial dose is 1 mg/kg and at least one of the continued doses is 1 mg/kg and the administration interval is one week, the initial dose is 1 mg/kg and at least one of the continued doses is 0.3 mg/kg and the administration interval is one week, the initial dose is 1 mg/kg and at least one of the continued doses is 0.1 mg/kg and the administration interval is one week, the initial dose is 10 mg/kg and at least one of the continued doses is 10 mg/kg and the administration interval is 2 weeks, the initial dose is 10 mg/kg and at least one of the continued doses is 3 mg/kg and the administration interval is 2 weeks, the initial dose is 10 mg/kg and at least one of the continued doses is 1 mg/kg and the administration interval is 2 weeks, the initial dose is 10 mg/kg and at least one of the continued doses is 0.3 mg/kg and the administration interval is 2 weeks, the initial dose is 10 mg/kg and at least one of the continued doses is 0.1 mg/kg and the administration interval is 2 weeks, the initial dose is 3 mg/kg and at least one of the continued doses is 3 mg/kg and the administration interval is 2 weeks, the initial dose is 3 mg/kg and at least one of the continued doses is 1 mg/kg and the administration interval is 2 weeks, the initial dose is 3 mg/kg and at least one of the continued doses is 0.3 mg/kg and the administration interval is 2 weeks, the initial dose is 3 mg/kg and at least one of the continued doses is 0.1 mg/kg and the administration interval is 2 weeks, the initial dose is 1 mg/kg and at least one of the continued doses is 1 mg/kg and the administration interval is 2 weeks, the initial dose is 1 mg/kg and at least one of the continued doses is 0.3 mg/kg and the administration interval is 2 weeks, the initial dose is 1 mg/kg and at least one of the continued doses is 0.1 mg/kg and the administration interval is 2 weeks, the initial dose is 10 mg/kg and at least one of the continued doses is 10 mg/kg and the administration interval is 3 weeks, the initial dose is 10 mg/kg and at least one of the continued

continued dose is 1 mg/kg and the administration interval is 4 weeks, the initial dose is 3 mg/kg and the continued dose is 0.3 mg/kg and the administration interval is 4 weeks, the initial dose is 3 mg/kg and the continued dose is 0.1 mg/kg and the administration interval is 4 weeks, the initial dose is 1 mg/kg and the continued dose is 1 mg/kg and the administration interval is 4 weeks, the initial dose is 1 mg/kg and the continued dose is 0.3 mg/kg and the administration interval is 4 weeks, the initial dose is 1 mg/kg and the continued dose is 0.1 mg/kg and the administration interval is 4 weeks, the initial dose is 10 mg/kg and the continued dose is 10 mg/kg and the administration interval is 1 month, the initial dose is 10 mg/kg and the continued dose is 3 mg/kg and the administration interval is 1 month, the initial dose is 10 mg/kg and the continued dose is 1 mg/kg and the administration interval is 1 month, the initial dose is 10 mg/kg and the continued dose is 0.3 mg/kg and the administration interval is 1 month, the initial dose is 10 mg/kg and the continued dose is 0.1 mg/kg and the administration interval is 1 month, the initial dose is 3 mg/kg and the continued dose is 3 mg/kg and the administration interval is 1 month, the initial dose is 3 mg/kg and the continued dose is 1 mg/kg and the administration interval is 1 month, the initial dose is 3 mg/kg and the continued dose is 0.3 mg/kg and the administration interval is 1 month, the initial dose is 3 mg/kg and the continued dose is 0.1 mg/kg and the administration interval is 1 month, the initial dose is 1 mg/kg and the continued dose is 1 mg/kg and the administration interval is 1 month, the initial dose is 1 mg/kg and the continued dose is 0.3 mg/kg and the administration interval is 1 month, the initial dose is 1 mg/kg and the continued dose is 0.1 mg/kg and the administration interval is 1 month, the initial dose is 10 mg/kg and the continued dose is 10 mg/kg and the administration interval is 2 months, the initial dose is 10 mg/kg and the continued dose is 3 mg/kg and the administration interval is 2 months, the initial dose is 10 mg/kg and the continued dose is 1 mg/kg and the administration interval is 2 months, the initial dose is 10 mg/kg and the continued dose is 0.3 mg/kg and the administration interval is 2 months, the initial dose is 10 mg/kg and the continued dose is 0.1 mg/kg and the administration interval is 2 months, the initial dose is 3 mg/kg and the continued dose is 3 mg/kg and the administration interval is 2 months, the initial dose is 3 mg/kg and the continued dose is 1 mg/kg and the administration interval is 2 months, the initial dose is 3 mg/kg and the continued dose is 0.3 mg/kg and the administration interval is 2 months, the initial dose is 3 mg/kg and the continued dose is 0.1 mg/kg and the administration interval is 2 months, the initial dose is 1 mg/kg and the continued dose is 1 mg/kg and the administration interval is 2 months, the initial dose is 1 mg/kg and the continued dose is 0.3 mg/kg and the administration interval is 2 months, or the initial dose is 1 mg/kg and the continued dose is 0.1 mg/kg and the administration interval is 2 months.

The dosage regimen is determined, for example, by considering the effects and safety. Furthermore, the dosage regimen is determined by considering the convenience of the patient,

within the range that does not impair the effectiveness and safety. For example, the dosage regimen for a hemophilia A patient can be determined by considering the effects of preventing bleeding in patients and clinically acceptable safety.

In the present invention, “nearly the same” means that the difference is approximately 20% or less, preferably the difference is 10% or less, or more preferably the difference is 5% or less, 4% or less, 3% or less, 2% or less, or 1% or less.

A disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII (FVIIIa) is, for example, hemophilia A, hemophilia A with emergence of an inhibitor against FVIII / FVIIIa, acquired hemophilia A, and von Willebrand disease, but the disease is not particularly limited thereto.

The present invention provides a product comprising at least (i) a container; (ii) a pharmaceutical composition in a container, which comprises a bispecific antigen-binding molecule that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X; and (iii) a document instructing administration of the antigen-binding molecule at an initial dose of approximately 0.001 to 100 mg/kg and multiple continued administrations of continued doses that are nearly the same as or less than the initial dose with administration intervals of at least one day or longer. In addition, a label, syringe, syringe needle, pharmaceutically acceptable medium, alcohol-soaked cotton, adhesive bandage, and such may be packaged in the product. The container is, for example, a bottle, a glass bottle, or a syringe, and can be produced from various materials such as glass or plastic. A pharmaceutical composition is stored in the container, and the mouth of the container is sealed with a rubber stopper or such. For example, a label indicating that the pharmaceutical composition is to be used for preventing or treating selected pathological conditions is attached to the container.

Treatment of hemophilia refers to, for example, stopping bleeding by administering the composition to a hemophilia patient who is actually showing bleeding symptoms (treatment of bleeding) and/or reducing the bleeding frequency by administering the composition to a patient who had shown bleeding to prevent manifestation of bleeding symptoms in advance (prevention of bleeding), but it is not limited thereto. Treatment and prevention of bleeding may be understood as having the same meaning in certain cases.

Herein, bleeding that is examined and counted as the number of bleeding events in a patient is, for example, bleeding that required hemostatic treatment by coagulation factor formulations. Coagulation factor formulations refer to, for example, FVIII formulations and bypassing agents (activated prothrombin complex formulations, recombinant FVIIa formulations, and such).

The number of bleedings per year (the Annualized Bleeding Rate (ABR)) is calculated as: (number of bleeding events x 365.25) / number of days of observation.

All prior art references cited herein are incorporated by reference into this description.

5 Examples

Herein below, the present invention will be specifically described with reference to the Examples, but it is not to be construed as being limited thereto.

10 Example 1: Preparation of a bispecific antibody that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X

ACE910 (Q499-z121/J327-z119/L404-k) which is a bispecific antibody described in a non-patent document (PLoS One. 2013;8(2):e57479) and a patent document (WO 2012/067176) (a bispecific antibody in which the H chain containing the amino acid sequence of SEQ ID NO: 20 and the L chain of SEQ ID NO: 32 are associated, and the H chain containing the amino acid sequence of SEQ ID NO: 25 and the L chain of SEQ ID NO: 32 are associated) was produced according to description in the aforementioned non-patent document or patent document. As described in the patent document, ACE910 has an activity that substitutes for the function of coagulation factor VIII.

20

Example 2: Single subcutaneous administration study in healthy adult Japanese and Caucasian males

A single dose of ACE910 at a volume ($\mu\text{L}/\text{kg}$) shown in Table 1 was subcutaneously administered to the abdomen in the test drug groups of Part A (Japanese) and Part B (Caucasians). ACE910 administration solutions were prepared at concentrations (mg/mL) shown in the table below, and administered at the indicated volumes ($\mu\text{L}/\text{kg}$). For administration of 0.1 mg/kg or less, a diluent (prepared by diluting an auxiliary diluent approximately 100-times with a physiological saline solution) was used; and for administration of 0.3 mg/kg , a physiological saline solution was used.

30

Table 1

Examination	ACE910 dose (mg/kg)	ACE910 dose solution concentration (mg/mL)	Dose volume (μL/kg)
A-1	0.001	0.08	12.5
A-2	0.01	0.8	12.5
A-3, B-1	0.1	8	12.5
A-4, B-2	0.3	24	12.5
A-5, B-3	1	80	12.5

Follow-up observations were performed for 4 weeks (A-1, A-2), 16 weeks (A-3, B-1), 20 weeks (A-4, B-2), and 24 weeks (A-5, B-3) after administration, and serious side effects were not particularly observed.

Example 3: Open-label, inter-individual, dose-ascending, multiple subcutaneous administration study in Japanese hemophilia A patients (Examinations 1 and 2)

Patients meeting the following criteria were selected as the study participants:

- (1) a patient with severe congenital hemophilia A;
- (2) a Japanese individual;
- (3) an individual whose body weight is 40 kg or more;
- (4) an individual whose record of bleeding episodes (bleeding period, bleeding site) and treatment with blood coagulation factor formulations is available for the six months prior to enrollment; and
- (5) an individual who meets either one of the following criteria at the time of enrollment:
 - (a) for a patient having inhibitors, an individual who has had six or more bleeding events during the six months prior to enrollment; and
 - (b) for a patient not having inhibitors, an individual who has received 150 or more administrations of FVIII formulations before enrollment and has been carrying out regular replacement therapy with FVIII formulations for the six months prior to enrollment.

Based on the latest body weight measurement, the dose volume of ACE910 shown in Table 2 was repeatedly administered subcutaneously to the abdomen at a frequency of once a week for 12 weeks (total of 12 times). The test drug used was 1.0 mL of a solution containing 80 mg of ACE910 in a single vial.

Table 2

Dose, dose solution concentration, and dose volume of ACE910

Examination	Initial administration			2nd and subsequent administrations		
	ACE910 dose (mg/kg)	ACE910 dose solution concentration (mg/mL)	Dose volume (μ L/kg)	ACE910 dose (mg/kg)	ACE910 dose solution concentration (mg/mL)	Dose volume (μ L/kg)
1	1	80	12.5	0.3	24	12.5
2	3	80	37.5	1	80	12.5

To administer 0.3 mg/kg, the 80-mg/mL ACE910-containing solution was adjusted to have the ACE910 administration solution concentration (mg/mL) shown in Table 2 using a physiological saline solution, and then this was administered at the administration volume (μ L/kg) shown in Table 2. The maximum volume that can be administered per administration site was set to 1.5 mL, and when a larger volume was to be administered, subcutaneous administrations were carried out at two or more separate sites. During the period of ACE910 administration, regular replacement therapy with FVIII formulations was discontinued.

The number of bleeding events for the six months prior to ACE910 administration, and the number of bleeding events during the ACE910 administration period (12 weeks) were investigated. Bleeding events that required hemostatic therapy with FVIII formulations or bypassing agents were investigated. The numbers of bleeding events before and after ACE910 administration were converted to annualized bleeding frequencies. Specifically, the annualized bleeding rate (ABR) was calculated as: (number of bleeding events x 365.25) / number of days of observation.

An interim analysis of Examination 1 showed that inhibitor patients who have not been given any prophylactic treatment against bleeding showed a dramatic decrease in the annualized bleeding frequency by ACE910 administration in comparison to when ACE910 was not administered. Moreover, in non-inhibitor patients who had been given regular replacement therapy with FVIII formulations, the annualized bleeding frequency was decreased by ACE910 administration in comparison to when FVIII formulations were administered (Fig. 1).

Examination 2 which was carried out with changing the ACE910 dose showed a dramatic decrease in the annualized bleeding frequency by ACE910 administration in both inhibitor patients who had not been given any prophylactic treatment against bleeding and non-inhibitor patients who had been given regular replacement therapy with FVIII formulations (Fig. 2).

Since ACE910 has a long half-life in blood, its administration frequency is low, it can be

administered subcutaneously, it is effective also for inhibitor patients, it may not induce inhibitors, and such; therefore, it is considered to be a prominent pharmaceutical agent.

Example 4: Open-label, inter-individual, dose-ascending, multiple subcutaneous administration study in Japanese hemophilia A patients (Examination 3)

Patients were selected according to the same criteria as in Example 3, Examination 3 described in Table 3 was performed, and the annualized bleeding rate was investigated.

Based on the latest body weight measurement, the dose volume of ACE910 shown in Table 3 was repeatedly administered subcutaneously to the abdomen at a frequency of once a week for 12 weeks (total of 12 times). The test drug used was 1.0 mL of a solution containing 80 mg of ACE910 in a single vial.

Table 3

Dose, dose solution concentration, and dose volume of ACE910

Examination	Initial administration			2nd and subsequent administrations		
	ACE910 dose (mg/kg)	ACE910 dose solution concentration (mg/mL)	Dose volume (μ L/kg)	ACE910 dose (mg/kg)	ACE910 dose solution concentration (mg/mL)	Dose volume (μ L/kg)
3	3	80	37.5	3	80	37.5

Preparation of the administration solution, investigation of the bleeding rate, and such were carried out according to Example 3. Regarding Examination 3, the annualized bleeding frequency was dramatically decreased by ACE910 administration in both inhibitor patients who had been given regular administration therapy with bypassing agents that prevent manifestation of bleeding (for 6 months prior to ACE910 administration) and non-inhibitor patients who had been given regular replacement therapy with FVIII formulations (for 6 months prior to ACE910 administration) (Fig. 3).

Industrial Applicability

The present invention provides a pharmaceutical composition comprising a bispecific antigen-binding molecule which recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X, as a more effective pharmaceutical composition for preventing and/or treating a disease which develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII, or a dosage regimen thereof.

CLAIMS

1. A pharmaceutical composition for use in preventing and/or treating a disease that develops and/or progresses due to a decrease or deficiency in the activity of blood coagulation factor VIII and/or activated blood coagulation factor VIII, wherein the composition comprises a bispecific antigen-binding molecule that recognizes blood coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor X and/or activated blood coagulation factor X, wherein the antigen-binding molecule is administered at an initial dose of approximately 0.001 to 100 mg/kg and is continually administered several times at continued doses that are nearly the same as or less than the initial dose, wherein the interval between individual administrations is at least one day or longer.
2. The pharmaceutical composition of claim 1, wherein the continued dose is a dose selected from the group consisting of the same dose as the initial dose, and approximately one-half, approximately one-third, approximately 0.3-times, approximately one-fourth, approximately one-fifth, and approximately one-tenth the initial dose.
3. The pharmaceutical composition of claim 2, wherein the initial dose is 1 mg/kg and at least one of the continued doses is 0.3 mg/kg.
4. The pharmaceutical composition of claim 2, wherein the initial dose is 3 mg/kg and at least one of the continued doses is 1 mg/kg.
5. The pharmaceutical composition of claim 2, wherein the initial dose is 3 mg/kg and at least one of the continued doses is 3 mg/kg.
6. The pharmaceutical composition of any one of claims 1 to 5, wherein at least one of the intervals between individual administrations is one week.
7. The pharmaceutical composition of any one of claims 1 to 6, wherein the disease is selected from the group consisting of hemophilia A, acquired hemophilia A, von Willebrand disease, and hemophilia A with emergence of an inhibitor against blood coagulation factor VIII and/or activated blood coagulation factor VIII.
8. The pharmaceutical composition of any one of claims 1 to 7, wherein the antigen-binding molecule is the bispecific antibody described below, wherein the first polypeptide and the third

polypeptide are associated and the second polypeptide and the fourth polypeptide are associated:
 a bispecific antibody comprising a first polypeptide which is an H chain comprising the amino
 acid sequence of SEQ ID NO: 20; a second polypeptide which is an H chain comprising the
 amino acid sequence of SEQ ID NO: 25; a third polypeptide and a fourth polypeptide which are
 5 a commonly shared L chain comprising the amino acid sequence of SEQ ID NO: 32.

9. The pharmaceutical composition of any one of claims 1 to 8, wherein the antigen-binding
 molecule is administered subcutaneously.

10. A product comprising (i) a container; (ii) a pharmaceutical composition in the container,
 wherein the composition comprises a bispecific antigen-binding molecule that recognizes blood
 coagulation factor IX and/or activated blood coagulation factor IX and blood coagulation factor
 X and/or activated blood coagulation factor X; and (iii) a document instructing administration of
 the antigen-binding molecule at an initial dose of approximately 0.001 to 100 mg/kg and several
 15 continued administrations of continued doses that are nearly the same as or less than the initial
 dose, wherein the interval between individual administrations is at least one day or longer.

11. The product of claim 10, wherein the initial dose is 1 mg/kg and at least one of the continued
 doses is 0.3 mg/kg.

12. The product of claim 10 or 11, wherein at least one of the intervals between individual
 administrations is one week.

13. The product of any one of claims 10 to 12, which further comprises a label attached to the
 25 container which indicates that the pharmaceutical composition can be used for preventing and/or
 treating a disease that develops and/or progresses due to a decrease or deficiency in the activity
 of blood coagulation factor VIII and/or activated blood coagulation factor VIII.

14. The product of claim 13, wherein the label indicates that the pharmaceutical composition
 30 can be used for the treatment of hemophilia A, acquired hemophilia A, von Willebrand disease,
 and hemophilia A with emergence of an inhibitor against blood coagulation factor VIII and/or
 activated blood coagulation factor VIII.

15. The product of any one of claims 10 to 14, wherein the antigen-binding molecule is the
 35 bispecific antibody described below, wherein the first polypeptide and the third polypeptide are
 associated and the second polypeptide and the fourth polypeptide are associated:

a bispecific antibody comprising a first polypeptide which is an H chain comprising the amino acid sequence of SEQ ID NO: 20; a second polypeptide which is an H chain comprising the amino acid sequence of SEQ ID NO: 25; and a third polypeptide and a fourth polypeptide which are commonly shared L chain comprising the amino acid sequence of SEQ ID NO: 32.

11806SG265 Sequence Listing.txt
SEQUENCE LISTING

<110> CHUGAI SEIYAKU KABUSHIKI KAISHA
<120> PHARMACEUTICAL COMPOSITION USED FOR PREVENTION AND/OR TREATMENT
OF DISEASES THAT DEVELOP AND/OR PROGRESS DUE TO A DECREASE OR
DEFICIENCY IN THE ACTIVITY OF BLOOD COAGULATION FACTOR VIII
AND/OR ACTIVATED BLOOD COAGULATION FACTOR VIII
<130> C1-X1404Y1P
<150> JP 2014-127240
<151> 2014-06-20
<150> JP 2014-226988
<151> 2014-11-07
<160> 36
<170> PatentIn version 3.5
<210> 1
<211> 448
<212> PRT
<213> Artificial
<220>
<223> artificial sequence
<400> 1

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

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

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

Ala Ser Ile Ser Pro Ser Gly Gly Ser Thr Tyr Tyr Arg His Ser Val
50 55 60

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

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

Ala Arg Arg Ala Gly His Asn Leu Gly Ala Gly Trp Tyr Phe Asp Phe
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
Page 1

11806SG265 Sequence Listing.txt

145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val
195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
210 215 220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
260 265 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
340 345 350

Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
Page 2

420

425

430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
 435 440 445

<210> 2

<211> 448

<212> PRT

<213> Artificial

<220>

<223> artificial sequence

<400> 2

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

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

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

Ala Ser Ile Ser Pro Ser Gly Gly Ser Thr Tyr Tyr Arg Arg Ser Val
 50 55 60

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

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

Ala Arg Arg Ala Gly His Asn Leu Gly Ala Gly Trp Tyr Phe Asp Phe
 100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
 115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
 130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
 145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
 165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
 180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val
 195 200 205

11806SG265 Sequence Listing.txt

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
210 215 220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Asp Val Ser Gln Glu
260 265 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
435 440 445

<210> 3
<211> 448
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

11806SG265 Sequence Listing.txt

<400> 3

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

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

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

Ala Ser Ile Ser Pro Ser Gly Gly Ser Thr Tyr Tyr Arg Arg Ser Val
50 55 60

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

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

Ala Arg Arg Ala Gly His Asn Phe Gly Ala Gly Trp Tyr Phe Asp Phe
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val
195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
210 215 220

Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
Page 5

260

265

270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
 290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
 325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 340 345 350

Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu
 355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
 405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
 435 440 445

<210> 4
 <211> 444
 <212> PRT
 <213> Artificial

<220>
 <223> artificial sequence

<400> 4

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
 20 25 30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

11806SG265 Sequence Listing.txt

Gly Asp Ile Asn Thr Arg Ser Gly Gly Ser Ile Tyr Asn Glu Glu Phe
50 55 60

Gln Asp Arg Val Ile Met Thr Val Asp Lys Ser Thr Gly Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr His Cys
85 90 95

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

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

11806SG265 Sequence Listing.txt

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Gln Cys Glu Met Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
435 440

<210> 5
<211> 444
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 5

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Thr Arg Ser Gly Gly Ser Ile Tyr Asn Glu Glu Phe
50 55 60

Gln Asp Arg Val Ile Met Thr Val Asp Lys Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr His Cys
85 90 95

Ala Arg Arg Lys Ser Tyr Gly Tyr His Leu Asp Glu Trp Gly Glu Gly
Page 8

100

105

110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
 115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
 130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
 145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
 165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
 180 185 190

Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
 195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
 210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
 225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
 260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
 290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
 325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 340 345 350

Ser Gln Cys Glu Met Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val
 355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 Page 9

370

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
435 440

<210> 6

<211> 444

<212> PRT

<213> Artificial

<220>

<223> artificial sequence

<400> 6

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Thr Arg Ser Gly Gly Ser Ile Tyr Asn Glu Glu Phe
50 55 60

Gln Asp Arg Val Ile Met Thr Val Asp Lys Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr His Cys
85 90 95

Ala Arg Arg Lys Ser Tyr Gly Asn His Leu Asp Glu Trp Gly Glu Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

11806SG265 Sequence Listing.txt

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

11806SG265 Sequence Listing.txt

Asn Arg Tyr Thr Gln Glu Ser Leu Ser Leu Ser Pro
435 440

<210> 7
<211> 444
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 7

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Thr Lys Ser Gly Gly Ser Ile Tyr Asn Glu Glu Phe
50 55 60

Gln Asp Arg Val Ile Met Thr Val Asp Lys Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr His Cys
85 90 95

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

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
Page 12

210

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn Arg Tyr Thr Gln Glu Ser Leu Ser Leu Ser Pro
435 440

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

<220>
<223> artificial sequence

<400> 8

11806SG265 Sequence Listing.txt

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1           5           10          15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Ile Tyr Lys Asn
20          25          30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
35          40          45
Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Ser Gly
50          55          60
Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65          70          75          80
Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Gly Leu Thr
85          90          95
Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
100         105         110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115        120        125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130        135        140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145        150        155        160
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165        170        175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180        185        190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195        200        205
Asn Arg Gly Glu Cys
210

```

```

<210> 9
<211> 214
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 9

```

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
Page 14

```

```

1              5              10              15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Ile Tyr Lys Asn
      20              25              30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Lys Leu Leu Ile
      35              40              45
Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Ser Gly
      50              55              60
Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
      65              70              75              80
Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Pro Pro Leu
      85              90              95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
      100              105              110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
      115              120              125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
      130              135              140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
      145              150              155              160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
      165              170              175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
      180              185              190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
      195              200              205
Phe Asn Arg Gly Glu Cys
      210

```

```

<210> 10
<211> 448
<212> PRT
<213> Artificial

```

```

<220>
<223> artificial sequence

```

```

<400> 10

```

```

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

```

11806SG265 Sequence Listing.txt

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

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

Ala Ser Ile Ser Pro Ser Gly Gly Ser Thr Tyr Tyr Arg Arg Ser Val
50 55 60

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

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

Ala Arg Arg Ala Gly His Asn Phe Gly Ala Gly Trp Tyr Phe Asp Phe
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val
195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
210 215 220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
260 265 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

11806SG265 Sequence Listing.txt

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
435 440 445

<210> 11
<211> 448
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 11

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

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

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

Ala Ser Ile Ser Pro Ser Gly Gly Ser Thr Tyr Tyr Arg Arg Ser Val
50 55 60

Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
Page 17

```

65              70              75              80
Leu Gln Met Asn Ser85 Leu Arg Ala Glu Asp90 Thr Ala Val Tyr Tyr Cys
Ala Arg Arg Ala100 Gly His Asn Tyr Gly105 Ala Gly Trp Tyr Phe110 Asp Tyr
Trp Gly Gln115 Gly Thr Leu Val Thr120 Val Ser Ser Ala Ser125 Thr Lys Gly
Pro Ser Val Phe Pro Leu Ala135 Pro Cys Ser Arg Ser140 Thr Ser Glu Ser
Thr Ala Ala Leu Gly Cys150 Leu Val Lys Asp Tyr155 Phe Pro Glu Pro Val160
Thr Val Ser Trp Asn165 Ser Gly Ala Leu Thr170 Ser Gly Val His Thr175 Phe
Pro Ala Val Leu180 Gln Ser Ser Gly Leu185 Tyr Ser Leu Ser Ser190 Val Val
Thr Val Pro195 Ser Ser Ser Leu Gly200 Thr Lys Thr Tyr Thr205 Cys Asn Val
Asp His210 Lys Pro Ser Asn Thr215 Lys Val Asp Lys Arg220 Val Glu Ser Lys
Tyr Gly Pro Pro Cys Pro230 Pro Cys Pro Ala Pro235 Glu Phe Leu Gly Gly240
Pro Ser Val Phe Leu245 Phe Pro Pro Lys Pro250 Lys Asp Thr Leu Met255 Ile
Ser Arg Thr Pro260 Glu Val Thr Cys Val265 Val Val Asp Val Ser270 Gln Glu
Asp Pro Glu275 Val Gln Phe Asn Trp Tyr Val Asp Gly Val285 Glu Val His
Asn Ala Lys Thr Lys Pro Arg295 Glu Glu Gln Phe Asn300 Ser Thr Tyr Arg
Val Val Ser Val Leu Thr310 Val Leu His Gln Asp315 Trp Leu Asn Gly Lys320
Glu Tyr Lys Cys Lys325 Val Ser Asn Lys Gly330 Leu Pro Ser Ser Ile335 Glu
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys

```

340

345

350

Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
 355 360 365

Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
 405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
 435 440 445

<210> 12
 <211> 448
 <212> PRT
 <213> Artificial

<220>
 <223> artificial sequence

<400> 12

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

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

Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ala Ser Ile Ser Pro Ser Gly Gly Ser Thr Tyr Tyr Arg Arg Ser Val
 50 55 60

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

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

Ala Thr Arg Ala Gly His Asn Tyr Gly Ala Gly Trp Tyr Phe Asp Tyr
 100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
 115 120 125

11806SG265 Sequence Listing.txt

Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser
	130					135					140				
Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val
145					150					155					160
Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe
				165					170					175	
Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val
			180					185					190		
Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val
		195					200					205			
Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys
	210					215					220				
Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly
225					230					235					240
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
				245					250					255	
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu
			260					265					270		
Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
		275					280					285			
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg
	290					295					300				
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
305					310					315					320
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu
				325					330					335	
Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Cys
			340					345					350		
Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu
		355					360					365			
Trp	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
	370					375					380				
Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val
385					390					395					400

11806SG265 Sequence Listing.txt

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
435 440 445

<210> 13
<211> 448
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 13

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

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

Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Pro Ser Gly Gln Ser Thr Tyr Tyr Arg Arg Glu Val
50 55 60

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

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

Ala Arg Arg Ser Gly His Asn Tyr Gly Gly Gly Trp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
Page 21

180

185

190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val
 195 200 205
 Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
 210 215 220
 Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
 225 230 235 240
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 245 250 255
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
 260 265 270
 Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 275 280 285
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
 290 295 300
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 305 310 315 320
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
 325 330 335
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 340 345 350
 Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu
 355 360 365
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 385 390 395 400
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 405 410 415
 Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
 435 440 445

<210> 14

11806SG265 Sequence Listing.txt

<211> 448

<212> PRT

<213> Artificial

<220>

<223> artificial sequence

<400> 14

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

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

Asp Ile Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Pro Ser Gly Gln Ser Thr Tyr Tyr Arg Arg Glu Val
50 55 60

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

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

Ala Arg Arg Ser Gly His Asn Tyr Gly Gly Gly Trp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val
195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
210 215 220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
225 230 235 240

11806SG265 Sequence Listing.txt

Pro Ser Val Phe Leu₂₄₅ Phe Pro Pro Lys Pro₂₅₀ Lys Asp Thr Leu Met₂₅₅ Ile

Ser Arg Thr Pro₂₆₀ Glu Val Thr Cys Val₂₆₅ Val Val Asp Val Ser₂₇₀ Gln Glu

Asp Pro Glu₂₇₅ Val Gln Phe Asn Trp₂₈₀ Tyr Val Asp Gly Val₂₈₅ Glu Val His

Asn Ala₂₉₀ Lys Thr Lys Pro Arg₂₉₅ Glu Glu Gln Phe Asn₃₀₀ Ser Thr Tyr Arg

Val Val Ser Val Leu Thr₃₁₀ Val Leu His Gln Asp₃₁₅ Trp Leu Asn Gly Lys₃₂₀

Glu Tyr Lys Cys Lys₃₂₅ Val Ser Asn Lys Gly₃₃₀ Leu Pro Ser Ser Ile₃₃₅ Glu

Lys Thr Ile Ser₃₄₀ Lys Ala Lys Gly Gln₃₄₅ Pro Arg Glu Pro Gln₃₅₀ Val Cys

Thr Leu Pro₃₅₅ Pro Ser Gln Glu Glu₃₆₀ Met Thr Lys Asn Gln₃₆₅ Val Ser Leu

Trp Cys₃₇₀ Leu Val Lys Gly Phe₃₇₅ Tyr Pro Ser Asp Ile₃₈₀ Ala Val Glu Trp

Glu Ser Asn Gly Gln Pro₃₉₀ Glu Asn Asn Tyr Lys₃₉₅ Thr Thr Pro Pro Val₄₀₀

Leu Asp Ser Asp Gly₄₀₅ Ser Phe Phe Leu Tyr₄₁₀ Ser Arg Leu Thr Val₄₁₅ Asp

Lys Ser Arg Trp₄₂₀ Gln Glu Gly Asn Val₄₂₅ Phe Ser Cys Ser Val₄₃₀ Met His

Glu Ala Leu₄₃₅ His Asn His Tyr Thr₄₄₀ Gln Lys Ser Leu Ser₄₄₅ Leu Ser Leu

<210> 15

<211> 448

<212> PRT

<213> Artificial

<220>

<223> artificial sequence

<400> 15

Gln Val Gln Leu Val₅ Glu Ser Gly Gly Gly₁₀ Leu Val Gln Pro Gly₁₅ Gly

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Tyr Tyr
Page 24

Asp Ile Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ser Ile Ser Pro Ser Gly Gln Ser Thr Tyr Tyr Arg Arg Glu Val
 50 55 60

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

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

Ala Arg Arg Ser Gly His Asn Tyr Gly Gly Gly Trp Tyr Phe Asp Tyr
 100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
 115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
 130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
 145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
 165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
 180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val
 195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
 210 215 220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
 225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
 260 265 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
 Page 25

290

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

<210> 16
<211> 448
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 16

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

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

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

Ser Ser Ile Ser Pro Ser Gly Gln Ser Thr Tyr Tyr Arg Arg Glu Val
50 55 60

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

11806SG265 Sequence Listing.txt

Leu Gln Met Asn Ser₈₅ Leu Arg Ala Glu₉₀ Asp Thr Ala Val Tyr Tyr Cys
 Ala Arg Arg Ser₁₀₀ Gly His Asn Phe Gly₁₀₅ Gly Gly Trp Tyr Phe₁₁₀ Asp Tyr
 Trp Gly Gln₁₁₅ Gly Thr Leu Val Thr₁₂₀ Val Ser Ser Ala Ser₁₂₅ Thr Lys Gly
 Pro Ser Val₁₃₀ Phe Pro Leu Ala₁₃₅ Pro Cys Ser Arg Ser₁₄₀ Thr Ser Glu Ser
 Thr Ala Ala Leu Gly Cys₁₅₀ Leu Val Lys Asp Tyr₁₅₅ Phe Pro Glu Pro Val₁₆₀
 Thr Val Ser Trp Asn₁₆₅ Ser Gly Ala Leu Thr₁₇₀ Ser Gly Val His Thr₁₇₅ Phe
 Pro Ala Val₁₈₀ Leu Gln Ser Ser Gly₁₈₅ Leu Tyr Ser Leu Ser Ser₁₉₀ Val Val
 Thr Val Pro₁₉₅ Ser Ser Ser Leu Gly₂₀₀ Thr Lys Thr Tyr Thr₂₀₅ Cys Asn Val
 Asp His₂₁₀ Lys Pro Ser Asn Thr₂₁₅ Lys Val Asp Lys Arg₂₂₀ Val Glu Ser Lys
 Tyr Gly Pro Pro Cys Pro₂₃₀ Pro Cys Pro Ala Pro₂₃₅ Glu Phe Leu Gly Gly₂₄₀
 Pro Ser Val₂₄₅ Phe Leu Phe Pro Pro Lys Pro₂₅₀ Lys Asp Thr Leu Met₂₅₅ Ile
 Ser Arg Thr Pro₂₆₀ Glu Val Thr Cys Val₂₆₅ Val Val Asp Val Ser₂₇₀ Gln Glu
 Asp Pro Glu₂₇₅ Val Gln Phe Asn Trp₂₈₀ Tyr Val Asp Gly Val₂₈₅ Glu Val His
 Asn Ala₂₉₀ Lys Thr Lys Pro Arg₂₉₅ Glu Glu Gln Phe Asn₃₀₀ Ser Thr Tyr Arg
 Val Val Ser Val Leu Thr₃₁₀ Val Leu His Gln Asp₃₁₅ Trp Leu Asn Gly Lys₃₂₀
 Glu Tyr Lys Cys Lys₃₂₅ Val Ser Asn Lys Gly₃₃₀ Leu Pro Ser Ser Ile₃₃₅ Glu
 Lys Thr Ile Ser₃₄₀ Lys Ala Lys Gly Gln₃₄₅ Pro Arg Glu Pro Gln₃₅₀ Val Cys

11806SG265 Sequence Listing.txt

Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
435 440 445

<210> 17
<211> 448
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 17

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

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

Asp Ile Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Pro Ser Gly Gln Ser Thr Tyr Tyr Arg Arg Glu Val
50 55 60

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

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

Ala Arg Arg Ser Gly Lys Ser Tyr Gly Gly Gly Trp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
Page 28

130

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val
195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
210 215 220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
260 265 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
Page 29

405

410

415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
 435 440 445

<210> 18

<211> 448

<212> PRT

<213> Artificial

<220>

<223> artificial sequence

<400> 18

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

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

Asp Ile Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ser Ile Ser Pro Ser Gly Gln Ser Thr Tyr Tyr Arg Arg Glu Val
 50 55 60

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

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

Ala Arg Arg Ser Gly Arg Glu Tyr Gly Gly Gly Trp Tyr Phe Asp Tyr
 100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
 115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
 130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
 145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
 165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
 180 185 190

11806SG265 Sequence Listing.txt

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val
195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
210 215 220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
260 265 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

<210> 19
<211> 448
<212> PRT

11806SG265 Sequence Listing.txt

<213> Artificial

<220>

<223> artificial sequence

<400> 19

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

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

Asp Ile Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Pro Ser Gly Gln Ser Thr Tyr Tyr Arg Arg Glu Val
50 55 60

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

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

Ala Arg Arg Thr Gly Arg Glu Tyr Gly Gly Gly Trp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val
195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
210 215 220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
Page 32

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
260 265 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

<210> 20
<211> 448
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 20

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

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

11806SG265 Sequence Listing.txt

Asp Ile Gln Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Pro Ser Gly Gln Ser Thr Tyr Tyr Arg Arg Glu Val
50 55 60

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

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

Ala Arg Arg Thr Gly Arg Glu Tyr Gly Gly Gly Trp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val
195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
210 215 220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
260 265 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

11806SG265 Sequence Listing.txt

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

<210> 21
<211> 444
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 21

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Thr Arg Ser Gly Gly Ser Ile Tyr Asn Glu Glu Phe
50 55 60

Gln Asp Arg Val Ile Met Thr Val Asp Lys Ser Thr Gly Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
Page 35

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

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Gln Cys Glu Met Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val

11806SG265 Sequence Listing.txt

355

360

365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
435 440

<210> 22
<211> 444
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 22

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Thr Arg Ser Gly Gly Ser Ile Tyr Asn Glu Glu Phe
50 55 60

Gln Asp Arg Val Ile Met Thr Val Asp Lys Ser Thr Gly Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr His Cys
85 90 95

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

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140

11806SG265 Sequence Listing.txt

Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
145					150					155					160
Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
				165					170					175	
Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
			180					185					190		
Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro
		195					200					205			
Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro
	210					215					220				
Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe
225					230					235					240
Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro
				245					250					255	
Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val
			260					265					270		
Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr
		275					280					285			
Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val
	290					295					300				
Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys
305					310					315					320
Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser
				325					330					335	
Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro
			340					345					350		
Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val
		355					360					365			
Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly
	370					375					380				
Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp
385					390					395					400
Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp
				405					410					415	

11806SG265 Sequence Listing.txt

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn Arg Tyr Thr Gln Glu Ser Leu Ser Leu Ser Pro
435 440

<210> 23
<211> 444
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 23

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Thr Arg Ser Gly Gly Ser Ile Tyr Asn Glu Glu Phe
50 55 60

Gln Asp Arg Val Ile Met Thr Val Asp Lys Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr His Cys
85 90 95

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

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
Page 39

11806SG265 Sequence Listing.txt

195

200

205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
 210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
 225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
 260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
 290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
 325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 340 345 350

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
 355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
 385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
 405 410 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 420 425 430

Asn Arg Tyr Thr Gln Glu Ser Leu Ser Leu Ser Pro
 435 440

<210> 24
 <211> 444
 <212> PRT
 <213> Artificial

11806SG265 Sequence Listing.txt

<220>

<223> artificial sequence

<400> 24

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Thr Arg Ser Gly Gly Ser Ile Tyr Asn Glu Glu Phe
50 55 60

Gln Asp Arg Val Ile Met Thr Val Asp Lys Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr His Cys
85 90 95

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

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

11806SG265 Sequence Listing.txt

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn Arg Tyr Thr Gln Glu Ser Leu Ser Leu Ser Pro
435 440

<210> 25
<211> 444
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 25

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
Page 42

35

40

45

Gly Asp Ile Asn Thr Arg Ser Gly Gly Ser Ile Tyr Asn Glu Glu Phe
50 55 60

Gln Asp Arg Val Ile Met Thr Val Asp Lys Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr His Cys
85 90 95

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

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
Page 43

11806SG265 Sequence Listing.txt

305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Glu Ser Leu Ser Leu Ser Pro
435 440

<210> 26
<211> 444
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 26

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Thr Arg Ser Gly Gly Ser Ile Tyr Asn Glu Glu Phe
50 55 60

Gln Asp Arg Val Ile Met Thr Val Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr His Cys
85 90 95

11806SG265 Sequence Listing.txt

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

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

11806SG265 Sequence Listing.txt

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Glu Ser Leu Ser Leu Ser Pro
435 440

<210> 27
<211> 444
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 27

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Thr Arg Ser Gly Gly Ser Ile Tyr Asn Glu Glu Phe
50 55 60

Gln Asp Arg Val Ile Met Thr Val Asp Lys Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr His Cys
85 90 95

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

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
Page 46

145 150 155 160

420

425

430

Asn Arg Tyr Thr Gln Glu Ser Leu Ser Leu Ser Pro
 435 440

<210> 28
 <211> 214
 <212> PRT
 <213> Artificial

<220>
 <223> artificial sequence

<400> 28

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

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Lys Asn Ile Glu Arg Asn
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

Tyr Arg Ala Ser Arg Lys Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
 50 55 60

Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Pro Pro Leu
 85 90 95

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

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

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

11806SG265 Sequence Listing.txt

Phe Asn Arg Gly Glu Cys
210

<210> 29

<211> 214

<212> PRT

<213> Artificial

<220>

<223> artificial sequence

<400> 29

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

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asn Ile Glu Arg Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Glu Leu Leu Ile
35 40 45

Tyr Arg Ala Asp Arg Lys Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Pro Pro Leu
85 90 95

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

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

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

Phe Asn Arg Gly Glu Cys

210

<210> 30
 <211> 214
 <212> PRT
 <213> Artificial

<220>
 <223> artificial sequence

<400> 30

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

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asn Ile Glu Arg Asn
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Glu Leu Leu Ile
 35 40 45

Tyr Gln Ala Ser Arg Lys Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
 50 55 60

Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Pro Pro Leu
 85 90 95

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

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

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

Phe Asn Arg Gly Glu Cys
 210

11806SG265 Sequence Listing.txt

<210> 31
 <211> 214
 <212> PRT
 <213> Artificial

<220>
 <223> artificial sequence

<400> 31

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

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asn Ile Glu Arg Gln
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Glu Leu Leu Ile
 35 40 45

Tyr Gln Ala Ser Arg Lys Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
 50 55 60

Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Pro Pro Leu
 85 90 95

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

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

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

Phe Asn Arg Gly Glu Cys
 210

<210> 32

11806SG265 Sequence Listing.txt

<211> 214
<212> PRT
<213> Artificial

<220>
<223> artificial sequence

<400> 32

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

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asn Ile Glu Arg Gln
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Glu Leu Leu Ile
35 40 45

Tyr Gln Ala Ser Arg Lys Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Asp Pro Pro Leu
85 90 95

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

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

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

Phe Asn Arg Gly Glu Cys
210

<210> 33
<211> 214
<212> PRT

11806SG265 Sequence Listing.txt

<213> Artificial

<220>

<223> artificial sequence

<400> 33

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

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asn Ile Glu Arg Gln
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Glu Leu Leu Ile
35 40 45

Tyr Arg Ala Ser Arg Lys Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Asp Pro Pro Leu
85 90 95

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

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

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

Phe Asn Arg Gly Glu Cys
210

<210> 34

<211> 214

<212> PRT

<213> Artificial

11806SG265 Sequence Listing.txt

<220>

<223> artificial sequence

<400> 34

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

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asn Ile Glu Arg Gln
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Glu Leu Leu Ile
35 40 45

Tyr Arg Ala Asp Arg Lys Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Asp Pro Pro Leu
85 90 95

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

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

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

Phe Asn Arg Gly Glu Cys
210

<210> 35

<211> 444

<212> PRT

<213> Artificial

<220>

<223> artificial sequence

11806SG265 Sequence Listing.txt

<400> 35

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Thr Arg Ser Gly Gly Ser Ile Tyr Asn Glu Glu Phe
50 55 60

Gln Asp Arg Val Thr Met Thr Ile Asp Lys Ser Thr Gly Thr Ala Tyr
65 70 75 80

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

Ala Arg Arg Arg Ser Tyr Gly Tyr Tyr His Asp Glu Trp Gly Glu Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
Page 55

260

265

270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
 290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
 325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 340 345 350

Ser Gln Cys Glu Met Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val
 355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
 385 390 395 400

Gly Ser Phe Phe Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
 405 410 415

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
 435 440

<210> 36

<211> 214

<212> PRT

<213> Artificial

<220>

<223> artificial sequence

<400> 36

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

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asn Ile Glu Arg Asn
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Glu Leu Leu Ile
 35 40 45

11806SG265 Sequence Listing.txt

Tyr Ser Ala Ser Arg Lys Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
 50 55 60
 Ser Arg Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Pro Pro Leu
 85 90 95
 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110
 Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125
 Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140
 Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160
 Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175
 Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190
 Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205
 Phe Asn Arg Gly Glu Cys
 210