A new variant of antihemophilic factor VIII having increased specific activity

FIELD OF THE INVENTION

The present invention is in the field of blood coagulation factors and hemophilia. It relates to a new variant of antihemophilic factor VIII (FVIII), designated herein rFVIIIv3, having an increased specific activity in comparison to known factor VIII products.

BACKGROUND OF THE INVENTION

Blood clotting begins when platelets adhere to the cut wall of an injured blood vessel at a lesion site. Subsequently, in a cascade of enzymatically regulated reactions, soluble fibrinogen molecules are converted by the enzyme thrombin to insoluble strands of fibrin that hold the platelets together in a thrombus. At each step in the cascade, a variant precursor is converted to a protease that cleaves the next variant precursor in the series. Cofactors are required at most of the steps.

Factor VIII (also called antihemophilic factor VIII or FVIII) circulates as an inactive precursor in blood, bound tightly and non-covalently to von Willebrand factor. Factor VIII is proteolytically activated by thrombin or factor Xa, which dissociates it from von Willebrand factor and activates its procoagulant function in the cascade. In its active form, the variant factor VIIIa is a cofactor that increases the catalytic efficiency of factor IXa toward factor X activation by several orders of magnitude.

Cloning of human FVIII has revealed that the variant contains 2332 amino acids organized within a number of domains with the sequence A1-A2-B-A3-C1-C2 (Vehar et al., 1984, Nature 312, 337-342; Toole et al., 1984, Nature 312, 342-347 and Wood et al., 1984, Nature 312, 330-337). Most of FVIII is heterodimeric in plasma, containing a light-chain and various heavy-chain derivatives. The heterodimeric structure is due to proteolytic cleavage of the precursor at arginine^{1648}, resulting in heavy- and light-chains comprising A_1-A_2-B and A_3-C_1-C_2, respectively. The heterogeneity within the heavy chain is explained by limited proteolysis within its carboxy-terminal B-domain.

In order to function as a co-factor for factor X activation, FVIII requires limited proteolysis by factor Xa or thrombin. This activation involves cleavage at arginine at positions 372 and 740 on the heavy-chain and at position 1689 on the light-chain. It has been established that in comparison with the inactive precursor, active FVIII

cofactor lacks a light chain fragment 1649-1689 and the whole B-domain (Mertens *et al.*, 1993).

People with deficiencies in factor VIII or antibodies against factor VIII who are not treated with factor VIII suffer uncontrolled internal bleeding that may cause a range of serious symptoms, from inflammatory reactions in joints to early death. Severe hemophiliacs, who number about 10,000 in the United States, can be treated with infusion of human factor VIII, which will restore the blood's normal clotting ability if administered with sufficient frequency and concentration. The classic definition of factor VIII, in fact, is the substance present in normal blood plasma that corrects the clotting defect in plasma derived from individuals with hemophilia A.

Several preparations of human plasma-derived factor VIII of varying degrees of purity are available commercially for the treatment of hemophilia A. These include a partially purified factor VIII derived from the pooled blood of many donors that is heat- and detergent treated for viruses but contain a significant level of antigenic variants; a monoclonal antibody purified factor VIII that has lower levels of antigenic impurities and viral contamination; and recombinant human factor VIII.

The development of antibodies ("inhibitors" or "inhibitory antibodies") that inhibit the activity of factor VIII is a serious complication in the management of patients with hemophilia.

Alloantibodies develop in approximately 20% of patients with hemophilia A in response to therapeutic infusions of factor VIII. In previously untreated patients with hemophilia A who develop inhibitors, the inhibitor usually develops within one year of treatment. Additionally, antibodies (autoantibodies) that inactivate factor VIII occasionally develop in individuals with previously normal factor VIII levels. If the inhibitor titer is low enough, patients can be managed by increasing the dose of factor VIII. However, often the inhibitor titer is so high that it cannot be overwhelmed by factor VIII. An alternative strategy is to bypass the need for factor VIII during normal hemostasis using activated prothrombin complex concentrate preparations (for example, KONYNE (Cutter Laboratories), FEIBA (Baxter Healthcare), PROPLEX (Baxter Healthcare)) or recombinant human factor VIIa. Additionally, since porcine factor VIII usually has substantially less reactivity with inhibitors than human factor VIII, a partially purified porcine factor VIII preparation (HYATE: C (IPSEN Pharma)) has been used. Many patients who have developed inhibitory antibodies to human factor VIII have been successfully treated with porcine factor VIII and have tolerated such treatment for long periods of time.

However, public health concerns regarding the risk of viruses or other blood-borne contaminants have limited the usefulness of porcine factor VIII purified from porcine blood. A recombinant porcine factor VIII variant has therefore been developed, which is designated "OBI-1" and described e.g. in WO 01/68109. OBI-1 is a partially B-domain deleted porcine FVIII. This molecule is presently in clinical development.

B-domain deleted factor VIII variants are known to keep the procoagulant and cofactor activity of factor VIII. In addition to this, Mertens et al. (British Journal of Haematology 1993, 85, 133-142) describe recombinant human factor VIII variants lacking the B-domain and the heavy-chain sequence spanning from Lysine 713 to Arginine 740.

Many hemophiliacs require daily replacement of factor VIII to prevent bleeding and the resulting deforming hemophilic arthropathy. In view of this, there is a need for a more potent factor VIII molecule.

SUMMARY OF THE INVENTION

In a first aspect, the invention relates to an isolated, recombinant, fully or partially B-domain deleted factor VIII (FVIII) variant, the FVIII variant being devoid of an up to 27 amino acid sequence corresponding to amino acids 716 to 742 of porcine factor VIII as depicted in Figure 2 or amino acids 714 to 740 of SEQ ID NO: 7. This 27 amino acid sequence, NTGDYYEDSYEDISAYLLSKNNAIEPR (SEQ ID NO:10), may be partially or completely deleted.

In one embodiment, the invention relates to an isolated, recombinant, fully or partially B-domain deleted FVIII variant, the FVIII variant being devoid of an up to 27 amino acid sequence corresponding to amino acids 716 to 742 of porcine factor VIII as depicted in Figure 2 or amino acids 714 to 740 of SEQ ID NO: 7, where 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acids may be deleted. In another embodiment, 27, 26, 25, 24, 23, 22, 21 or 20 amino acids are deleted. In another embodiment, 27, 26, or 25 amino acids are deleted. In another embodiment, the 27 amino acids corresponding to DIGDYYDNTYEDIPGFLLSGKNVIEPR (SEQ ID NO:10) are deleted.

In one embodiment, the invention relates to an isolated, recombinant, fully or partially B-domain deleted FVIII variant, the FVIII variant being devoid of an up to 27 amino acid sequence corresponding to amino acids 716 to 742 of human factor VIII as depicted in Figure 2 or amino acids 714 to 740 of SEQ ID NO: 8, where 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acids may be deleted. In another embodiment, 27, 26, 25, 24, 23, 22, 21 or

20 amino acids are deleted. In another embodiment, 27, 26, or 25 amino acids are deleted. In another embodiment, the 27 amino acids corresponding to NTGDYYEDSYEDISAYLLSKNNAIEPR (SEQ ID NO:11) are deleted.

In another embodiment, the invention relates to an isolated, recombinant, fully or partially B-domain deleted porcine FVIII variant being completely devoid of the 27 amino acids corresponding to DIGDYYDNTYEDIPGFLLSGKNVIEPR (SEQ ID NO:10).

In another embodiment, the invention relates to an isolated, recombinant, fully or partially B-domain deleted human FVIII variant being completely devoid of the 27 amino acids corresponding to NTGDYYEDSYEDISAYLLSKNNAIEPR (SEQ ID NO:11).

In another embodiment, the invention relates to an isolated, recombinant, fully or partially B-domain deleted canine FVIII variant being completely devoid of the 27 amino acids corresponding to NIDDYYEDTYEDIPTPLLNENNVIKPR (SEQ ID NO:12).

A second aspect of the invention relates to a polynucleotide encoding a polypeptide as defined in the first aspect and the embodiments described.

In a third aspect, the invention relates to an expression vector comprising a polynucleotide as defined in the second aspect.

A fourth aspect of the invention relates to a mammalian cell comprising an expression vector as defined in the third aspect.

In a fifth aspect, the invention relates to a method for producing a FVIII as defined in the first aspect, comprising the steps of:

a. Culturing a mammalian cell according to the fourth aspect; and

b. Isolating from the mammalian cell the FVIII variant.

A sixth aspect of the invention relates to a pharmaceutical composition comprising a FVIII variant as defined in the first aspect.

In a seventh aspect, the invention relates to a method of treating a patient suffering from hemophilia comprising administering a therapeutically effective amount of FVIII variant according to the first aspect of the invention to a patient in need thereof, thereby treating the hemophilia in said patient.

In an eighth aspect, the invention relates to a FVIII variant according to the first aspect for use in treating hemophilia.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the amount of protein in µg per dose required for 5 known FVIII products (blank columns) and the new rpFVIIIv3 (hashed column). BDD=B-domain deleted; FL=full length; u=µ;

Fig. 2 a-e are continuations of the same sequence. Fig 2a-e shows a sequence alignment between the factor VIII sequences from human (homo sapiens), pig (sus scrofa), mouse (mus musculus) and dog (canis familiaris). This sequence alignment is taken from HADB (aka HAMSTeRS) 2010, home page of the Haemophilia A Mutation Database and a resource site for work on factor VIII (hadb.org.uk). The numbering follows the human sequence and is not identical to the amino acid numbers of the sequences in the Sequence Listing. The bold plus double underlined sequence depicts the sequence missing in the recombinant FVIIIv3 variants of the invention. The underlined sequence is the sequence of the B-domain. The sequence highlighted in grey is the portion from the B-domain which can be retained in the partially B-domain deleted FIIIv3 sequences of the invention; and

Fig. 3 shows typical example of the SEC profile of the calibration standards and the linear regression of the calibration curve as described in Example 5.

BRIEF DESCRIPTION OF THE SEQUENCES

SEQ ID NO: 1 shows the sequence of porcine partially B-domain deleted FVIIIv3;

SEQ ID NO: 2 shows the sequence of a human B-domain deleted FVIIIv3;

SEQ ID NO: 3 shows the sequence of a canine B-domain deleted FVIIIv3;

SEQ ID NO: 4 shows the sequence from the porcine FVIII B-domain that can be present in a partially B-domain deleted FVIII molecule of the invention (the so called "B-domain linker");

SEQ ID NO: 5 shows a B-domain linker sequence from the human FVIII B-domain that can be present in a partially B-domain deleted FVIII molecule of the invention;

SEQ ID NO: 6 shows a B-domain linker sequence from the canine FVIII B-domain that can be present in a partially B-domain deleted FVIII molecule of the invention;

SEQ ID NO: 7 shows the amino acid sequence of full-length porcine FVIII;

SEQ ID NO: 8 shows the amino acid sequence of full-length human FVIII;

SEQ ID NO: 9 shows the amino acid sequence of full-length canine FVIII;

SEQ ID NO:10 shows the 27 peptide sequence which corresponds to amino acids 716 to 742 of porcine factor VIII as depicted in Figure 2 or amino acids 714 to 740 of SEQ ID NO: 7;

SEQ ID NO:11 shows the 27 peptide sequence which corresponds to amino acids 714 to 740 of human factor VIII as depicted in Figure 2 or amino acids 714 to 740 of SEQ ID NO: 8; and

SEQ ID NO:12 shows the 27 peptide sequence which corresponds to amino acids 714 to 740 of canine factor VIII as depicted in Figure 2 or amino acids 708 to 734 of SEQ ID NO: 9.

DETAILED DESCRIPTION OF THE INVENTION

The invention is based on the finding of a variant of a partially B-domain deleted recombinant porcine factor VIII protein which contains a particular 27 amino acid deletion. This variant, which is herein designated rpFVIIIv3, has been shown to have an increased specific activity as compared to a similar protein containing the 27 amino acid stretch, namely a partially B-domain deleted recombinant porcine FVIII called "OBI-1". OBI-1, its amino acid sequence and polynucleotides encoding OBI-1 are known e.g. from US 6,458,563.

The invention relates to an isolated, recombinant, fully or partially B-domain deleted factor VIII (FVIII) variant, wherein the FVIII variant is devoid of an amino acid sequence corresponding to amino acids 716 to 742 of porcine factor VIII as depicted in Figure 2 or amino acids 714 to 740 of SEQ ID NO: 7.

Additionally, the invention relates to an isolated, recombinant, fully or partially B-domain deleted FVIII variant, the FVIII variant being devoid of a 27 amino acid sequence corresponding to amino acids 716 to 742 of porcine factor VIII as depicted in Figure 2 or amino acids 714 to 740 of SEQ ID NO: 7, where 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acids may be deleted. In one variant, 27, 26, 25, 24, 23, 22, 21 or 20 amino acids are deleted. In another variant, 27, 26, or 25 amino acids are deleted. In the rpFVIIIv3 variant, the 27 amino acids corresponding to DIGDYYDNTYEDIPGFLLSGKNVIEPR (SEQ ID NO:10) are deleted.

Additionally, the invention relates to an isolated, recombinant, fully or partially B-domain deleted FVIII variant, the FVIII variant being devoid of a 27 amino acid sequence corresponding to amino acids 714 to 740 of human factor VIII as depicted

in Figure 2 or amino acids 714 to 740 of SEQ ID NO: 8, where 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acids may be deleted. In one variant, 27, 26, 25, 24, 23, 22, 21 or 20 amino acids are deleted. In another variant, 27, 26, or 25 amino acids are deleted. In a human FVIIIv3 variant (rhFVIIIv3), the 27 amino acids corresponding to NTGDYYEDSYEDISAYLLSKNNAIEPR (SEQ ID NO:11) are deleted.

Additionally, the invention relates to an isolated, recombinant, fully or partially B-domain deleted FVIII variant, the FVIII variant being devoid of a 27 amino acid sequence corresponding to amino acids 714 to 740 of canine factor VIII as depicted in Figure 2 or amino acids 708 to 734 of SEQ ID NO: 9, where 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acids may be deleted. In one variant, 27, 26, 25, 24, 23, 22, 21 or 20 amino acids are deleted. In another variant, 27, 26, or 25 amino acids are deleted. In a canine FVIIIv3 variant (rcFVIIIv3), the 27 amino acids corresponding to NIDDYYEDTYEDIPTPLLNENNVIKPR (SEQ ID NO:12) are deleted.

Such variants have an elevated specific activity as compared to similar variants containing the intact 27 amino acid sequence. Preferably, the specific activity is increased by more than 25 % or 30 % or 35 % or 40 % or 45 % or 50 % or 55 % or 60 %.

The term "specific activity," as used herein, refers to the activity that will correct the coagulation defect of human factor VIII deficient plasma. Specific activity is measured in units of clotting activity per milligram total factor VIII variant in a standard assay in which the clotting time of human factor VIII deficient plasma is compared to that of normal human plasma. A suitable standard assay for measuring the potency of FVIII products, which is accepted by the FDA for high purity FVIII concentrates, is called the one-stage clotting assay (OSCA; see Example 5; Langdell RD, Wagner RH, Brinkhous KM., Effect of antihemophilic factor on one-stage clotting tests: a presumptive test for hemophilia and a simple one-stage antihemophilic assay procedure, J Lab Clin Med, 1953; 41:637–47; Brand JT, Measurement of factor VIII: a potential risk factor for vascular disease, Arch Pathol Lab Med, 1993; 117:48–51; Preston FE, Kitchen S, Quality control and factor VIII assays, Haemophilia, 1998; 4:651–3; National Committee for Clinical Laboratory Standards (NCCLS USA). Determination of factor coagulant activities; Approved guideline, NCCLS Document H-48-A 1997; 17:1–36.). The amount of FVIII protein present in a sample can be measured *e.g.* by SEC HPLC (size-exclusion high-performance liquid chromatography).

One unit of factor VIII activity is the activity present in one milliliter of normal human plasma. In the assay, the shorter the time for clot formation, the greater the activity of the factor VIII being assayed. Porcine factor VIII has coagulation activity in a human factor VIII assay.

In line with the present invention, the terms "protein" and "polypeptide" are being used interchangeably.

Being "devoid of an amino acid sequence corresponding to amino acids 716 to 742 as depicted in Fig. 2" means that amino acids 716 and 742, as well as the amino acids between these positions, are deleted, *i.e.* not included, in the FVIII variant of the invention. This stretch of amino acids consists thus of 27 amino acids, of which the FVIII variants of the invention are devoid.

The factor VIII variants of the invention are herein globally designated "FVIII variant(s)" or "FVIIIv3" or "rFVIIIv3". They can be of porcine, human, canine, murine or any other origin which is appropriate for human or animal therapy. Fig. 2 depicts a sequence alignment of FVIII sequences of human, porcine, murine and canine origin.

The sequence deleted in the FVIII variants of the invention is highlighted in bold and double underlined. This stretch of amino acids can be identified for the FVIII variants of other species by the person skilled in the art by aligning the FVIII sequences of further species with *e.g.* the porcine or human sequence and taking the amino acids that correspond to amino acids 716 to 742 as per Fig. 2 of the present patent application.

Embodiments of the invention relate to FVIII variants of porcine, human or canine origin.

In an embodiment, the FVIII variant according to the invention comprises the sequence of SEQ ID NO:1, or a variant thereof comprising a sequence being at least 90% identical to SEQ ID NO: 1. It is understood that the 10% variability concerns the sequences outside of the deleted stretch of amino acids, *i.e.* that the variant is completely devoid of DIGDYYDNTYEDIPGFLLSGKNVIEPR (SEQ ID NO:10), an amino acid sequence corresponding to amino acids 716 to 742 of porcine factor VIII as depicted in Figure 2 or amino acids 714 to 740 of SEQ ID NO: 7.

In a further embodiment, the FVIII variant of the invention comprises the sequence of SEQ ID NO:2, or a variant thereof comprising a sequence being at least 90% identical to SEQ ID NO: 2. Again, the variant is understood to be completely devoid of an amino acid sequence NTGDYYEDSYEDISAYLLSKNNAIEPR (SEQ ID NO:11),

corresponding to amino acids 714 to 740 of human factor VIII as depicted in Fig. 2 or amino acids 714 to 740 of SEQ ID NO: 8.

In yet a further embodiment, the FVIII variant of the invention comprises the sequence of SEQ ID NO:3, or a variant thereof comprising a sequence being at least 90% identical to SEQ ID NO: 3. Again, the variant is understood to be completely devoid of an amino acid sequence NIDDYYEDTYEDIPTPLLNENNVIKPR (SEQ ID NO:12) corresponding to amino acids 714 to 740 of canine factor VIII as depicted in Fig. 2 or amino acids 708 to 734 of SEQ ID NO: 9.

The FVIII variants of the invention can also comprise sequences that are at least 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, 99.6, 99.7, 99.8 or 99.9% identical to the sequences of SEQ ID NO: 7, 8 or 9.

To determine the percent identity of two polypeptides/proteins, the amino acid sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid sequence for optimal alignment with a second amino acid sequence). The amino acid residues at corresponding amino acid positions are then compared. When a position in the first sequence is occupied by the same amino acid residue as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity=# of identical positions/total # of positions (*e.g.*, (overlapping positions)×100).

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) Proc. Natl. Acad. Sci. USA 87:2264–2268, modified as in Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873–5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, *et al.* (1990) J. Mol. Biol. 215:403–410. BLAST nucleotide searches can be performed with the NBLAST program, score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST variant searches can be performed with the XBLAST program, score=50, wordlength=3 to obtain amino acid sequences homologous to a variant molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (1997) Nucleic Acids Res. 25:3389–3402. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant

relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) CABIOS 4:11–17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) Proc. Natl. Acad. Sci. USA 85:2444–2448. When using the FASTA algorithm for comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a k-tuple value of 2.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

The FVIII variant of the invention can be partially or fully B-domain deleted. This means that either the whole B-domain is deleted, or a part of the B-domain is retained in the FVIII variant. The remaining (retained) part of the B-domain is e.g. selected from the 20, 15, 12, 10 or 5 N-terminal amino acids and the 20, 15, 12, 10 or 5 C-terminal amino acids of the B-domain, fused in frame with each other.

Hence, preferably, in the partially B-domain deleted FVIII variants of the invention, significant portions of the approximately 900 amino acid B-domain are being removed. In embodiments of the invention, less than 5% or less than 4% or less than 3% or less than 2 % or less than 1 % of the B-domain remain present in the FVIII variants.

In embodiments of the invention, the remaining portion of the B-domain is selected from a sequence consisting of SEQ ID NO: 4 or SEQ ID NO:5 or SEQ ID NO: 6.

In a further aspect, the invention relates to a polynucleotide encoding a polypeptide/protein as described above. A polynucleotide can be an RNA or DNA molecule whose nucleotide sequence embodies coding information to a host cell for the amino acid sequence of the variant of the invention, according to the known relationships of the genetic code.

In a further aspect, the invention relates to an expression vector comprising a polynucleotide as described above.

An "expression vector" is a DNA element, often of circular structure, having the ability to replicate autonomously in a desired host cell, or to integrate into a host cell genome and also possessing certain well-known features which permit expression of a coding DNA inserted into the vector sequence at the proper site and in proper orientation. Such features can include, but are not limited to, one or more promoter sequences to direct transcription initiation of the coding DNA and other DNA elements such as enhancers, polyadenylation sites and the like, all as well known in the art. The term "expression vector" is used to denote both a vector having a DNA coding sequence to be expressed inserted within its sequence, and a vector having the requisite expression control elements so arranged with respect to an insertion site that it can serve to express any coding DNA inserted into the site, all as well-known in the art. Thus, for example, a vector lacking a promoter can become an expression vector by the insertion of a promoter combined with a coding DNA. An expression vector, as used herein, can also be a viral vector.

Expression of the recombinant FVIII variants of the invention is preferably carried out in mammalian cell culture.

Therefore, in a further aspect, the invention relates to a mammalian cell comprising an expression vector as described above. For instance, CHO (Chinese hamster ovary) cells and BHK cells (baby hamster kidney cells) are mammalian cells that are suitable host cells in the context of the present invention.

In accordance with another aspect of the invention, a method for producing a FVIII variant of the invention comprises the steps of:

a. Culturing a mammalian cell as described above; and

b. Isolating from the mammalian cell the FVIII variant.

In an embodiment, the method further comprises the step of

c. Formulating the factor VIII variant together with appropriate excipients into a pharmaceutical composition.

Excipients suitable for human or animal administration are e.g. pharmaceutical stabilization compounds, preservatives, delivery vehicles, and/or carrier vehicles. One suitable formulation for factor VIII products is e.g. described in WO 03/080108, which is incorporated by reference herein.

In a further aspect, the invention relates to a pharmaceutical composition comprising a FVIII variant of the invention.

A further aspect of the invention relates to a method of treating a patient suffering from factor VIII deficiency comprising administering a therapeutically effective amount of FVIII variant of the invention to a patient in need thereof, thereby treating the factor VIII deficiency in said patient.

The term "therapeutically effective amount" as used herein, means the level of FVIII in the plasma of a patient having FVIII deficiency, who has received a pharmaceutical composition of FVIII variant, that is sufficient to exhibit a measurable improvement or protective effect in the patient (e.g., to stop bleeding). The patients having FVIII deficiency are typically congenital hemophilia A patients but also include those subjects diagnosed with "acquired hemophilia", a condition in which those who are not congenital hemophiliacs spontaneously develop inhibitory antibodies to their FVIII, creating a serious FVIII deficiency.

The invention also relates to a FVIII variant of the invention for use in treating factor VIII deficiency.

Treatment can take the form of a single intravenous administration of the composition or periodic or continuous administration over an extended period of time, as required. Preferably, administration of the FVIII variant is by intravenous route.

"Factor VIII deficiency," as used herein, includes deficiency in clotting activity caused by production of defective factor VIII, by inadequate or no production of factor VIII, or by partial or total inhibition of factor VIII by inhibitors. Hemophilia A is a type of factor VIII deficiency resulting from a defect in an X-linked gene and the absence or deficiency of the factor VIII variant it encodes.

The FVIII variants of the invention are used to treat uncontrolled bleeding due to factor VIII deficiency (*e.g.,* intraarticular, intracranial, or gastrointestinal hemorrhage) in hemophiliacs.

In an embodiment of the invention, the factor VIII deficiency is hemophilia A.

In another embodiment, the factor VIII deficiency is acquired hemophilia.

In an embodiment, the factor VIII deficiency is treated in patients having developed human FVIII antibodies.

As mentioned above, the FVIII variants of the invention have increased specific activity. It is therefore possible to administer reduced amounts of FVIII variant in order to treat VIII deficiency in accordance with the present invention. The amounts of FVIII variant can be reduced by at least 30%, 35%, 40%, 45%, 50%, 55%, 60% as

compared to therapy with a FVIII product that does not contain the up to 27 amino acid deletion of the invention.

Reducing the amount of FVIII variant therapy has the advantage of expected reduced immunogenicity, *i.e.* it is expected that the probability of generation of inhibitory antibodies against the FVIII replacement therapy in the patient is significantly reduced.

In an embodiment, a factor VIII variant of the invention is administered in an amount of no more than 200 µg/dose or 150 µg/dose or 145 µg/dose or 140 µg/dose or 136 µg/dose or 130 µg/dose.

Having now fully described this invention, it will be appreciated by those skilled in the art that the same can be performed within a wide range of equivalent parameters, concentrations and conditions without departing from the spirit and scope of the invention and without undue experimentation.

While this invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications. This application is intended to cover any variations, uses or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth as follows in the scope of the appended claims.

All references cited herein, including journal articles or abstracts, published or unpublished U. S. or foreign patent application, issued U. S. or foreign patents or any other references, are entirely incorporated by reference herein, including all data, tables, figures and text presented in the cited references. Additionally, the entire contents of the references cited within the references cited herein are also entirely incorporated by reference.

Reference to known method steps, conventional methods steps, known methods or conventional methods is not any way an admission that any aspect, description or embodiment of the present invention is disclosed, taught or suggested in the relevant art.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art (including the contents of the references cited herein), readily modify and/or adapt for various application such specific embodiments, without undue experimentation,

without departing from the general concept of the present invention. Therefore, such adaptations and modifications are intended to be within the meaning a range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance presented herein, in combination with the knowledge of one of ordinary skill in the art.

EXAMPLES

Example 1: Expression of recombinant porcine partially B-domain deleted FVIII (OBI-1) and isolation of three variant proteins (rpVIIIv1, v2 and v3)

Expression of OBI-1 in BHK cells was carried out essentially as described in US 6,458,563. Three variants were detected in the produced material (rpVIIIv1, v2 and v3). The variants were isolated and purified to >95% purity ion exchange chromatography. For purification, an AKTA Explorer system (AKTA Explorer 10, GE Healthcare Lifesciences # 17-5167-01) using a MonoQ HR10/10 semi-preparative anion exchange column (now Mono Q 10/100 GL ,GE Healthcare Lifesciences # 17-5167-01) was used. Elution was carried out on a gradient with the two following buffers:

Buffer A: 10 mM TRIS, pH 7.0, 0.01% Polysorbate 80

Buffer B: Buffer A and 1 M sodium chloride.

The purification method characteristics are summarized in Table 1.

Table 1: rpFVIII Variant Purification Method

AKTA Method:	LoopMQ1010	
Flow:	4 ml/min	
Equilibrium Column	8 CV	
Load flow	4ml/min	
Sample Volume	40 - 1000 ml	
Wash Column	10CV	
Gradient	Column Volume (CV)	%B
	7	45
	4	50
	4	50
	6	52
	4	52
	2	55
	7	60
	1	65

	5	65
	1	70
	5	70
	1	100
	7	100
	1	10
	4	10
Total Run	59 CV	
Column Temp	Not controlled	

Example 2: Variant 3 (rpVIIIv3) has a significantly higher specific activity than variants 1 and 2

The specific activity of each variant was assessed by dividing the potency assessed by one stage coagulation assay (OSCA) by the protein concentration as measured by the SEC HPLC per method. The OSCA and SEC HPLC methods were carried out as described in "Materials and Methods" Example 5.

RESULTS

The results for the specific activities are indicated in Table 2.

Table 2: Specific Activities (OSCA method)for Purified Variants 1, 2 and 3 obtained from two different lots of rpFVIII

Sample based on SEC	OSCA units/ml	%RSD*	Specific activity units/ml	%RSD*
V1 – lot 1	1060	1.5	11956	1.7
V2 – lot 1	715	2.7	17267	3.3
V3 – lot 1	216	1.2	25926	2.8
OBI-1	513	1	18150	1.3
V1 – lot 2	980	1.2	12532	1.5
V2 – lot 2	613	0.6	16089	1.3
V3 – lot 2	280	2.9	19718	4.1
OBI-1	565	4.0	14427	4.4

*relative standard deviation

The observation of significantly higher specific activity for variant 3 in the OSCA assay is distinct and consistent. Since the OSCA method is predictive and representative for the coagulation process in humans, it is expected that variant 3 is a product of significant value. It is expected that 1.5-2.0 fold increase in potency reduce the amount of FVIII administered to patients and might therefore indirectly reduce the occurrence of immunological side effects.

Example 3: Sequence determination of rpFVIIIv3

The sequence of purified v3 was determined by peptide map followed by LCMS (liquid chromatography mass spectrometry) and LCMS/MS (liquid chromatography mass spectrometry/mass spectrometry) on a Q-TOF Ultima Mass Spectrometer, running MassLynx 4.0 (Waters Corporation, Milford, MA).

Approximately 250 µg of Variant 3 was concentrated using an Amicon, Centricon YM-10 concentrator with a 10,000 MWCO filter (Millipore Corporation, Billerica, MA) to a volume of < 100 µL. The samples were mixed with 450 µL of 6 M guanidine HCl/ 0.002 M EDTA (ethylenediaminetetraacetic acid) /0.02 M Tris buffer pH 8 and transferred to 2.0 mL polypropylene tubes. 1 M DTT (dithiothreitol) was added to each sample to a final concentration of 10 mM and incubated for 1 hour at 37 °C. After reduction, 2 M iodoacetamide was added to each tube to a final concentration of 20 mM and incubated for an additional hour at room temperature. The reduced and alkylated samples were transferred to dialysis cassettes and dialyzed for 1 hour against 1 L of 50 mM ammonium bicarbonate dialysis buffer containing 1.0 M urea, pH 8. The samples were then dialyzed against 1 L of dialysis buffer overnight at room temperature while maintaining constant stirring. After dialysis the final volumes were approximately 0.5 mL each. Samples were divided into two 125 µg aliquots.

After dialysis, the protein sample was contained in a matrix that is optimal for proteolytic digestion with trypsin. Trypsin was added to each sample at an enzyme to substrate ratio of 1:20 (w:w) and incubated for 8 hours at 37 °C. All samples were transferred to HPLC vials and analyzed by HPLC-MS.

Reduced and alkylated protein was injected onto a Vydac C18 reverse phase column (Grace, Deerfield, IL). Prior to the sample injection, a blank sample (Mobile Phase A; deionized water containing 0.2% (v:v) formic acid) was analyzed to equilibrate the column and demonstrate the absence of interfering peaks.

Mass spectrometry data was collected on a Q-TOF API-US mass spectrometer or a Q-TOF Ultima mass spectrometer (Waters Corporation, Milford, MA) using electrospray ionization (ESI) in the positive ion mode. Prior to sample analysis, the mass spectrometer was calibrated using a 5th order fit on the fragment ions of Glu-Fibrinogen peptide covering a range of 175 to 1285 m/z. For the calibration to pass specifications, a RMS (root mean square) error for the mass of the peptide fragments less than 5 ppm was required. The software package Masslynx 4.0™ SP2 and SP4 (Waters Corporation, Milford, MA) were used for data acquisition and analysis.

Both MS and MS/MS data were collected using a single liquid chromatography (LC) run. Full mass spectrometer (MS) survey scans were collected from 200-1950 m/z.

The sequence of rpFVIII was determined to correspond to SEQ ID NO: 1. This sequence contains a 27 amino acid deletion in comparison with the OBI-1 sequence.

Example 4: rpFVIIIv3 has a higher specific activity than other known FVIII products

The specific activity of rpFVIIIv3 was compared to three commercially available FVIII products, namely Xynthia® (a recombinant, B-domain deleted human FVIII from Wyeth Pharmaceuticals (Philadelphia, PA)), Kogenate FS® (a full-length human FVIII from Bayer Healthcare (Tarrytown, NY)) and Advate® (a full-length human FVIII from Baxter (Westlake Village, CA)), as well as to OBI-1 (a recombinant partially B-domain deleted porcine FVIII), which is presently under clinical development, and a B-domain deleted canine factor VIII (Denise E. Sabatino *et.al.*, Recombinant canine B-domain–deleted FVIII exhibits high specific activity and is safe in the canine hemophilia A model, Blood, 12 November 2009, Vol. 114, No. 20, pp. 4562-4565).

The specific activity of OBI-1 and rpFVIIIv3 was determined by the methods as described in Example 5.

The results are depicted in Table 3 and Fig. 1. Due to its increased specific activities, lower amounts of prVIIIv3 per dose can be administered to a patient. It is expected that this decrease in dose will lead to a reduced immunogenicity, *i.e.* result in a lower probability that patients develop inhibitory antibodies.

Table 3: Specific activities of FVIII products as compared to rpVIIIv3

	Specific Activity in IU/mg Protein	Amt protein µg/dose^
Xynthia	7500	400
Kogenate FS	4000	750
Advate	4000	750
OBI-1	11000	273
rpVIIIv3	22000	136
Canine BDD* FVIII	34000	88

^Amt Protein = xxxx µg/dose. The numbers shown in the column for rpVIII3 mean that an amount of 136 µg per dose will be required. One dose is the required amount to raise the blood factor VIII level from 0% to 100%, i.e. the higher the specific activity (XXX units/mg), the less amount (in terms of µg) is required. Note that 1 mg = 1000µg. Given that a typical dose is 3000 units per patient, the amount of actual protein required = 3000/22000 = 0.136 mg = 136 µg.

*BDD stands for B-domain deleted and FL stands for full length

In conclusion, these results show that rpVIIIv3 has a significantly higher specific activity than the tested products that are presently commercialized, or under clinical development, for FVIII replacement therapy.

In particular, it is highly surprising a deletion of 27 amino acids, present in rpVIIIv3 but not in OBI-1, leads to a 50% increase in specific activity (as measured by the OSCA assay).

Example 5: Materials and methods

ONE-STAGE COAGULATION ASSAY - OSCA - METHOD

1. Dilute Reference Standard in Assay Buffer (10% Factor VIII deficient plasma + Owren's Veronal Buffer, per liter, 28 mmol of sodium barbital and 125 mmol of NaCl, pH 7.35) to target potency of 1.0 units/mL.
2. Dilute check standards, activity controls and samples in Assay Buffer to the target potency.
3. Load the calibration standard (reference) and reagents into the appropriate wells inside a Symex instrument. (Sysmex CA-1500, Coagulation Analyzer, Dade Behring # B4260-1500 (Siemans Corporation, Deerfield, IL)).
4. Load check standard, controls and samples into racks outside of the Sysmex instrument.
5. Assay sequence occurs automatically inside the instrument as follows:
    a. 5 uL of sample is diluted into 45 ul of assay buffer inside the reaction tube
    b. 50ul of factor VIII deficient plasma is added to the reaction tube
    c. 50ul of Dade Actin FS (purified soy phosphatides in 1.0 X 10^{-4}M Ellagic acid activator, Dade Behring, Liederbach, Germany) activated partial thromboplastin time reagent is added to the reaction tube and incubated for 60 seconds.

d. 50ul of Calcium Chloride (0.025M, Dade Behring, Liederbach, Germany) is added to the reaction tube and incubated for 240 seconds.

e. The clot time is measured up to a maximum time of 300 seconds.

6. The clot time is then correlated to the potency generated by the reference standard calibration curve.

SIZE-EXCLUSION (SEC) HPLC METHOD

An Agilent 1100 (Agilent Technologies, Santa Clara,CA) or a Waters Bioalliance HPLC system (Waters Corporation, Milford, MA) was and is typically used for the size exclusion method for determination of protein concentration. The typical size exclusion column used was a Superdex 200 from GE (Superdex 200 10.300 GL, 10 X 300mm, Cat # 17-5175-01 (GE Healthcare Lifesciences, Piscataway, NJ)). A general assay protocol is as follows:

1. A typical mobile phase was prepared that contained 400mM NaCl with 20mM TRIS, pH 7.4 and 0.01% polysorbate 80.
2. *The mobile phase was run through the HPLC system and column until* equilibration of the baseline was observed.
3. Standards were run to establish system suitability with a typical run time of 30 minutes for each sample.
4. Samples were typically loaded onto an auto sampler with a control chamber temperature of 4°C.
5. A calibration standard of known concentrations containing various amounts of standard samples, typically from 1, 3, 5, 10 and 25 µg of protein were loaded onto the column in volumes between 10 to 50 µl.
6. Samples of unknown concentrations were also loaded into the columns typically in volumes between 30 to 50 µl.
7. The HPLC system was programmed to run the samples automatically according the sequence set up.
8. The peak area of the calibration standards and the unknown samples were determined based on fluorescence detection with excitation and emission at 280nm and 340nm respectively.

9. A linear regression of the calibration standards was generated and the concentration of the unknown sample was determined against this calibration curve.

A typical example of the SEC profile of the calibration standards and the linear regression of the calibration curve is shown in Figure 3.

Example 6: Binding to von Willebrand Factor

Von Willebrand factor (vWF) is a multifunctional glycoprotein which circulates in plasma as a multimeric form complexed with Factor VIII (FVIII/vWF complex). The FVIII/vWF complex serves to protect the bound FVIII from early proteolysis in circulation *in vivo*.

Size exclusion chromatography (SEC) is used to characterize the binding in FIII/vWF complexes. A Superose 6 column (Superose 6 10/300GL, GE Healthcare #17-5172-01, flow rate = 0.5 mL/min) was selected for its known biocompatibility and high exclusion limit of 40 million Daltons (Mobile Phase formulation buffer: 2 mM CaCl2, 10 mM Tris pH 7.0, 300 mM NaCl, 0.01% PSB-80, 11 mM sucrose, 10 mM trisodium citrate). The differences in molecular weight between von Willebrand factor (dimeric @ ~ 500KD, Fitzgerald Cat# 30C-CP4003U, Lot # A09121050, Monomer Mol. Wt = ~260kD, Conc. = 77 µg/mL) and rpFVIII (~ 160 KD) is sufficient to resolve the two species.

The stoichiometry of binding was determined by titration of constant amount of vWF with increasing amounts of rpFVIII. The profile of the complexation formation between rpFVIII and vWF was determined from the SEC chromatogram and integration of the appropriate peaks. The soluble form of the resultant mixtures in the supernatant were used to determine the end point of the complexation from titration with increasing amounts of rpFVIII. The larger, stable complexes formed between rpFVIII and vWF migrate from the normal retention time to the exclusion limit of the column. When saturation occurs, increasing amounts of unbound rpFVIII will be observed in the SEC chromatogram. This method is used to distinguish differences and similarities in the properties of the variants.

Example 7: Thrombin Digestion Kinetics

SDS-PAGE

Recombinant porcine factor VIII (rpFVIII) molecules are heterodimers of approximately 160kD composed of a 78.5kD molecular weight light chain (A3-C1-C2, 765-1448) and a heavy chain ranging in molecular weight from 86.7kD (A1-A2). The

heavy chain of rpFVIII is heterogeneous and composed of three main variants which are formed upon secretion from the cell and may be cleaved by membrane bound proteases of the subtilisin family designated PACE (Paired Basic Amino Acid Cleavage Enzyme).

Like the human factor VIII, rpFVIII is transformed into an active form by limited proteolysis from thrombin. Thrombin activation of rpFVIII is specific for the cleavage site of the heavy chain at Arg(372)-Ser(373). The cleavage region for the Light Chain at Arg(805)-Ser(806) liberates a small 40 amino acid peptide fraction ranging from 765-804 (~4.4kD). The combination of these initial cleavages by thrombin form the activated recombinant porcine factor VIII as a heterotrimer of subunits designated as A1 (~50kD), A2 (~40kD), and A3-C1-C2 (~70kD). The cleaved rpFVIII A1 and A3-C1-C2 subunits retain the divalent metal ion-dependent linkage, whereas the A2 subunit is weakly associated with the A1–A3-C1-C2 dimer by primarily electrostatic interactions. In SDS-PAGE, these subunits are displayed as three distinct bands. The efficiency in conversion of the rpFVIII (2 peptide units) to three peptide units is characteristic of thrombin activation of the product. This method distinguishes the similarity and differences between the individual variants.

Two other orthogonal methods can be and were used to map the kinetics of thrombin digestion of FVIII. Denaturing reverse phase HPLC may be used; the peak profiles are expected to be similar to that of SDS-PAGE. Anion exchange chromatography, which retains the native form of the peptides, may also be used.

Reverse Phase HPLC

Equipment:

1. HPLC 1100 series: Agilent Technologies, Santa Clara, CA, USA; Model No. 61312A, Serial No. DE10907753.
2. Poroshell 5um 2.1X75mm column: Agilent Technologies, Santa Clara, CA, USA; Part No. 660750-909, Serial No. USVV001988.

Reagents:

1. Buffer A: 0.1% TFA (JT B Baker, Phillisburg, NJ; Cat No. 94700-00, Lot No. J23J00) in water
2. Buffer B: 0.1% TFA in Acetonitrile (JT Baker, Phillisburg, NJ; Cat No. 9017-03, Lot No. J38807).

Procedure:

1. Equilibrate the column for 60 minutes using 99%A and 1%B at 1ml/min.
2. Sample injections were 50µl in volume; 25 µl of reference standard was used as control.

3. An example of the method used to run the samples is shown Table 4.

Table 4:

Injection	Time (min)	Flow (ml/min)	%A	%B
1	0.00	2	99	1
2	2.00	2	99	1
3	3.00	2	64	36
4	3.50	2	64	36
5	4.00	2	61	39
6	5.00	2	61	39
7	5.10	2	58	42
8	6.50	2	58	42
9	6.51	2	56	44
10	7.20	2	56	44
11	7.21	2	40	60
12	8.50	2	40	60
13	8.51	2	10	90
14	9.00	2	10	90
15	9.10	2	99	1
16	10.00	2	99	1

Anion Exchange Chromatography

Equipment:

1. AllianceBio HPLC, Waters corporation, Milford, MA, USA; Model No. 2796; Serial No M08BA1199M.
2. Protein Pak Hi Res Q 5um 4.6X100mm column: Waters Corporation, Milford, MA, USA; Part No. 186004931, Serial No. 502N112561VE04.

Reagents:

Buffer A:

10mM Tris base (1.211g/L)

2mM Calcium Chloride (0.588g/L)

0.01% polysorbate 80 (1ml of 10% PS-80/L)

Filtered water up to 1L, pH 7.0

Buffer B:

10mM Tris base (1.211g/L)

2mM Calcium Chloride (0.588g/L)

0.01% polysorbate 80 (1ml of 10% PS-80/L)

1M Sodium Chloride (58.44g/L)

Filtered water upto 1L, pH 7.0

Procedure:

1. Equilibrate the column for 60min using 70%A and 30%B at 0.5ml/min
2. Sample injections were 50µl in volume; 10 µl of reference standard was used as control.
3. An example of the method used to run the samples is shown Table 5.

Table 5:

Injection	Time (min)	Flow (ml/min)	%A	%B
1	0.01	0.5	70	30
2	0.50	0.5	70	30
3	3.50	0.5	60	40
4	5.00	0.5	60	40
5	10.00	0.5	30	70
6	10.10	0.5	1	99
7	12.00	0.5	1	99
8	12.10	0.5	70	30
9	17.00	0.5	70	30

The skilled artisan would know and appreciate that these and other methods may be used to arrive at understanding recombinant Factor VIII proteins as described herein.

CLAIMS

1. An isolated, recombinant, fully or partially B-domain deleted factor VIII (FVIII) variant, the FVIII variant being devoid of an amino acid sequence corresponding to amino acids 716 to 742 of porcine factor VIII as depicted in Figure 2 or amino acids 714 to 740 of SEQ ID NO: 7.

2. The FVIII variant according to claim 1, comprising a sequence being at least 90% identical to SEQ ID NO: 1, the variant being devoid of the amino acid sequence corresponding to amino acids 716 to 742 of porcine factor VIII as depicted in Figure 2 or amino acids 714 to 740 of SEQ ID NO: 7.

3. The FVIII variant according to claim 2, wherein said variant shares at least 95, 96, 97, 98, 99, 99.5, 99.6, 99.7, 99.8 or 99.9% identity to SEQ ID NO:1.

4. The FVIII variant according to claim 3, wherein said variant shares 99.5, 99.6, 99.7, 99.8 or 99.9% identity to SEQ ID NO:1.

5. The FVIII variant according to claim 4, wherein said variant is SEQ ID NO:1.

6. An isolated, recombinant, fully or partially B-domain deleted factor VIII (FVIII) variant, the FVIII variant being devoid of an amino acid sequence corresponding to amino acids 716 to 742 of human factor VIII as depicted in Figure 2 or amino acids 714 to 740 of SEQ ID NO: 8.

7. The FVIII variant according to claim 6, comprising a sequence being at least 90% identical to SEQ ID NO: 1, the variant being devoid of the amino acid sequence corresponding to amino acids 716 to 742 of porcine factor VIII as depicted in Figure 2 or amino acids 714 to 740 of SEQ ID NO: 8.

8. The FVIII variant according to claim 7, wherein said variant shares at least 95, 96, 97, 98, 99, 99.5, 99.6, 99.7, 99.8 or 99.9% identity to SEQ ID NO:2.

9. The FVIII variant according to claim 8, wherein said variant shares 99.5, 99.6, 99.7, 99.8 or 99.9% identity to SEQ ID NO:2.

10. The FVIII variant according to claim 9, wherein said variant is SEQ ID NO:2.

11. The FVIII variant according to any one of the preceding claims, wherein the FVIII variant is partially B-domain deleted and the remaining portion of the B-domain is selected from a sequence consisting of SEQ ID NO: 4 or SEQ ID NO:5.

12. A polynucleotide encoding a polypeptide according any one of the preceding claims.

13. An expression vector comprising a polynucleotide according to claim 12.

14. A mammalian cell comprising an expression vector according to claim 13.

15. A method for producing a FVIII variant according to any one of claims 1 to 10, comprising the steps of :

a. Culturing a mammalian cell according to claim 14; and

b. Isolating from the mammalian cell the FVIII variant.

16. The method according to claim 15, further comprising the step of

c. Formulating the factor VIII variant together with appropriate excipients into a pharmaceutical composition.

17. A pharmaceutical composition comprising a factor VIII variant according to any one of claims 1 to 10.

18. A method of treating a patient suffering from hemophilia comprising administering a therapeutically effective amount of FVIII variant according to any one of claims 1 to 10 to a patient in need thereof, thereby treating the hemophilia in said patient.

19. A FVIII variant according to any one of claims 1 to 10 for use in treating hemophilia.

20. The method or use according to claim 18 or 19, wherein said hemophilia is hemophilia A.

21. The method or use according to claim 18 or 19, wherein said hemophilia is acquired hemophilia.

22. The method or use according to any one of claims 18 to 21, wherein said hemophilia is treated in patients having developed human FVIII antibodies.

23. The method or use according to any one of claims 18 to 22, wherein the factor VIII is administered in an amount of no more than 200 µg/dose or 150 µg/dose or 140 µg/dose.

SEQUENCE LISTING

<110> Ipsen Pharma S.A.S.

<120> A new variant of antihemophilic factor VIII having increased specific activity

<130> IPH 021

<160> 12

<170> PatentIn version 3.5

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<212> PRT
<213> sus scrofa

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Ala Thr Ala Pro Gly Ala Leu Pro Leu Gly Pro Ser Val Leu Tyr Lys
        35                  40                  45

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

Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu
65                  70                  75                  80

Val Tyr Asp Thr Val Val Val Thr Leu Lys Asn Met Ala Ser His Pro
                85                  90                  95

Val Ser Leu His Ala Val Gly Val Ser Phe Trp Lys Ser Ser Glu Gly
            100                 105                 110

Ala Glu Tyr Glu Asp His Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys
        115                 120                 125

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

Asn Gly Pro Thr Ala Ser Asp Pro Pro Cys Leu Thr Tyr Ser Tyr Leu
145                 150                 155                 160

Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala
                165                 170                 175
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Leu Leu Val Cys Arg Glu Gly Ser Leu Thr Arg Glu Arg Thr Gln Asn
            180                 185                 190

Leu His Glu Phe Val Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser
        195                 200                 205

Trp His Ser Ala Arg Asn Asp Ser Trp Thr Arg Ala Met Asp Pro Ala
    210                 215                 220

Pro Ala Arg Ala Gln Pro Ala Met His Thr Val Asn Gly Tyr Val Asn
225                 230                 235                 240

Arg Ser Leu Pro Gly Leu Ile Gly Cys His Lys Lys Ser Val Tyr Trp
                245                 250                 255

His Val Ile Gly Met Gly Thr Ser Pro Glu Val His Ser Ile Phe Leu
            260                 265                 270

Glu Gly His Thr Phe Leu Val Arg His His Arg Gln Ala Ser Leu Glu
        275                 280                 285

Ile Ser Pro Leu Thr Phe Leu Thr Ala Gln Thr Phe Leu Met Asp Leu
    290                 295                 300

Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His His His Gly Gly
305                 310                 315                 320

Met Glu Ala His Val Arg Val Glu Ser Cys Ala Glu Glu Pro Gln Leu
                325                 330                 335

Arg Arg Lys Ala Asp Glu Glu Glu Asp Tyr Asp Asp Asn Leu Tyr Asp
            340                 345                 350

Ser Asp Met Asp Val Val Arg Leu Asp Gly Asp Asp Val Ser Pro Phe
        355                 360                 365

Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val His
    370                 375                 380

Tyr Ile Ser Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Ala Val Pro
385                 390                 395                 400

Ser Pro Ser Asp Arg Ser Tyr Lys Ser Leu Tyr Leu Asn Ser Gly Pro
                405                 410                 415

Gln Arg Ile Gly Arg Lys Tyr Lys Lys Ala Arg Phe Val Ala Tyr Thr
            420                 425                 430
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Asp Val Thr Phe Lys Thr Arg Lys Ala Ile Pro Tyr Glu Ser Gly Ile
        435                 440                 445

Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile
    450                 455                 460

Phe Lys Asn Lys Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile
465                 470                 475                 480

Thr Asp Val Ser Ala Leu His Pro Gly Arg Leu Leu Lys Gly Trp Lys
                485                 490                 495

His Leu Lys Asp Met Pro Ile Leu Pro Gly Glu Thr Phe Lys Tyr Lys
            500                 505                 510

Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys
        515                 520                 525

Leu Thr Arg Tyr Tyr Ser Ser Ser Ile Asn Leu Glu Lys Asp Leu Ala
    530                 535                 540

Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp
545                 550                 555                 560

Gln Arg Gly Asn Gln Met Met Ser Asp Lys Arg Asn Val Ile Leu Phe
                565                 570                 575

Ser Val Phe Asp Glu Asn Gln Ser Trp Tyr Leu Ala Glu Asn Ile Gln
            580                 585                 590

Arg Phe Leu Pro Asn Pro Asp Gly Leu Gln Pro Gln Asp Pro Glu Phe
        595                 600                 605

Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp Ser
    610                 615                 620

Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu
625                 630                 635                 640

Ser Val Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr
                645                 650                 655

Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro
            660                 665                 670

Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp
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675 680 685

Val Leu Gly Cys His Asn Ser Asp Leu Arg Asn Arg Gly Met Thr Ala
690 695 700

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Pro Pro Ser Ala Ser Ala Pro Lys Pro Pro Val Leu Arg Arg His Gln
725 730 735

Arg Asp Ile Ser Leu Pro Thr Phe Gln Pro Glu Glu Asp Lys Met Asp
740 745 750

Tyr Asp Asp Ile Phe Ser Thr Glu Thr Lys Gly Glu Asp Phe Asp Ile
755 760 765

Tyr Gly Glu Asp Glu Asn Gln Asp Pro Arg Ser Phe Gln Lys Arg Thr
770 775 780

Arg His Tyr Phe Ile Ala Ala Val Glu Gln Leu Trp Asp Tyr Gly Met
785 790 795 800

Ser Glu Ser Pro Arg Ala Leu Arg Asn Arg Ala Gln Asn Gly Glu Val
805 810 815

Pro Arg Phe Lys Lys Val Val Phe Arg Glu Phe Ala Asp Gly Ser Phe
820 825 830

Thr Gln Pro Ser Tyr Arg Gly Glu Leu Asn Lys His Leu Gly Leu Leu
835 840 845

Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr Phe
850 855 860

Lys Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser
865 870 875 880

Tyr Pro Asp Asp Gln Glu Gln Gly Ala Glu Pro Arg His Asn Phe Val
885 890 895

Gln Pro Asn Glu Thr Arg Thr Tyr Phe Trp Lys Val Gln His His Met
900 905 910

Ala Pro Thr Glu Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe Ser
915 920 925

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Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro Leu
    930                 935                 940

Leu Ile Cys Arg Ala Asn Thr Leu Asn Ala Ala His Gly Arg Gln Val
945                 950                 955                 960

Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr Lys
                965                 970                 975

Ser Trp Tyr Phe Thr Glu Asn Val Glu Arg Asn Cys Arg Ala Pro Cys
            980                 985                 990

His Leu Gln Met Glu Asp Pro Thr  Leu Lys Glu Asn Tyr  Arg Phe His
        995                 1000                1005

Ala Ile  Asn Gly Tyr Val Met  Asp Thr Leu Pro Gly  Leu Val Met
    1010                1015                1020

Ala Gln  Asn Gln Arg Ile Arg  Trp Tyr Leu Leu Ser  Met Gly Ser
    1025                1030                1035

Asn Glu  Asn Ile His Ser Ile  His Phe Ser Gly His  Val Phe Ser
    1040                1045                1050

Val Arg  Lys Lys Glu Glu Tyr  Lys Met Ala Val Tyr  Asn Leu Tyr
    1055                1060                1065

Pro Gly  Val Phe Glu Thr Val  Glu Met Leu Pro Ser  Lys Val Gly
    1070                1075                1080

Ile Trp  Arg Ile Glu Cys Leu  Ile Gly Glu His Leu  Gln Ala Gly
    1085                1090                1095

Met Ser  Thr Thr Phe Leu Val  Tyr Ser Lys Glu Cys  Gln Ala Pro
    1100                1105                1110

Leu Gly  Met Ala Ser Gly Arg  Ile Arg Asp Phe Gln  Ile Thr Ala
    1115                1120                1125

Ser Gly  Gln Tyr Gly Gln Trp  Ala Pro Lys Leu Ala  Arg Leu His
    1130                1135                1140

Tyr Ser  Gly Ser Ile Asn Ala  Trp Ser Thr Lys Asp  Pro His Ser
    1145                1150                1155

Trp Ile  Lys Val Asp Leu Leu  Ala Pro Met Ile Ile  His Gly Ile
    1160                1165                1170
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Met Thr  Gln Gly Ala Arg Gln  Lys Phe Ser Ser Leu  Tyr Ile Ser
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Gln Phe  Ile Ile Met Tyr Ser  Leu Asp Gly Arg Asn  Trp Gln Ser
    1190                 1195                 1200

Tyr Arg  Gly Asn Ser Thr Gly  Thr Leu Met Val Phe  Phe Gly Asn
    1205                 1210                 1215

Val Asp  Ala Ser Gly Ile Lys  His Asn Ile Phe Asn  Pro Pro Ile
    1220                 1225                 1230

Val Ala  Arg Tyr Ile Arg Leu  His Pro Thr His Tyr  Ser Ile Arg
    1235                 1240                 1245

Ser Thr  Leu Arg Met Glu Leu  Met Gly Cys Asp Leu  Asn Ser Cys
    1250                 1255                 1260

Ser Met  Pro Leu Gly Met Gln  Asn Lys Ala Ile Ser  Asp Ser Gln
    1265                 1270                 1275

Ile Thr  Ala Ser Ser His Leu  Ser Asn Ile Phe Ala  Thr Trp Ser
    1280                 1285                 1290

Pro Ser  Gln Ala Arg Leu His  Leu Gln Gly Arg Thr  Asn Ala Trp
    1295                 1300                 1305

Arg Pro  Arg Val Ser Ser Ala  Glu Glu Trp Leu Gln  Val Asp Leu
    1310                 1315                 1320

Gln Lys  Thr Val Lys Val Thr  Gly Ile Thr Thr Gln  Gly Val Lys
    1325                 1330                 1335

Ser Leu  Leu Ser Ser Met Tyr  Val Lys Glu Phe Leu  Val Ser Ser
    1340                 1345                 1350

Ser Gln  Asp Gly Arg Arg Trp  Thr Leu Phe Leu Gln  Asp Gly His
    1355                 1360                 1365

Thr Lys  Val Phe Gln Gly Asn  Gln Asp Ser Ser Thr  Pro Val Val
    1370                 1375                 1380

Asn Ala  Leu Asp Pro Pro Leu  Phe Thr Arg Tyr Leu  Arg Ile His
    1385                 1390                 1395

Pro Thr  Ser Trp Ala Gln His  Ile Ala Leu Arg Leu  Glu Val Leu
    1400                 1405                 1410
```

Gly Cys Glu Ala Gln Asp Leu Tyr
1415 1420

<210> 2
<211> 1397
<212> PRT
<213> homo sapiens

<400> 2

Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr
1 5 10 15

Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg Phe Pro Pro
20 25 30

Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val Tyr Lys Lys
35 40 45

Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile Ala Lys Pro
50 55 60

Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu Val
65 70 75 80

Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val
85 90 95

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

Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val
115 120 125

Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu Asn
130 135 140

Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu Ser
145 150 155 160

His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala Leu
165 170 175

Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr Leu
180 185 190

His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser Trp
195 200 205

```
His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala Ser
    210                 215                 220

Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn Arg
225                 230                 235                 240

Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val Tyr Trp His
                245                 250                 255

Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu
            260                 265                 270

Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile
        275                 280                 285

Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met Asp Leu Gly
    290                 295                 300

Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met
305                 310                 315                 320

Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg
                325                 330                 335

Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp Leu Thr Asp
            340                 345                 350

Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser Pro Ser Phe
        355                 360                 365

Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val His
    370                 375                 380

Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Leu Val Leu
385                 390                 395                 400

Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn Asn Gly Pro
                405                 410                 415

Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr
            420                 425                 430

Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly Ile
        435                 440                 445

Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile
```

```
450                 455                 460

Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile
465                 470                 475                 480

Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys Gly Val Lys
                485                 490                 495

His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys
            500                 505                 510

Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys
        515                 520                 525

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

Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp
545                 550                 555                 560

Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe
                565                 570                 575

Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu Asn Ile Gln
            580                 585                 590

Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp Pro Glu Phe
        595                 600                 605

Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp Ser
    610                 615                 620

Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu
625                 630                 635                 640

Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr
                645                 650                 655

Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro
            660                 665                 670

Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp
        675                 680                 685

Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly Met Thr Ala
    690                 695                 700
```

```
Leu Leu Lys Val Ser Ser Cys Asp Lys Glu Ile Thr Arg Thr Thr Leu
705                 710                 715                 720

Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu
                725                 730                 735

Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser
            740                 745                 750

Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val
        755                 760                 765

Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg
    770                 775                 780

Asn Arg Ala Gln Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe
785                 790                 795                 800

Gln Glu Phe Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu
                805                 810                 815

Leu Asn Glu His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val
            820                 825                 830

Glu Asp Asn Ile Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr
        835                 840                 845

Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly
    850                 855                 860

Ala Glu Pro Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr
865                 870                 875                 880

Phe Trp Lys Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp
                885                 890                 895

Cys Lys Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val
            900                 905                 910

His Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu
        915                 920                 925

Asn Pro Ala His Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe
    930                 935                 940

Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met
945                 950                 955                 960
```

```
Glu Arg Asn Cys Arg Ala Pro Cys Asn Ile Gln Met Glu Asp Pro Thr
                965                 970                 975

Phe Lys Glu Asn Tyr Arg Phe His Ala Ile Asn Gly Tyr Ile Met Asp
            980                 985                 990

Thr Leu Pro Gly Leu Val Met Ala  Gln Asp Gln Arg Ile  Arg Trp Tyr
        995                 1000                1005

Leu Leu  Ser Met Gly Ser Asn  Glu Asn Ile His Ser  Ile His Phe
    1010                1015                1020

Ser Gly  His Val Phe Thr Val  Arg Lys Lys Glu Glu  Tyr Lys Met
    1025                1030                1035

Ala Leu  Tyr Asn Leu Tyr Pro  Gly Val Phe Glu Thr  Val Glu Met
    1040                1045                1050

Leu Pro  Ser Lys Ala Gly Ile  Trp Arg Val Glu Cys  Leu Ile Gly
    1055                1060                1065

Glu His  Leu His Ala Gly Met  Ser Thr Leu Phe Leu  Val Tyr Ser
    1070                1075                1080

Asn Lys  Cys Gln Thr Pro Leu  Gly Met Ala Ser Gly  His Ile Arg
    1085                1090                1095

Asp Phe  Gln Ile Thr Ala Ser  Gly Gln Tyr Gly Gln  Trp Ala Pro
    1100                1105                1110

Lys Leu  Ala Arg Leu His Tyr  Ser Gly Ser Ile Asn  Ala Trp Ser
    1115                1120                1125

Thr Lys  Glu Pro Phe Ser Trp  Ile Lys Val Asp Leu  Leu Ala Pro
    1130                1135                1140

Met Ile  Ile His Gly Ile Lys  Thr Gln Gly Ala Arg  Gln Lys Phe
    1145                1150                1155

Ser Ser  Leu Tyr Ile Ser Gln  Phe Ile Ile Met Tyr  Ser Leu Asp
    1160                1165                1170

Gly Lys  Lys Trp Gln Thr Tyr  Arg Gly Asn Ser Thr  Gly Thr Leu
    1175                1180                1185

Met Val  Phe Phe Gly Asn Val  Asp Ser Ser Gly Ile  Lys His Asn
    1190                1195                1200
```

```
Ile Phe  Asn Pro Pro Ile Ile  Ala Arg Tyr Ile Arg  Leu His Pro
    1205                 1210                 1215

Thr His  Tyr Ser Ile Arg Ser  Thr Leu Arg Met Glu  Leu Met Gly
    1220                 1225                 1230

Cys Asp  Leu Asn Ser Cys Ser  Met Pro Leu Gly Met  Glu Ser Lys
    1235                 1240                 1245

Ala Ile  Ser Asp Ala Gln Ile  Thr Ala Ser Ser Tyr  Phe Thr Asn
    1250                 1255                 1260

Met Phe  Ala Thr Trp Ser Pro  Ser Lys Ala Arg Leu  His Leu Gln
    1265                 1270                 1275

Gly Arg  Ser Asn Ala Trp Arg  Pro Gln Val Asn Asn  Pro Lys Glu
    1280                 1285                 1290

Trp Leu  Gln Val Asp Phe Gln  Lys Thr Met Lys Val  Thr Gly Val
    1295                 1300                 1305

Thr Thr  Gln Gly Val Lys Ser  Leu Leu Thr Ser Met  Tyr Val Lys
    1310                 1315                 1320

Glu Phe  Leu Ile Ser Ser Ser  Gln Asp Gly His Gln  Trp Thr Leu
    1325                 1330                 1335

Phe Phe  Gln Asn Gly Lys Val  Lys Val Phe Gln Gly  Asn Gln Asp
    1340                 1345                 1350

Ser Phe  Thr Pro Val Val Asn  Ser Leu Asp Pro Pro  Leu Leu Thr
    1355                 1360                 1365

Arg Tyr  Leu Arg Ile His Pro  Gln Ser Trp Val His  Gln Ile Ala
    1370                 1375                 1380

Leu Arg  Met Glu Val Leu Gly  Cys Glu Ala Gln Asp  Leu Tyr
    1385                 1390                 1395


<210>  3
<211>  1397
<212>  PRT
<213>  Canis familiaris

<400>  3

Ala Thr Arg Lys Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr
1               5                  10                  15
```

```
Met Gln Ser Asp Leu Leu Ser Ala Leu His Ala Asp Thr Ser Phe Ser
            20                  25                  30

Ser Arg Val Pro Gly Ser Leu Pro Leu Thr Thr Ser Val Thr Tyr Arg
        35                  40                  45

Lys Thr Val Phe Val Glu Phe Thr Asp Asp Leu Phe Asn Ile Ala Lys
    50                  55                  60

Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu
65                  70                  75                  80

Val Tyr Asp Thr Val Val Ile Val Leu Lys Asn Met Ala Ser His Pro
                85                  90                  95

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

Ala Glu Tyr Glu Asp Gln Thr Ser Gln Lys Glu Lys Glu Asp Asp Asn
        115                 120                 125

Val Ile Pro Gly Glu Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu
    130                 135                 140

Asn Gly Pro Met Ala Ser Asp Pro Pro Cys Leu Thr Tyr Ser Tyr Phe
145                 150                 155                 160

Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala
                165                 170                 175

Leu Leu Val Cys Lys Glu Gly Ser Leu Ala Lys Glu Arg Thr Gln Thr
            180                 185                 190

Leu Gln Glu Phe Val Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser
        195                 200                 205

Trp His Ser Glu Thr Asn Ala Ser Leu Thr Gln Ala Glu Ala Gln His
    210                 215                 220

Glu Leu His Thr Ile Asn Gly Tyr Val Asn Arg Ser Leu Pro Gly Leu
225                 230                 235                 240

Thr Val Cys His Lys Arg Ser Val Tyr Trp His Val Ile Gly Met Gly
                245                 250                 255

Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu Gly His Thr Phe Leu
```

260 265 270

Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile Thr Phe
275 280 285

Leu Thr Ala Gln Thr Phe Leu Met Asp Leu Gly Gln Phe Leu Leu Phe
290 295 300

Cys His Ile Pro Ser His Gln His Asp Gly Met Glu Ala Tyr Val Lys
305 310 315 320

Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg Met Lys Asn Asn Glu
325 330 335

Asp Lys Asp Tyr Asp Asp Gly Leu Tyr Asp Ser Asp Met Asp Val Val
340 345 350

Ser Phe Asp Asp Asp Ser Ser Ser Pro Phe Ile Gln Ile Arg Ser Val
355 360 365

Ala Lys Lys His Pro Lys Thr Trp Val His Tyr Ile Ala Ala Glu Glu
370 375 380

Glu Asp Trp Asp Tyr Ala Pro Ser Gly Pro Thr Pro Asn Asp Arg Ser
385 390 395 400

His Lys Asn Leu Tyr Leu Asn Asn Gly Pro Gln Arg Ile Gly Lys Lys
405 410 415

Tyr Lys Lys Val Arg Phe Val Ala Tyr Thr Asp Glu Thr Phe Lys Thr
420 425 430

Arg Glu Ala Ile Gln Tyr Glu Ser Gly Ile Leu Gly Pro Leu Leu Tyr
435 440 445

Gly Glu Val Gly Asp Thr Leu Leu Ile Ile Phe Lys Asn Gln Ala Ser
450 455 460

Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile Asn Tyr Val Thr Pro Leu
465 470 475 480

His Thr Gly Arg Leu Pro Lys Gly Val Lys His Leu Lys Asp Met Pro
485 490 495

Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys Trp Thr Val Thr Val Glu
500 505 510

```
Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys Leu Thr Arg Tyr Tyr Ser
        515                 520                 525

Ser Phe Ile Asn Leu Glu Arg Asp Leu Ala Ser Gly Leu Ile Gly Pro
    530                 535                 540

Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp Gln Arg Gly Asn Gln Met
545                 550                 555                 560

Met Ser Asp Lys Arg Asn Val Ile Leu Phe Ser Val Phe Asp Glu Asn
                565                 570                 575

Arg Ser Trp Tyr Leu Thr Glu Asn Met Gln Arg Phe Leu Pro Asn Ala
            580                 585                 590

Asp Val Val Gln Pro His Asp Pro Glu Phe Gln Leu Ser Asn Ile Met
        595                 600                 605

His Ser Ile Asn Gly Tyr Val Phe Asp Asn Leu Gln Leu Ser Val Cys
    610                 615                 620

Leu His Glu Val Ala Tyr Trp Tyr Ile Leu Ser Val Gly Ala Gln Thr
625                 630                 635                 640

Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr Thr Phe Lys His Lys Met
                645                 650                 655

Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro Phe Ser Gly Glu Thr Val
            660                 665                 670

Phe Met Ser Met Glu Asn Pro Gly Leu Trp Val Leu Gly Cys His Asn
        675                 680                 685

Ser Asp Phe Arg Asn Phe Val Ile Ile Ile Asn Arg Gly Met Thr Ala
    690                 695                 700

Leu Leu Lys Val Ser Ser Cys Asn Arg Glu Ile Thr Val Thr Thr Leu
705                 710                 715                 720

Gln Pro Glu Glu Asp Lys Phe Glu Tyr Asp Asp Thr Phe Ser Ile Glu
                725                 730                 735

Met Lys Arg Glu Asp Phe Asp Ile Tyr Gly Asp Tyr Glu Asn Gln Gly
            740                 745                 750

Leu Arg Ser Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val
        755                 760                 765
```

```
Glu Arg Leu Trp Asp Tyr Gly Met Ser Arg Ser Pro His Ile Leu Arg
    770                 775                 780

Asn Arg Ala Gln Ser Gly Asp Val Gln Gln Phe Lys Lys Val Val Phe
785                 790                 795                 800

Gln Glu Phe Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu
                805                 810                 815

Leu Asn Glu His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val
            820                 825                 830

Glu Asp Asn Ile Val Val Thr Phe Lys Asn Gln Ala Ser Arg Pro Tyr
        835                 840                 845

Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Asp Glu Asp Glu Gly Gln Gly
    850                 855                 860

Ala Glu Pro Arg Arg Lys Phe Val Asn Pro Asn Glu Thr Lys Ile Tyr
865                 870                 875                 880

Phe Trp Lys Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp
                885                 890                 895

Cys Lys Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val
            900                 905                 910

His Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Arg Ser Asn Thr Leu
        915                 920                 925

Asn Pro Ala His Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu Val
    930                 935                 940

Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Leu
945                 950                 955                 960

Glu Arg Asn Cys Arg Ala Pro Cys Asn Val Gln Lys Glu Asp Pro Thr
                965                 970                 975

Leu Lys Glu Asn Phe Arg Phe His Ala Ile Asn Gly Tyr Val Lys Asp
            980                 985                 990

Thr Leu Pro Gly Leu Val Met Ala  Gln Asp Gln Lys Val  Arg Trp Tyr
        995                 1000                1005

Leu Leu  Ser Met Gly Ser Asn  Glu Asn Ile His Ser  Ile His Phe
    1010                1015                1020
```

```
Ser Gly  His Val Phe Thr Val  Arg Lys Lys Glu Glu  Tyr Lys Met
    1025                 1030                 1035

Ala Val  Tyr Asn Leu Tyr Pro  Gly Val Phe Glu Thr  Val Glu Met
    1040                 1045                 1050

Leu Pro  Ser Gln Val Gly Ile  Trp Arg Ile Glu Cys  Leu Ile Gly
    1055                 1060                 1065

Glu His  Leu Gln Ala Gly Met  Ser Thr Leu Phe Leu  Val Tyr Ser
    1070                 1075                 1080

Lys Lys  Cys Gln Thr Pro Leu  Gly Met Ala Ser Gly  His Ile Arg
    1085                 1090                 1095

Asp Phe  Gln Ile Thr Ala Ser  Gly Gln Tyr Gly Gln  Trp Ala Pro
    1100                 1105                 1110

Lys Leu  Ala Arg Leu His Tyr  Ser Gly Ser Ile Asn  Ala Trp Ser
    1115                 1120                 1125

Thr Lys  Asp Pro Phe Ser Trp  Ile Lys Val Asp Leu  Leu Ala Pro
    1130                 1135                 1140

Met Ile  Ile His Gly Ile Met  Thr Gln Gly Ala Arg  Gln Lys Phe
    1145                 1150                 1155

Ser Ser  Leu Tyr Val Ser Gln  Phe Ile Ile Met Tyr  Ser Leu Asp
    1160                 1165                 1170

Gly Asn  Lys Trp His Ser Tyr  Arg Gly Asn Ser Thr  Gly Thr Leu
    1175                 1180                 1185

Met Val  Phe Phe Gly Asn Val  Asp Ser Ser Gly Ile  Lys His Asn
    1190                 1195                 1200

Ile Phe  Asn Pro Pro Ile Ile  Ala Gln Tyr Ile Arg  Leu His Pro
    1205                 1210                 1215

Thr His  Tyr Ser Ile Arg Ser  Thr Leu Arg Met Glu  Leu Leu Gly
    1220                 1225                 1230

Cys Asp  Phe Asn Ser Cys Ser  Met Pro Leu Gly Met  Glu Ser Lys
    1235                 1240                 1245

Ala Ile  Ser Asp Ala Gln Ile  Thr Ala Ser Ser Tyr  Leu Ser Ser
```

1250 1255 1260

Met Leu Ala Thr Trp Ser Pro Ser Gln Ala Arg Leu His Leu Gln
1265 1270 1275

Gly Arg Thr Asn Ala Trp Arg Pro Gln Ala Asn Asn Pro Lys Glu
1280 1285 1290

Trp Leu Gln Val Asp Phe Arg Lys Thr Met Lys Val Thr Gly Ile
1295 1300 1305

Thr Thr Gln Gly Val Lys Ser Leu Leu Ile Ser Met Tyr Val Lys
1310 1315 1320

Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Asn Trp Thr Leu
1325 1330 1335

Phe Leu Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Arg Asp
1340 1345 1350

Ser Ser Thr Pro Val Arg Asn Arg Leu Glu Pro Pro Leu Val Ala
1355 1360 1365

Arg Tyr Val Arg Leu His Pro Gln Ser Trp Ala His His Ile Ala
1370 1375 1380

Leu Arg Leu Glu Val Leu Gly Cys Asp Thr Gln Gln Pro Ala
1385 1390 1395

<210> 4
<211> 24
<212> PRT
<213> sus scrofa

<400> 4

Ser Phe Ala Gln Asn Ser Arg Pro Pro Ser Ala Ser Ala Pro Lys Pro
1 5 10 15

Pro Val Leu Arg Arg His Gln Arg
20

<210> 5
<211> 24
<212> PRT
<213> homo sapiens

<400> 5

Ser Phe Ser Gln Asn Ser Arg His Pro Ser Thr Arg Ser Gln Asn Pro
1 5 10 15

Pro Val Leu Lys Arg His Gln Arg
20

<210> 6
<211> 24
<212> PRT
<213> Canis familiaris

<400> 6

Ser Phe Ser Gln Asn Ser Arg His Pro Ser Thr Lys Ser Gln Asn Pro
1 5 10 15

Pro Val Ser Lys His His Gln Arg
20

<210> 7
<211> 2114
<212> PRT
<213> Sus scrofa

<400> 7

Ala Ile Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr
1 5 10 15

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

Ala Thr Ala Pro Gly Ala Leu Pro Leu Gly Pro Ser Val Leu Tyr Lys
35 40 45

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

Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu
65 70 75 80

Val Tyr Asp Thr Val Val Val Thr Leu Lys Asn Met Ala Ser His Pro
85 90 95

Val Ser Leu His Ala Val Gly Val Ser Phe Trp Lys Ser Ser Glu Gly
100 105 110

Ala Glu Tyr Glu Asp His Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys
115 120 125

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

```
Asn Gly Pro Thr Ala Ser Asp Pro Pro Cys Leu Thr Tyr Ser Tyr Leu
145                 150                 155                 160

Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala
                165                 170                 175

Leu Leu Val Cys Arg Glu Gly Ser Leu Thr Arg Glu Arg Thr Gln Asn
            180                 185                 190

Leu His Glu Phe Val Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser
        195                 200                 205

Trp His Ser Ala Arg Asn Asp Ser Trp Thr Arg Ala Met Asp Pro Ala
    210                 215                 220

Pro Ala Arg Ala Gln Pro Ala Met His Thr Val Asn Gly Tyr Val Asn
225                 230                 235                 240

Arg Ser Leu Pro Gly Leu Ile Gly Cys His Lys Lys Ser Val Tyr Trp
                245                 250                 255

His Val Ile Gly Met Gly Thr Ser Pro Glu Val His Ser Ile Phe Leu
            260                 265                 270

Glu Gly His Thr Phe Leu Val Arg His His Arg Gln Ala Ser Leu Glu
        275                 280                 285

Ile Ser Pro Leu Thr Phe Leu Thr Ala Gln Thr Phe Leu Met Asp Leu
    290                 295                 300

Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His His His Gly Gly
305                 310                 315                 320

Met Glu Ala His Val Arg Val Glu Ser Cys Ala Glu Glu Pro Gln Leu
                325                 330                 335

Arg Arg Lys Ala Asp Glu Glu Glu Asp Tyr Asp Asp Asn Leu Tyr Asp
            340                 345                 350

Ser Asp Met Asp Val Val Arg Leu Asp Gly Asp Asp Val Ser Pro Phe
        355                 360                 365

Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val His
    370                 375                 380

Tyr Ile Ser Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Ala Val Pro
385                 390                 395                 400
```

```
Ser Pro Ser Asp Arg Ser Tyr Lys Ser Leu Tyr Leu Asn Ser Gly Pro
                405                 410                 415

Gln Arg Ile Gly Arg Lys Tyr Lys Lys Ala Arg Phe Val Ala Tyr Thr
            420                 425                 430

Asp Val Thr Phe Lys Thr Arg Lys Ala Ile Pro Tyr Glu Ser Gly Ile
        435                 440                 445

Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile
    450                 455                 460

Phe Lys Asn Lys Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile
465                 470                 475                 480

Thr Asp Val Ser Ala Leu His Pro Gly Arg Leu Leu Lys Gly Trp Lys
                485                 490                 495

His Leu Lys Asp Met Pro Ile Leu Pro Gly Glu Thr Phe Lys Tyr Lys
            500                 505                 510

Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys
        515                 520                 525

Leu Thr Arg Tyr Tyr Ser Ser Ser Ile Asn Leu Glu Lys Asp Leu Ala
    530                 535                 540

Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp
545                 550                 555                 560

Gln Arg Gly Asn Gln Met Met Ser Asp Lys Arg Asn Val Ile Leu Phe
                565                 570                 575

Ser Val Phe Asp Glu Asn Gln Ser Trp Tyr Leu Ala Glu Asn Ile Gln
            580                 585                 590

Arg Phe Leu Pro Asn Pro Asp Gly Leu Gln Pro Gln Asp Pro Glu Phe
        595                 600                 605

Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp Ser
    610                 615                 620

Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu
625                 630                 635                 640

Ser Val Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr
```

645 650 655

Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro
660 665 670

Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp
675 680 685

Val Leu Gly Cys His Asn Ser Asp Leu Arg Asn Arg Gly Met Thr Ala
690 695 700

Leu Leu Lys Val Tyr Ser Cys Asp Arg Asp Ile Gly Asp Tyr Tyr Asp
705 710 715 720

Asn Thr Tyr Glu Asp Ile Pro Gly Phe Leu Leu Ser Gly Lys Asn Val
725 730 735

Ile Glu Pro Arg Ser Phe Ala Gln Asn Ser Arg Pro Pro Ser Ala Ser
740 745 750

Gln Lys Gln Phe Gln Thr Ile Thr Ser Pro Glu Asp Asp Val Glu Leu
755 760 765

Asp Pro Gln Ser Gly Glu Arg Thr Gln Ala Leu Glu Glu Leu Ser Val
770 775 780

Pro Ser Gly Asp Gly Ser Met Leu Leu Gly Gln Asn Pro Ala Pro His
785 790 795 800

Gly Ser Ser Ser Ser Asp Leu Gln Glu Ala Arg Asn Glu Ala Asp Asp
805 810 815

Tyr Leu Pro Gly Ala Arg Glu Arg Asn Thr Ala Pro Ser Ala Ala Ala
820 825 830

Arg Leu Arg Pro Glu Leu His His Ser Ala Glu Arg Val Leu Thr Pro
835 840 845

Glu Pro Glu Lys Glu Leu Lys Lys Leu Asp Ser Lys Met Ser Ser Ser
850 855 860

Ser Asp Leu Leu Lys Thr Ser Pro Thr Ile Pro Ser Asp Thr Leu Ser
865 870 875 880

Ala Glu Thr Glu Arg Thr His Ser Leu Gly Pro Pro His Pro Gln Val
885 890 895

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Asn Phe Arg Ser Gln Leu Gly Ala Ile Val Leu Gly Lys Asn Ser Ser
            900                 905                 910

His Phe Ile Gly Ala Gly Val Pro Leu Gly Ser Thr Glu Glu Asp His
        915                 920                 925

Glu Ser Ser Leu Gly Glu Asn Val Ser Pro Val Glu Ser Asp Gly Ile
    930                 935                 940

Phe Glu Lys Glu Arg Ala His Gly Pro Ala Ser Leu Thr Lys Asp Asp
945                 950                 955                 960

Val Leu Phe Lys Val Asn Ile Ser Leu Val Lys Thr Asn Lys Ala Arg
                965                 970                 975

Val Tyr Leu Lys Thr Asn Arg Lys Ile His Ile Asp Asp Ala Ala Leu
            980                 985                 990

Leu Thr Glu Asn Arg Ala Ser Ala  Thr Phe Met Asp Lys  Asn Thr Thr
        995                 1000                1005

Ala Ser  Gly Leu Asn His Val  Ser Asn Trp Ile Lys  Gly Pro Leu
    1010                1015                1020

Gly Lys  Asn Pro Leu Ser Ser  Glu Arg Gly Pro Ser  Pro Glu Leu
    1025                1030                1035

Leu Thr  Ser Ser Gly Ser Gly  Lys Ser Val Lys Gly  Gln Ser Ser
    1040                1045                1050

Gly Gln  Gly Arg Ile Arg Val  Ala Val Glu Glu Glu  Glu Leu Ser
    1055                1060                1065

Lys Gly  Lys Glu Met Met Leu  Pro Asn Ser Glu Leu  Thr Phe Leu
    1070                1075                1080

Thr Asn  Ser Ala Asp Val Gln  Gly Asn Asp Thr His  Ser Gln Gly
    1085                1090                1095

Lys Lys  Ser Arg Glu Glu Met  Glu Arg Arg Glu Lys  Leu Val Gln
    1100                1105                1110

Glu Lys  Val Asp Leu Pro Gln  Val Tyr Thr Ala Thr  Gly Thr Lys
    1115                1120                1125

Asn Phe  Leu Arg Asn Ile Phe  His Gln Ser Thr Glu  Pro Ser Val
    1130                1135                1140
```

```
Glu Gly  Phe Asp Gly Gly Ser  His Ala Pro Val Pro  Gln Asp Ser
    1145                 1150                 1155

Arg Ser  Leu Asn Asp Ser Ala  Glu Arg Ala Glu Thr  His Ile Ala
    1160                 1165                 1170

His Phe  Ser Ala Ile Arg Glu  Glu Ala Pro Leu Glu  Ala Pro Gly
    1175                 1180                 1185

Asn Arg  Thr Gly Pro Gly Pro  Arg Ser Ala Val Pro  Arg Arg Val
    1190                 1195                 1200

Lys Gln  Ser Leu Lys Gln Ile  Arg Leu Pro Leu Glu  Glu Ile Lys
    1205                 1210                 1215

Pro Glu  Arg Gly Val Val Leu  Asn Ala Thr Ser Thr  Arg Trp Ser
    1220                 1225                 1230

Glu Ser  Ser Pro Ile Leu Gln  Gly Ala Lys Arg Asn  Asn Leu Ser
    1235                 1240                 1245

Leu Pro  Phe Leu Thr Leu Glu  Met Ala Gly Gly Gln  Gly Lys Ile
    1250                 1255                 1260

Ser Ala  Leu Gly Lys Ser Ala  Ala Gly Pro Leu Ala  Ser Gly Lys
    1265                 1270                 1275

Leu Glu  Lys Ala Val Leu Ser  Ser Ala Gly Leu Ser  Glu Ala Ser
    1280                 1285                 1290

Gly Lys  Ala Glu Phe Leu Pro  Lys Val Arg Val His  Arg Glu Asp
    1295                 1300                 1305

Leu Leu  Pro Gln Lys Thr Ser  Asn Val Ser Cys Ala  His Gly Asp
    1310                 1315                 1320

Leu Gly  Gln Glu Ile Phe Leu  Gln Lys Thr Arg Gly  Pro Val Asn
    1325                 1330                 1335

Leu Asn  Lys Val Asn Arg Pro  Gly Arg Thr Pro Ser  Lys Leu Leu
    1340                 1345                 1350

Gly Pro  Pro Met Pro Lys Glu  Trp Glu Ser Leu Glu  Lys Ser Pro
    1355                 1360                 1365

Lys Ser  Thr Ala Leu Arg Thr  Lys Asp Ile Ile Ser  Leu Pro Leu
    1370                 1375                 1380
```

```
Asp Arg His Glu Ser Asn His Ser Ile Ala Ala Lys Asn Glu Gly
1385                1390                1395

Gln Ala Glu Thr Gln Arg Glu Ala Ala Trp Thr Lys Gln Gly Gly
1400                1405                1410

Pro Gly Arg Leu Cys Ala Pro Lys Pro Pro Val Leu Arg Arg His
1415                1420                1425

Gln Arg Asp Ile Ser Leu Pro Thr Phe Gln Pro Glu Glu Asp Lys
1430                1435                1440

Met Asp Tyr Asp Asp Ile Phe Ser Thr Glu Thr Lys Gly Glu Asp
1445                1450                1455

Phe Asp Ile Tyr Gly Glu Asp Glu Asn Gln Asp Pro Arg Ser Phe
1460                1465                1470

Gln Lys Arg Thr Arg His Tyr Phe Ile Ala Ala Val Glu Gln Leu
1475                1480                1485

Trp Asp Tyr Gly Met Ser Glu Ser Pro Arg Ala Leu Arg Asn Arg
1490                1495                1500

Ala Gln Asn Gly Glu Val Pro Arg Phe Lys Lys Val Val Phe Arg
1505                1510                1515

Glu Phe Ala Asp Gly Ser Phe Thr Gln Pro Ser Tyr Arg Gly Glu
1520                1525                1530

Leu Asn Lys His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu
1535                1540                1545

Val Glu Asp Asn Ile Met Val Thr Phe Lys Asn Gln Ala Ser Arg
1550                1555                1560

Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Pro Asp Asp Gln
1565                1570                1575

Glu Gln Gly Ala Glu Pro Arg His Asn Phe Val Gln Pro Asn Glu
1580                1585                1590

Thr Arg Thr Tyr Phe Trp Lys Val Gln His His Met Ala Pro Thr
1595                1600                1605

Glu Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe Ser Asp Val
```

```
1610                1615                1620

Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro Leu Leu
1625                1630                1635

Ile Cys Arg Ala Asn Thr Leu Asn Ala Ala His Gly Arg Gln Val
1640                1645                1650

Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
1655                1660                1665

Lys Ser Trp Tyr Phe Thr Glu Asn Val Glu Arg Asn Cys Arg Ala
1670                1675                1680

Pro Cys His Leu Gln Met Glu Asp Pro Thr Leu Lys Glu Asn Tyr
1685                1690                1695

Arg Phe His Ala Ile Asn Gly Tyr Val Met Asp Thr Leu Pro Gly
1700                1705                1710

Leu Val Met Ala Gln Asn Gln Arg Ile Arg Trp Tyr Leu Leu Ser
1715                1720                1725

Met Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His
1730                1735                1740

Val Phe Ser Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Val Tyr
1745                1750                1755

Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser
1760                1765                1770

Lys Val Gly Ile Trp Arg Ile Glu Cys Leu Ile Gly Glu His Leu
1775                1780                1785

Gln Ala Gly Met Ser Thr Thr Phe Leu Val Tyr Ser Lys Glu Cys
1790                1795                1800

Gln Ala Pro Leu Gly Met Ala Ser Gly Arg Ile Arg Asp Phe Gln
1805                1810                1815

Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala
1820                1825                1830

Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Asp
1835                1840                1845
```

```
Pro His  Ser Trp Ile Lys Val  Asp Leu Leu Ala Pro  Met Ile Ile
    1850                1855                1860

His Gly  Ile Met Thr Gln Gly  Ala Arg Gln Lys Phe  Ser Ser Leu
    1865                1870                1875

Tyr Ile  Ser Gln Phe Ile Ile  Met Tyr Ser Leu Asp  Gly Arg Asn
    1880                1885                1890

Trp Gln  Ser Tyr Arg Gly Asn  Ser Thr Gly Thr Leu  Met Val Phe
    1895                1900                1905

Phe Gly  Asn Val Asp Ala Ser  Gly Ile Lys His Asn  Ile Phe Asn
    1910                1915                1920

Pro Pro  Ile Val Ala Arg Tyr  Ile Arg Leu His Pro  Thr His Tyr
    1925                1930                1935

Ser Ile  Arg Ser Thr Leu Arg  Met Glu Leu Met Gly  Cys Asp Leu
    1940                1945                1950

Asn Ser  Cys Ser Met Pro Leu  Gly Met Gln Asn Lys  Ala Ile Ser
    1955                1960                1965

Asp Ser  Gln Ile Thr Ala Ser  Ser His Leu Ser Asn  Ile Phe Ala
    1970                1975                1980

Thr Trp  Ser Pro Ser Gln Ala  Arg Leu His Leu Gln  Gly Arg Thr
    1985                1990                1995

Asn Ala  Trp Arg Pro Arg Val  Ser Ser Ala Glu Glu  Trp Leu Gln
    2000                2005                2010

Val Asp  Leu Gln Lys Thr Val  Lys Val Thr Gly Ile  Thr Thr Gln
    2015                2020                2025

Gly Val  Lys Ser Leu Leu Ser  Ser Met Tyr Val Lys  Glu Phe Leu
    2030                2035                2040

Val Ser  Ser Ser Gln Asp Gly  Arg Arg Trp Thr Leu  Phe Leu Gln
    2045                2050                2055

Asp Gly  His Thr Lys Val Phe  Gln Gly Asn Gln Asp  Ser Ser Thr
    2060                2065                2070

Pro Val  Val Asn Ala Leu Asp  Pro Pro Leu Phe Thr  Arg Tyr Leu
    2075                2080                2085
```

```
Arg Ile  His Pro Thr Ser Trp  Ala Gln His Ile Ala  Leu Arg Leu
    2090                 2095                 2100

Glu Val  Leu Gly Cys Glu Ala  Gln Asp Leu Tyr
    2105                 2110


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<212>  PRT
<213>  homo sapiens

<400>  8

Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr
1               5                  10                  15

Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg Phe Pro Pro
            20                  25                  30

Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val Tyr Lys Lys
        35                  40                  45

Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile Ala Lys Pro
    50                  55                  60

Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu Val
65                  70                  75                  80

Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val
                85                  90                  95

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

Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val
        115                 120                 125

Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu Asn
    130                 135                 140

Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu Ser
145                 150                 155                 160

His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala Leu
                165                 170                 175

Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr Leu
            180                 185                 190
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His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser Trp
        195                 200                 205

His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala Ser
    210                 215                 220

Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn Arg
225                 230                 235                 240

Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val Tyr Trp His
                245                 250                 255

Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu
            260                 265                 270

Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile
        275                 280                 285

Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met Asp Leu Gly
    290                 295                 300

Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met
305                 310                 315                 320

Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg
                325                 330                 335

Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp Leu Thr Asp
            340                 345                 350

Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser Pro Ser Phe
        355                 360                 365

Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val His
    370                 375                 380

Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Leu Val Leu
385                 390                 395                 400

Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn Asn Gly Pro
                405                 410                 415

Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr
            420                 425                 430

Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly Ile
        435                 440                 445
```

```
Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile
    450                 455                 460

Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile
465                 470                 475                 480

Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys Gly Val Lys
                485                 490                 495

His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys
            500                 505                 510

Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys
        515                 520                 525

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

Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp
545                 550                 555                 560

Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe
                565                 570                 575

Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu Asn Ile Gln
            580                 585                 590

Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp Pro Glu Phe
        595                 600                 605

Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp Ser
    610                 615                 620

Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu
625                 630                 635                 640

Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr
                645                 650                 655

Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro
            660                 665                 670

Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp
        675                 680                 685

Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly Met Thr Ala
```

690 695 700

Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp Tyr Tyr Glu
705 710 715 720

Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala
725 730 735

Ile Glu Pro Arg Ser Phe Ser Gln Asn Ser Arg His Pro Ser Thr Arg
740 745 750

Gln Lys Gln Phe Asn Ala Thr Thr Ile Pro Glu Asn Asp Ile Glu Lys
755 760 765

Thr Asp Pro Trp Phe Ala His Arg Thr Pro Met Pro Lys Ile Gln Asn
770 775 780

Val Ser Ser Ser Asp Leu Leu Met Leu Leu Arg Gln Ser Pro Thr Pro
785 790 795 800

His Gly Leu Ser Leu Ser Asp Leu Gln Glu Ala Lys Tyr Glu Thr Phe
805 810 815

Ser Asp Asp Pro Ser Pro Gly Ala Ile Asp Ser Asn Asn Ser Leu Ser
820 825 830

Glu Met Thr His Phe Arg Pro Gln Leu His His Ser Gly Asp Met Val
835 840 845

Phe Thr Pro Glu Ser Gly Leu Gln Leu Arg Leu Asn Glu Lys Leu Gly
850 855 860

Thr Thr Ala Ala Thr Glu Leu Lys Lys Leu Asp Phe Lys Val Ser Ser
865 870 875 880

Thr Ser Asn Asn Leu Ile Ser Thr Ile Pro Ser Asp Asn Leu Ala Ala
885 890 895

Gly Thr Asp Asn Thr Ser Ser Leu Gly Pro Pro Ser Met Pro Val His
900 905 910

Tyr Asp Ser Gln Leu Asp Thr Thr Leu Phe Gly Lys Lys Ser Ser Pro
915 920 925

Leu Thr Glu Ser Gly Gly Pro Leu Ser Leu Ser Glu Glu Asn Asn Asp
930 935 940

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Ser Lys Leu Leu Glu Ser Gly Leu Met Asn Ser Gln Glu Ser Ser Trp
945                 950                 955                 960

Gly Lys Asn Val Ser Ser Thr Glu Ser Gly Arg Leu Phe Lys Gly Lys
                965                 970                 975

Arg Ala His Gly Pro Ala Leu Leu Thr Lys Asp Asn Ala Leu Phe Lys
            980                 985                 990

Val Ser Ile Ser Leu Leu Lys Thr  Asn Lys Thr Ser Asn  Asn Ser Ala
        995                 1000                1005

Thr Asn  Arg Lys Thr His Ile  Asp Gly Pro Ser Leu  Leu Ile Glu
    1010                1015                1020

Asn Ser  Pro Ser Val Trp Gln  Asn Ile Leu Glu Ser  Asp Thr Glu
    1025                1030                1035

Phe Lys  Lys Val Thr Pro Leu  Ile His Asp Arg Met  Leu Met Asp
    1040                1045                1050

Lys Asn  Ala Thr Ala Leu Arg  Leu Asn His Met Ser  Asn Lys Thr
    1055                1060                1065

Thr Ser  Ser Lys Asn Met Glu  Met Val Gln Gln Lys  Lys Glu Gly
    1070                1075                1080

Pro Ile  Pro Pro Asp Ala Gln  Asn Pro Asp Met Ser  Phe Phe Lys
    1085                1090                1095

Met Leu  Phe Leu Pro Glu Ser  Ala Arg Trp Ile Gln  Arg Thr His
    1100                1105                1110

Gly Lys  Asn Ser Leu Asn Ser  Gly Gln Gly Pro Ser  Pro Lys Gln
    1115                1120                1125

Leu Val  Ser Leu Gly Pro Glu  Lys Ser Val Glu Gly  Gln Asn Phe
    1130                1135                1140

Leu Ser  Glu Lys Asn Lys Val  Val Val Gly Lys Gly  Glu Phe Thr
    1145                1150                1155

Lys Asp  Val Gly Leu Lys Glu  Met Val Phe Pro Ser  Ser Arg Asn
    1160                1165                1170

Leu Phe  Leu Thr Asn Leu Asp  Asn Leu His Glu Asn  Asn Thr His
    1175                1180                1185
```

```
Asn Gln  Glu Lys Lys Ile Gln  Glu Glu Ile Glu Lys  Lys Glu Thr
    1190                 1195                 1200

Leu Ile  Gln Glu Asn Val Val  Leu Pro Gln Ile His  Thr Val Thr
    1205                 1210                 1215

Gly Thr  Lys Asn Phe Met Lys  Asn Leu Phe Leu Leu  Ser Thr Arg
    1220                 1225                 1230

Gln Asn  Val Glu Gly Ser Tyr  Asp Gly Ala Tyr Ala  Pro Val Leu
    1235                 1240                 1245

Gln Asp  Phe Arg Ser Leu Asn  Asp Ser Thr Asn Arg  Thr Lys Lys
    1250                 1255                 1260

His Thr  Ala His Phe Ser Lys  Lys Gly Glu Glu Glu  Asn Leu Glu
    1265                 1270                 1275

Gly Leu  Gly Asn Gln Thr Lys  Gln Ile Val Glu Lys  Tyr Ala Cys
    1280                 1285                 1290

Thr Thr  Arg Ile Ser Pro Asn  Thr Ser Gln Gln Asn  Phe Val Thr
    1295                 1300                 1305

Gln Arg  Ser Lys Arg Ala Leu  Lys Gln Phe Arg Leu  Pro Leu Glu
    1310                 1315                 1320

Glu Thr  Glu Leu Glu Lys Arg  Ile Ile Val Asp Asp  Thr Ser Thr
    1325                 1330                 1335

Gln Trp  Ser Lys Asn Met Lys  His Leu Thr Pro Ser  Thr Leu Thr
    1340                 1345                 1350

Gln Ile  Asp Tyr Asn Glu Lys  Glu Lys Gly Ala Ile  Thr Gln Ser
    1355                 1360                 1365

Pro Leu  Ser Asp Cys Leu Thr  Arg Ser His Ser Ile  Pro Gln Ala
    1370                 1375                 1380

Asn Arg  Ser Pro Leu Pro Ile  Ala Lys Val Ser Ser  Phe Pro Ser
    1385                 1390                 1395

Ile Arg  Pro Ile Tyr Leu Thr  Arg Val Leu Phe Gln  Asp Asn Ser
    1400                 1405                 1410

Ser His  Leu Pro Ala Ala Ser  Tyr Arg Lys Lys Asp  Ser Gly Val
    1415                 1420                 1425
```

```
Gln Glu  Ser Ser His Phe Leu  Gln Gly Ala Lys Lys  Asn Asn Leu
    1430                 1435                 1440

Ser Leu  Ala Ile Leu Thr Leu  Glu Met Thr Gly Asp  Gln Arg Glu
    1445                 1450                 1455

Val Gly  Ser Leu Gly Thr Ser  Ala Thr Asn Ser Val  Thr Tyr Lys
    1460                 1465                 1470

Lys Val  Glu Asn Thr Val Leu  Pro Lys Pro Asp Leu  Pro Lys Thr
    1475                 1480                 1485

Ser Gly  Lys Val Glu Leu Leu  Pro Lys Val His Ile  Tyr Gln Lys
    1490                 1495                 1500

Asp Leu  Phe Pro Thr Glu Thr  Ser Asn Gly Ser Pro  Gly His Leu
    1505                 1510                 1515

Asp Leu  Val Glu Gly Ser Leu  Leu Gln Gly Thr Glu  Gly Ala Ile
    1520                 1525                 1530

Lys Trp  Asn Glu Ala Asn Arg  Pro Gly Lys Val Pro  Phe Leu Arg
    1535                 1540                 1545

Val Ala  Thr Glu Ser Ser Ala  Lys Thr Pro Ser Lys  Leu Leu Asp
    1550                 1555                 1560

Pro Leu  Ala Trp Asp Asn His  Tyr Gly Thr Gln Ile  Pro Lys Glu
    1565                 1570                 1575

Glu Trp  Lys Ser Gln Glu Lys  Ser Pro Glu Lys Thr  Ala Phe Lys
    1580                 1585                 1590

Lys Lys  Asp Thr Ile Leu Ser  Leu Asn Ala Cys Glu  Ser Asn His
    1595                 1600                 1605

Ala Ile  Ala Ala Ile Asn Glu  Gly Gln Asn Lys Pro  Glu Ile Glu
    1610                 1615                 1620

Val Thr  Trp Ala Lys Gln Gly  Arg Thr Glu Arg Leu  Cys Ser Gln
    1625                 1630                 1635

Asn Pro  Pro Val Leu Lys Arg  His Gln Arg Glu Ile  Thr Arg Thr
    1640                 1645                 1650

Thr Leu  Gln Ser Asp Gln Glu  Glu Ile Asp Tyr Asp  Asp Thr Ile
```

1655 1660 1665

Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp
1670 1675 1680

Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr
1685 1690 1695

Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser
1700 1705 1710

Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser Val Pro
1715 1720 1725

Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser Phe
1730 1735 1740

Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
1745 1750 1755

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val
1760 1765 1770

Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser
1775 1780 1785

Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg
1790 1795 1800

Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys
1805 1810 1815

Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys
1820 1825 1830

Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His
1835 1840 1845

Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu
1850 1855 1860

Asn Pro Ala His Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu
1865 1870 1875

Phe Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu
1880 1885 1890

```
Asn Met  Glu Arg Asn Cys Arg  Ala Pro Cys Asn Ile  Gln Met Glu
    1895                 1900                 1905

Asp Pro  Thr Phe Lys Glu Asn  Tyr Arg Phe His Ala  Ile Asn Gly
    1910                 1915                 1920

Tyr Ile  Met Asp Thr Leu Pro  Gly Leu Val Met Ala  Gln Asp Gln
    1925                 1930                 1935

Arg Ile  Arg Trp Tyr Leu Leu  Ser Met Gly Ser Asn  Glu Asn Ile
    1940                 1945                 1950

His Ser  Ile His Phe Ser Gly  His Val Phe Thr Val  Arg Lys Lys
    1955                 1960                 1965

Glu Glu  Tyr Lys Met Ala Leu  Tyr Asn Leu Tyr Pro  Gly Val Phe
    1970                 1975                 1980

Glu Thr  Val Glu Met Leu Pro  Ser Lys Ala Gly Ile  Trp Arg Val
    1985                 1990                 1995

Glu Cys  Leu Ile Gly Glu His  Leu His Ala Gly Met  Ser Thr Leu
    2000                 2005                 2010

Phe Leu  Val Tyr Ser Asn Lys  Cys Gln Thr Pro Leu  Gly Met Ala
    2015                 2020                 2025

Ser Gly  His Ile Arg Asp Phe  Gln Ile Thr Ala Ser  Gly Gln Tyr
    2030                 2035                 2040

Gly Gln  Trp Ala Pro Lys Leu  Ala Arg Leu His Tyr  Ser Gly Ser
    2045                 2050                 2055

Ile Asn  Ala Trp Ser Thr Lys  Glu Pro Phe Ser Trp  Ile Lys Val
    2060                 2065                 2070

Asp Leu  Leu Ala Pro Met Ile  Ile His Gly Ile Lys  Thr Gln Gly
    2075                 2080                 2085

Ala Arg  Gln Lys Phe Ser Ser  Leu Tyr Ile Ser Gln  Phe Ile Ile
    2090                 2095                 2100

Met Tyr  Ser Leu Asp Gly Lys  Lys Trp Gln Thr Tyr  Arg Gly Asn
    2105                 2110                 2115

Ser Thr  Gly Thr Leu Met Val  Phe Phe Gly Asn Val  Asp Ser Ser
    2120                 2125                 2130
```

```
Gly Ile  Lys His Asn Ile Phe  Asn Pro Pro Ile Ile  Ala Arg Tyr
    2135                2140                2145

Ile Arg  Leu His Pro Thr His  Tyr Ser Ile Arg Ser  Thr Leu Arg
    2150                2155                2160

Met Glu  Leu Met Gly Cys Asp  Leu Asn Ser Cys Ser  Met Pro Leu
    2165                2170                2175

Gly Met  Glu Ser Lys Ala Ile  Ser Asp Ala Gln Ile  Thr Ala Ser
    2180                2185                2190

Ser Tyr  Phe Thr Asn Met Phe  Ala Thr Trp Ser Pro  Ser Lys Ala
    2195                2200                2205

Arg Leu  His Leu Gln Gly Arg  Ser Asn Ala Trp Arg  Pro Gln Val
    2210                2215                2220

Asn Asn  Pro Lys Glu Trp Leu  Gln Val Asp Phe Gln  Lys Thr Met
    2225                2230                2235

Lys Val  Thr Gly Val Thr Thr  Gln Gly Val Lys Ser  Leu Leu Thr
    2240                2245                2250

Ser Met  Tyr Val Lys Glu Phe  Leu Ile Ser Ser Ser  Gln Asp Gly
    2255                2260                2265

His Gln  Trp Thr Leu Phe Phe  Gln Asn Gly Lys Val  Lys Val Phe
    2270                2275                2280

Gln Gly  Asn Gln Asp Ser Phe  Thr Pro Val Val Asn  Ser Leu Asp
    2285                2290                2295

Pro Pro  Leu Leu Thr Arg Tyr  Leu Arg Ile His Pro  Gln Ser Trp
    2300                2305                2310

Val His  Gln Ile Ala Leu Arg  Met Glu Val Leu Gly  Cys Glu Ala
    2315                2320                2325

Gln Asp  Leu Tyr
    2330
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<212> PRT
<213> canis familiaris

<400> 9

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Ala Thr Arg Lys Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr
1               5                  10                  15

Met Gln Ser Asp Leu Leu Ser Ala Leu His Ala Asp Thr Ser Phe Ser
            20                  25                  30

Ser Arg Val Pro Gly Ser Leu Pro Leu Thr Thr Ser Val Thr Tyr Arg
        35                  40                  45

Lys Thr Val Phe Val Glu Phe Thr Asp Asp Leu Phe Asn Ile Ala Lys
    50                  55                  60

Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu
65                  70                  75                  80

Val Tyr Asp Thr Val Val Ile Val Leu Lys Asn Met Ala Ser His Pro
                85                  90                  95

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

Ala Glu Tyr Glu Asp Gln Thr Ser Gln Lys Glu Lys Glu Asp Asp Asn
        115                 120                 125

Val Ile Pro Gly Glu Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu
    130                 135                 140

Asn Gly Pro Met Ala Ser Asp Pro Pro Cys Leu Thr Tyr Ser Tyr Phe
145                 150                 155                 160

Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala
                165                 170                 175

Leu Leu Val Cys Lys Glu Gly Ser Leu Ala Lys Glu Arg Thr Gln Thr
            180                 185                 190

Leu Gln Glu Phe Val Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser
        195                 200                 205

Trp His Ser Glu Thr Asn Ala Ser Leu Thr Gln Ala Glu Ala Gln His
    210                 215                 220

Glu Leu His Thr Ile Asn Gly Tyr Val Asn Arg Ser Leu Pro Gly Leu
225                 230                 235                 240

Thr Val Cys His Lys Arg Ser Val Tyr Trp His Val Ile Gly Met Gly
                245                 250                 255
```

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Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu Gly His Thr Phe Leu
            260                 265                 270

Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile Thr Phe
        275                 280                 285

Leu Thr Ala Gln Thr Phe Leu Met Asp Leu Gly Gln Phe Leu Leu Phe
    290                 295                 300

Cys His Ile Pro Ser His Gln His Asp Gly Met Glu Ala Tyr Val Lys
305                 310                 315                 320

Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg Met Lys Asn Asn Glu
                325                 330                 335

Asp Lys Asp Tyr Asp Asp Gly Leu Tyr Asp Ser Asp Met Asp Val Val
            340                 345                 350

Ser Phe Asp Asp Asp Ser Ser Ser Pro Phe Ile Gln Ile Arg Ser Val
        355                 360                 365

Ala Lys Lys His Pro Lys Thr Trp Val His Tyr Ile Ala Ala Glu Glu
    370                 375                 380

Glu Asp Trp Asp Tyr Ala Pro Ser Gly Pro Thr Pro Asn Asp Arg Ser
385                 390                 395                 400

His Lys Asn Leu Tyr Leu Asn Asn Gly Pro Gln Arg Ile Gly Lys Lys
                405                 410                 415

Tyr Lys Lys Val Arg Phe Val Ala Tyr Thr Asp Glu Thr Phe Lys Thr
            420                 425                 430

Arg Glu Ala Ile Gln Tyr Glu Ser Gly Ile Leu Gly Pro Leu Leu Tyr
        435                 440                 445

Gly Glu Val Gly Asp Thr Leu Leu Ile Ile Phe Lys Asn Gln Ala Ser
    450                 455                 460

Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile Asn Tyr Val Thr Pro Leu
465                 470                 475                 480

His Thr Gly Arg Leu Pro Lys Gly Val Lys His Leu Lys Asp Met Pro
                485                 490                 495

Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys Trp Thr Val Thr Val Glu
```

500 505 510

Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys Leu Thr Arg Tyr Tyr Ser
515 520 525

Ser Phe Ile Asn Leu Glu Arg Asp Leu Ala Ser Gly Leu Ile Gly Pro
530 535 540

Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp Gln Arg Gly Asn Gln Met
545 550 555 560

Met Ser Asp Lys Arg Asn Val Ile Leu Phe Ser Val Phe Asp Glu Asn
565 570 575

Arg Ser Trp Tyr Leu Thr Glu Asn Met Gln Arg Phe Leu Pro Asn Ala
580 585 590

Asp Val Val Gln Pro His Asp Pro Glu Phe Gln Leu Ser Asn Ile Met
595 600 605

His Ser Ile Asn Gly Tyr Val Phe Asp Asn Leu Gln Leu Ser Val Cys
610 615 620

Leu His Glu Val Ala Tyr Trp Tyr Ile Leu Ser Val Gly Ala Gln Thr
625 630 635 640

Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr Thr Phe Lys His Lys Met
645 650 655

Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro Phe Ser Gly Glu Thr Val
660 665 670

Phe Met Ser Met Glu Asn Pro Gly Leu Trp Val Leu Gly Cys His Asn
675 680 685

Ser Asp Phe Arg Asn Arg Gly Met Thr Ala Leu Leu Lys Val Ser Ser
690 695 700

Cys Asn Arg Asn Ile Asp Asp Tyr Tyr Glu Asp Thr Tyr Glu Asp Ile
705 710 715 720

Pro Thr Pro Leu Leu Asn Glu Asn Asn Val Ile Lys Pro Arg Ser Phe
725 730 735

Ser Gln Asn Ser Arg His Pro Ser Thr Lys Glu Lys Gln Leu Lys Ala
740 745 750

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Thr Thr Thr Pro Glu Asn Asp Ile Glu Lys Ile Asp Leu Gln Ser Gly
        755                 760                 765

Glu Arg Thr Gln Leu Ile Lys Ala Gln Ser Val Ser Ser Ser Asp Leu
    770                 775                 780

Leu Met Leu Leu Gly Gln Asn Pro Thr Pro Arg Gly Leu Phe Leu Ser
785                 790                 795                 800

Asp Leu Arg Glu Ala Thr Asp Arg Ala Asp Asp His Ser Arg Gly Ala
                805                 810                 815

Ile Glu Arg Asn Lys Gly Pro Pro Glu Val Ala Ser Leu Arg Pro Glu
            820                 825                 830

Leu Arg His Ser Glu Asp Arg Glu Phe Thr Pro Glu Pro Glu Leu Gln
        835                 840                 845

Leu Arg Leu Asn Glu Asn Leu Gly Thr Asn Thr Thr Val Glu Leu Lys
    850                 855                 860

Lys Leu Asp Leu Lys Ile Ser Ser Ser Ser Asp Ser Leu Met Thr Ser
865                 870                 875                 880

Pro Thr Ile Pro Ser Asp Lys Leu Ala Ala Ala Thr Glu Lys Thr Gly
                885                 890                 895

Ser Leu Gly Pro Pro Asn Met Ser Val His Phe Asn Ser His Leu Gly
            900                 905                 910

Thr Ile Val Phe Gly Asn Asn Ser Ser His Leu Ile Gln Ser Gly Val
        915                 920                 925

Pro Leu Glu Leu Ser Glu Glu Asp Asn Asp Ser Lys Leu Leu Glu Ala
    930                 935                 940

Pro Leu Met Asn Ile Gln Glu Ser Ser Leu Arg Glu Asn Val Leu Ser
945                 950                 955                 960

Met Glu Ser Asn Arg Leu Phe Lys Glu Glu Arg Ile Arg Gly Pro Ala
                965                 970                 975

Ser Leu Ile Lys Asp Asn Ala Leu Phe Lys Val Asn Ile Ser Ser Val
            980                 985                 990

Lys Thr Asn Arg Ala Pro Val Asn  Leu Thr Thr Asn Arg  Lys Thr Arg
        995                 1000                1005
```

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Val Ala Ile Pro Thr Leu Leu Ile Glu Asn Ser Thr Ser Val Trp
    1010                1015                1020

Gln Asp Ile Met Leu Glu Arg Asn Thr Glu Phe Lys Glu Val Thr
    1025                1030                1035

Ser Leu Ile His Asn Glu Thr Phe Met Asp Arg Asn Thr Thr Ala
    1040                1045                1050

Leu Gly Leu Asn His Val Ser Asn Lys Thr Thr Leu Ser Lys Asn
    1055                1060                1065

Val Glu Met Ala His Gln Lys Lys Glu Asp Pro Val Pro Leu Arg
    1070                1075                1080

Ala Glu Asn Pro Asp Leu Ser Ser Ser Lys Ile Pro Phe Leu Pro
    1085                1090                1095

Asp Trp Ile Lys Thr His Gly Lys Asn Ser Leu Ser Ser Glu Gln
    1100                1105                1110

Arg Pro Ser Pro Lys Gln Leu Thr Ser Leu Gly Ser Glu Lys Ser
    1115                1120                1125

Val Lys Asp Gln Asn Phe Leu Ser Glu Glu Lys Val Val Val Gly
    1130                1135                1140

Glu Asp Glu Phe Thr Lys Asp Thr Glu Leu Gln Glu Ile Phe Pro
    1145                1150                1155

Asn Asn Lys Ser Ile Phe Phe Ala Asn Leu Ala Asn Val Gln Glu
    1160                1165                1170

Asn Asp Thr Tyr Asn Gln Glu Lys Lys Ser Pro Glu Glu Ile Glu
    1175                1180                1185

Arg Lys Glu Lys Leu Thr Gln Glu Asn Val Ala Leu Pro Gln Ala
    1190                1195                1200

His Thr Met Ile Gly Thr Lys Asn Phe Leu Lys Asn Leu Phe Leu
    1205                1210                1215

Leu Ser Thr Lys Gln Asn Val Ala Gly Leu Glu Glu Gln Pro Tyr
    1220                1225                1230

Thr Pro Ile Leu Gln Asp Thr Arg Ser Leu Asn Asp Ser Pro His
    1235                1240                1245
```

```
Ser Glu  Gly Ile His Met Ala  Asn Phe Ser Lys Ile  Arg Glu Glu
    1250                 1255                 1260

Ala Asn  Leu Glu Gly Leu Gly  Asn Gln Thr Asn Gln  Met Val Glu
    1265                 1270                 1275

Arg Phe  Pro Ser Thr Thr Arg  Met Ser Ser Asn Ala  Ser Gln His
    1280                 1285                 1290

Val Ile  Thr Gln Arg Gly Lys  Arg Ser Leu Lys Gln  Pro Arg Leu
    1295                 1300                 1305

Ser Gln  Gly Glu Ile Lys Phe  Glu Arg Lys Val Ile  Ala Asn Asp
    1310                 1315                 1320

Thr Ser  Thr Gln Trp Ser Lys  Asn Met Asn Tyr Leu  Ala Gln Gly
    1325                 1330                 1335

Thr Leu  Thr Gln Ile Glu Tyr  Asn Glu Lys Glu Lys  Arg Ala Ile
    1340                 1345                 1350

Thr Gln  Ser Pro Leu Ser Asp  Cys Ser Met Arg Asn  His Val Thr
    1355                 1360                 1365

Ile Gln  Met Asn Asp Ser Ala  Leu Pro Val Ala Lys  Glu Ser Ala
    1370                 1375                 1380

Ser Pro  Ser Val Arg His Thr  Asp Leu Thr Lys Ile  Pro Ser Gln
    1385                 1390                 1395

His Asn  Ser Ser His Leu Pro  Ala Ser Ala Cys Asn  Tyr Thr Phe
    1400                 1405                 1410

Arg Glu  Arg Thr Ser Gly Val  Gln Glu Gly Ser His  Phe Leu Gln
    1415                 1420                 1425

Glu Ala  Lys Arg Asn Asn Leu  Ser Leu Ala Phe Val  Thr Leu Gly
    1430                 1435                 1440

Ile Thr  Glu Gly Gln Gly Lys  Phe Ser Ser Leu Gly  Lys Ser Ala
    1445                 1450                 1455

Thr Asn  Gln Pro Met Tyr Lys  Lys Leu Glu Asn Thr  Val Leu Leu
    1460                 1465                 1470

Gln Pro  Gly Leu Ser Glu Thr  Ser Asp Lys Val Glu  Leu Leu Ser
```

1475 1480 1485

Gln Val His Val Asp Gln Glu Asp Ser Phe Pro Thr Lys Thr Ser
1490 1495 1500

Asn Asp Ser Pro Gly His Leu Asp Leu Met Gly Lys Ile Phe Leu
1505 1510 1515

Gln Lys Thr Gln Gly Pro Val Lys Met Asn Lys Thr Asn Ser Pro
1520 1525 1530

Gly Lys Val Pro Phe Leu Lys Trp Ala Thr Glu Ser Ser Glu Lys
1535 1540 1545

Ile Pro Ser Lys Leu Leu Gly Val Leu Ala Trp Asp Asn His Tyr
1550 1555 1560

Asp Thr Gln Ile Pro Ser Glu Glu Trp Lys Ser Gln Lys Lys Ser
1565 1570 1575

Gln Thr Asn Thr Ala Phe Lys Arg Lys Asp Thr Ile Leu Pro Leu
1580 1585 1590

Gly Pro Cys Glu Asn Asn Asp Ser Thr Ala Ala Ile Asn Glu Gly
1595 1600 1605

Gln Asp Lys Pro Gln Arg Glu Ala Met Trp Ala Lys Gln Gly Glu
1610 1615 1620

Pro Gly Arg Leu Cys Ser Gln Asn Pro Pro Val Ser Lys His His
1625 1630 1635

Gln Arg Glu Ile Thr Val Thr Thr Leu Gln Pro Glu Glu Asp Lys
1640 1645 1650

Phe Glu Tyr Asp Asp Thr Phe Ser Ile Glu Met Lys Arg Glu Asp
1655 1660 1665

Phe Asp Ile Tyr Gly Asp Tyr Glu Asn Gln Gly Leu Arg Ser Phe
1670 1675 1680

Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu
1685 1690 1695

Trp Asp Tyr Gly Met Ser Arg Ser Pro His Ile Leu Arg Asn Arg
1700 1705 1710

```
Ala Gln  Ser Gly Asp Val Gln  Gln Phe Lys Lys Val  Val Phe Gln
     1715                 1720                 1725

Glu Phe  Thr Asp Gly Ser Phe  Thr Gln Pro Leu Tyr  Arg Gly Glu
     1730                 1735                 1740

Leu Asn  Glu His Leu Gly Leu  Leu Gly Pro Tyr Ile  Arg Ala Glu
     1745                 1750                 1755

Val Glu  Asp Asn Ile Val Val  Thr Phe Lys Asn Gln  Ala Ser Arg
     1760                 1765                 1770

Pro Tyr  Ser Phe Tyr Ser Ser  Leu Ile Ser Tyr Asp  Glu Asp Glu
     1775                 1780                 1785

Gly Gln  Gly Ala Glu Pro Arg  Arg Lys Phe Val Asn  Pro Asn Glu
     1790                 1795                 1800

Thr Lys  Ile Tyr Phe Trp Lys  Val Gln His His Met  Ala Pro Thr
     1805                 1810                 1815

Lys Asp  Glu Phe Asp Cys Lys  Ala Trp Ala Tyr Phe  Ser Asp Val
     1820                 1825                 1830

Asp Leu  Glu Lys Asp Val His  Ser Gly Leu Ile Gly  Pro Leu Leu
     1835                 1840                 1845

Ile Cys  Arg Ser Asn Thr Leu  Asn Pro Ala His Gly  Arg Gln Val
     1850                 1855                 1860

Thr Val  Gln Glu Phe Ala Leu  Val Phe Thr Ile Phe  Asp Glu Thr
     1865                 1870                 1875

Lys Ser  Trp Tyr Phe Thr Glu  Asn Leu Glu Arg Asn  Cys Arg Ala
     1880                 1885                 1890

Pro Cys  Asn Val Gln Lys Glu  Asp Pro Thr Leu Lys  Glu Asn Phe
     1895                 1900                 1905

Arg Phe  His Ala Ile Asn Gly  Tyr Val Lys Asp Thr  Leu Pro Gly
     1910                 1915                 1920

Leu Val  Met Ala Gln Asp Gln  Lys Val Arg Trp Tyr  Leu Leu Ser
     1925                 1930                 1935

Met Gly  Ser Asn Glu Asn Ile  His Ser Ile His Phe  Ser Gly His
     1940                 1945                 1950
```

Val Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Val Tyr
1955 1960 1965

Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser
1970 1975 1980

Gln Val Gly Ile Trp Arg Ile Glu Cys Leu Ile Gly Glu His Leu
1985 1990 1995

Gln Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Lys Lys Cys
2000 2005 2010

Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln
2015 2020 2025

Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala
2030 2035 2040

Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Asp
2045 2050 2055

Pro Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile
2060 2065 2070

His Gly Ile Met Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu
2075 2080 2085

Tyr Val Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Asn Lys
2090 2095 2100

Trp His Ser Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe
2105 2110 2115

Phe Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn
2120 2125 2130

Pro Pro Ile Ile Ala Gln Tyr Ile Arg Leu His Pro Thr His Tyr
2135 2140 2145

Ser Ile Arg Ser Thr Leu Arg Met Glu Leu Leu Gly Cys Asp Phe
2150 2155 2160

Asn Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser
2165 2170 2175

Asp Ala Gln Ile Thr Ala Ser Ser Tyr Leu Ser Ser Met Leu Ala
2180 2185 2190

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Thr Trp  Ser Pro Ser Gln Ala  Arg Leu His Leu Gln  Gly Arg Thr
    2195                 2200                 2205

Asn Ala  Trp Arg Pro Gln Ala  Asn Asn Pro Lys Glu  Trp Leu Gln
    2210                 2215                 2220

Val Asp  Phe Arg Lys Thr Met  Lys Val Thr Gly Ile  Thr Thr Gln
    2225                 2230                 2235

Gly Val  Lys Ser Leu Leu Ile  Ser Met Tyr Val Lys  Glu Phe Leu
    2240                 2245                 2250

Ile Ser  Ser Ser Gln Asp Gly  His Asn Trp Thr Leu  Phe Leu Gln
    2255                 2260                 2265

Asn Gly  Lys Val Lys Val Phe  Gln Gly Asn Arg Asp  Ser Ser Thr
    2270                 2275                 2280

Pro Val  Arg Asn Arg Leu Glu  Pro Pro Leu Val Ala  Arg Tyr Val
    2285                 2290                 2295

Arg Leu  His Pro Gln Ser Trp  Ala His His Ile Ala  Leu Arg Leu
    2300                 2305                 2310

Glu Val  Leu Gly Cys Asp Thr  Gln Gln Pro Ala
    2315                 2320
```

<210> 10
<211> 27
<212> PRT
<213> Sus scrofa

<400> 10

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Asp Ile Gly Asp Tyr Tyr Asp Asn Thr Tyr Glu Asp Ile Pro Gly Phe
1               5                  10                  15

Leu Leu Ser Gly Lys Asn Val Ile Glu Pro Arg
            20                  25
```

<210> 11
<211> 27
<212> PRT
<213> Homo sapiens

<400> 11

```
Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr
1               5                  10                  15
```

Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg
20 25

<210> 12
<211> 27
<212> PRT
<213> Canis familiaris

<400> 12

Asn Ile Asp Asp Tyr Tyr Glu Asp Thr Tyr Glu Asp Ile Pro Thr Pro
1 5 10 15

Leu Leu Asn Glu Asn Asn Val Ile Lys Pro Arg
20 25