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(54) **Title**: VARIANT FACTOR VIII POLYPEPTIDES AND METHODS OF THEIR PRODUCTION AND USE

(57) **Abstract**: This disclosure relates to variant Factor VIII polypeptides comprising an amino acid substitution at one or more positions within one or both of the thrombin cleavage site and the activation loop. In certain embodiments, the variant Factor VIII polypeptide comprises one or more amino acid substitutions within both the thrombin cleavage site and the activation loop. In further embodiments, the variant factor VIII polypeptide further comprises one or more amino acid substitutions within the A1-A2 domain interface and the A2-A3 domain interface. The present disclosure further relates to methods of producing and/or using such variant Factor VIII polypeptides; nucleic acids encoding the polypeptides; vectors and/or recombinant cells, tissues, or organisms containing such nucleic acids; and kits and pharmaceutical compositions containing such polypeptides and/or nucleic acids.

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VARIANT FACTOR VIII POLYPEPTIDES AND METHODS OF THEIR PRODUCTION AND USE

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/789,112, filed March 15, 2013, which is hereby incorporated by reference herein in its entirety.

FIELD OF THE DISCLOSURE

[0002] Human coagulation Factor VIII variants and the polynucleotides encoding such variants, vectors, and host cells comprising and expressing such variants, methods of obtaining such variants, methods of using such variants, compositions of the variants, and additional inventive features related thereto are provided herein.

BACKGROUND

[0003] Blood coagulation is a process consisting of complex interactions between various blood components (or factors) that eventually gives rise to a fibrin clot. Generally, the blood components that participate in what is frequently referred to as the coagulation "cascade" are enzymatically inactive proteins (proenzymes or zymogens) that are converted to proteolytic enzymes by the action of an activator, which itself is often an activated clotting factor. One peptide that is critical to the coagulation cascade is Factor VIII or FVIII. In fact, Hemophilia A, which is the most common hereditary coagulation disorder, is caused by deficiency or structural defects in Factor VIII. The biochemistry of Factor VIII allows for a rapid on/off switch for coagulation. It circulates as an inactive cofactor which is activated to FVIIIa by thrombin, the penultimate enzyme of the coagulation cascade. FVIIIa participates in a short-lived enzymatic complex (FXase) with FIXa, a membrane or phospholipid (PL) surface and Ca^{+2} to convert FX to FXa. The major function of FVIIIa as a participant in the FXase complex is to markedly amplify FXa, which then allows for thrombin generation. Factor VIII is encoded by a ~186 kb gene consisting of 26 exons (Thompson, Seminars in Thrombosis and Hemostasis, 29:11-22 (2003) (references 11 and 16-18)). Translation of the mRNA of this gene, followed by removal of a 19 amino acid signal sequence, leads to a mature protein of 2332 amino acids. The protein consists of 6 major domains, which, from

the amino terminus, are: A1, A2, B, A3, C1, and C2. Additional short acidic regions a1, a2, and a3, which are involved in activation, are interspersed between the A1 and A2, A2 and B, and B and A3 domains, respectively. The 2332 amino acid primary translation product is processed into a heterodimer consisting of a heterogeneous heavy chain, which contains the intact A1,a1 A2,a2 domains and various lengths of the B-domain, and a homogenous 80kD light chain, which contains of a3, A3, C1, and C2 domain. The heterogeneity of the B-domain results from proteolysis during secretion.

[0004] Activation of Factor VIII to Factor VIIIa generally occurs via proteolysis of the procofactor by thrombin. Thrombin recognizes certain amino acid regions that define thrombin cleavage sites along the Factor VIII peptide chain. Factor VIII has three thrombin cleavage sites. Examination of other thrombin substrates reveals a variety of residues that can be accommodated by thrombin. Though the amino acids within these thrombin cleavage sites can vary to some degree, certain amino acids are much more common within these cleavage sites than others, and certain amino acid residues result in a more efficient cleavage of the peptide by thrombin. (See, e.g., Newell-Caito et al., "P3-P3' Residues flanking Scissile Bonds in Factor VIII Modulate Rates of Substrate Cleavage and Profactor Activation by Thrombin," Biochemistry 51:3451-59 (2012); Gallwitz et al., "The Extended Cleavage Specificity of Human Thrombin," PLoS ONE 7:e31756 (2012)). One of the three thrombin cleavage sites in Factor VIII lies at or near the a1-A2 junction, which is at or near amino acid positions 370-375 of the mature wild-type human Factor VIII peptide.

[0005] Following cleavage, active Factor VIIIa is a heterotrimer comprised of the A1 subunit, the A2 subunit, and the A3C1C2 subunit. This heterotrimer is supported by both electrostatic and hydrophobic interactions between the subunits at the regions in which they interact with one another, termed the "domain interfaces." The heterotrimer is known to include at least A1-A2 and A2-A3 domain interfaces. (See, e.g., U.S. Patent No. 8,338,571 (filed Jul. 25, 2008) (issued Dec. 25, 2012)).

[0006] Human Factor VIII has been produced recombinantly as a single-chain molecule of approximately 300 kD. The precursor product is processed into two polypeptide chains of 200 kD (heavy) and 80 kD (light) in the Golgi Apparatus, with the two chains held together by metal ions (Kaufman et al., J. Biol. Chem. 263:6352 (1988); Andersson et al., Proc. Natl. Acad. Sci. 83:2979 (1986)). The B-domain of FVIII seems to be dispensable, as B-domain deleted FVIII (FVIII-BDD; 90 kD A1-A2 heavy chain plus 80 kD light chain) has also been shown to be effective as a replacement therapy for hemophilia A. One well-known

B-domain deleted Factor VIII sequence referred to as "BDD-SQ" or simply "BDD" contains a deletion of all but 14 amino acids of the B-domain.

[0007] Treatment of hemophilia A currently involves intravenous (iv) administration of Factor VIII on demand or as a prophylactic therapy. Despite its large size of greater than 300 kD for the full-length protein, Factor VIII has a half-life in humans of only about 11 hours. (Ewenstein et al., Semin. Hematol. 41:1-16 (2004)). As such, Factor VIII must be administered relatively frequently for prophylactic treatment of clotting disorders. Factor VIII is typically administered two to three times a week with dosing based upon Factor VIII activity. This need for frequent iv injection creates tremendous barriers to patient compliance. It would be more convenient for patients if a Factor VIII product could be developed that required less frequent administration. Furthermore, reducing the number of dosages required would also reduce the cost of treatment. Additionally, even with these frequent administrations, due to its short half-life, patients undergoing Factor VIII replacement therapy often achieve large swings in plasma Factor VIII activity levels, potentially putting them at risk for thrombosis (at peak levels) and bleeding (at trough levels).

[0008] Additionally, an alternate, non-iv route of administration, such as subcutaneous (sc) administration, could both increase ease of treatment and decrease the potential risks of thrombosis and bleeding by maintaining plasma Factor VIII levels at a more constant level. One challenge of sc delivery is increasing the bioavailability of the administered Factor VIII. A Factor VIII peptide with enhanced activity could be useful in enhancing bioavailability, and therefore could be useful in sc delivery of Factor VIII. Due to its higher specific activity, such a Factor VIII peptide could allow for a decrease in the volume needed for administration, as the activity concentration of the drug is higher. Reduced injection volume could decrease patient discomfort. Furthermore, the reduction in volume would also translate to a reduction in the cost of goods. Finally, an enhanced activity Factor VIII molecule could also confer additional protection above that of wild-type Factor VIII, by prolonging the duration of cofactor activity if dosing is by mass rather than by activity. As an example, with equal mass dosing, the enhanced activity FVIII variants with 2-fold specific activity enhancement would offer the same protection at the 0.5% level as the protection provided at the 1% level for the wild-type FVIII, thus extending the interval between Factor VIII doses.

[0009] Numerous Factor VIII variants have been produced in an attempt to address one or more shortcomings of the current medical therapy. For example, U.S. Patent No. 8,338,571 (filed Jul. 25, 2008; issued Dec. 25, 2012) describes a recombinant factor VIII that

includes one or more mutations that result in enhanced stability of both Factor VIII and Factor VIIIa. Similarly, U.S. Patent Publication No. 2012/0190623 (filed Jan. 27, 2011) describes Factor VIII muteins that are resistant to inactivation, including muteins "wherein the APC cleavage sites, Arg336 and Ile562, are mutated." U.S. Patent Publication No. 2011/0124565 (filed Apr. 10, 2006) relates to modified nucleic acid sequences coding for coagulation factors, in particular human Factor VIII and their derivatives with improved stability, including a Factor VIII peptide with a modification that reportedly prevents thrombin cleavage between the A1 and the A2 domain of FVIII. Other efforts have produced, for example, modified Factor VIII polypeptides that reportedly have increased circulating half-lives due to the introduction of mutations that permit PEGylation of the peptide (Mei et al., Blood 116:270-279 (2010)) and modified Factor VIII polypeptides that reportedly possess increased stability due to mutations to the amino acids that make up the domain interfaces of the active FVIIIa heterotrimer (Wakabayashi et al., J. Thromb. Haemost. 7:438-444 (2009)).

[0010] For the reasons stated above, there exists a need for improved Factor VIII variants, for instance a variant that possesses increased activity and/or a variant that need not be administered as frequently and/or at as high a dose. Furthermore, it is desirable that such a protein be produced as a homogeneous product in a consistent manner.

BRIEF SUMMARY

[0011] In one embodiment, the present disclosure relates to a variant of a Factor VIII polypeptide which is a functional Factor VIII, the Factor VIII polypeptide comprising a thrombin cleavage site at amino acid positions 370-375 and an activation loop at amino acid positions 558-565, wherein these amino acid position numbers are in reference to the amino acid sequence set forth in SEQ ID NO: 1; and wherein the variant comprises an amino acid substitution at one or more residues within the thrombin cleavage site and an amino acid substitution at one or more residues within the activation loop.

[0012] In certain examples, the substitution within the thrombin cleavage site of the variant Factor VIII polypeptide does not include a substitution at amino acid position 372. In other examples, the substitution within the thrombin cleavage site comprises a substitution at one or more of positions 370, 371, or 374, while in other examples the substitution within the thrombin cleavage site comprises a substitution at two or more of positions 370, 371, or 374.

[0013] In further examples, the substitution within the activation loop comprises a substitution at one or more of positions 559, 562, and 565, while in other examples, the

substitution within the activation loop comprises a substitution at two or more of positions 559, 562, and 565.

[0014] In other examples, the variant Factor VIII polypeptide further comprises an A1-A2 domain interface comprising amino acid residues E272 and D519 and an A2-A3 domain interface comprising amino acid residues E665 and E1984, wherein these amino acid position numbers are in reference to the amino acid sequence set forth in SEQ ID NO: 1; and the variant further comprises a substitution at one or more amino acid residues of the A1-A2 domain interface and a substitution at one or more amino acid residues of the A2-A3 domain interface. In additional examples, the substitution of the A1-A2 domain interface comprises one or more substitutions selected from the group consisting of E272A, E272V, D519A, and D519V. In other examples, the substitution of the A2-A3 domain interface comprises one or more substitutions selected from the group consisting of E665A, E665V, E1984A, and E1984V. In still further examples, the substitution of the A1-A2 domain interface comprises D519V and the substitution of the A2-A3 domain interface comprises E665V.

[0015] In particular examples, the variant Factor VIII polypeptide comprises an amino acid substitution at one or more of positions 370, 371, and 374, and an amino acid substitution at one or more of positions 559, 562, and 565. In other examples, the variant comprises an amino acid substitution at two or more of positions 370, 371, and 374, and an amino acid substitution at two or more of positions 559, 562, and 565. In still further examples, the variant comprises amino acid substitutions selected from the group consisting of: Q370M, I371P, V374F, V559L, R562W, R562F, R562K, and Q565E. In additional examples, the variant comprises amino acid substitutions within the thrombin cleavage site selected from the group consisting of: (i) Q370M and I371P, and (ii) I371P and V374F. In further examples, the variant comprises amino acid substitutions within the activation loop selected from the group consisting of: (i) V559L and R562F, (ii) V559L and R562W, (iii) V559L and Q565E, (iv) V559L, R562W, and Q565E, and (v) V559L, R562F, and Q565E.

[0016] In certain particular examples, the variant comprises the amino acid substitutions I371P, V374F, V559L, R562W, and Q565E. In other particular examples, the variant comprises the amino acid substitutions I371P, V374F, V559L, R562W, Q565E, D519V, and E665V. In still further examples, the variant further comprises an amino acid substitution at amino acid position 336. In certain examples, the amino acid substitution at amino acid position 336 comprises an R336I substitution.

[0017] In certain examples, the variant Factor VIII polypeptide comprises an amino acid sequence at least 90% identical to the sequence of SEQ ID NO: 1, 2, or 3. In other

examples, the variant Factor VIII polypeptide comprises the amino acid sequence of SEQ ID NO: 53.

[0018] In certain examples the variant Factor VIII polypeptide has increased specific activity as compared to the unmodified Factor VIII polypeptide.

[0019] In an additional embodiment, the present disclosure relates to a pharmaceutical composition comprising a variant Factor VIII polypeptide as described herein and a pharmaceutically acceptable excipient.

[0020] In another embodiment, the present disclosure relates to an isolated nucleic acid encoding a variant Factor VIII polypeptide as described herein.

[0021] In a further embodiment, the present disclosure relates to a vector comprising a nucleic acid sequence encoding a variant Factor VIII polypeptide as described herein. In certain examples, the vector is an expression vector.

[0022] In yet another embodiment, the present disclosure relates to a recombinant host cell comprising an isolated nucleic acid or vector as described herein.

[0023] In a further embodiment, the present disclosure relates to a method of producing a variant Factor VIII polypeptide, the method comprising culturing a recombinant host cell as described herein under conditions appropriate for expression of the variant Factor VIII polypeptide and isolating the variant.

[0024] In still another embodiment, the present disclosure relates to a method for preventing or treating a bleeding disorder comprising administering to a subject an effective amount of a variant Factor VIII polypeptide or the pharmaceutical composition as described herein. In certain examples, the bleeding disorder is a chronic bleeding disorder. In other examples, the bleeding disorder is an acute bleeding episode.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] **FIG. 1** presents the aPTT specific activities of various Factor VIII polypeptides and variants, presented as fold activity over wild-type Factor VIII. The designations have the following meanings: "A" indicates that the polypeptide possessed I371P and V374F amino acid substitutions in the Thrombin cleavage site; "B" indicates that the polypeptide possessed V559L, R562W, and Q565E amino acid substitutions in the activation site; and "C" indicates that the polypeptide possessed D519V and E665V amino acid substitutions. All amino acid position designations are based upon position numbers in wt-FVIII (SEQ ID NO: 1).

[0026] FIG. 2 presents specific activities of various Factor VIII polypeptides and variants, presented as fold activity over wild-type Factor VIII, as determined by a chromogenic assay. The designations have the same meanings as for FIG. 1.

[0027] FIG. 3 presents thrombin generation profiles for FVIII-BDD (SEQ ID NO: 3), D519VE665V-FVIII (SEQ ID NO: 5), and Var97, a variant of D519VE665V-FVIII which possesses the following amino acid substitutions: I371P, V374F, V559L, R562W, and Q565E (SEQ ID NO: 53).

[0028] FIG. 4 presents data demonstrating the concentration of various Factor VIII polypeptides and variants needed to elicit a defined quantity of peak thrombin. The Factor VIII polypeptides investigated are FVIII-BDD (SEQ ID NO: 3), D519VE665V-FVIII (SEQ ID NO: 5), a modified FVIII-BDD with D519V and E665V amino acid substitutions, and Var97, a variant of D519VE665V-FVIII which possesses the following amino acid substitutions: I371P, V374F, V559L, R562W, and Q565E (SEQ ID NO: 53).

[0029] FIG. 5 presents kinetic profiles of the clot formation rates for FVIII-BDD (SEQ ID NO: 3), D519VE665V-FVIII (SEQ ID NO: 5), and Var97, a variant of D519VE665V-FVIII which possesses the following additional amino acid substitutions: I371P, V374F, V559L, R562W, and Q565E (SEQ ID NO: 53). The approximately 10-fold greater activity of Var97 relative to BDD and D519VE665V is evident in the time needed to achieve maximal rate of clot formation.

[0030] FIG. 6 presents binding affinity results for FVIII-BDD (SEQ ID NO: 3), D519VE665V-FVIII (SEQ ID NO: 5), and Var97, a variant of D519VE665V-FVIII which possesses the following additional amino acid substitutions: I371P, V374F, V559L, R562W, and Q565E (SEQ ID NO: 53).

[0031] FIG. 7 presents turbidity profiles (absorbance units versus time) for clot formation using either normal plasma, FVIII-deficient plasma, or FVIII-deficient plasma containing 50 mU/mL (5%) of one of the following FVIII variants: FVIII-BDD, D519VE665V-FVIII, Var97, or Var97-R336I.

[0032] FIG. 8 presents plots of 24-hour survival (%) of HemA mice following vascular injury after administration of various dosages, measured either by mass (left panel) or units (right panel), of either FVIII-BDD (gray circles) or Var97 (black triangles).

[0033] FIG. 9 presents an image of an SDS-PAGE gel of variant Factor VIII polypeptides from an FXase reaction in the presence (+) or absence (-) of excess FIXa. The FVIII polypeptides investigated are FVIII-BDD (lanes 2 and 3), D519VE665V-FVIII (lanes 4

and 5), Var97 (lanes 6 and 7), and Var97-R336I (lanes 8 and 9), with a mass marker in lane 1.

[0034] FIG. 10 presents thrombin generation profiles for FVIII-BDD (SEQ ID NO: 3), D519VE665V-FVIII (SEQ ID NO: 5), Var97 (SEQ ID NO: 53), and Var97-R336I (SEQ ID NO: 55).

[0035] FIG. 11 presents data demonstrating the concentration of various Factor VIII polypeptides and variants needed to elicit a defined quantity of peak thrombin. The Factor VIII polypeptides investigated are FVIII-BDD (SEQ ID NO: 3), D519VE665V-FVIII (SEQ ID NO: 5), Var97 (SEQ ID NO: 53), and Var97-R336I (SEQ ID NO: 55).

BRIEF DESCRIPTION OF THE SEQUENCES

[0036] SEQ ID NO: 1 comprises a wild-type human Factor VIII polypeptide sequence. This polypeptide is generally referred to herein as "wild-type Factor VIII," "wt-FVIII," or simply "Factor VIII" or "FVIII."

[0037] SEQ ID NO: 2 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 1.

[0038] SEQ ID NO: 3 comprises a modified form of the wt-FVIII polypeptide sequence of SEQ ID NO: 1 that has a deletion in the B-domain. This is a nearly complete deletion of the B-domain with only 14 amino acids of the B-domain remaining. This polypeptide is generally referred to herein as "B-domain deleted Factor VIII," "Factor VIII BDD," or "FVIII-BDD."

[0039] SEQ ID NO: 4 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 3.

[0040] SEQ ID NO: 5 comprises a modified form of the FVIII-BDD of SEQ ID NO: 3 that contains two amino acid substitutions: D519V and E665V. This polypeptide is generally referred to herein as "D519VE665V Factor VIII" or "D519VE665V-FVIII."

[0041] SEQ ID NO: 6 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 5.

[0042] SEQ ID NO: 7 is a variant of the wt-FVIII of SEQ ID NO: 1 that contains the following amino acid substitutions: Q370M and I371P.

[0043] SEQ ID NO: 8 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 7.

[0044] SEQ ID NO: 9 is a variant of the FVIII-BDD of SEQ ID NO: 3 that contains the following amino acid substitutions: Q370M and I371P.

[0045] SEQ ID NO: 10 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 9.

[0046] SEQ ID NO: 11 is a variant of the D519VE665V-FVIII of SEQ ID NO: 5 that contains the following additional amino acid substitutions: Q370M and I371P.

[0047] SEQ ID NO: 12 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 11.

[0048] SEQ ID NO: 13 is a variant of the wt-FVIII of SEQ ID NO: 1 that contains the following amino acid substitutions: I371 P and V374F.

[0049] SEQ ID NO: 14 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 13.

[0050] SEQ ID NO: 15 is a variant of the FVIII-BDD of SEQ ID NO: 3 that contains the following amino acid substitutions: I371P and V374F.

[0051] SEQ ID NO: 16 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 15.

[0052] SEQ ID NO: 17 is a variant of the D519VE665V-FVIII of SEQ ID NO: 5 that contains the following additional amino acid substitutions: I371 P and V374F.

[0053] SEQ ID NO: 18 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 17.

[0054] SEQ ID NO: 19 is a variant of the wt-FVIII of SEQ ID NO: 1 that contains the following amino acid substitutions: V559L and R562F.

[0055] SEQ ID NO: 20 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 19.

[0056] SEQ ID NO: 21 is a variant of the FVIII-BDD of SEQ ID NO: 3 that contains the following amino acid substitutions: V559L and R562F.

[0057] SEQ ID NO: 22 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 21.

[0058] SEQ ID NO: 23 is a variant of the D519VE665V-FVIII of SEQ ID NO: 5 that contains the following additional amino acid substitutions: V559L and R562F.

[0059] SEQ ID NO: 24 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 23.

[0060] SEQ ID NO: 25 is a variant of the wt-FVIII of SEQ ID NO: 1 that contains the following amino acid substitutions: V559L and R562W.

[0061] SEQ ID NO: 26 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 25.

[0062] SEQ ID NO: 27 is a variant of the FVIII-BDD of SEQ ID NO: 3 that contains the following amino acid substitutions: V559L and R562W.

[0063] SEQ ID NO: 28 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 27.

[0064] SEQ ID NO: 29 is a variant of the D519VE665V-FVIII of SEQ ID NO: 5 that contains the following additional amino acid substitutions: V559L and R562W.

[0065] SEQ ID NO: 30 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 29.

[0066] SEQ ID NO: 31 is a variant of the wt-FVIII of SEQ ID NO: 1 that contains the following amino acid substitutions: V559L and Q565E.

[0067] SEQ ID NO: 32 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 31.

[0068] SEQ ID NO: 33 is a variant of the FVIII-BDD of SEQ ID NO: 3 that contains the following amino acid substitutions: V559L and Q565E.

[0069] SEQ ID NO: 34 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 33.

[0070] SEQ ID NO: 35 is a variant of the D519VE665V-FVIII of SEQ ID NO: 5 that contains the following additional amino acid substitutions: V559L and Q565E.

[0071] SEQ ID NO: 36 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 35.

[0072] SEQ ID NO: 37 is a variant of the wt-FVIII of SEQ ID NO: 1 that contains the following amino acid substitutions: V559L, R562W, and Q565E.

[0073] SEQ ID NO: 38 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 37.

[0074] SEQ ID NO: 39 is a variant of the FVIII-BDD of SEQ ID NO: 3 that contains the following amino acid substitutions: V559L, R562W, and Q565E.

[0075] SEQ ID NO: 40 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 39.

[0076] SEQ ID NO: 41 is a variant of the D519VE665V-FVIII of SEQ ID NO: 5 that contains the following additional amino acid substitutions: V559L, R562W, and Q565E.

[0077] SEQ ID NO: 42 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 41.

[0078] SEQ ID NO: 43 is a variant of the wt-FVIII of SEQ ID NO: 1 that contains the following amino acid substitutions: V559L, R562F, and Q565E.

[0079] SEQ ID NO: 44 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 43.

[0080] SEQ ID NO: 45 is a variant of the FVIII-BDD of SEQ ID NO: 3 that contains the following amino acid substitutions: V559L, R562F, and Q565E.

[0081] SEQ ID NO: 46 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 45.

[0082] SEQ ID NO: 47 is a variant of the D519VE665V-FVIII of SEQ ID NO: 5 that contains the following additional amino acid substitutions: V559L, R562F, and Q565E.

[0083] SEQ ID NO: 48 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 47.

[0084] SEQ ID NO: 49 is a variant of the wt-FVIII of SEQ ID NO: 1 that contains the following amino acid substitutions: I371P, V374F, V559L, R562W, and Q565E.

[0085] SEQ ID NO: 50 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 49.

[0086] SEQ ID NO: 51 is a variant of the FVIII-BDD of SEQ ID NO: 3 that contains the following amino acid substitutions: I371P, V374F, V559L, R562W, and Q565E.

[0087] SEQ ID NO: 52 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 51.

[0088] SEQ ID NO: 53 is a variant of the D519VE665V-FVIII of SEQ ID NO: 5 that contains the following additional amino acid substitutions: I371P, V374F, V559L, R562W, and Q565E.

[0089] SEQ ID NO: 54 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 53.

[0090] SEQ ID NO: 55 is a variant of the D519VE665V-FVIII of SEQ ID NO: 5 that contains the following additional amino acid substitutions: I371P, V374F, V559L, R562W, Q565E, and R336I.

[0091] SEQ ID NO: 56 comprises a nucleotide sequence that encodes for the polypeptide of SEQ ID NO: 55.

DETAILED DESCRIPTION

[0092] Before describing the present invention in detail, it is to be understood that this disclosure is not limited to particular embodiments, which can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting. Unless defined otherwise, all technical

and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, and nucleic acid chemistry and hybridization are those well-known and commonly employed in the art. Standard techniques are used for nucleic acid and polypeptide synthesis. The nomenclature used herein and the laboratory procedures described below are those well-known and commonly employed in the art. Procedures used for genetic engineering are well known and can be found for example in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor, N.Y.).

[0093] As used in this specification and the appended claims, terms in the singular and the singular forms "a," "an," and "the," for example, include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "polypeptide," "the polypeptide," or "a polypeptide" also includes a plurality of polypeptides. Additionally, as used herein, the term "comprises" is intended to indicate a non-exhaustive list of components or steps, thus indicating that the given composition or method includes the listed components or steps and may also include additional components or steps not specifically listed. As an example, a composition "comprising a polypeptide" may also include additional components or polypeptides. The term "comprising" is also intended to encompass embodiments "consisting essentially of" and "consisting of" the listed components or steps. Similarly, the term "consisting essentially of" is also intended to encompass embodiments "consisting of" the listed components or steps.

[0094] Numeric ranges recited within the specification are inclusive of the numbers defining the range (the end point numbers) and also are intended to include each integer or any non-integer fraction within the defined range.

[0095] In describing and claiming the particular embodiments, the following terminology will be used in accordance with the definitions set out below.

[0096] As used herein, "B-domain deleted Factor VIII" or "FVIII-BDD" refers to a Factor VIII polypeptide which contains a deletion of at least some portion of the B-domain. In the examples set forth herein, FVIII-BDD specifically refers to a deletion of all but 14 amino acids of the B-domain of Factor VIII. (Lind et al., Eur. J. Biochem. 232:19-27 (1995)), the polypeptide sequence of which is set forth in SEQ ID NO: 3, which is encoded by the nucleotide sequence of SEQ ID NO: 4. However, while this particular FVIII-BDD sequence was employed in the examples herein, it is to be understood that Factor VIII polypeptides with modifications as compared to SEQ ID NO: 3, including differences in the

B-domain deletion, could also be employed. For example, a Factor VIII polypeptide with more or fewer than 14 amino acids of the B-domain remaining could also be useful in some embodiments if Factor VIII procoagulant activity is retained.

[0097] As used herein, "Factor VIII" or "FVIII" refers to a blood clotting factor which is a glycoprotein synthesized and released into the bloodstream by the liver. In its immature form, FVIII contains a signal sequence, which is proteolytically cleaved during the translation process. Following removal of that 19 amino acid signal sequence, the Factor VIII polypeptide is in its mature form, in which the first amino acid of the secreted FVIII product is an alanine. This mature form of Factor VIII will be referred to herein as "mature Factor VIII." Mature wild-type human FVIII has the amino acid sequence set forth in SEQ ID NO:1, although allelic variants are possible, as are modified versions, such as those set forth in SEQ ID NOs: 3 and 5.

[0098] As used herein, a "functional Factor VIII polypeptide" denotes a polypeptide or combination of polypeptides that is/are capable, *in vivo* or *in vitro*, of correcting human Factor VIII deficiencies, characterized, for example, by hemophilia A. Factor VIII has multiple degradation or processed forms in the natural state. These are proteolytically derived from a precursor, one chain protein, as demonstrated herein. A functional Factor VIII polypeptide includes such single chain protein and also provides for these various degradation products that have the biological activity of correcting human factor VIII deficiencies. Allelic variations likely exist. The functional Factor VIII polypeptides include all such allelic variations, glycosylated versions, modifications, and fragments resulting in derivatives of Factor VIII so long as they contain the functional segment of Factor VIII and the essential, characteristic Factor VIII functional activity remains unaffected in kind. Those derivatives of Factor VIII possessing the requisite functional activity can readily be identified by straightforward *in vitro* tests described herein. Furthermore, functional Factor VIII polypeptide is capable of catalyzing the conversion of Factor X to Xa in the presence of Factor IXa, calcium, and phospholipid, as well as correcting the coagulation defect in plasma derived from hemophilia A affected individuals. From the disclosure of the sequence of the human Factor VIII amino acid sequences and the functional regions herein, the fragments that can be derived via restriction enzyme cutting of the DNA or proteolytic or other degradation of human Factor VIII protein will be apparent to those skilled in the art.

[0099] As used herein, "thrombin cleavage site" refers to a portion of the Factor VIII peptide chain which is a target cleavage site for thrombin. In certain embodiments, the thrombin cleavage site is located at or near the a1-A2 junction of the Factor VIII polypeptide.

In other embodiments, the thrombin cleavage site is located at amino acid residues 370-375 of the mature wild-type human Factor VIII peptide (SEQ ID NO: 1). In further embodiments, the thrombin cleavage site may be a homologous site in a homologous Factor VIII polypeptide, such as an allelic variant or modified polypeptide.

[00100] As used herein, "activation loop" refers to a portion of the A2 subunit of the Factor VIII peptide chain which is capable of interfacing with Factor IXa. In certain embodiments, the activation loop is located at amino acid residues 558-565 of the mature wild-type human Factor VIII peptide (SEQ ID NO: 1). In further embodiments, the activation loop may be a homologous site in a homologous Factor VIII polypeptide, such as an allelic variant or modified polypeptide.

[00101] As used herein, "domain interface" refers to the regions or residues on the respective subunits of the Factor VIIIa heterotrimer which interact with the other subunits of the heterotrimer. As such, "A1-A2 domain interface" refers to the regions or residues on each of the A1 and A2 subunits that interact with the corresponding regions or residues on the other subunit. Similarly, "A2-A3 domain interface" refers to the regions or residues on each of the A2 and A3 subunits that interact with the corresponding regions or residues on the other subunit. In certain examples, the A1-A2 domain interface includes residues E272 and D519 (based on the wild-type Factor VIII sequence of SEQ ID NO: 1). In other examples, the A2-A3 domain interface includes residues E665 and E1984 (based on the wild-type Factor VIII sequence of SEQ ID NO: 1).

[00102] As used herein, "Factor IX" or "FIX" means Coagulation Factor IX, which is also known as Human Clotting Factor IX or Plasma Thromboplastin Component.

[00103] As used herein, "Factor X" or "FX" means Coagulation Factor X, which is also known by the names Human Clotting Factor X and by the eponym Stuart-Prower factor.

[00104] "Pharmacokinetics" or "PK" is used herein to describe the properties of absorption, distribution, metabolism, and elimination of a drug in a body. An improvement to a drug's pharmacokinetics means an improvement in those characteristics that make the drug more effective *in vivo* as a therapeutic agent, especially its useful duration in the body.

[00105] The terms "polypeptide," "peptide," and "protein" are generally used interchangeably herein and they refer to a polymer in which the monomers are amino acids that are joined together through amide bonds. Additionally, unnatural amino acids, for example, β-alanine, phenylglycine, and homoarginine are also included. Amino acids that are

not gene-encoded can also be used with the technology disclosed herein. Furthermore, amino acids that have been modified to include reactive groups, glycosylation sites, polymers, therapeutic moieties, biomolecules, and the like can also be used. All of the amino acids used herein can be either the D- or L-isomer. The L-isomer is generally preferred. As used herein, "polypeptide," "peptide," and "protein" refer to both glycosylated and unglycosylated forms.

[00106] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. "Amino acid analogs" refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that function in a manner similar to a naturally occurring amino acid.

[00107] "Variant" and "mutein" are used interchangeably herein and they each refer to a genetically engineered polypeptide or nucleotide sequence encoding a polypeptide arising as a result of a laboratory induced change to the nucleotide or polypeptide sequence. In describing amino acids, the standard one-letter or three-letter amino acid codes that are well-known in the art may be used in place of the full name of an amino acid. Additionally, a one-letter amino acid code followed by a number may be used to indicate a particular amino acid at a particular position in the starting sequence. For instance "V374" would indicate the valine at amino acid position 374 of the wt-FVIII sequence (SEQ ID NO: 1). Further, the one-letter code of the substituted amino acid may be included after the position number to indicate a particular amino acid substitution that was made. For instance, "V374F" would indicate that a phenylalanine residue has been substituted for the valine at position 374. "Substitution" as used herein refers to replacement of one amino acid with another amino acid and does not include deletions or additions unless expressly stated otherwise.

[00108] It should also be noted that, unless the language of a particular example specifically indicates otherwise, the amino acid positions disclosed herein are all

based on the corresponding position in the amino acid sequence of the mature wild-type Factor VIII peptide, as provided in SEQ ID NO: 1, as is conventionally done in the art.

[00109] The variant polypeptides of the present disclosure include one or more amino acid substitutions in one or both of the thrombin cleavage site and the activation loop. In certain examples, the variant polypeptides include one or more amino acid substitutions in one or both of 1) the thrombin cleavage site, represented by amino acid positions 370-375 of SEQ ID NO: 1, and 2) the activation loop, represented by amino acid positions 558-565 of SEQ ID NO: 1. With regard to the thrombin cleavage site at residues 370-375, cleavage typically occurs immediately after the R372 residue, which makes this residue important for proper cleavage at this site. As such, in certain embodiments, the variant polypeptide will include one or more amino acid substitutions within the thrombin cleavage site represented by amino acid positions 370-375 of SEQ ID NO: 1, wherein the substitution is not at position 372. In certain embodiments, the amino acid substitution may be a substitution at one or more of the following positions in the starting sequence (with the position numbers based on the wt-FVIII sequence of SEQ ID NO: 1): Q370, I371, S373, V374, A375, S558, V559, D560, Q561, R562, G563, N564, and Q565. In certain other embodiments, there may be substitutions at 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 of those positions. In additional embodiments, the variant may comprise at least one substitution in each of the thrombin cleavage site (370-375) and the activation loop (558-565). In certain examples, the variant may comprise a substitution of at least one of Q370, I371, S373, V374, and A375, and a substitution of at least one of S558, V559, D560, Q561, R562, G563, N564, and Q565. In further embodiments, the variant may comprise more than one substitution within either the thrombin cleavage site (370-375) or the activation loop (558-565), for example 2, 3, 4, 5, 6, 7, or 8 substitutions. In particular examples, the variant comprises two substitutions within the thrombin cleavage site (370-375) and two substitutions within the activation loop (558-565). In other examples, the variant comprises two substitutions within the thrombin cleavage site (370-375) and three substitutions within the activation loop (558-565). In particular examples, the substitutions within the thrombin cleavage site are Q370M, I371P, V374F, Q370M/I371P, or I371P/V374F. In other examples, the substitutions within the activation loop are V559L, R562W, R562F, R562K, Q565E, V559L/R562F, V559L/R562W, V559L/Q565E, V559L/R562W/Q565E, or V559L/R562F/Q565E.

[00110] In further examples, the variant Factor VIII polypeptide further includes one or more substitutions to amino acid residues within each of the A1-A2 and A2-A3 domain interfaces. In particular examples, the substitution within the A1-A2 domain

interface comprises a substitution of one or both of residues E272 and D519 (based on the wild-type Factor VIII sequence of SEQ ID NO: 1). In certain embodiments, these substitutions replace one or both of the charged aspartic acid (D) or glutamic acid (E) residues at E272 and D519 with a hydrophobic residue, and particularly a hydrophobic residue such as alanine, leucine, proline, methionine, glycine, valine, isoleucine, phenylalanine, or tryptophan. In certain examples, the one or more substitutions within the A1-A2 domain interface are selected from the group consisting of E272A, E272V, D519A, and D519V. In additional examples, the substitution within the A2-A3 domain interface comprises a substitution of one or both of residues E665 and E1984 (based on the wild-type Factor VIII sequence of SEQ ID NO: 1). In certain embodiments, these substitutions replace one or both of the charged glutamic acid (E) residues at E665 and E1984 with a hydrophobic residue, and particularly a hydrophobic residue such as alanine, leucine, proline, methionine, glycine, valine, isoleucine, phenylalanine, or tryptophan. In further examples, the one or more substitutions within the A2-A3 domain interface are selected from the group consisting of E665A, E665V, E1984A, and E1984V. In certain examples, the variant Factor VIII polypeptide comprises D519A/E665A substitutions, D519A/E665V substitutions, D519V/E665A substitutions, or D519V/E665V substitutions.

[00111] In certain examples, preparation of the variant Factor VIII polypeptides involves site-directed mutagenesis of a nucleic acid sequence encoding a Factor VIII polypeptide. Such site-directed mutation of a nucleotide sequence may occur by any method known in the art and persons skilled in the art would be capable of readily determining an appropriate mutagenesis technique to employ for the specific application at hand. In certain examples, the mutagenesis is accomplished using a commercially available site-directed mutagenesis kit such as the Stratagene QuickChange™ II site-directed mutagenesis kit, the Clontech Transformer site-directed mutagenesis kit no. K1600-1, the Invitrogen GenTaylor site-directed mutagenesis system no. 12397014, the Promega Altered Sites II in vitro mutagenesis system kit no. Q6210, or the Takara Mirus Bio LA PCR mutagenesis kit no. TAK RR016.

[00112] In certain embodiments, the variant Factor VIII polypeptides will have an increased activity in at least one activity assay when compared with the starting Factor VIII polypeptide. Any suitable assay for testing Factor VIII activity can be employed with the variant polypeptides of the present disclosure, and such assays are well known in the art. Such activity assays include, but are not limited to: aPTT; chromogenic or fluorogenic substrate assay for FVIII, either assembled from individual components of the FXase

complex or as a kit; thrombin generation assay or test (TGA or TGT) or calibrated automated thrombography (CAT); and rotational thromboelastometry (ROTEM) or rotational thromboelastography (ROTEG).

[00113] The aPTT can refer to the one-stage or the less common two-stage assay, where coagulation is detected as the time needed to achieve a predefined sample turbidity or viscosity (clot time or CT). As the aPTT is a plasma-based assay, it has been used to assess potential Factor VIII activity and function in plasma. In the typical one-stage aPTT, a plasma sample containing FVIII is incubated with a negatively charged surface or particles and Ca^{+2} to initiate coagulation. In the one-stage assay, FXIa, FVIIIa, FXa, thrombin, and fibrin generation occur in one reaction. In the two-stage assay FXIa, FVIIIa, and FXa generation occur at the first stage and thrombin and fibrin formation occur in the second stage. Modifications of the one-stage and two-stage aPTT may be possible to make the assays specific for FVIII quantitation, as in a FVIII-specific factor assay.

[00114] The chromogenic substrate assay (chromo assay) is a two-stage assay designed to assess FVIII function in the context of FXase complex (FIXa, PL, Ca+2, and FX). In this assay, FVIIIa is fully activated, and FIXa and PL are in excess, a situation not typically encountered physiologically. In this assay, FVIIIa is combined with purified or relatively purified components of the FXase complex to generate FXa in the first stage. In the second stage, the level of FXa generated is quantified by a substrate that yields color when cleaved by FXa. Variation of the chromogenic assay includes replacement of the chromogenic substrate with a fluorogenic substrate, and fluorescence emission is detected (fluorogenic assay).

[00115] TGA, another assay of FVIII procoagulant function, is performed by activating plasma containing FVIII with a physiologic initiator such as tissue factor (TF) or FXIa in the presence of phospholipid (PL) (40:40:20, v/v/v phosphatidlyserine:phosphatidylcholine: phosphatidylethanolamine) to simulate the membrane surface of activated platelets. Thrombin generation (and coagulation) commences with the addition of Ca^{+2} and a fluorogenic substrate for thrombin to the sample. In CAT, the fluorescence change over time is then related back to thrombin concentration by monitoring the rate of fluorescence change in parallel samples containing defined levels of thrombin. Parameters describing the kinetic change in thrombin generation profiles can include the time before the onset of the response (lag) and the peak thrombin achieved (peak).

[00116] ROTEM/ROTEG is analogous to TGA, except that the development of viscosity with coagulation is monitored rather than thrombin generation. Again, coagulation

is initiated in plasma containing FVIII by Ca^{+2}, or TF-PL mixture. Parameters describing the kinetic changes in viscosity can include clot initiation time (CT) and the rate of viscosity change (α angle).

[00117] In certain examples, activity of the variant Factor VIII polypeptide will be tested by one or more assays. Note that due to the changes in the mechanism of action for these FVIII variants and to the differences in the ability of assays to detect specific aspects of FVIII function, only certain assays will detect marked enhancements in Factor VIII activity. As such, in certain examples, the variant Factor VIII polypeptide may have comparable activity to wt-FVIII in one assay while possessing increased activity in another assay. For example, the variant may have activity that is comparable to that of wt-FVIII in a chromogenic assay while possessing increased activity when tested using an aPTT assay or thrombin generation assay. This can occur, for example, when a variant has enhanced catalytic activity but is also more susceptible to proteolytic degradation. For some variants, the assays most sensitive to enhanced activity may be the one-stage aPTT and the TGA, but not the chromogenic assay. Such a discrepancy in assay performance of coagulation proteins is not uncommon, particularly when mutations are in domains impacting specific functions but not others (Leong et al., Biochemistry 31:2567 (1992); Stone et al., Biochemistry 30:6392 (1991); Henriksen and Mann, Biochemistry 28:2078 (1989)). These results may suggest that these variants may have the advantage of being easier to activate, i.e., the conversion from FVIII to FVIIIa is accelerated, which could then translate to enhanced thrombin generation.

[00118] In certain examples, the variant Factor VIII polypeptide will possess an activity greater than that of the starting Factor VIII polypeptide, wt-FVIII, FVIII-BDD, or D519VE665E-FVIII. These activities will be measured using polypeptides produced under comparable conditions, such as recombinant expression of the variant and starting polypeptide in the same type of cell line under comparable conditions. In certain embodiments, the activity will be increased by at least 1.1-fold over that of the starting Factor VIII polypeptide, wt-FVIII, FVIII-BDD, or D519VE665E-FVIII in at least one assay. In other embodiments, the activity will be increased by at least about 1.2-fold, 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2.0-fold, 2.5-fold, 3.0-fold, 3.5-fold, 4.0-fold, 4.5-fold, 5.0-fold, 5.5-fold, 6.0-fold, 6.5-fold, 7.0-fold, 7.5-fold, 8.0-fold, 8.5-fold, 9.0-fold, 9.5-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold, 20-fold, 21-fold, 22-fold, 23-fold, 24-fold, 25-fold, 26-fold, 27-fold, 28-fold, 29-fold, 30-fold, 31-fold, 32-fold, 33-fold, 34-fold, 35-fold, 36-fold, 37-fold, 38-fold, 39-fold, 40-fold, 41-fold, 42-fold, 43-fold, 44-fold, 45-fold, 46-fold, 47-fold, 48-fold, 49-fold, 50-fold,

55-fold, 60-fold, 65-fold, 70-fold, 75-fold, 80-fold, 85-fold, 90-fold, 100-fold, 110-fold, 120-fold, 130-fold, 140-fold, 150-fold, 160-fold, 170-fold, 180-fold, 190-fold, 200-fold, 210-fold, 220-fold, 230-fold, 240-fold, 250-fold, 260-fold, 270-fold, 280-fold, 290-fold, 300-fold, 310-fold, 320-fold, 330-fold, 340-fold, 350-fold, 360-fold, 370-fold, 380-fold, 390-fold, 400-fold, 450-fold, 500-fold, or more over that of the starting Factor VIII polypeptide, wt-FVIII, FVIII-BDD, or D519VE665E-FVIII in at least one assay.

[00119] In still further embodiments, the activity will be increased by about 1.2 to 10-fold, 1.2 to 12-fold, 1.2 to 14-fold, 1.2 to 16-fold, 1.2 to 18-fold, 1.2 to 20-fold, 1.2 to 30-fold, 1.2 to 40-fold, 1.2 to 50-fold, 1.2 to 60-fold, 1.2 to 70-fold, 1.2 to 80-fold, 1.2 to 90-fold, 1.2 to 100-fold, 1.3 to 10-fold, 1.3 to 12-fold, 1.3 to 14-fold, 1.3 to 16-fold, 1.3 to 18-fold, 1.3 to 20-fold, 1.3 to 30-fold, 1.3 to 40-fold, 1.3 to 50-fold, 1.3 to 60-fold, 1.3 to 70-fold, 1.3 to 80-fold, 1.3 to 90-fold, 1.3 to 100-fold, 1.4 to 10-fold, 1.4 to 12-fold, 1.4 to 14-fold, 1.4 to 16-fold, 1.4 to 18-fold, 1.4 to 20-fold, 1.4 to 30-fold, 1.4 to 40-fold, 1.4 to 50-fold, 1.4 to 60-fold, 1.4 to 70-fold, 1.4 to 80-fold, 1.4 to 90-fold, 1.4 to 100-fold, 1.5 to 10-fold, 1.5 to 12-fold, 1.5 to 14-fold, 1.5 to 16-fold, 1.5 to 18-fold, 1.5 to 20-fold, 1.5 to 30-fold, 1.5 to 40-fold, 1.5 to 50-fold, 1.5 to 60-fold, 1.5 to 70-fold, 1.5 to 80-fold, 1.5 to 90-fold, 1.5 to 100-fold, 1.6 to 10-fold, 1.6 to 12-fold, 1.6 to 14-fold, 1.6 to 16-fold, 1.6 to 18-fold, 1.6 to 20-fold, 1.6 to 30-fold, 1.6 to 40-fold, 1.6 to 50-fold, 1.6 to 60-fold, 1.6 to 70-fold, 1.6 to 80-fold, 1.6 to 90-fold, 1.6 to 100-fold, 1.8 to 10-fold, 1.8 to 12-fold, 1.8 to 14-fold, 1.8 to 16-fold, 1.8 to 18-fold, 1.8 to 20-fold, 1.8 to 30-fold, 1.8 to 40-fold, 1.8 to 50-fold, 1.8 to 60-fold, 1.8 to 70-fold, 1.8 to 80-fold, 1.8 to 90-fold, 1.8 to 100-fold, 2 to 10-fold, 2 to 12-fold, 2 to 14-fold, 2 to 16-fold, 2 to 18-fold, 2 to 20-fold, 2 to 30-fold, 2 to 40-fold, 2 to 50-fold, 2 to 60-fold, 2 to 70-fold, 22 to 80-fold, 2 to 90-fold, 2 to 100-fold, 4 to 10-fold, 4 to 12-fold, 4 to 14-fold, 4 to 16-fold, 4 to 18-fold, 4 to 20-fold, 4 to 30-fold, 4 to 40-fold, 4 to 50-fold, 4 to 60-fold, 4 to 70-fold, 4 to 80-fold, 4 to 90-fold, 4 to 100-fold, 5 to 10-fold, 5 to 12-fold, 5 to 14-fold, 5 to 16-fold, 5 to 18-fold, 5 to 20-fold, 5 to 30-fold, 5 to 40-fold, 5 to 50-fold, 5 to 60-fold, 5 to 70-fold, 5 to 80-fold, 5 to 90-fold, 5 to 100-fold, 6 to 12-fold, 6 to 14-fold, 6 to 16-fold, 6 to 18-fold, 6 to 20-fold, 6 to 30-fold, 6 to 40-fold, 6 to 50-fold, 6 to 60-fold, 6 to 70-fold, 6 to 80-fold, 6 to 90-fold, 6 to 100-fold, 8 to 16-fold, 8 to 18-fold, 8 to 20-fold, 8 to 30-fold, 8 to 40-fold, 8 to 50-fold, 8 to 60-fold, 8 to 70-fold, 8 to 80-fold, 8 to 90-fold, 8 to 100-fold, 10 to 20-fold, 10 to 30-fold, 10 to 40-fold, 10 to 50-fold, 10 to 60-fold, 10 to 70-fold, 10 to 80-fold, 10 to 90-fold, 10 to 100-fold, 12 to 20-fold, 12 to 30-fold, 12 to 40-fold, 12 to 50-fold, 12 to 60-fold, 12 to 70-fold, 12 to 80-fold, 12 to 90-fold, 12 to 100-fold, 15 to 30-fold, 15 to 40-fold, 15 to 50-fold, 15 to 60-fold, 5 to 70-fold, 15 to 80-fold, 15

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[00120] The Factor VIII variants described herein can be designed using any functional Factor VIII polypeptide as a starting polypeptide. In certain embodiments, the Factor VIII polypeptide is a human Factor VIII polypeptide. In further embodiments, the Factor VIII polypeptide is human wt-FVIII (SEQ ID NO: 1), FVIII-BDD (SEQ ID NO: 3), or D519VE665E-FVIII (SEQ ID NO: 5). The starting polypeptide may have deletions, insertions, and/or additions compared with the amino acid sequence of wild type Factor VIII. As non-limiting examples, the starting polypeptide may include Factor VIII mutants with mutations further stabilizing the A2 domain (see, e.g., WO 97/40145), Factor VIII mutants resulting in increased expression (see, e.g., Swaroop et al., JBC 272:24121-24124 (1997)), Factor VIII mutants reducing the immunogenicity relative to wild type (see, e.g., Lollar, Thromb. Haemost. 82:505-508 (1999)), Factor VIII reconstituted from differently expressed heavy and light chains (see, e.g., Oh et al., Exp. Mol. Med. 31:95-100 (1999), or Factor VIII mutants having reduced binding to receptors leading to catabolism of Factor VIII like HSPG (heparan sulfate proteoglycans) and/or LRP (low density lipoprotein receptor related protein) (see, e.g., Ananyeva et al., TCM 11:251-257 (2001)). In certain examples, the Factor VIII polypeptide may also contain additional amino acid substitutions, such as, for example, a substitution at or near the R336 residue, for example an R336I substitution. Additionally, useful starting polypeptides can be modified forms of these that still possess Factor VIII functionality, including polypeptides comprising an amino acid sequence at least about 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 77%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 69%, 68%, 67%, or 66% identical to the sequence of wt-FVIII (SEQ ID NO: 1), FVIII-BDD (SEQ ID NO: 3),

or D519VE665E-FVIII (SEQ ID NO: 5). Further, variant Factor VIII polypeptides of the present disclosure include any variant polypeptide with at least about 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 77%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 69%, 68%, 67%, or 66% identity to the sequence of wt-FVIII (SEQ ID NO: 1), FVIII-BDD (SEQ ID NO: 3), or D519VE665E-FVIII (SEQ ID NO: 5) and which also contain one or more of the amino acid substitutions discussed herein, or in a further embodiment contain one or more amino acid substitutions in both the thrombin cleavage site and the activation loop. In another embodiment, variant Factor VIII polypeptides of the present disclosure include any variant polypeptide with more than 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 77%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 69%, 68%, 67%, or 66% identity to the sequence of wt-FVIII (SEQ ID NO: 1), FVIII-BDD (SEQ ID NO: 3), or D519VE665E-FVIII (SEQ ID NO: 5) and which also contain one or more of the amino acid substitutions discussed herein, or in a further embodiment contain one or more amino acid substitutions in both the thrombin cleavage site and the activation loop.

[00121] In another embodiment, the present disclosure relates to nucleic acid sequences encoding the variant Factor VIII polypeptides. In one embodiment, the Factor VIII variants are encoded by a nucleotide sequence having at least about 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 77%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 69%, 68%, 67%, or 66% identity across the full length to the nucleotide sequence of wt-FVIII (SEQ ID NO: 2), FVIII-BDD (SEQ ID NO: 4), or D519VE665E-FVIII (SEQ ID NO: 6), and which encodes a polypeptide containing one or more of the amino acid alterations discussed herein, or in a further embodiment contain one or more amino acid substitutions in both the thrombin cleavage site and the activation loop. In another embodiment, the Factor VIII variant is encoded by a nucleotide sequence having more than 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 79%, 78%, 77%, 76%, 75%, 74%, 73%, 72%, 71%, 70%, 69%, 68%, 67%, or 66% identity across the full length to the nucleotide sequence of wt-FVIII (SEQ ID NO: 2), FVIII-BDD (SEQ ID NO: 4), or D519VE665E FVIII (SEQ ID NO: 6), and which encodes a polypeptide containing one or more of the amino acid alterations discussed herein, or in a further embodiment contain one or more amino acid substitutions in both the thrombin cleavage site and the activation loop.

[00122] The percent identity values are calculated over the entire amino acid or nucleic acid sequence region. A series of programs based on a variety of algorithms is

available to the skilled worker for comparing different sequences. In at least one embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch algorithm (Needleman J. Mol. Biol. 48:444-453 (1970)) which has been incorporated into the needle program in the EMBOSS software package (Rice et al., "EMBOSS: The European Molecular Biology Open Software Suite," Trends in Genetics 16:276-277 (2000)), using either a BLOSUM 45 or PAM250 scoring matrix for distantly related proteins, or either a BLOSUM 62 or PAM160 scoring matrix for closer related proteins, and a gap opening penalty of 16, 14, 12, 10, 8, 6, or 4 and a gap extension penalty of 0.5, 1, 2, 3, 4, 5, or 6. Guides for local installation of the EMBOSS package as well as links to WEB-Services can be found at emboss.sourceforge.net. A non-limiting example of parameters to be used for aligning two amino acid sequences using the needle program are the default parameters, including the EBLOSUM62 scoring matrix, a gap opening penalty of 10 and a gap extension penalty of 0.5. In yet another embodiment, the percent identity between two nucleotide sequences is determined using the needle program in the EMBOSS software package (Rice et al., "EMBOSS: The European Molecular Biology Open Software Suite," Trends in Genetics 16:276-277 (2000)), using the EDNAFULL scoring matrix and a gap opening penalty of 16, 14, 12, 10, 8, 6, or 4 and a gap extension penalty of 0.5, 1, 2, 3, 4, 5, or 6. A non-limiting example of parameters to be used in conjunction for aligning two amino acid sequences using the needle program are the default parameters, including the EDNAFULL scoring matrix, a gap opening penalty of 10 and a gap extension penalty of 0.5. The nucleic acid and protein sequences can further be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the BLAST series of programs (version 2.2) of Altschul (Altschul et al., J. Mol. Biol. 215:403-10 (1990)). BLAST using nucleic acid sequences of the present disclosure as query sequence can be performed with the BLASTn, BLASTx, or the tBLASTx program using default parameters to obtain either nucleotide sequences (BLASTn, tBLASTx) or amino acid sequences (BLASTx) homologous to sequences encoded by the nucleic acid sequences of the present disclosure. BLAST using protein sequences encoded by the nucleic acid sequences of the present disclosure as query sequence can be performed with the BLASTp or the tBLASTn program using default parameters to obtain either amino acid sequences (BLASTp) or nucleic acid sequences (tBLASTn) homologous to sequences of the present disclosure. To obtain gapped alignments for comparison purposes, Gapped BLAST using default parameters can be utilized as described in Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997).

[00123] In certain embodiments, the polynucleotides of the present disclosure either essentially consist of the aforementioned nucleotide sequences or comprise the aforementioned nucleotide sequences. Thus, they can contain further nucleotide sequences as well. In certain embodiments, the polynucleotide can comprise, in addition to an open reading frame, further untranslated sequence at the 3' and at the 5' terminus of the coding gene region, for example at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, or more nucleotides of the sequence upstream of the 5' terminus of the coding region and/or at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, or more nucleotides of the sequence downstream of the 3' terminus of the coding gene region. Furthermore, the polynucleotides can encode proteins that comprise so called "tags" which may serve as a detectable marker or as an auxiliary measure for purification purposes. Tags for different purposes are well known in the art and include, for example, FLAG-tags, 6-histidine-tags, MYC-tags, and the like. In one embodiment, the polynucleotide further comprises an expression control sequence operatively linked to the nucleotide sequence.

[00124] In certain embodiments, a nucleic acid sequence encoding the variant Factor VIII polypeptide is inserted into a suitable vector. Numerous vectors useful for various purposes are well known in the art and persons skilled in the art would be able to readily select an appropriate vector for their desired application. In certain examples, the vector may be a cloning vector or an expression vector. In other examples, the vector may be a plasmid, a viral vector, a cosmid, or an artificial chromosome. Examples of suitable vectors include Tat/Tar-oriP expression vectors, such as pSS185 (Cho et al., Biotechnol. Prog. 19:229-232 (2003)) and pSS207 (Mei et al., Mol. Biotech. 34:165-178 (2006)), as well as pcDNA3.1, pCINeo, pEAK, pCEP4, and pUCOE vectors. In certain examples, the nucleic acid encoding the variant Factor VIII polypeptide may be placed adjacent to and/or under the control of an appropriate promoter. Numerous promoters useful for various purposes are well known in the art and persons skilled in the art would be able to readily select an appropriate promoter for their desired application. In certain examples, the promoter may be a constitutive promoter, an inducible promoter, or a tissue specific promoter. Examples of suitable promoters include the human or murine CMV promoter/enhancer, SV40 promoter/enhancer, EIf1alpha promoter, MPSV promoter, and SRalpha promoter.

[00125] In certain embodiments, the variant Factor VIII polypeptides are recombinantly produced in a cell, tissue, or organism. In certain embodiments, such recombinant production is accomplished by transforming or transfecting a host cell with a nucleic acid molecule encoding the variant polypeptide or a vector containing such a nucleic

acid. Numerous methods of transformation and transfection are well known in the art and persons skilled in the art would be able to readily select an appropriate method for their desired application. Examples of suitable transformation methods include liposome mediated transfection (e.g., 293Fectin™ from Invitrogen), calcium phosphate transfection, electroporation, and DEAE-dextran transfection.

[00126] Such recombinant production can also be accomplished using any suitable host cell, tissue, or organism. Suitable cells, tissues, and organisms are well known in the art and persons skilled in the art would be able to readily select an appropriate host for their desired application. In some embodiments, the host cell is mammalian. Examples of suitable mammalian cell lines are the COS-1 (ATCC CRL 1650), baby hamster kidney (BHK) cell lines, such as BHK21, HKB11 (Cho et al., J. Biomed. Sci. 9:631 (2002)), HEK293 (ATCC CRL-1573; Graham et al., J. Gen. Virol. 36:59-72 (1977)), HEK293T (ATCC CRL 11268; DSM ACC 2494), and HEK293F (Invitrogen R79007) cells. A useful BHK cell line is the tk^{31} ts13 BHK cell line (Waechter and Baserga, Proc. Natl. Acad. Sci. USA 79:1106-1110 (1982), incorporated herein by reference), hereinafter referred to as BHK 570 cells. The BHK 570 cell line has been deposited with the American Type Culture Collection, 12301 Parklawn Dr., Rockville, Md. 20852, under ATCC accession number CRL 10314. A tk^- ts13 BHK cell line is also available from the ATCC under accession number CRL 1632. In addition, a number of other cell lines can be used within the present disclosure, including Rat Hep I (Rat hepatoma; ATCC CRL 1600), Rat Hep II (Rat hepatoma; ATCC CRL 1548), TCMK (ATCC CCL 139), Human lung (ATCC HB 8065), NCTC 1469 (ATCC CCL 9.1), CHO (ATCC CCL 61), CHO K1 (ATCC CCI61), DUKX cells (Urlaub and Chasin, Proc. Natl. Acad. Sci. USA 77:4216-4220 (1980)) and CHO-DG44 cells (Urlaub et al., Cell 33:405-412 (1983)).

[00127] In another embodiment, the present disclosure relates to pharmaceutical formulations of the Factor VIII variants, as well as pharmaceutical compositions comprising a therapeutically effective amount of the Factor VIII variant and a pharmaceutically acceptable excipient or carrier. Pharmaceutically acceptable excipients or carriers generally include substances that may be added to the active ingredient to help formulate or stabilize the preparation and which cause no significant adverse toxicological effects to the patient. Numerous suitable excipients and carriers are well known in the art and persons skilled in the art would be able to readily identify a suitable excipient or carrier to employ for a particular formulation or composition. Examples of suitable excipients or carriers include water, sugars such as maltose or sucrose; albumin; and salts. Specific

examples of suitable formulations include the formulations described in U.S. Patent No. 5,763,401 (filed Jul. 12, 1996; issued Jun. 9, 1998), which is incorporated herein by reference in its entirety.

[00128] In one embodiment, the pharmaceutical formulations/compositions are for parenteral administration, such as by iv, sc, or intramuscular (im) administration, and dosing may be as a single bolus dose, intermittent dosing, or as a continuous iv infusion. Topical formulations are also useful. In one embodiment the pharmaceutical formulation comprises an isolated Factor VIII variant as described herein, or comprises a composition of Factor VIII variants as described herein, in a lyophilized preparation that is reconstituted at the time of use. Alternatively, the pharmaceutical formulation can be a stable liquid ready-to-use formulation not requiring reconstitution. The pharmaceutical formulation can be provided in single-use vials of lyophilized powder or vials of ready-to-use solution of about 25 IU, 50 IU, 75 IU, 100 IU, 125 IU, 150 IU, 175 IU, 200 IU, 250 IU, 300 IU, 350 IU, 400 IU, 450 IU, 500 IU, 550 IU, 600 IU, 650 IU, 700 IU, 750 IU, 800 IU, 850 IU, 900 IU, 950 IU, 1000 IU, 1050 IU, 1100 IU, 1150 IU, 1200 IU, 1250 IU, 1300 IU, 1350 IU, 1400 IU, 1450 IU, 1500 IU, 1550 IU, 1600 IU, 1650 IU, 1700 IU, 1750 IU, 1800 IU, 1850 IU, 1900 IU, 1950 IU, 2000 IU, 2050 IU, 2100 IU, 2150 IU, 2200 IU, 2250 IU, 2300 IU, 2350 IU, 2400 IU, 2450 IU, 2500 IU, 2550 IU, 2600 IU, 2650 IU, 2700 IU, 2750 IU, 2800 IU, 2850 IU, 2900 IU, 2950 IU, 3000 IU, 3050 IU, 3100 IU, 3150 IU, 3200 IU, 3250 IU, 3300 IU, 3350 IU, 3400 IU, 3450 IU, 3500 IU, 3550 IU, 3600 IU, 3650 IU, 3700 IU, 3750 IU, 3800 IU, 3850 IU, 3900 IU, 3950 IU, 4000 IU, 4050 IU, 4100 IU, 4150 IU, 4200 IU, 4250 IU, 4300 IU, 4350 IU, 4400 IU, 4450 IU, 4500 IU, 4550 IU, 4600 IU, 4650 IU, 4700 IU, 4750 IU, 4800 IU, 4850 IU, 4900 IU, 4950 IU, 5000 IU, 5500 IU, 6000 IU, 6500 IU, 7000 IU, 7500 IU, 8000 IU, 8500 IU, 9000 IU, 9500 IU, 10000 IU, 10500 IU, 11000 IU, 11500 IU, 12000 IU, 12500 IU, 13000 IU, 13500 IU, 14000 IU, 14500 IU, or 15000 IU, and vials containing any range of the above amounts identified by two of the above numbers are included herein (e.g., a range of 25-75 IU, 100-200 IU, etc.). "IU" is understood in the field as an International Unit and is defined by the WHO International Standard. Actual methods for preparing parenterally administrable compositions will be known or apparent to those skilled in the art and are described in more detail in, for example, Remington's Pharmaceutical Sciences, 21st ed., published by Lippincott Williams & Wilkins (2005). Topical application, such as can be advisable in the case of trauma or surgery, can be carried out by means of a spray, perfusion, catheters, stent, vascular graft or stent, ointment, or other preparation known in the art. In certain examples, topical administration can be by way of a

solid or semi-solid matrix, such as a surgical sponge or collagen matrix, which has been treated with, infused with, coated with, or soaked in a composition comprising the variant Factor VIII polypeptide. Methods of preparing such matrices are well known in the art (see, e.g., Thrombosis/Hemostasis 12:445 (2006)). The composition of the disclosure would then be applied to the matrix using known technology, such as spraying an aqueous formulation onto the matrix.

[00129] In one embodiment, the present disclosure relates to kits comprising the variant Factor VIII polypeptide. In certain examples, the kit contains a vial containing the lyophilized variant Factor VIII polypeptide, or a lyophilized formulation comprising the polypeptide, and also a diluent for reconstitution. In other examples, the kit contains a topical formulation of the Factor VIII polypeptide, for example, an ointment, spray, or liquid, and a matrix such as a sponge or other medical matrix to which the topical formulation may be applied before administration to the patient.

[00130] Proper dosage for administration to a patient suffering from Hemophilia A or another clotting disorder caused by a deficiency in a particular clotting factor can be readily determined by persons skilled in the art based upon, for example, the weight of the patient, the severity of the bleeding episode, the factor deficiency, and the specific activity of the particular variant being employed. In certain examples, dosing can be about 5 IU/kg, 10 IU/kg, 15 IU/kg, 20 IU/kg, 25 IU/kg, 30 IU/kg, 35 IU/kg, 40 IU/kg, 45 IU/kg, 50 IU/kg, 55 IU/kg, 60 IU/kg, 65 IU/kg, 70 IU/kg, 75 IU/kg, 80 IU/kg, 85 IU/kg, 90 IU/kg, 95 IU/kg, 100 IU/kg, or more when administered parenterally. The dosage may also be within a range of dosages in which each endpoint of the range is selected from the above dosages, such as, i.e., 5-15 IU/kg, 10-20 IU/kg, etc. In certain embodiments, for a patient having hemophilia A, the dosages administered iv are about 40 IU per kilogram for pre-operative indications, 15 to 20 IU per kilogram for minor hemorrhaging, and 20 to 40 IU per kilogram administered over an 8-hour period for a maintenance dose. These dosages may be administered as frequently as needed based on the pharmacokinetic profile of the variant Factor VIII preparation being administered. For example, such preparations may be administered intravenously twice per day, daily, every other day, every third day, three times per week, twice per week, or once per week for prophylactic use. Frequency of dosaging would be determined based upon the severity of the Hemophilia A condition, the pharmacokinetics of the variant being administered, and the prolongation of action achieved due to enhanced activity.

[00131] The Factor VIII variants and compositions herein are useful for the treatment of blood clotting disorders and those disorders that benefit from blood coagulation, and are particularly useful in situations where a Factor VIII with increased clotting activity is needed. Accordingly, the Factor VIII variants and compositions herein are useful for prophylactic treatment in patients with clotting disorders, as well as for treatment of acute bleeding episodes in patients with or without an underlying clotting deficiency. In certain embodiments, the variant Factor VIII polypeptides can be employed to treat bleeding caused by or related to penetrating traumatic injury; blunt traumatic injury; bleeding in elective surgery; bleeding in cardiac surgery; bleeding in spinal surgery; orthopedic surgery; neurosurgery; oncology surgery; post-partum surgery; menorrhagia; bleeding in stem cell transplantation; bleeding in liver transplantation; gastrointestinal bleeding; active variceal bleeding in cirrhosis; non variceal bleeding in cirrhosis; diffuse alveolar hemorrhage; aortic aneurysm; intracerebral hemorrhage; traumatic brain injury; brain contusion; reversal of warfarin; reversal of heparin; reversal of anticoagulants; reversal of anti-thrombotics; Factor VIII deficiency; specific types of von Willebrand disease; hereditary hemorrhagic telangiectasis; various arteriovenous malformations; burns; prophylaxis in hemophilia patients with inhibitors; partial hepatectomy for non-cirrhotic and cirrhotic patients; acquired hemophilia; idiopathic thrombocytopenic purpura; defects in platelet-mediated hemostasis (e.g., defects in platelet number or response); Glanzmann's Thrombasthenia; Glanzmann's Thrombasthenia refractory to platelet transfusion; Bernard-Soulier Syndrome; and Dengue hemorrhagic fever.

[00132] The following examples are offered to illustrate, but not to limit, the claimed embodiments. It is to be understood that the examples and embodiments described herein are for illustrative purposes only, and persons skilled in the art will recognize various parameters that can be altered without departing from the spirit of the disclosure or the scope of the appended claims.

EXAMPLES

Example 1: Mutagenesis of thrombin cleavage site and activation loop

Thrombin Cleavage Site Mutagenesis

[00133] Expression constructs for a variety of FVIII variants carrying amino acid substitutions at positions within the thrombin cleavage site were generated by standard site-directed mutagenesis using the Quick Change Site-Directed Mutagenesis Kit (Agilent Technologies cat. # 200251) and using FVIII-BDD as a starting polypeptide. The constructs

were originally created in a pcDNA3.1 vector. Following mutagenesis, the nucleic acid sequence encoding the variant Factor VIII was cut out of the pcDNA3.1 using appropriate restriction enzymes and was ligated into a pSS207 expression vector. The resulting plasmids were transiently transfected into HEK293 cells in a 96 well-based format. FVIII expression levels were quantitated by standard sandwich ELISAs.

Activation Loop Mutagenesis

[00134] Gene libraries individually randomizing amino acid positions 558-65 were generated using FVIII-BDD as a starting polypeptide and the standard mutagenesis technique described above. Clonal DNA preparations of the eight libraries were transiently transfected into HEK293 cells. FVIII expression levels were quantitated by standard sandwich ELISAs, as described above.

Inclusion of Additional Mutations

[00135] In addition to producing substitutions within the thrombin cleavage site and activation loop, certain substitutions at other positions along the Factor VIII polypeptide chain were also made in order to investigate the effects of such additional mutations. In one instance, a pcDNA3.1 vector containing a nucleic acid encoding a D519VE665V-FVIII polypeptide with I371P, V374F, V559L, R562W, and Q565E substitutions was further subjected to site directed mutagenesis, as described above, to produce an R336I substitution. The resulting nucleic acid was then transferred to the expression vector pSS207.

Combination of Mutations of Interest

[00136] Following creation of the distinct variant sets, mutations of interest were combined and characterized in a variety of permutations using essentially identical protocols. Overall, roughly 2000 FVIII variants were generated and characterized.

Factor VIII Activity Assays

[00137] FVIII activity was measured by both chromogenic and aPTT assays. For purified proteins, chromogenic activity was determined by Coatest FVIII:C (Instrumentation Laboratory; Bedford, MA), using 02-122 as a calibrator (NIBSC; Potters Bar, Hertfordshire, UK). Details of the chromogenic assay principles are described above. The aPTT activity of purified proteins was determined on the ACL TOP, using FVIII-BDD as a calibrator and the APTT-SP kit (Instrumentation Laboratory; Bedford, MA). Further details of the one-stage aPTT assay principles are described above. Specific activity of purified proteins was calculated using A280 to determine the protein concentrations.

Results

[00138] Numerous variants of FVIII-BDD with amino acid substitutions at positions within the thrombin cleavage site at amino acids 370-375 were produced and investigated (see Table 1). Preferred thrombin cleavage sequences were based on the ability of thrombin to cleave specific linear peptide sequences over others using kinetic fluorogenic substrate assay (Bianchini et al., J. Biol. Chem. 277:20527 (2002)). Surprisingly, one variant that was previously predicted to be containing an "optimal" thrombin cleavage site (Bianchini et al., J. Biol. Chem. 277:20527 (2002)) showed poor aPTT activity (variant "a" in Table 1). Other variants with partial correspondence to the predicted "optimal" consensus sequence (variants b and c in Table 1) displayed enhanced aPTT activity. Without wanting to be limited in any way by theory, the discrepancy from the predicted "optimal" thrombin cleavage site may be due partly to the limited capacity to extrapolate from thrombin interaction with small, linear peptide sequences to thrombin's interaction with large, three-dimensional proteins. Nevertheless, the enhanced aPTT activity of "b" and "c" indicated that these FVIII mutants were more efficiently activated under aPTT conditions, e.g., limited activated coagulation factor initiation.

Table 1

Variant Name	**Amino Acid Sequence within the Thrombin Cleavage Site (370-375)**	**Specific Activity (aPTT, fold over FVIII-BDD)**
FVIII-BDD	QIRSVA	1
a	MPRFSR	0.27
b	MPRSVA	2.0
c	QPRSFA	2.5

[00139] Roughly 1600 Factor VIII variants with amino acid substitutions in the activation loop at positions 558-565 were produced and characterized. While the primary screen was done using a chromogenic assay, aPTT assays identified variants with enhanced procoagulant activity. Table 2 lists the aPTT activities of certain variants produced and characterized.

Table 2

Variant	Specific Activity (aPTT, fold over FVIII-BDD)
FVIII-BDD	1
R562W	1.7
R562F	2.0
Q565E	2.0
R562K	2.8
V559L	3.6

[00140] Subsequently, the effects of combining multiple amino acid substitutions within the activation loop was investigated. Table 3 lists the activities of selected combinations of variants.

Table3

Variant	Specific Activity (aPTT, fold over FVIII-BDD)
FVIII-BDD	1
V559L, R562F	3.2
V559L, R562W	3.1
V559L, Q565E	4.8
V559L, R562W, Q565E	7.9
V559L, R562F, Q565E	9.5

[00141] Finally, combinations of variants at both the thrombin cleavage site and the activation loop were characterized. Many of the resulting variants showed only modest activity increases as assessed by chromogenic assay (**FIG. 2**), but showed substantial activity increases when characterized by the aPTT assay (**FIG. 1**). The modest change in chromogenic assay activity versus the markedly enhanced aPTT activity might be consistent with the activation advantage of these FVIII variants, as FVIII is fully pre-activated in the chromogenic assay but not in the aPTT assay.

Example 2: Further characterization of Var97

[00142] Another particular variant, termed Var97, which utilized D519VE665V-FVIII as the starting polypeptide and which possessed I371P, V374F, V559L, R562W, and Q565E amino acid substitutions, was further characterized. The selected variant was first cloned into the pSS207 expression vector and transfected into HKB11 cells to obtain

a stably expressing pool of cells used to inoculate a 10L wave fermenter. Purified Var97 protein was obtained and characterized both *in vitro* and *in vivo* as described below.

[00143] In the initial studies, it was found that purified Var97 protein has significantly enhanced aPTT activity compared to its chromogenic assay activity relative to the starting Factor VIII polypeptide. The ratio of specific activity for both these assays indicated that the degree of aPTT activity over chromogenic assay activity for the variant Var97 protein was about 30 times that of FVIII-BDD activity (Table 4).

Table 4

Protein	**Ratio of aPTT activity to chromogenic assay activity**	**Standard deviation of ratio**
FVIII-BDD	0.76	0.40
D519VE665V-FVIII	2.01	0.18
Var97	33.1	2.69

[00144] Further assessment of Var97 potency in coagulation was performed by TGA using tissue factor (TF) as an initiator. TGA was performed as recommended by the manufacturer (Diagnostica Stago; Asnières sur Seine, France). In brief, FVIII (BDD, D519VE665V, or variant) was spiked into human hemophilia A plasma with 1 pM TF 4 μM PL mixture, final concentration, as described above. Reactions were initiated by adding a mixture of thrombin substrate and $CaCl_2$ (Flu-Ca), and monitored for 60 min. The TGA results reported herein represent the mean of triplicate experiments. Due to the use of low levels of TF, the TGA is likely to more closely reflect physiologic coagulation. By TGA, Var97 was clearly more potent than either FVIII-BDD or D519VE665V-FVIII proteins, eliciting a very rapid increase in thrombin generation relative to those parent molecules (**FIG. 3**). Comparison of the thrombin profiles between Var97 and its parent, D519VE665V-FVIII, clearly demonstrated the contribution of the additional mutations by increasing the ease of thrombin activation (shorter lag) and the enhanced FXa generation (faster rate of rise, and the larger extent of thrombin generation).

[00145] Despite its enhanced capacity to elicit a thrombin response, the overall Var97 thrombin profile was qualitatively very similar to FVIII-BDD and D519VE665V-FVIII, where the rate of return toward baseline thrombin levels was related to peak thrombin levels (**FIG. 3**). This suggests that Var97 did not alter the mechanisms regulating thrombin levels in plasma. These results predict that Var97 is likely to pose no additional

thrombogenic risk or systemic coagulation risk above that of the FVIII-BDD or D519VE665V-FVIII proteins.

[00146] Quantitative comparisons of Var97 potency relative to other FVIII molecules tested indicate agreement between the procoagulant assay (TGA and aPTT) results. Comparison of the concentration of Var97 needed to elicit a defined quantity of peak thrombin indicated that Var97 was ~10x more potent than its parent D519VE665V-FVIII, and ~100x more potent than FVIII-BDD (**FIG. 4**). A similar assessment by aPTT indicated that ~10x less Var97 was required to elicit the same clot time as D519VE665V-FVIII (**FIG. 5**).

[00147] The function of the Var97 variant in its physiologic enzyme complex was examined using FXase kinetic assays. These FXase kinetic assays were performed in 10 mM HEPES pH 7.4, 150 mM NaCl, 5 mM CaCl2, 0.01% Tween 20, 0.01% BSA and 10 μM PL (40:40:20, v/v/v PS:PC:PE). In these FXase kinetic assays, purified FVIIIa proteins were generated by incubation with 20 nM thrombin. The FVIII level was held fixed at 10 pM and reacted with varying concentrations of FIXa (0-10 nM), or the FIXa level was held fixed at (100 pM) and the level of thrombin activated FVIIIa was varied (0-10 nM). FX (150 nM) was added to either types of reactions, and after 1 min., the FXase reactions were stopped by addition to EDTA. The amount of FXa generated in these reactions were measured using the S-2765 chromogenic substrate. FXa generation was then extrapolated from a standard curve relating FXa level to rates of chromogenic substrate cleavage. The data was fit to a standard Michaelis-Menten equation to derive kinetic constants. This data was plotted to show how FXa activity generation varied with FIXa concentration. Results of this analysis are shown in Table 5 and **FIG. 6**. As Table 5 demonstrates, the Var97 variant has an enhanced rate of FX activation as opposed to the wt-FVIII or FVIII-BDD polypeptides. Additionally, **FIG. 6** illustrates that the Var97 variant shows an increased binding affinity for FIXa. In fact, Var97 shows at least a 4-fold greater binding affinity for FIXa over the FVIII-BDD polypeptide.

Table 5:

	Vmax (nM/sec)	sem	Km (nM)	sem	Kcat (s-1)	sem
Var97	0.325	0.007	16.770	1.554	3.25	0.067
D519VE665V-FVIII	0.186	0.003	10.990	0.894	1.859	0.031
FVIII-BDD	0.147	0.002	9.493	0.779	1.472	0.023

[00148] The turbidity of a clotting solution over a time course can be analyzed to investigate both clotting kinetics and the structure of a resulting clot. It has been previously demonstrated that changes in the turbidity versus time profile during clotting can be induced by lowering the concentration of clotting factors as compared to physiological levels, and further that such changes in the turbidity profile correlate with changes in the fibrin structure of the clot. *See, e.g.,* Weisel and Nagsawami, Biophys. J., 63:111-28 (1992). Turbidity analysis was performed as described by Weisel and Nagsawami using either normal plasma, FVIII-deficient plasma, or FVIII-deficient plasma containing 50 mU/mL of the various Factor VIII variants. As shown in **FIG. 7**, introduction of either 50 mU/mL BDD or D519VE665V to FVIII-deficient plasma produced a turbidity profile (absorbance units [AU] versus time [sec]) which differs from that of normal serum; the rise in turbidity in these two variants was not nearly as rapid as was observed in the normal serum sample. In addition to indicating that the clotting kinetics of BDD and D519VE665V are not as rapid as in normal serum, this suggests that the presence of 50 mU/mL of the BDD or D519VE665V variant may produce a different clot structure and architecture than is produced during normal clotting. In contrast, introduction of 50 mU/mL Var97 Factor VIII variant produced a turbidity profile that is quite similar to that of the normal serum sample, indicating clotting kinetics and clot structure that closely resembles that of a normal clot.

[00149] As a further characterization of the Var97 variant, a study was performed to compare the ability of BDD and Var97 to protect against death from vascular injury in HemA mice. HemA mice were dosed with different concentrations of the various FVIII and 24 hours later, tail veins of HemA mice were transected as described (Mei et al., Blood (2010) 116: 270-279.). HemA mice survival was monitored for 24 hours and FVIII variant efficacy was assessed as 24 hour survival. The survival rate at the various dosages administered was then plotted (both in μg/kg and IU/kg) and the dosage of BDD and Var97 required to result in 50% survival (ED50) was determined from the plot (**FIG. 8** and Table 6). As this shows, a 50% survival rate is achieved at ~2-3-fold lower dose with Var97 than with BDD. This correlates well with the results of the other tests discussed herein, which indicated enhanced potency of Var97 and improved clot structure produced by Var97.

Table 6:

	ED50 (μg/kg)	ED50 (IU/kg)
Var97	0.33	2.47
BDD	0.96	4.93
Difference	~3-fold	~2-fold

[00150] The kinetic FXase results (not shown) with variable FIXa and fixed FVIIIa suggested that proteolysis might account for the discrepant aPTT versus chromogenic assay activity of Var97. To investigate cleavage of the variant Factor VIII polypeptide, the physical changes in FVIII in the presence of excess FIXa in a FXase reaction were visualized. For the detection of FVIIIa cleavage by FIXa present in FXase, Factor VIII polypeptides being examined were adjusted to 0.1 μg/ml final concentration in the standard Xase reaction buffer without bovine serum albumin present. The FVIII solution (25 μL) was added to 5 μl of 120nM IXa or buffer. The reactants were allowed to incubate at 37°C for 1 hr., and 4X nupage buffer was added to stop the reaction. The samples were then subjected to SDS-PAGE, followed by Coomassie Blue staining (**FIG. 9**). This analysis demonstrated that the Var97 Factor VIII variant shows enhanced proteolytic cleavage by FIXa relative to one or both of BDD and D519VE665V variant FVIII.

Example 3: Characterization of Var97-R336I

[00151] In an attempt to reduce the enhanced proteolytic cleavage of Var97, an additional substitution, R336I, was made within the Var97 peptide chain (Var97-R336I; SEQ ID NO: 55). This is a substitution within a known cleavage site for activated protein C (aPC). As can be seen in the SDS-PAGE gel image of **FIG. 9**, in the FIXa digestion assay, proteolytic cleavage of Var97-R336I was markedly reduced as compared to Var97.

[00152] The potency of the Var97-R336I variant in coagulation variant was also assessed by TGA using tissue factor (TF) as an initiator, as described above. By TGA, Var97-R336I was more potent than BDD, though somewhat less potent than Var97 and D519VE665V (**FIG. 10**). Additionally, the overall Var97-R336I thrombin profile was again qualitatively very similar to BDD, D519VE665V, and Var97, where the rate of return toward baseline thrombin levels was related to peak thrombin levels (**FIG. 10**). Quantitative comparisons of the concentration of BDD, D519VE665V, Var97, and Var97-R336I Factor

VIII variants needed to elicit a defined quantity of peak thrombin indicated that Var97-R336I was of similar potency to D519VE665V-FVIII (**FIG. 11**).

[00153] To further characterize the Var97-R336I variant, the turbidity profile of this variant was compared to the other variants, as well as normal serum control, as described above. As shown in **FIG. 7**, the turbidity profile of the Var97-R336I variant closely resembles that of the BDD and D519VE665V variants, indicating similar clotting kinetics and clot structure.

[00154] The variant polypeptides described herein, including Var97, have application for a variety of clinical indications. For hemophilia A, such a molecule with a rapid and enhanced thrombin response profile could be used either acutely or prophylactically, with either iv or sc routes of administration. These variants also could be used to treat other bleeding disorders, whether arising from a platelet or coagulation defect. In the cases of defects in platelet-mediated hemostasis, whether due to insufficiency in platelet number or response, the enhanced capacity of these variants to generate thrombin could potentially compensate by enhancing platelet activity and by providing more fibrin "glue" to hold the platelet plug needed for effective hemostasis.

[00155] In addition to hemophilia and other hemostatic disorders, the ability of these variants to elicit such a rapid thrombin response suggests possible utility in more acute situations, such as trauma and surgery. In those settings, the rapidity and robustness with which these variants can support a thrombin response, with minimal impact on the mechanisms regulating thrombin levels, could be an advantage. In those settings, these variants could be administered in a variety of manners, including iv, sc, and topically, either in the form of a spray or soaked in matrices, such as surgical sponges or collagen. Other indications where these variants could have utility include the treatment of hemorrhagic syndromes, such as Dengue hemorrhagic fever, where massive vascular permeability, impaired platelet function, and enhanced fibrinolysis can result in life-threatening internal bleeding.

CLAIMS

We claim:

1. A variant of a Factor VIII polypeptide, wherein said Factor VIII polypeptide is a functional Factor VIII comprising a thrombin cleavage site at amino acid positions 370-375 and an activation loop at amino acid positions 558-565, wherein said amino acid position numbering is with reference to the amino acid sequence set forth in SEQ ID NO: 1; and wherein said variant comprises an amino acid substitution at one or more residues within the thrombin cleavage site and an amino acid substitution at one or more residues within the activation loop.

2. The variant of claim 1, wherein said substitution within the thrombin cleavage site does not include a substitution at amino acid position 372.

3. The variant of claim 1 or 2, wherein said Factor VIII polypeptide further comprises an A1-A2 domain interface comprising amino acid residues E272 and D519 and an A2-A3 domain interface comprising amino acid residues E665 and E1984, wherein said amino acid position numbering is with reference to the amino acid sequence set forth in SEQ ID NO: 1; and wherein said variant further comprises a substitution at one or more amino acid residues of the A1-A2 domain interface and a substitution at one or more amino acid residues of the A2-A3 domain interface.

4. The variant of any one of claims 1-3, wherein said substitution within the thrombin cleavage site comprises a substitution at one or more positions selected from the group consisting of 370, 371, and 374.

5. The variant of any one of claims 1-3, wherein said substitution within the thrombin cleavage site comprises a substitution at two or more positions selected from the group consisting of 370, 371, and 374.

6. The variant of any of claims 1-5, wherein said substitution within the activation loop comprises a substitution at one or more positions selected from the group consisting of 559, 562, and 565.

7. The variant of any one of claims 1-5, wherein said substitution within the activation loop comprises a substitution at two or more positions selected from the group consisting of 559, 562, and 565.

8. The variant of any one of claims 3-7, wherein said substitution of the A1-A2 domain interface comprises one or more substitutions selected from the group consisting of E272A, E272V, D519A, and D519V.

9. The variant of any one of claims 3-8, wherein said substitution of the A2-A3 domain interface comprises one or more substitutions selected from the group consisting of E665A, E665V, E1984A, and E1984V.

10. The variant of any one of claims 3-7, wherein said substitution of the A1-A2 domain interface comprises D519V and wherein said substitution of the A2-A3 domain interface comprises E665V.

11. The variant of any one of claims 1-10, wherein said variant comprises an amino acid substitution at one or more positions selected from the group consisting of 370, 371, and 374, and an amino acid substitution at one or more positions selected from the group consisting of 559, 562, and 565.

12. The variant of any one of claims 1-10, wherein said variant comprises an amino acid substitution at two or more positions selected from the group consisting of 370, 371, and 374, and an amino acid substitution at two or more positions selected from the group consisting of 559, 562, and 565.

13. The variant of any one of claims 1-12, wherein said amino acid substitutions are selected from the group consisting of Q370M, I371P, V374F, V559L, R562W, R562F, R562K, and Q565E.

14. The variant of any one of claims 1-12, wherein said variant comprises amino acid substitutions within the thrombin cleavage site selected from the group consisting of:

(i) Q370M and I371P, and

(ii) I371P and V374F;

and comprises amino acid substitutions within the activation loop selected from the group consisting of:

(i) V559L and R562F,

(ii) V559L and R562W,

(iii) V559L and Q565E,

(iv) V559L, R562W, and Q565E, and

(v) V559L, R562F, and Q565E.

15. The variant of any one of claims 1-10, wherein said variant comprises the amino acid substitutions I371P, V374F, V559L, R562W, and Q565E.

16. The variant of any one of claims 1-10, wherein said variant comprises the amino acid substitutions I371P, V374F, V559L, R562W, Q565E, D519V, and E665V.

17. The variant of any one of claims 1-16, wherein said variant further comprises an amino acid substitution at amino acid position 336.

18. The variant of claim 17, wherein said amino acid substitution at amino acid position 336 comprises an R336I substitution.

19. The variant of any one of claims 1-18, wherein said Factor VIII polypeptide comprises an amino acid sequence at least 90% identical to the sequence of SEQ ID NO: 1, 2, or 3.

20. The variant of claim 1, wherein said Factor VIII polypeptide comprises the amino acid sequence of SEQ ID NO: 53.

21. The variant of any one of claims 1-20, wherein said variant has increased specific activity as compared to the unmodified Factor VIII polypeptide.

22. A pharmaceutical composition comprising the variant Factor VIII polypeptide of any one of claims 1-21 and a pharmaceutically acceptable excipient.

23. An isolated nucleic acid encoding the variant Factor VIII polypeptide of any one of claims 1-21.

24. A vector comprising the nucleic acid sequence of claim 23.

25. The vector of claim 24, wherein said vector is an expression vector.

26. A recombinant host cell comprising the isolated nucleic acid of claim 23 or the vector of claim 24 or 25.

27. A method of producing a variant Factor VIII polypeptide, said method comprising (a) culturing the recombinant host cell of claim 26 under conditions appropriate for expression of the variant Factor VIII polypeptide, and (b) isolating the variant.

28. A method for preventing or treating a bleeding disorder comprising administering to a subject an effective amount of the variant Factor VIII polypeptide of any of claims 1-21 or the pharmaceutical composition of claim 22.

29. The method of claim 28, wherein said bleeding disorder is a chronic bleeding disorder.

30. The method of claim 29, wherein said bleeding disorder is an acute bleeding episode.

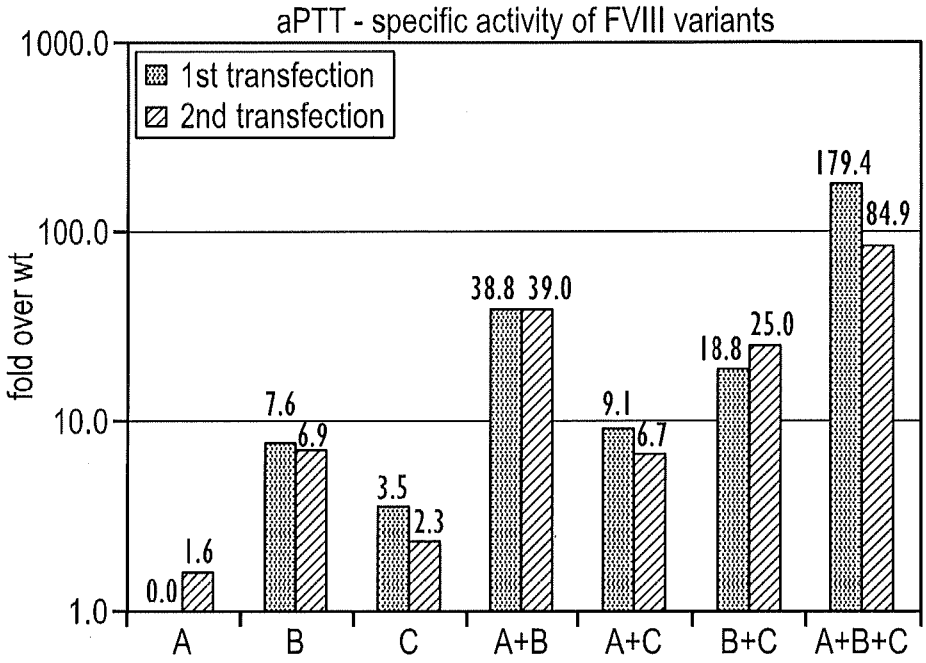

aPTT - specific activity of FVIII variants
1st transfection
2nd transfection
fold over wt
1000.0
100.0
10.0
1.0
0.0
1.6
7.6
6.9
3.5
2.3
38.8
39.0
9.1
6.7
18.8
25.0
179.4
84.9
A
B
C
A+B
A+C
B+C
A+B+C

FIG. 1

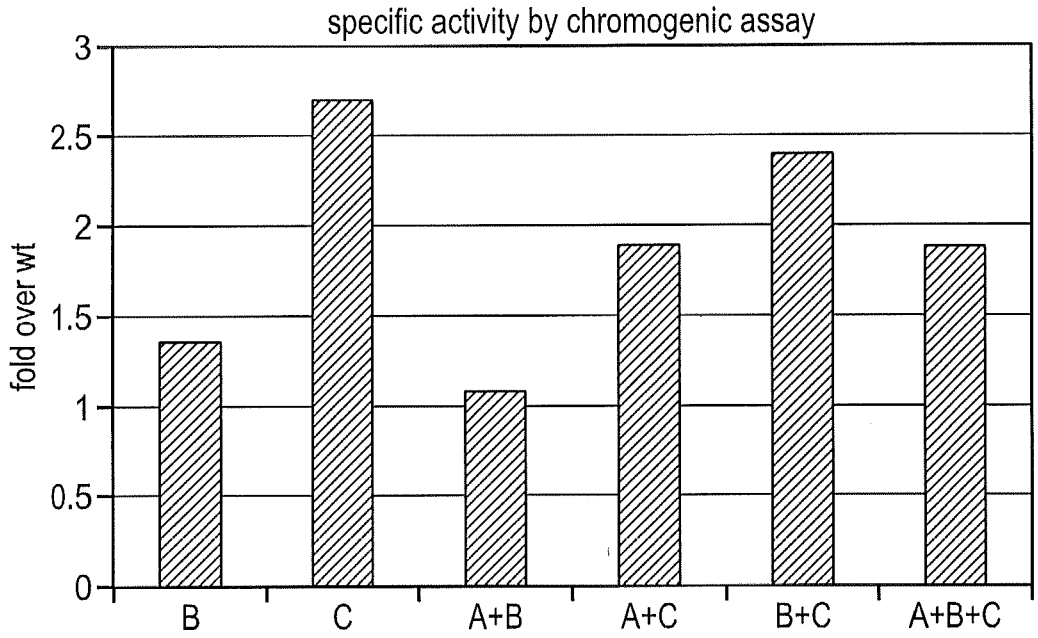

specific activity by chromogenic assay
fold over wt
3
2.5
2
1.5
1
0.5
0
B
C
A+B
A+C
B+C
A+B+C

FIG. 2

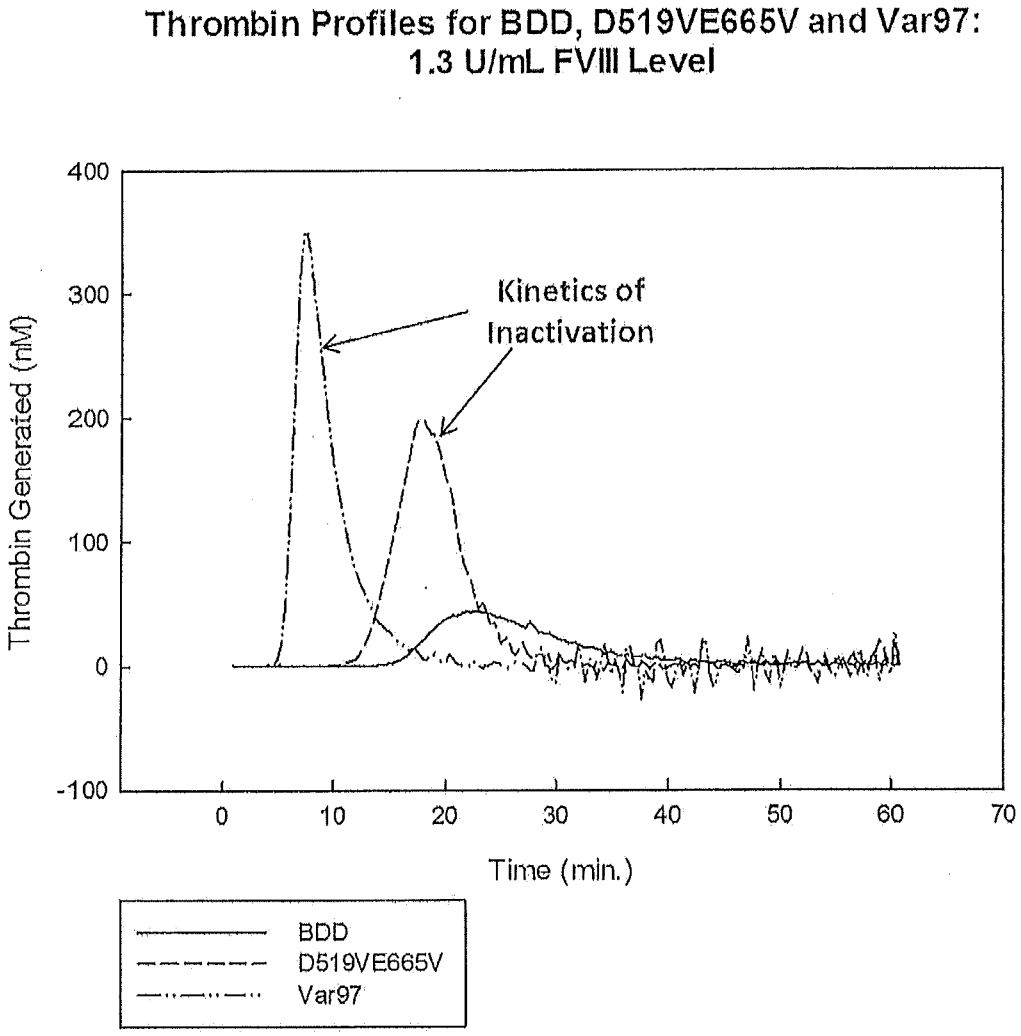

Thrombin Profiles for BDD, D519VE665V and Var97:
1.3 U/mL FVIII Level
Thrombin Generated (nM)
400
300
200
100
0
-100
0
10
20
30
40
50
60
70
Time (min.)
Kinetics of
Inactivation
BDD
D519VE665V
Var97

FIG. 3

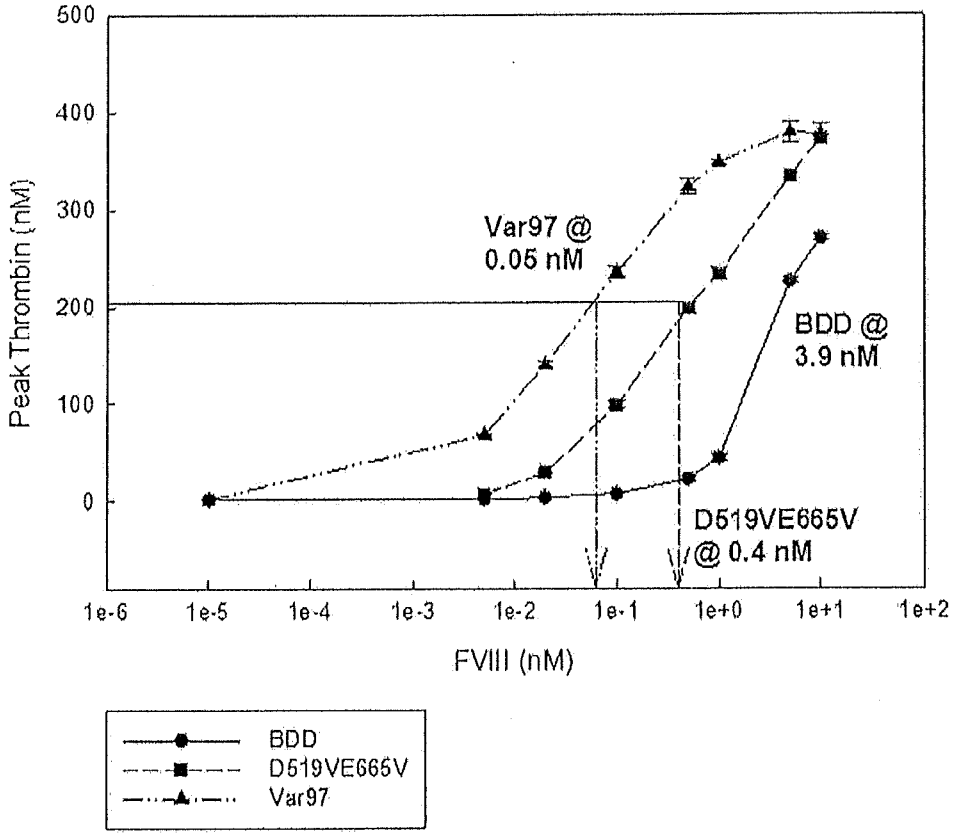
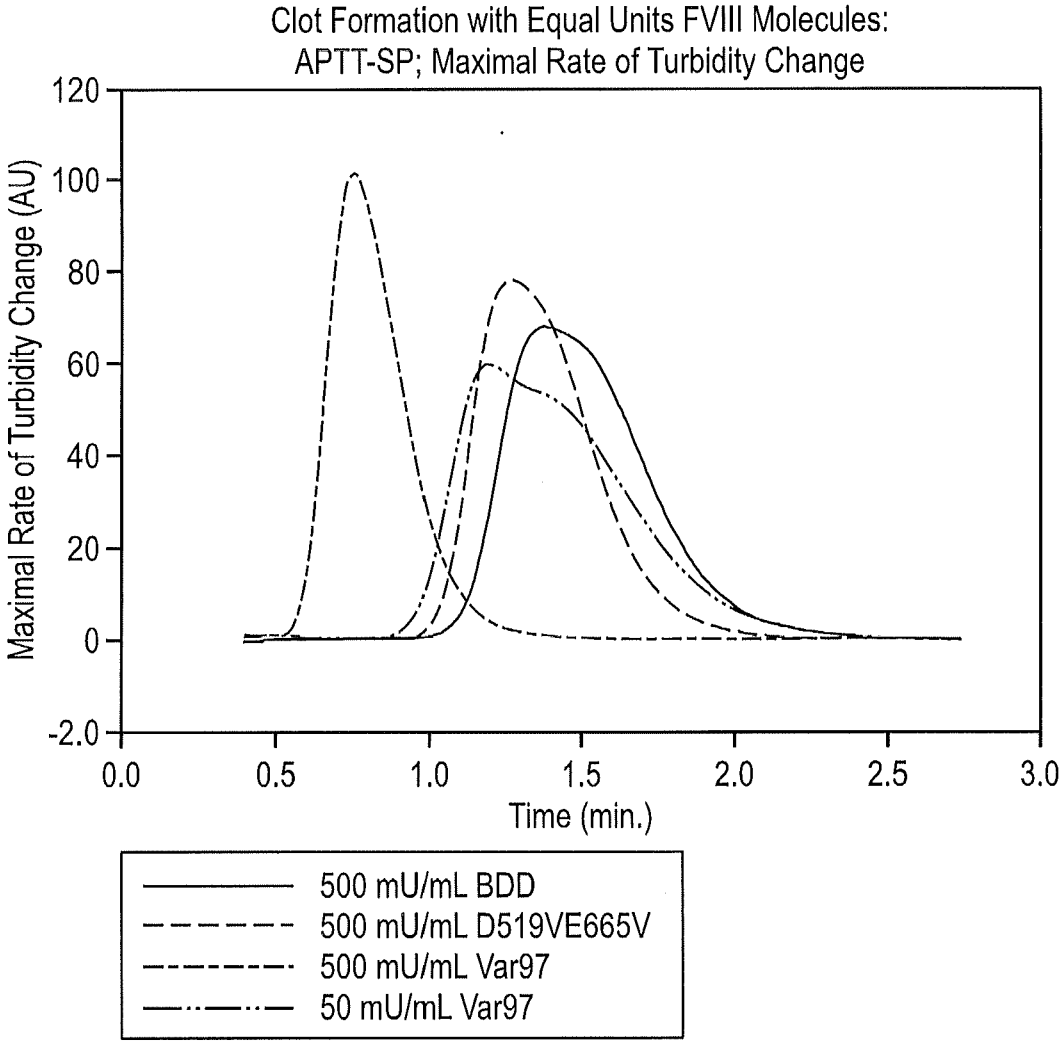

Comparison of D519VE665V or Var97 with BDD by Mass:
Peak Thrombin; with 1 pM TF-4 µM Phospholipid Initiation
Peak Thrombin (nM)
500
400
300
200
100
0
Var97 @
0.05 nM
BDD @
3.9 nM
D519VE665V
@ 0.4 nM
1e-6
1e-5
1e-4
1e-3
1e-2
1e-1
1e+0
1e+1
1e+2
FVIII (nM)
BDD
D519VE665V
Var97

FIG. 4

FIG. 5


Clot Formation with Equal Units FVIII Molecules:
APTT-SP; Maximal Rate of Turbidity Change
Maximal Rate of Turbidity Change (AU)
120
100
80
60
40
20
0
-2.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Time (min.)
500 mU/mL BDD
500 mU/mL D519VE665V
500 mU/mL Var97
50 mU/mL Var97

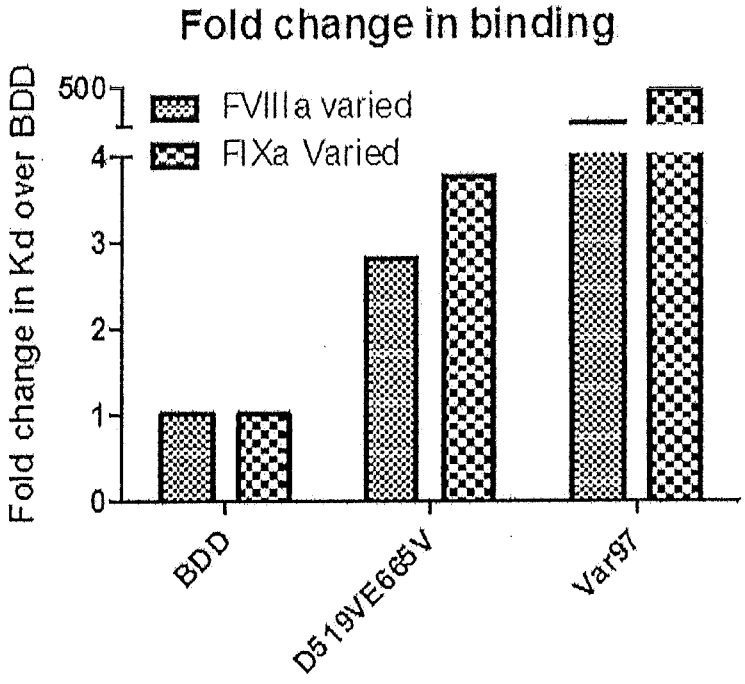
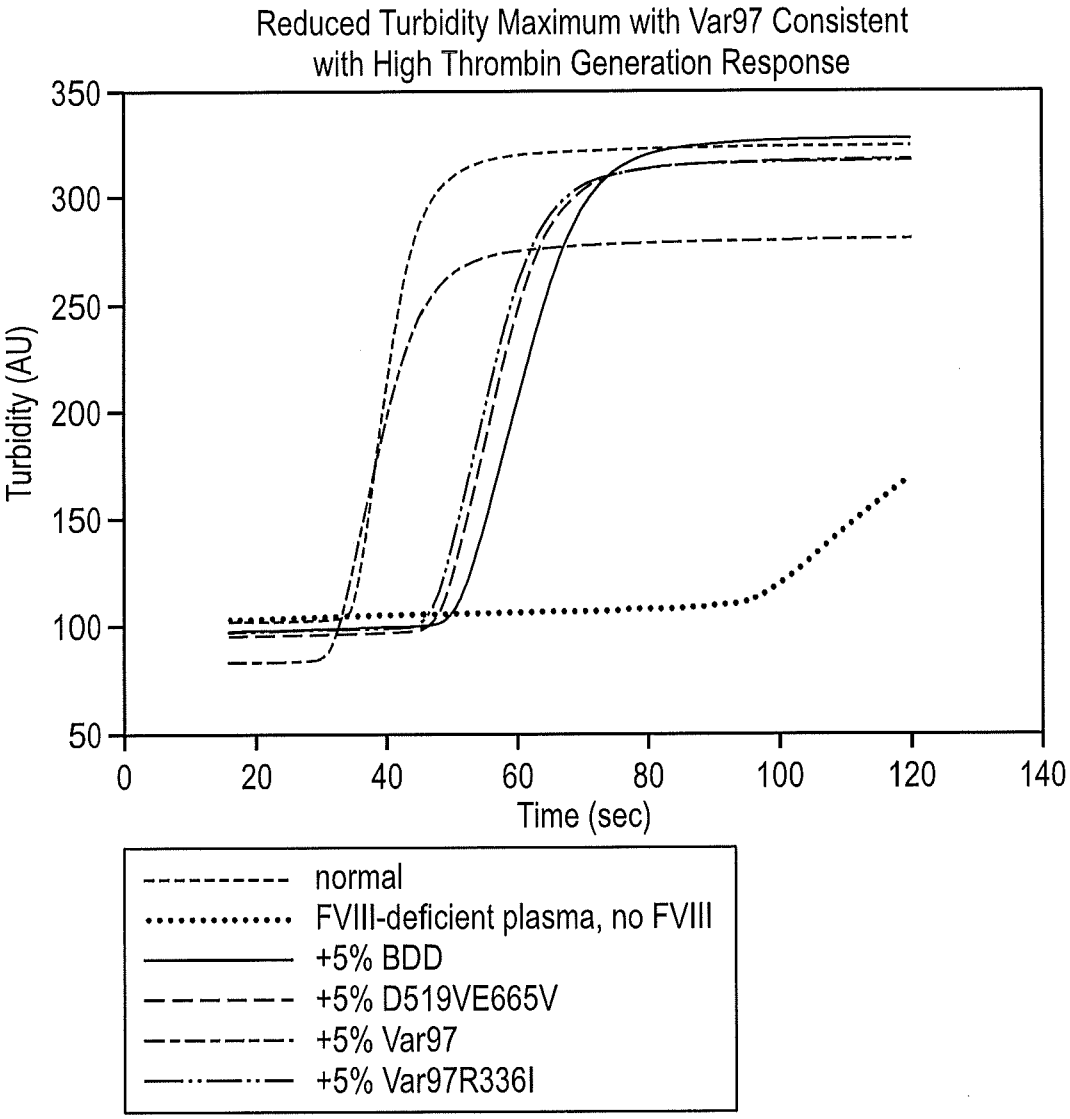

Fold change in binding
Fold change in Kd over BDD
500
4
3
2
1
0
FVIIIa varied
FIXa Varied
BDD
D519VE665V
Var97

FIG. 6

FIG. 7


Reduced Turbidity Maximum with Var97 Consistent with High Thrombin Generation Response
Turbidity (AU)
350
300
250
200
150
100
50
0
20
40
60
80
100
120
140
Time (sec)
normal
FVIII-deficient plasma, no FVIII
+5% BDD
+5% D519VE665V
+5% Var97
+5% Var97R336I

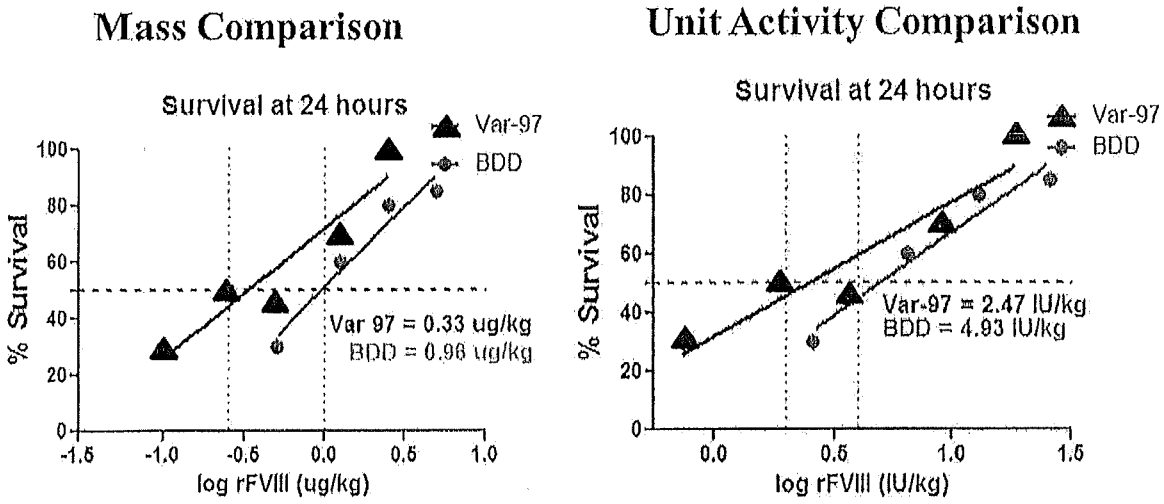

Mass Comparison
Survival at 24 hours
Var-97
BDD
% Survival
Var 97 = 0.33 ug/kg
BDD = 0.96 ug/kg
log rFVIII (ug/kg)
Unit Activity Comparison
Survival at 24 hours
Var-97
BDD
% Survival
Var-97 = 2.47 IU/kg
BDD = 4.93 IU/kg
log rFVIII (IU/kg)

FIG. 8

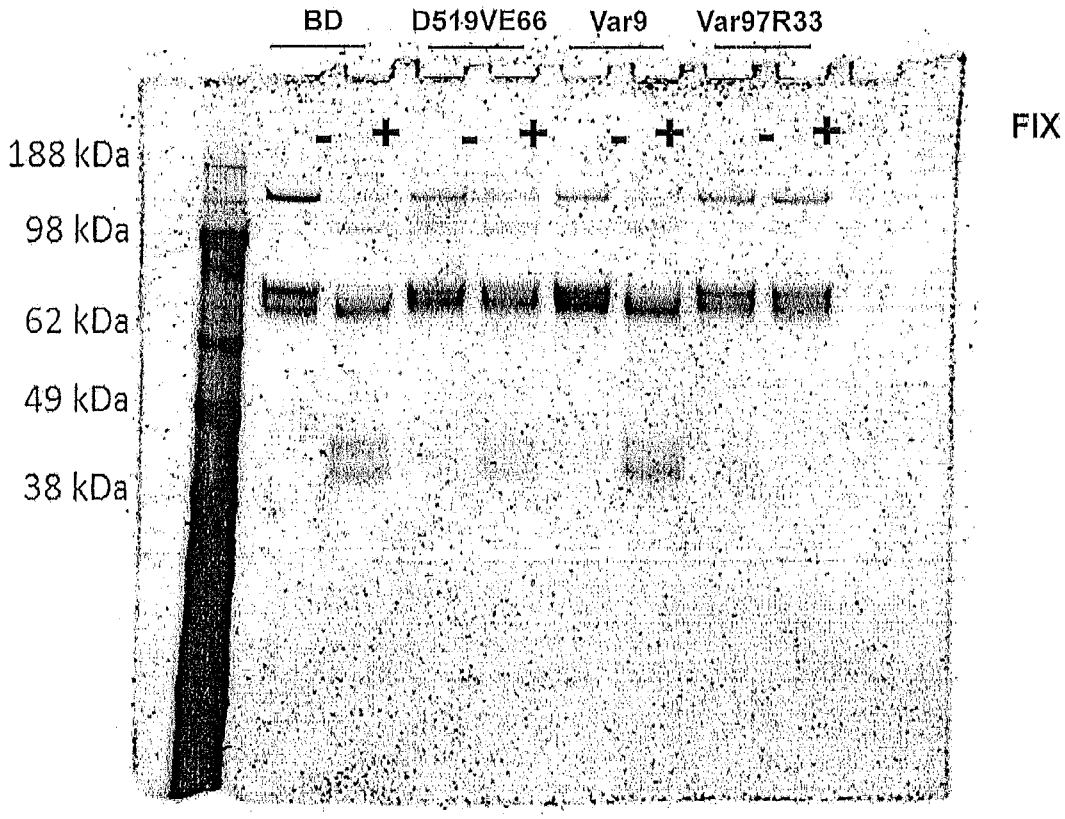

BD
D519VE66
Var9
Var97R33
- + - + - + - +
FIX
188 kDa
98 kDa
62 kDa
49 kDa
38 kDa

FIG. 9

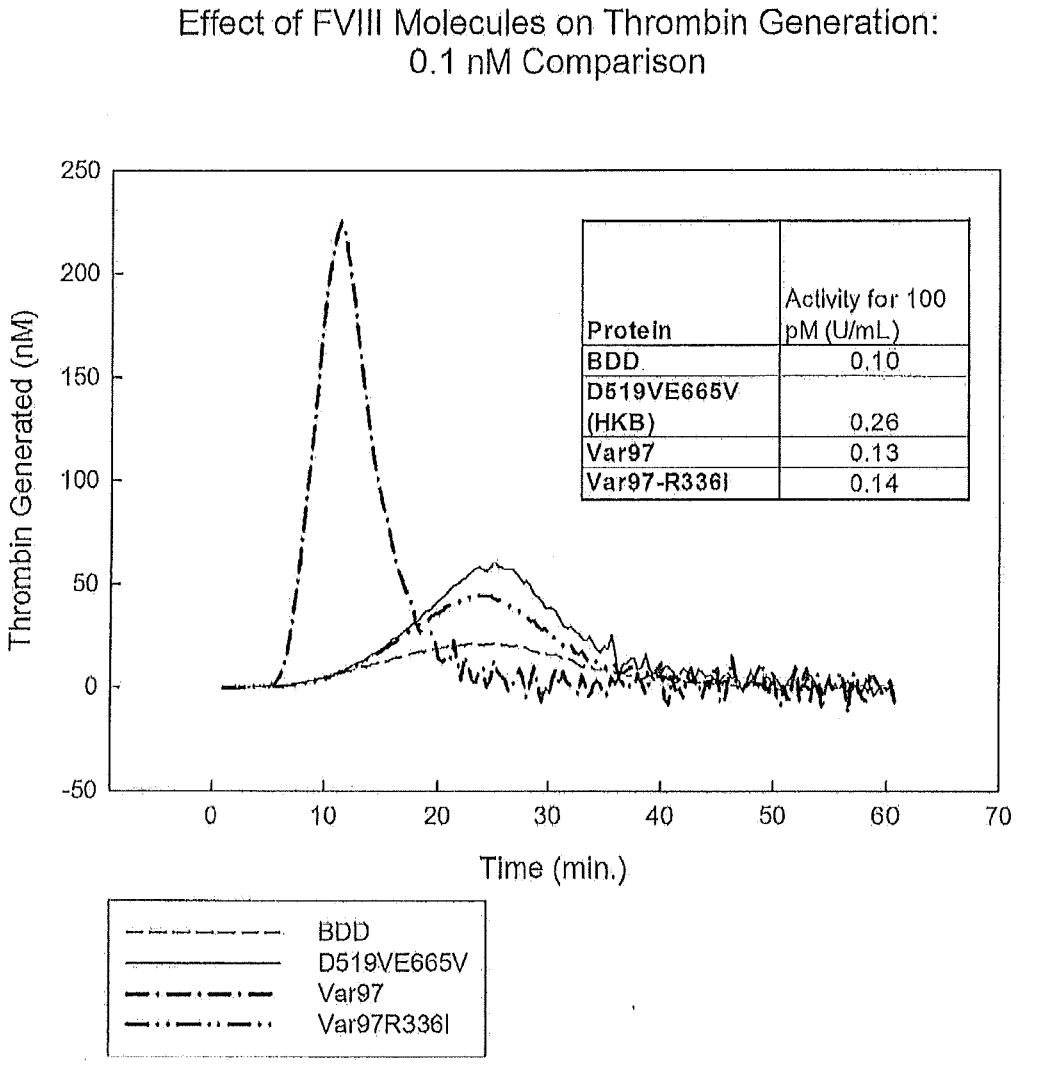

Effect of FVIII Molecules on Thrombin Generation:
0.1 nM Comparison
Thrombin Generated (nM)
250
200
150
100
50
0
-50
0
10
20
30
40
50
60
70
Time (min.)
Protein
Activity for 100 pM (U/mL)
BDD
0.10
D519VE665V (HKB)
0.26
Var97
0.13
Var97-R336I
0.14
BDD
D519VE665V
Var97
Var97R336I

FIG. 10

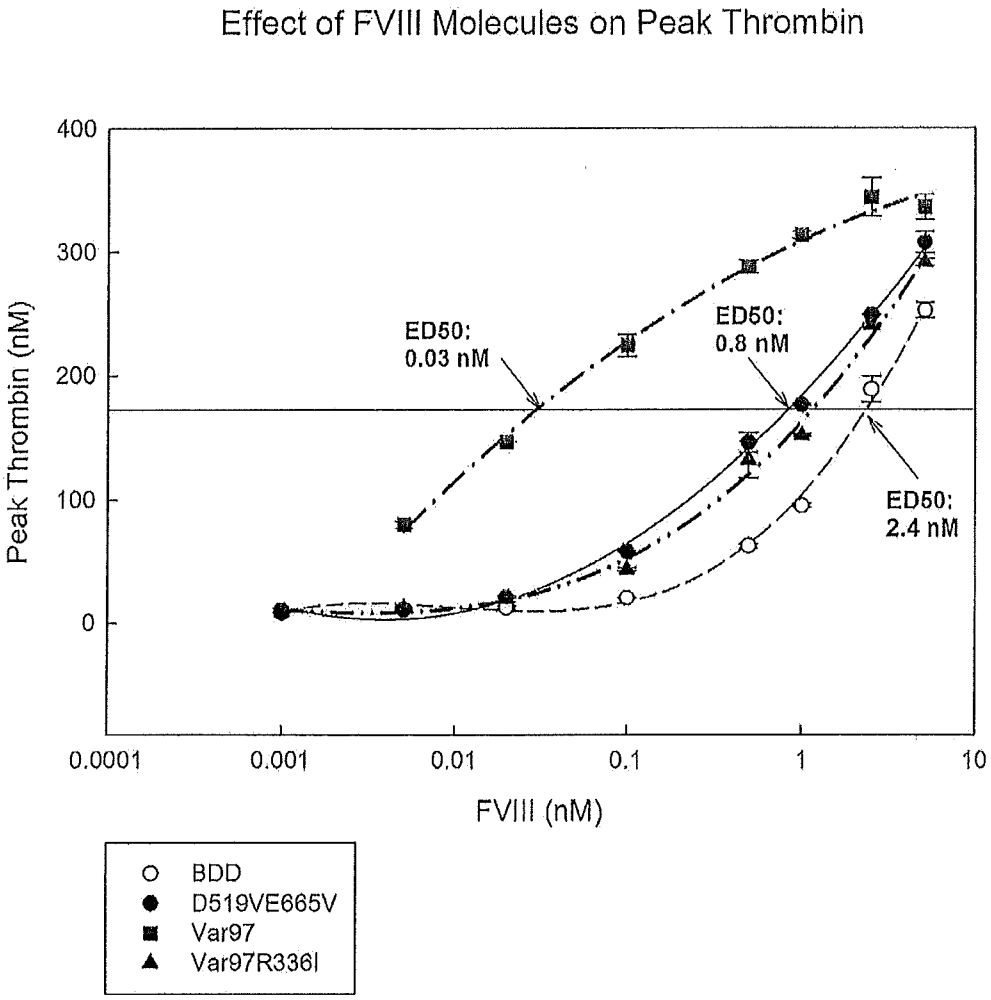

Effect of FVIII Molecules on Peak Thrombin
Peak Thrombin (nM)
400
300
200
100
0
0.0001
0.001
0.01
0.1
1
10
FVIII (nM)
ED50:
0.03 nM
ED50:
0.8 nM
ED50:
2.4 nM
BDD
D519VE665V
Var97
Var97R336I

FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/27443

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 35/14, C07K 1/00, C07K 14/00, A61K 38/37, C07K 14/755 (2014.01)
USPC - 530/383, 514/14.1, 514/21.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC- 530/383, 514/14.1, 514/21.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 530/350, 435/69.6

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(PGPB,USPT,USOC,EPAB,JPAB); PatBase, Google/Scholar: GRITZAN, Uwe; KRETSCHMER, Peter; Factor VIII; increased activity; thrombin cleavage site, amino acids 370-375, 558-565, activation loop, A1-A2, A2-A3 interface
GenCore 6.4: SEQ ID NO:53

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	Newell-Caito, et al. P3-P3' residues flanking scissile bonds in factor VIII modulate rates of substrate cleavage and procofactor activation by thrombin. Biochemistry 2012, 51(16):3451-9; Abstract, pg 5 [of the posted document], para 2; pg 18, Table 1; pg 19, Table 2	1-3 ----- 20
Y	US 2012/0065136 A1 (FAY, et al.) 15 March 2012 (15.03.2012) claims 1, 6, 7, 9, 14, para [0079]	1-3
A	WO 2003/087161 A1 (JONES et al.) 23 October 2003 (23.10.2003) Fig 10	20
A	US 2012/0028900 A1 (KAUFMAN, et al.) 02 February 2012 (02.02.2012) para [0097], [0174]	20
A	Wakabayashi, et al. Enhancing factor VIII and VIIIa stability by combining mutations at the A2 domain interface and A1-C2 domain interface. J Thromb Haemost. 2012, 10(3):492-5; pg 1 [of the posted document], last para	20
A	Jagannathan, et al. Identification of residues in the 558-loop of factor VIIIa A2 subunit that interact with factor IXa. Biol Chem. 2009, 284(47):32248-55; pg 32251, Fig 2 and its legend	20

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2014 (27.06.2014)	11 AUG 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/27443

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-19, 21-30
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

SEQUENCE LISTING

<110> Bayer HealthCare
Gritzan, Uwe
Leong, Lilley
Patel, Chandra
Kretschmer, Peter

<120> VARIANT FACTOR VIII POLYPEPTIDES AND METHODS OF THEIR PRODUCTION AND USE

<130> BHC125004

<160> 56

<170> PatentIn version 3.5

<210> 1
<211> 2332
<212> PRT
<213> Homo sapiens

<400> 1

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
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Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala
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ctcatctcca gcagtcaaga tggccatcag tggactctct tttttcagaa tggcaaagta 6840

aaggtttttc agggaaatca agactccttc acacctgtgg tgaactctct agacccaccg 6900

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atggaggttc tgggctgcga ggcacaggac ctctac 6996

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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 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 Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
805 810 815

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
835 840 845

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
865 870 875 880

Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile
885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
900 905 910

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
915 920 925

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
930 935 940

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
945 950 955 960

Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
965 970 975

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
980 985 990

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
995 1000 1005

Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
1010 1015 1020

Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
1025 1030 1035

Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
1040 1045 1050

Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
1055 1060 1065

Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn
1070 1075 1080

Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys
1085 1090 1095

Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His

1100 1105 1110

Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln
1115 1120 1125

Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile
1130 1135 1140

Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg
1145 1150 1155

Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro
1160 1165 1170

Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His
1175 1180 1185

Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
1190 1195 1200

Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
1205 1210 1215

Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
1220 1225 1230

Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
1235 1240 1245

Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
1250 1255 1260

Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn
1265 1270 1275

Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp
1280 1285 1290

Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
1295 1300 1305

Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn
1310 1315 1320

Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
1325 1330 1335

Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly
1340 1345 1350

Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile
1355 1360 1365

Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn
1370 1375 1380

Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
1385 1390 1395

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

Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu
1415 1420 1425

Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
1430 1435

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atcgctaagc caaggccacc ctggatgggt ctgctaggtc ctaccatcca ggctgaggtt 240

tatgatacag tggtcattac acttaagaac atggcttccc atcctgtcag tcttcatgct 300

gttggtgtat cctactggaa agcttctgag ggagctgaat atgatgatca gaccagtcaa 360

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catgtggacc tggtaaaaga cttgaattca ggcctcattg gagccctact agtatgtaga 540

gaagggagtc tggccaagga aaagacacag accttgcaca aatttatact acttttgct 600

gtatttgatg aagggaaaag ttggcactca gaaacaaaga actccttgat gcaggatagg 660

gatgctgcat ctgctcgggc ctggcctaaa atgcacacag tcaatggtta tgtaaacagg 720

tctctgccag gtctgattgg atgccacagg aaatcagtct attggcatgt gattggaatg 780

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catcgccagg cgtccttgga aatctcgcca ataactttcc ttactgctca aacactcttg 900

atggaccttg gacagtttct actgttttgt catatctctt cccaccaaca tgatggcatg 960

gaagcttatg tcaaagtaga cagctgtcca gaggaacccc aactacgaat gaaaaataat 1020

gaagaagcgg aagactatga tgatgatctt actgattctg aaatggatgt ggtcaggttt 1080

gatgatgaca actctccttc ctttatccaa attcgctcag ttgccaagaa gcatcctaaa 1140

acttgggtac attacattgc tgctgaagag gaggactggg actatgctcc cttagtcctc 1200

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aactctctag acccaccgtt actgactcgc taccttcgaa ttcaccccca gagttgggtg 4260

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<213> Artificial Sequence

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<223> Variant peptide

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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 Val 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 Val 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 Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
805 810 815

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser

835 840 845

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
865 870 875 880

Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile
885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
900 905 910

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
915 920 925

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
930 935 940

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
945 950 955 960

Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
965 970 975

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
980 985 990

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
995 1000 1005

Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
1010 1015 1020

Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
1025 1030 1035

Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
1040 1045 1050

Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
1055 1060 1065

Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn
1070 1075 1080

Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys
1085 1090 1095

Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His
1100 1105 1110

Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln
1115 1120 1125

Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile
1130 1135 1140

Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg
1145 1150 1155

Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro
1160 1165 1170

Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His
1175 1180 1185

Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
1190 1195 1200

Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
1205 1210 1215

Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
1220 1225 1230

Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
1235 1240 1245

Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
1250 1255 1260

Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn
1265 1270 1275

Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp

1280 1285 1290

Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
1295 1300 1305

Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn
1310 1315 1320

Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
1325 1330 1335

Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly
1340 1345 1350

Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile
1355 1360 1365

Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn
1370 1375 1380

Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
1385 1390 1395

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

Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu
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Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
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gatgctgcat ctgctcgggc ctggcctaaa atgcacacag tcaatggtta tgtaaacagg 720

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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 Met Pro 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

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
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Gly Thr Lys Asn Phe Met Lys Asn Leu Phe Leu Leu Ser Thr Arg
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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
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Val Gly Ser Leu Gly Thr Ser Ala Thr Asn Ser Val Thr Tyr Lys

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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

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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
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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
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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
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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
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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
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Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser Pro Ser Lys Ala
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Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln Val
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Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met
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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
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His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe
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Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val Asn Ser Leu Asp
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Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His Pro Gln Ser Trp
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catgtggacc tggtaaaaga cttgaattca ggcctcattg gagccctact agtatgtaga 540

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tctctgccag gtctgattgg atgccacagg aaatcagtct attggcatgt gattggaatg 780

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atggaccttg gacagtttct actgttttgt catatctctt cccaccaaca tgatggcatg 960

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Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val
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Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe
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Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp
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Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
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Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
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Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
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atgtatgtga aggagttcct catctccagc agtcaagatg gccatcagtg gactctcttt 4140

tttcagaatg gcaaagtaaa ggtttttcag ggaaatcaag actccttcac acctgtggtg 4200

aactctctag acccaccgtt actgactcgc taccttcgaa ttcaccccca gagttgggtg 4260

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<213> Artificial Sequence

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<223> Variant peptide

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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 Met Pro 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 Val 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 Val 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 Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys

785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
805 810 815

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
835 840 845

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
865 870 875 880

Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile
885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
900 905 910

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
915 920 925

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
930 935 940

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
945 950 955 960

Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
965 970 975

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
980 985 990

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
995 1000 1005

Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
1010 1015 1020

Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
1025 1030 1035

Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
1040 1045 1050

Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
1055 1060 1065

Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn
1070 1075 1080

Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys
1085 1090 1095

Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His
1100 1105 1110

Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln
1115 1120 1125

Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile
1130 1135 1140

Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg
1145 1150 1155

Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro
1160 1165 1170

Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His
1175 1180 1185

Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
1190 1195 1200

Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
1205 1210 1215

Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
1220 1225 1230

Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro

1235 1240 1245

Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
1250 1255 1260

Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn
1265 1270 1275

Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp
1280 1285 1290

Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
1295 1300 1305

Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn
1310 1315 1320

Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
1325 1330 1335

Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly
1340 1345 1350

Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile
1355 1360 1365

Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn
1370 1375 1380

Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
1385 1390 1395

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

Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu
1415 1420 1425

Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
1430 1435

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<212> DNA

<213> Artificial Sequence

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<223> Variant nucleotide

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atcgctaagc caaggccacc ctggatgggt ctgctaggtc ctaccatcca ggctgaggtt 240

tatgatacag tggtcattac acttaagaac atggcttccc atcctgtcag tcttcatgct 300

gttggtgtat cctactggaa agcttctgag ggagctgaat atgatgatca gaccagtcaa 360

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ctgaaagaga atggtccaat ggcctctgac ccactgtgcc ttacctactc atatctttct 480

catgtggacc tggtaaaaga cttgaattca ggcctcattg gagccctact agtatgtaga 540

gaagggagtc tggccaagga aaagacacag accttgcaca aatttatact acttttgct 600

gtatttgatg aagggaaaag ttggcactca gaaacaaaga actccttgat gcaggatagg 660

gatgctgcat ctgctcgggc ctggcctaaa atgcacacag tcaatggtta tgtaaacagg 720

tctctaccag gtctgattgg atgccacagg aaatcagtct attggcatgt gattggaatg 780

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catcgccagg cgtccttgga aatctcgcca ataactttcc ttactgctca aacactcttg 900

atggaccttg gacagtttct actgttttgt catatctctt cccaccaaca tgatggcatg 960

gaagcttatg tcaaagtaga cagctgtcca gaggaacccc aactacgaat gaaaaataat 1020

gaagaagcgg aagactatga tgatgatctt actgattctg aaatggatgt ggtcaggttt 1080

gatgatgaca actctccttc ctttatcatg ccccgctcag ttgccaagaa gcatcctaaa 1140

acttgggtac attacattgc tgctgaagag gaggactggg actatgctcc cttagtcctc 1200

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ctgttgatta tatttaagaa tcaagcaagc agaccatata acatctaccc tcacggaatc 1440

actgatgtcc gtcctttgta ttcaaggaga ttaccaaaag gtgtaaaaca tttgaaggat 1500

tttccaattc tgccaggaga aatattcaaa tataaatgga cagtgactgt agaagttggg 1560

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tactttacca atatgtttgc cacctggtct ccttcaaaag ctcgacttca cctccaaggg 3960

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cagaagacaa tgaaagtcac aggagtaact actcagggag taaaatctct gcttaccagc 4080

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aactctctag acccaccgtt actgactcgc taccttcgaa ttcaccccca gagttgggtg 4260

caccagattg ccctgaggat ggaggttctg ggctgcgagg cacaggacct ctac 4314

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<212> PRT
<213> Artificial Sequence

<220>
<223> Variant peptide

<400> 13

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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 Pro Arg Ser Phe 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

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
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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
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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
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Asp Leu Val Glu Gly Ser Leu Leu Gln Gly Thr Glu Gly Ala Ile
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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
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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
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Val Thr Trp Ala Lys Gln Gly Arg Thr Glu Arg Leu Cys Ser Gln
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Asn Pro Pro Val Leu Lys Arg His Gln Arg Glu Ile Thr Arg Thr
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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
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Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser
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Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser Val Pro
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Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser Phe
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Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
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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
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Met Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn
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Ser Thr Gly Thr Leu Met Val Phe Phe Gly Asn Val Asp Ser Ser
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Gly Ile Lys His Asn Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr
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Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg Ser Thr Leu Arg
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Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser
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Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser Pro Ser Lys Ala
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Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln Val
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Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met
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Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu Leu Thr
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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
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Gln Asp Leu Tyr
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tatgatacag tggtcattac acttaagaac atggcttccc atcctgtcag tcttcatgct 300

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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 Pro Arg Ser Phe 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
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Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn Asn Gly Pro
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Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr
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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
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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
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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
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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
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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 Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
805 810 815

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
835 840 845

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
865 870 875 880

Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile
885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
900 905 910

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
915 920 925

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
930 935 940

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
945 950 955 960

Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
965 970 975

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
980 985 990

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
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Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg

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Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
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Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
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Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn
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Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys
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Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His
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1145 1150 1155

Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro
1160 1165 1170

Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His
1175 1180 1185

Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
1190 1195 1200

Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
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Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
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Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
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Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
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Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
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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
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Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val
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Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser Glu Gly Ala
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Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val
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Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu Asn
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Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu Ser
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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
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Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn Arg
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Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val Tyr Trp His
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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

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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 Pro Arg Ser Phe Ala Lys Lys His Pro Lys Thr Trp Val His
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Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Leu Val Leu
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Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn Asn Gly Pro
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Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr
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Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly Ile
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Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile
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Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile
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Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys Gly Val Lys
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His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys
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Trp Thr Val Thr Val Glu Val Gly Pro Thr Lys Ser Asp Pro Arg Cys
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Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu Ala
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Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe
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Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp Pro Glu Phe
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Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu
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Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr
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Thr Phe Lys His Lys Met Val Tyr Val 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
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Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala
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Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu Lys Arg His

740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
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820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
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Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
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Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
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885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
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Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
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Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
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Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
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Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
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Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
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Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
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Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
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Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
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Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
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Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr

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Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu Val
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Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val
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Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val
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Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu Asn
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Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu Ser
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Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr Leu
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His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala Ser
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Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn Arg
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Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg
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Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser Pro Ser Phe
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Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Leu Val Leu
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Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr
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Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly Ile
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Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile

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His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys
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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
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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
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Val Ser Ser Ser Asp Leu Leu Met Leu Leu Arg Gln Ser Pro Thr Pro
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His Gly Leu Ser Leu Ser Asp Leu Gln Glu Ala Lys Tyr Glu Thr Phe
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Leu Thr Glu Ser Gly Gly Pro Leu Ser Leu Ser Glu Glu Asn Asn Asp

930 935 940

Ser Lys Leu Leu Glu Ser Gly Leu Met Asn Ser Gln Glu Ser Ser Trp
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Phe Lys Lys Val Thr Pro Leu Ile His Asp Arg Met Leu Met Asp
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Pro Leu Ser Asp Cys Leu Thr Arg Ser His Ser Ile Pro Gln Ala

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Ile Arg Pro Ile Tyr Leu Thr Arg Val Leu Phe Gln Asp Asn Ser
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Ser His Leu Pro Ala Ala Ser Tyr Arg Lys Lys Asp Ser Gly Val
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Gln Glu Ser Ser His Phe Leu Gln Gly Ala Lys Lys Asn Asn Leu
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Val Gly Ser Leu Gly Thr Ser Ala Thr Asn Ser Val Thr Tyr Lys
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Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp
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Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser
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Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys
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1895 1900 1905

Asp Pro Thr Phe Lys Glu Asn Tyr Arg Phe His Ala Ile Asn Gly
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Glu Cys Leu Ile Gly Glu His Leu His Ala Gly Met Ser Thr Leu
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ctcatctcca gcagtcaaga tggccatcag tggactctct tttttcagaa tggcaaagta 6840

aaggtttttc agggaaatca agactccttc acacctgtgg tgaactctct agacccaccg 6900

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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 Leu Asp
545 550 555 560

Gln Phe 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 Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
805 810 815

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
835 840 845

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
865 870 875 880

Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile
885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
900 905 910

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
915 920 925

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
930 935 940

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
945 950 955 960

Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln

965 970 975

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
980 985 990

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
995 1000 1005

Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
1010 1015 1020

Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
1025 1030 1035

Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
1040 1045 1050

Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
1055 1060 1065

Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn
1070 1075 1080

Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys
1085 1090 1095

Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His
1100 1105 1110

Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln
1115 1120 1125

Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile
1130 1135 1140

Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg
1145 1150 1155

Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro
1160 1165 1170

Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His
1175 1180 1185

Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
1190 1195 1200

Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
1205 1210 1215

Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
1220 1225 1230

Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
1235 1240 1245

Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
1250 1255 1260

Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn
1265 1270 1275

Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp
1280 1285 1290

Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
1295 1300 1305

Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn
1310 1315 1320

Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
1325 1330 1335

Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly
1340 1345 1350

Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile
1355 1360 1365

Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn
1370 1375 1380

Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
1385 1390 1395

Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg

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Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu
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Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
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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
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Trp Thr Val Thr Val Glu Val 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 Leu Asp
545 550 555 560

Gln Phe 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 Val 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 Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
805 810 815

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
835 840 845

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
865 870 875 880

Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile
885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
900 905 910

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
915 920 925

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
930 935 940

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
945 950 955 960

Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
965 970 975

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
980 985 990

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
995 1000 1005

Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
1010 1015 1020

Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
1025 1030 1035

Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
1040 1045 1050

Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
1055 1060 1065

Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn
1070 1075 1080

Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys
1085 1090 1095

Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His
1100 1105 1110

Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln
1115 1120 1125

Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile
1130 1135 1140

Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg

1145 1150 1155

Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro
1160 1165 1170

Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His
1175 1180 1185

Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
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Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
1205 1210 1215

Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
1220 1225 1230

Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
1235 1240 1245

Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
1250 1255 1260

Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn
1265 1270 1275

Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp
1280 1285 1290

Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
1295 1300 1305

Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn
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Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
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Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly
1340 1345 1350

Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile
1355 1360 1365

Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn
1370 1375 1380

Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
1385 1390 1395

Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg
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tatgatacag tggtcattac acttaagaac atggcttccc atcctgtcag tcttcatgct 300

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gtatttgatg aagggaaaag ttggcactca gaaacaaaga actccttgat gcaggatagg 660

gatgctgcat ctgctcgggc ctggcctaaa atgcacacag tcaatggtta tgtaaacagg 720

tctctaccag gtctgattgg atgccacagg aaatcagtct attggcatgt gattggaatg 780

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acttgggtac attacattgc tgctgaagag gaggactggg actatgctcc cttagtcctc 1200

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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 Leu Asp
545 550 555 560

Gln Trp 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

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
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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
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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
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Gly Thr Lys Asn Phe Met Lys Asn Leu Phe Leu Leu Ser Thr Arg
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Gln Asn Val Glu Gly Ser Tyr Asp Gly Ala Tyr Ala Pro Val Leu
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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
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Gln Arg Ser Lys Arg Ala Leu Lys Gln Phe Arg Leu Pro Leu Glu
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Glu Thr Glu Leu Glu Lys Arg Ile Ile Val Asp Asp Thr Ser Thr

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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
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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
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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
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Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg Ser Thr Leu Arg
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Met Glu Leu Met Gly Cys Asp Leu Asn Ser Cys Ser Met Pro Leu
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Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser
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Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser Pro Ser Lys Ala

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Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln Val
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Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu Leu Thr
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Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly
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His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe
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Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val Asn Ser Leu Asp
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Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His Pro Gln Ser Trp
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atcgctaagc caaggccacc ctggatgggt ctgctaggtc ctaccatcca ggctgaggtt 240

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Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu Val
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Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val
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Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val
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His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser Trp
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His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala Ser
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Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met
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Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly Ile
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Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile

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Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile
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His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys
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Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu Ala
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Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp
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Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly Met Thr Ala
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Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp Tyr Tyr Glu
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Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala
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740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
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Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
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Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
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Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
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cagaagacaa tgaaagtcac aggagtaact actcagggag taaaatctct gcttaccagc 4080

atgtatgtga aggagttcct catctccagc agtcaagatg gccatcagtg gactctcttt 4140

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aactctctag acccaccgtt actgactcgc taccttcgaa ttcaccccca gagttgggtg 4260

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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 Val 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 Leu Asp
545 550 555 560

Gln Trp 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 Val 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 Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
805 810 815

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
835 840 845

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
865 870 875 880

Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile
885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
900 905 910

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
915 920 925

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
930 935 940

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
945 950 955 960

Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
965 970 975

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
980 985 990

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
995 1000 1005

Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
1010 1015 1020

Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
1025 1030 1035

Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
1040 1045 1050

Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
1055 1060 1065

Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn
1070 1075 1080

Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys
1085 1090 1095

Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His

1100 1105 1110

Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln
1115 1120 1125

Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile
1130 1135 1140

Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg
1145 1150 1155

Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro
1160 1165 1170

Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His
1175 1180 1185

Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
1190 1195 1200

Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
1205 1210 1215

Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
1220 1225 1230

Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
1235 1240 1245

Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
1250 1255 1260

Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn
1265 1270 1275

Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp
1280 1285 1290

Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
1295 1300 1305

Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn
1310 1315 1320

Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
1325 1330 1335

Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly
1340 1345 1350

Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile
1355 1360 1365

Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn
1370 1375 1380

Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
1385 1390 1395

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

Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu
1415 1420 1425

Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
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gatgctgcat ctgctcgggc ctggcctaaa atgcacacag tcaatggtta tgtaaacagg 720

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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 Leu Asp
545 550 555 560

Gln Arg Gly Asn Glu 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

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
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Gln Asp Phe Arg Ser Leu Asn Asp Ser Thr Asn Arg Thr Lys Lys
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Gln Ile Asp Tyr Asn Glu Lys Glu Lys Gly Ala Ile Thr Gln Ser
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Pro Leu Ser Asp Cys Leu Thr Arg Ser His Ser Ile Pro Gln Ala
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Ile Arg Pro Ile Tyr Leu Thr Arg Val Leu Phe Gln Asp Asn Ser
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Ser His Leu Pro Ala Ala Ser Tyr Arg Lys Lys Asp Ser Gly Val
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Gln Glu Ser Ser His Phe Leu Gln Gly Ala Lys Lys Asn Asn Leu
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Ser Leu Ala Ile Leu Thr Leu Glu Met Thr Gly Asp Gln Arg Glu
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Val Gly Ser Leu Gly Thr Ser Ala Thr Asn Ser Val Thr Tyr Lys
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Ser Gly Lys Val Glu Leu Leu Pro Lys Val His Ile Tyr Gln Lys
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Asp Leu Val Glu Gly Ser Leu Leu Gln Gly Thr Glu Gly Ala Ile
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Lys Trp Asn Glu Ala Asn Arg Pro Gly Lys Val Pro Phe Leu Arg
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Val Ala Thr Glu Ser Ser Ala Lys Thr Pro Ser Lys Leu Leu Asp
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Pro Leu Ala Trp Asp Asn His Tyr Gly Thr Gln Ile Pro Lys Glu
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Glu Trp Lys Ser Gln Glu Lys Ser Pro Glu Lys Thr Ala Phe Lys
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Lys Lys Asp Thr Ile Leu Ser Leu Asn Ala Cys Glu Ser Asn His
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Ala Ile Ala Ala Ile Asn Glu Gly Gln Asn Lys Pro Glu Ile Glu
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Val Thr Trp Ala Lys Gln Gly Arg Thr Glu Arg Leu Cys Ser Gln
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Asn Pro Pro Val Leu Lys Arg His Gln Arg Glu Ile Thr Arg Thr
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Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile
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Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp
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Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr
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Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser
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Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser Val Pro

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Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val
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Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser
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Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys
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Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His
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Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu
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1865 1870 1875

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

Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile Ala Lys Pro
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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
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Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met
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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
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Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn Asn Gly Pro

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

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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
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Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys
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Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu Ala
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Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Leu Asp
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Gln Arg Gly Asn Glu Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe
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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
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Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp Ser
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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
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Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro
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675 680 685

Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly Met Thr Ala
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Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp Tyr Tyr Glu
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Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala
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Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
805 810 815

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
835 840 845

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865 870 875 880

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Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
900 905 910

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
915 920 925

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
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Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
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Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
965 970 975

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
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Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
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Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
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Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
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Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
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Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
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Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile
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Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His
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Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
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Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
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Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
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Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
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Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
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Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn
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Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp
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Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
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Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn

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Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
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Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly
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Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile
1355 1360 1365

Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn
1370 1375 1380

Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
1385 1390 1395

Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg
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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
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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
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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
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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
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Trp Thr Val Thr Val Glu Val Gly Pro Thr Lys Ser Asp Pro Arg Cys
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Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu Ala
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Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Leu Asp
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Gln Arg Gly Asn Glu Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe
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Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu Asn Ile Gln
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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
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Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu
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Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr
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Thr Phe Lys His Lys Met Val Tyr Val 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
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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 Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
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Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
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Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
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885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
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Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
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Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
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Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
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Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile
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Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
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Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile Ala Lys Pro
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Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu Val
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Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val
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Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser Glu Gly Ala
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Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val
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Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu Asn
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Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu Ser
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His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala Leu
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Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr Leu
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His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser Trp
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His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala Ser
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Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn Arg
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Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val Tyr Trp His
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Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu
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Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile
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Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met
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Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg

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Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser Pro Ser Phe
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Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val His
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Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Leu Val Leu
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Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr
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Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly Ile
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Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile
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Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys Gly Val Lys
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His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys
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Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys
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Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu Ala
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Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu Asn Ile Gln
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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
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Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr
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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
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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

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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

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
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Arg Ala His Gly Pro Ala Leu Leu Thr Lys Asp Asn Ala Leu Phe Lys
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Val Ser Ile Ser Leu Leu Lys Thr Asn Lys Thr Ser Asn Asn Ser Ala
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Phe Lys Lys Val Thr Pro Leu Ile His Asp Arg Met Leu Met Asp
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Lys Asn Ala Thr Ala Leu Arg Leu Asn His Met Ser Asn Lys Thr
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Pro Ile Pro Pro Asp Ala Gln Asn Pro Asp Met Ser Phe Phe Lys
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Gly Lys Asn Ser Leu Asn Ser Gly Gln Gly Pro Ser Pro Lys Gln
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Pro Leu Ser Asp Cys Leu Thr Arg Ser His Ser Ile Pro Gln Ala
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Val Gly Ser Leu Gly Thr Ser Ala Thr Asn Ser Val Thr Tyr Lys
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Ser Gly Lys Val Glu Leu Leu Pro Lys Val His Ile Tyr Gln Lys
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Glu Trp Lys Ser Gln Glu Lys Ser Pro Glu Lys Thr Ala Phe Lys
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Lys Lys Asp Thr Ile Leu Ser Leu Asn Ala Cys Glu Ser Asn His
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Ala Ile Ala Ala Ile Asn Glu Gly Gln Asn Lys Pro Glu Ile Glu
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Val Thr Trp Ala Lys Gln Gly Arg Thr Glu Arg Leu Cys Ser Gln
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Asn Pro Pro Val Leu Lys Arg His Gln Arg Glu Ile Thr Arg Thr
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Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile
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Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp

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Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr
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Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser
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Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser Val Pro
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Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser Phe
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Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
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Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val
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Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser
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Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg
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Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys
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Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys
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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
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Asn Pro Ala His Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu
1865 1870 1875

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1895 1900 1905

Asp Pro Thr Phe Lys Glu Asn Tyr Arg Phe His Ala Ile Asn Gly
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His Ser Ile His Phe Ser Gly His Val Phe Thr Val Arg Lys Lys
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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
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Phe Leu Val Tyr Ser Asn Lys Cys Gln Thr Pro Leu Gly Met Ala
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Ser Gly His Ile Arg Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr
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Gly Gln Trp Ala Pro Lys Leu Ala Arg Leu His Tyr Ser Gly Ser
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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 Leu Asp
545 550 555 560

Gln Trp Gly Asn Glu 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 Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
805 810 815

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser

820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
835 840 845

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
865 870 875 880

Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile
885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
900 905 910

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
915 920 925

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
930 935 940

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
945 950 955 960

Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
965 970 975

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
980 985 990

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
995 1000 1005

Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
1010 1015 1020

Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
1025 1030 1035

Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
1040 1045 1050

Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
1055 1060 1065

Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn
1070 1075 1080

Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys
1085 1090 1095

Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His
1100 1105 1110

Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln
1115 1120 1125

Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile
1130 1135 1140

Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg
1145 1150 1155

Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro
1160 1165 1170

Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His
1175 1180 1185

Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
1190 1195 1200

Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
1205 1210 1215

Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
1220 1225 1230

Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
1235 1240 1245

Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
1250 1255 1260

Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn

1265 1270 1275

Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp
1280 1285 1290

Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
1295 1300 1305

Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn
1310 1315 1320

Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
1325 1330 1335

Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly
1340 1345 1350

Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile
1355 1360 1365

Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn
1370 1375 1380

Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
1385 1390 1395

Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg
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Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu
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Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
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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
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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
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Trp Thr Val Thr Val Glu Val Gly Pro Thr Lys Ser Asp Pro Arg Cys
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Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu Ala
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Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Leu Asp

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Gln Trp Gly Asn Glu Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe
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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 Val 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
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Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala
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Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
805 810 815

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
835 840 845

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
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Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile
885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
900 905 910

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
915 920 925

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
930 935 940

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
945 950 955 960

Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
965 970 975

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
980 985 990

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
995 1000 1005

Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg

1010 1015 1020

Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
1025 1030 1035

Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
1040 1045 1050

Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
1055 1060 1065

Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn
1070 1075 1080

Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys
1085 1090 1095

Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His
1100 1105 1110

Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln
1115 1120 1125

Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile
1130 1135 1140

Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg
1145 1150 1155

Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro
1160 1165 1170

Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His
1175 1180 1185

Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
1190 1195 1200

Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
1205 1210 1215

Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
1220 1225 1230

Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
1235 1240 1245

Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
1250 1255 1260

Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn
1265 1270 1275

Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp
1280 1285 1290

Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
1295 1300 1305

Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn
1310 1315 1320

Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
1325 1330 1335

Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly
1340 1345 1350

Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile
1355 1360 1365

Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn
1370 1375 1380

Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
1385 1390 1395

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

Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu
1415 1420 1425

Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
1430 1435

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aacacctcag tcgtgtacaa aaagactctg tttgtagaat tcacggatca ccttttcaac 180

atcgctaagc caaggccacc ctggatgggt ctgctaggtc ctaccatcca ggctgaggtt 240

tatgatacag tggtcattac acttaagaac atggcttccc atcctgtcag tcttcatgct 300

gttggtgtat cctactggaa agcttctgag ggagctgaat atgatgatca gaccagtcaa 360

agggagaaag aagatgataa agtcttccct ggtggaagcc atacatatgt ctggcaggtc 420

ctgaaagaga atggtccaat ggcctctgac ccactgtgcc ttacctactc atatctttct 480

catgtggacc tggtaaaaga cttgaattca ggcctcattg gagccctact agtatgtaga 540

gaagggagtc tggccaagga aaagacacag accttgcaca aatttatact acttttgct 600

gtatttgatg aagggaaaag ttggcactca gaaacaaaga actccttgat gcaggatagg 660

gatgctgcat ctgctcgggc ctggcctaaa atgcacacag tcaatggtta tgtaaacagg 720

tctctaccag gtctgattgg atgccacagg aaatcagtct attggcatgt gattggaatg 780

ggcaccactc ctgaagtgca ctcaatattc ctcgaaggtc acacatttct tgtgaggaac 840

catcgccagg cgtccttgga aatctcgcca ataactttcc ttactgctca aacactcttg 900

atggaccttg gacagtttct actgttttgt catatctctt cccaccaaca tgatggcatg 960

gaagcttatg tcaaagtaga cagctgtcca gaggaacccc aactacgaat gaaaaataat 1020

gaagaagcgg aagactatga tgatgatctt actgattctg aaatggatgt ggtcaggttt 1080

gatgatgaca actctccttc ctttatccaa attcgctcag ttgccaagaa gcatcctaaa 1140

acttgggtac attacattgc tgctgaagag gaggactggg actatgctcc cttagtcctc 1200

gcccccgatg acagaagtta taaaagtcaa tatttgaaca atggccctca gcggattggt 1260

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gctattcagc atgaatcagg aatcttggga cctttacttt atggggaagt tggagacaca 1380

ctgttgatta tatttaagaa tcaagcaagc agaccatata acatctaccc tcacggaatc 1440

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tttccaattc tgccaggaga aatattcaaa tataaatgga cagtgactgt agaagttggg 1560

ccaactaaat cagatccgcg gtgcctgacc cgctattact ctagtttcgt taatatggag 1620

agagatctag cttcaggact cattggccct ctcctcatct gctacaaaga atctctggat 1680

caatggggaa acgagataat gtcagacaag aggaatgtca tcctgttttc tgtatttgat 1740

gagaaccgaa gctggtacct cacagagaat atacaacgct ttctccccaa tccagctgga 1800

gtgcagcttg aggatccaga gttccaagcc tccaacatca tgcacagcat caatggctat 1860

gtttttgata gtttgcagtt gtcagtttgt ttgcatgagg tggcatactg gtacattcta 1920

agcattggag cacagactga cttcctttct gtcttcttct ctggatatac cttcaaacac 1980

aaaatggtct atgtagacac actcacccta ttcccattct caggagaaac tgtcttcatg 2040

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gacagttacg aagatatttc agcatacttg ctgagtaaaa acaatgccat tgaacctagg 2220

agcttctctc agaatccacc agtcttgaaa cgccatcaac gggaaataac tcgtacgact 2280

cttcagtcag atcaagagga aattgactat gatgatacca tatcagttga aatgaagaag 2340

gaagattttg acatttatga tgaggatgaa aatcagagcc cccgcagctt tcaaaagaaa 2400

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ccacatgttc taagaaacag ggctcagagt ggcagtgtcc ctcagttcaa gaaagttgtt 2520

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gatcagaggc aaggagcaga acctagaaaa aactttgtca agcctaatga aaccaaaact 2760

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cttctggtct gccacactaa cacactgaac cctgctcatg ggagacaagt gacagtacag 2940

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aattatcgct tccatgcaat caatggctac ataatggata cactacctgg cttagtaatg 3120

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ctggtgtaca gcaataagtg tcagactccc ctgggaatgg cttctggaca cattagagat 3420

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ataaaacaca atatttttaa ccctccaatt attgctcgat acatccgttt gcacccaact 3780

cattatagca ttcgcagcac tcttcgcatg gagttgatgg gctgtgattt aaatagttgc 3840

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tactttacca atatgtttgc cacctggtct ccttcaaaag ctcgacttca cctccaaggg 3960

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cagaagacaa tgaaagtcac aggagtaact actcagggag taaaatctct gcttaccagc 4080

atgtatgtga aggagttcct catctccagc agtcaagatg gccatcagtg gactctcttt 4140

tttcagaatg gcaaagtaaa ggtttttcag ggaaatcaag actccttcac acctgtggtg 4200

aactctctag acccaccgtt actgactcgc taccttcgaa ttcaccccca gagttgggtg 4260

caccagattg ccctgaggat ggaggttctg ggctgcgagg cacaggacct ctac 4314

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<212> PRT
<213> Artificial Sequence

<220>
<223> Variant peptide

<400> 43

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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 Leu Asp
545 550 555 560

Gln Phe Gly Asn Glu 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

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
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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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<220>
<223> Variant nucleotide

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His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser Trp
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Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly Ile
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His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys
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Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly Met Thr Ala
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Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp Tyr Tyr Glu
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Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala
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Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
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Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp

770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
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Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
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Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
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Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
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Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
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Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
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cagaagacaa tgaaagtcac aggagtaact actcagggag taaaatctct gcttaccagc 4080

atgtatgtga aggagttcct catctccagc agtcaagatg gccatcagtg gactctcttt 4140

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aactctctag acccaccgtt actgactcgc taccttcgaa ttcaccccca gagttgggtg 4260

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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 Val 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 Leu Asp
545 550 555 560

Gln Phe Gly Asn Glu 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 Val 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 Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
805 810 815

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
835 840 845

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
865 870 875 880

Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile
885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
900 905 910

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
915 920 925

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
930 935 940

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
945 950 955 960

Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln

965 970 975

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
980 985 990

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
995 1000 1005

Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
1010 1015 1020

Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
1025 1030 1035

Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
1040 1045 1050

Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
1055 1060 1065

Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn
1070 1075 1080

Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys
1085 1090 1095

Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His
1100 1105 1110

Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln
1115 1120 1125

Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile
1130 1135 1140

Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg
1145 1150 1155

Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro
1160 1165 1170

Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His
1175 1180 1185

Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
1190 1195 1200

Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
1205 1210 1215

Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
1220 1225 1230

Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
1235 1240 1245

Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
1250 1255 1260

Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn
1265 1270 1275

Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp
1280 1285 1290

Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
1295 1300 1305

Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn
1310 1315 1320

Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
1325 1330 1335

Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly
1340 1345 1350

Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile
1355 1360 1365

Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn
1370 1375 1380

Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
1385 1390 1395

Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg

1400 1405 1410

Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu
1415 1420 1425

Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
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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 Pro Arg Ser Phe 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
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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
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Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys
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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 Leu Asp
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Gln Trp Gly Asn Glu Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe
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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
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Tyr Asp Ser Gln Leu Asp Thr Thr Leu Phe Gly Lys Lys Ser Ser Pro
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Leu Thr Glu Ser Gly Gly Pro Leu Ser Leu Ser Glu Glu Asn Asn Asp
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Ser Lys Leu Leu Glu Ser Gly Leu Met Asn Ser Gln Glu Ser Ser Trp
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Gly Lys Asn Val Ser Ser Thr Glu Ser Gly Arg Leu Phe Lys Gly Lys
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Arg Ala His Gly Pro Ala Leu Leu Thr Lys Asp Asn Ala Leu Phe Lys
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Val Ser Ile Ser Leu Leu Lys Thr Asn Lys Thr Ser Asn Asn Ser Ala
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Thr Asn Arg Lys Thr His Ile Asp Gly Pro Ser Leu Leu Ile Glu
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Asn Ser Pro Ser Val Trp Gln Asn Ile Leu Glu Ser Asp Thr Glu
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Phe Lys Lys Val Thr Pro Leu Ile His Asp Arg Met Leu Met Asp
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Lys Asn Ala Thr Ala Leu Arg Leu Asn His Met Ser Asn Lys Thr
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Met Leu Phe Leu Pro Glu Ser Ala Arg Trp Ile Gln Arg Thr His
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Gln Asp Phe Arg Ser Leu Asn Asp Ser Thr Asn Arg Thr Lys Lys
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Asn Arg Ser Pro Leu Pro Ile Ala Lys Val Ser Ser Phe Pro Ser
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Ile Arg Pro Ile Tyr Leu Thr Arg Val Leu Phe Gln Asp Asn Ser
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Ser His Leu Pro Ala Ala Ser Tyr Arg Lys Lys Asp Ser Gly Val
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Gln Glu Ser Ser His Phe Leu Gln Gly Ala Lys Lys Asn Asn Leu
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Ser Leu Ala Ile Leu Thr Leu Glu Met Thr Gly Asp Gln Arg Glu
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Val Gly Ser Leu Gly Thr Ser Ala Thr Asn Ser Val Thr Tyr Lys
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Ser Gly Lys Val Glu Leu Leu Pro Lys Val His Ile Tyr Gln Lys
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Glu Trp Lys Ser Gln Glu Lys Ser Pro Glu Lys Thr Ala Phe Lys

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Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp
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Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr
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Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser Val Pro
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Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val
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Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser
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Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys
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Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu
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1865 1870 1875

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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
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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

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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
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Gly Gln Trp Ala Pro Lys Leu Ala Arg Leu His Tyr Ser Gly Ser
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Gly Ile Lys His Asn Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr
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Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly
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His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe
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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
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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
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Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met Asp Leu Gly
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Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met
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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
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Ile Gln Pro Arg Ser Phe Ala Lys Lys His Pro Lys Thr Trp Val His
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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
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Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys
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Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu Ala
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Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Leu Asp
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Gln Trp Gly Asn Glu Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe
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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
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Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp Ser
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Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu
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Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr
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Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro
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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 Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
805 810 815

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
835 840 845

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
865 870 875 880

Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile
885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
900 905 910

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
915 920 925

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
930 935 940

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
945 950 955 960

Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
965 970 975

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
980 985 990

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
995 1000 1005

Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
1010 1015 1020

Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
1025 1030 1035

Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
1040 1045 1050

Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
1055 1060 1065

Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn
1070 1075 1080

Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys
1085 1090 1095

Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His
1100 1105 1110

Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln
1115 1120 1125

Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile
1130 1135 1140

Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg
1145 1150 1155

Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro
1160 1165 1170

Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His

1175 1180 1185

Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
1190 1195 1200

Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
1205 1210 1215

Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
1220 1225 1230

Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
1235 1240 1245

Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
1250 1255 1260

Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn
1265 1270 1275

Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp
1280 1285 1290

Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
1295 1300 1305

Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn
1310 1315 1320

Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
1325 1330 1335

Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly
1340 1345 1350

Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile
1355 1360 1365

Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn
1370 1375 1380

Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
1385 1390 1395

Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg
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Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu
1415 1420 1425

Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
1430 1435

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atcgctaagc caaggccacc ctggatgggt ctgctaggtc ctaccatcca ggctgaggtt 240

tatgatacag tggtcattac acttaagaac atggcttccc atcctgtcag tcttcatgct 300

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gatgatgaca actctccttc ctttatccaa ccccgctcat tcgccaagaa gcatcctaaa 1140

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aactctctag acccaccgtt actgactcgc taccttcgaa ttcaccccca gagttgggtg 4260

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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 Pro Arg Ser Phe 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 Val 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 Leu Asp
545 550 555 560

Gln Trp Gly Asn Glu 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 Val 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 Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
805 810 815

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
835 840 845

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
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Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile
885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
900 905 910

Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His

915 920 925

Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
930 935 940

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro
945 950 955 960

Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln
965 970 975

Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
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Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
995 1000 1005

Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
1010 1015 1020

Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu
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Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
1040 1045 1050

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

Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His
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Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr
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Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
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Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
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Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
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Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
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Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp
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Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
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Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
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Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly
1340 1345 1350

Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile

1355 1360 1365

Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn
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Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro
1385 1390 1395

Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg
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Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
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Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile Ala Lys Pro
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Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu Val
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Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val
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Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser Glu Gly Ala
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Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val
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Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu Asn
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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
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His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala Ser
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Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn Arg
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Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met
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Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Ile
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Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp Leu Thr Asp
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Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser Pro Ser Phe
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Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr
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Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly Ile
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Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile
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Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile
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His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr Lys
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Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu Ala
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Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Leu Asp
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Gln Trp Gly Asn Glu Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe
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Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu Asn Ile Gln
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Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp Pro Glu Phe
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Thr Phe Lys His Lys Met Val Tyr Val 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
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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 Pro Pro Val Leu Lys Arg His
740 745 750

Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
755 760 765

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
770 775 780

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
785 790 795 800

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
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Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
820 825 830

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser
835 840 845

Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
850 855 860

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr
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885 890 895

Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe
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Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His
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Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
930 935 940

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Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro
995 1000 1005

Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg
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Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met
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Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val
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Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His

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Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe
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Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro
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Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser
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Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr
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Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val
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摘要

本公开涉及变体因子 VIII 多肽，其在凝血酶切割位点和活化环之一或两者中的一个或多个位置处包含氨基酸取代。在某些实施方案中，该变体因子 VIII 多肽包含在凝血酶切割位点和活化环两者中的一个或多个氨基酸取代。在进一步的实施方案中，所述变体因子 VIII 多肽还包含在 A1-A2 域界面和 A2-A3 域界面内的一个或多个氨基酸取代。本公开还涉及产生和 / 或使用这类变体因子 VIII 多肽的方法 ：编码该多肽的核酸 ；含有这类核酸的载体和 / 或重组细胞、组织或生物体 ；和含有这类多肽和 / 或核酸的试剂盒和药物组合物。