

(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 2019270184 B2**

(54) Title
Methods of treating hemophilia A

(51) International Patent Classification(s)
A61K 38/36 (2006.01) **A61P 7/04** (2006.01)
A61K 38/37 (2006.01)

(21) Application No: **2019270184** (22) Date of Filing: **2019.05.17**

(87) WIPO No: **WO19/222682**

(30) Priority Data

(31) Number	(32) Date	(33) Country
62/801,576	2019.02.05	US
62/712,880	2018.07.31	US
62/773,785	2018.11.30	US
62/673,670	2018.05.18	US

(43) Publication Date: **2019.11.21**

(44) Accepted Journal Date: **2025.05.22**

(71) Applicant(s)
Bioverativ Therapeutics Inc.

(72) Inventor(s)
INNES, Alison;KATRAGADDA, Suresh;RICE, Kara;RUDIN, Dan;SETH CHHABRA, Ekta;WONG, Nancy

(74) Agent / Attorney
Griffith Hack, Level 15 376-390 Collins St, MELBOURNE, VIC, 3000, AU

(56) Related Art
WO 2015/106052 A1
WO 2015/021423 A2
WO 2013/106787 A1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

21 November 2019 (21.11.2019)



(10) International Publication Number

WO 2019/222682 A1

(51) International Patent Classification:

A61K 38/36 (2006.01)

A61P 7/04 (2006.01)

A61K 38/37 (2006.01)

(21) International Application Number:

PCT/US2019/032956

(22) International Filing Date:

17 May 2019 (17.05.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/673,670 18 May 2018 (18.05.2018) US

62/712,880 31 July 2018 (31.07.2018) US

62/773,785 30 November 2018 (30.11.2018) US

62/801,576 05 February 2019 (05.02.2019) US

(71) Applicant: BIOVERATIV THERAPEUTICS INC.

[US/US]; 225 Second Avenue, Waltham, Massachusetts 02451 (US).

(72) Inventors: INNES, Alison; c/o Bioverativ Therapeutics

Inc., 225 Second Avenue, Waltham, Massachusetts 02451

(US). KATRAGADDA, Suresh; c/o Bioverativ Therapeu-

tics Inc., 225 Second Avenue, Waltham, Massachusetts

02451 (US). RICE, Kara; c/o Bioverativ Therapeutics Inc.,

225 Second Avenue, Waltham, Massachusetts 02451 (US).

RUDIN, Dan; c/o Bioverativ Therapeutics Inc., 225 Second

Avenue, Waltham, 02451 (US). SETH CHHABRA, Ekta;

1550 Worcester Road, Unit 128, Framingham, Massachu-

setts 01702 (US). WONG, Nancy; c/o Bioverativ Thera-

peutics Inc., 225 Second Avenue, Waltham, Massachusetts

02451 (US).

(74) Agent: VELEMA, James H.; 28 State Street, Boston,

Massachusetts 02109 (US).

(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,

CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,

DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,

HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP,

KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,

MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,

OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,

SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,

TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH,

GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,

(54) Title: METHODS OF TREATING HEMOPHILIA A

(57) Abstract: The present disclosure provides a method of treating hemophilia A in a human subject in need thereof comprising administering to the subject a chimeric polypeptide comprising (i) a factor VIII (FVIII) protein and (ii) a von Willebrand factor (VWF) fragment comprising a D' domain of VWF and a D3 domain of VWF at a dosing interval.



WO 2019/222682 A1

METHODS OF TREATING HEMOPHILIA A

REFERENCE TO PRIORITY APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 62/673,670, filed May 18, 2018, U.S. Provisional Application No. 62/712,880, filed July 31, 2018, U.S. Provisional Application No. 62/773,785 filed Nov. 30, 2018, and U.S. Provisional Application No. 62/801,576, filed Feb. 5, 2019, each of which are incorporated herein by reference in their entireties.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0002] The content of the electronically submitted sequence listing in ASCII text file (Name: SA9-461PC_SeqListing.txt; Size: 922 kilobytes; Date of Creation: May 14, 2019) is incorporated herein by reference in its entirety.

BACKGROUND OF THE DISCLOSURE

[0003] Hemophilia A is a bleeding disorder caused by defects in the gene encoding coagulation factor VIII (FVIII) and affects 1-2 in 10,000 male births. Graw *et al.*, *Nat. Rev. Genet.* 6(6): 488-501 (2005). Patients affected with hemophilia A can be treated with infusions of purified or recombinantly produced FVIII. Many commercially available FVIII products are known to have a half-life of about 8-12 hours, requiring frequent intravenous administration to the patients. See Weiner M.A. and Cairo, M.S., *Pediatric Hematology Secrets*, Lee, M.T., 12. Disorders of Coagulation, Elsevier Health Sciences, 2001; Lillicrap, D. *Thromb. Res.* 122 Suppl 4:S2-8 (2008). In addition, a number of approaches have been tried in order to extend the FVIII half-life. For example, the approaches in development to extend the half-life of clotting factors include pegylation, glycopegylation, and conjugation with albumin. See Dumont *et al.*, *Blood.* 119(13): 3024-3030 (2012). Consistent results have been demonstrated in humans, for example, rFVIIIIFc was reported to improve half-life up to ~1.7-fold compared with ADVATE® in hemophilia A patients. See Powell *et al.*, *Blood.* 119(13): 3031-3037 (2012). Therefore, the half-life increases, despite minor improvements, indicate the presence of other half-life limiting factors. See Liu, T. *et al.*, 2007 ISTH meeting, abstract #P-M-035; Henrik, A. *et al.*, 2011 ISTH meeting, abstract #P=MO-181; Liu, T. *et al.*, 2011 ISTH meeting abstract #P-WE-131.

[0004] The current recommended standard of care involves the regular administration (routine prophylaxis) of FVIII to minimize the number of bleeding episodes. Routine prophylaxis has been associated with improvements in long-term outcomes, but is a demanding regimen limited by the need for frequent intravenous (IV) administration. See Manco-Johnson et al., *N Engl J Med.* 357(6):535-44 (2007). Extended half-life FVIII products have reduced the frequency of FVIII administration for prophylaxis; however, all interact with von Willebrand factor (VWF) and have comparable circulating half-lives, consistent with an upper limit on the half-life of rFVIII variants due to the half-life of endogenous VWF. See, e.g., Pipe et al., *Blood.* 128(16):2007-16 (2016). Prophylactic dosing for these FVIII products is every 3 to 5 days.

[0005] Next-generation extended half-life FVIII products that prevent and control bleeding episodes for longer periods of time, resulting in less frequent administration, would potentially address the challenges of adherence to demanding prophylactic regimens, which in turn could improve the quality of life for hemophilia patients.

BRIEF SUMMARY OF THE DISCLOSURE

[0006] Certain aspects of the present disclosure are directed to a method of treating hemophilia A in a human subject in need thereof comprising administering to the subject multiple doses of a chimeric polypeptide comprising (i) a factor VIII (FVIII) protein and (ii) a von Willebrand factor (VWF) fragment comprising a D' domain of VWF and a D3 domain of VWF at a dosing interval, wherein at least one of the multiple doses is from about 15 IU/kg to about 100 IU/kg and the dosing interval is at least about every 7 days.

[0007] In some embodiments, the multiple doses comprise at least two doses, at least three doses, at least four doses, at least five doses, at least six doses, at least seven doses, at least eight doses, at least nine doses, at least ten doses, at least eleven doses, at least twelve doses, at least thirteen doses, at least fourteen doses, at least fifteen doses, at least sixteen doses, at least seventeen doses, at least eighteen doses, at least nineteen doses, at least twenty doses, or more.

[0008] In some embodiments, the treatment of hemophilia A comprises controlling or decreasing the incidence or frequency of a bleeding episode in a human subject in need thereof. In some embodiments, the treatment of hemophilia A comprises preventing or treating a bleeding episode in a human subject in need thereof.

[0009] In some embodiments, at least one of the multiple doses is from about 20 IU/kg to about 95 IU/kg, from about 20 IU/kg to about 90 IU/kg, from about 20 IU/kg to about 85 IU/kg, from about 20 IU/kg to about 80 IU/kg, from about 20 IU/kg to about 75 IU/kg, from about 20 IU/kg to about 70 IU/kg, from about 20 IU/kg to about 65 IU/kg, from about 20 IU/kg to about 60 IU/kg, from about 20 IU/kg to about 55 IU/kg, from about 20 IU/kg to about 50 IU/kg, from about 20 IU/kg to about 45 IU/kg, from about 20 IU/kg to about 40 IU/kg, from about 20 IU/kg to about 35 IU/kg, from about 20 IU/kg to about 30 IU/kg, or from about 20 IU/kg to about 25 IU/kg. In some embodiments, at least one of the multiple doses is from about 20 IU/kg to about 100 IU/kg, from about 25 IU/kg to about 100 IU/kg, from about 30 IU/kg to about 100 IU/kg, from about 35 IU/kg to about 100 IU/kg, from about 40 IU/kg to about 100 IU/kg, from about 45 IU/kg to about 100 IU/kg, from about 50 IU/kg to about 100 IU/kg, from about 55 IU/kg to about 100 IU/kg, from about 60 IU/kg to about 100 IU/kg, from about 65 IU/kg to about 100 IU/kg, from about 70 IU/kg to about 100 IU/kg, from about 75 IU/kg to about 100 IU/kg, from about 80 IU/kg to about 100 IU/kg, from about 85 IU/kg to about 100 IU/kg, or from about 90 IU/kg to about 100 IU/kg.

[0010] In some embodiments, at least one of the multiple doses is from about 20 IU/kg to about 80 IU/kg, from about 25 IU/kg to about 75 IU/kg, from about 30 IU/kg to about 70 IU/kg, from about 35 IU/kg to about 65 IU/kg, from about 40 IU/kg to about 60 IU/kg, or from about 45 IU/kg to about 55 IU/kg. In some embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg.

[0011] In some embodiments, at least one of the multiple doses is about 20 IU/kg, about 25 IU/kg, about 30 IU/kg, about 35 IU/kg, about 40 IU/kg, about 45 IU/kg, about 50 IU/kg, about 55 IU/kg, about 60 IU/kg, about 65 IU/kg, about 70 IU/kg, about 75 IU/kg, about 80 IU/kg, about 85 IU/kg, about 90 IU/kg, about 95 IU/kg, or about 100 IU/kg. In some embodiments, at least one of the multiple doses is about 25 IU/kg. In some embodiments, at least one of the multiple doses is about 50 IU/kg. In some embodiments, at least one of the multiple doses is about 65 IU/kg. In some embodiments, at least one of the multiple doses is about 80 IU/kg.

[0012] In some embodiments, the dosing interval is at least about 5 days, at least about 6 days, at least about 7 days, at least about 8 days, at least about 9 days, at least about 10 days, at least about 11 days, at least about 12 days, at least about 13 days, at least about 14 days, at least about 15 days, at least about 16 days, at least about 17 days, at least about 18 days, at least about 19 days, at least about 20 days, at least about 21 days, at least about 22 days, at least about 23 days, at least

about 24 days, at least about 25 days, at least about 26 days, at least about 27 days, at least about 28 days, at least about 29 days, at least about 30 days, or at least about 31 days.

[0013] In some embodiments, the dosing frequency is at least once every week, at least once every 2 weeks, at least once every 3 weeks, or at least once every 4 weeks. In some embodiments, the dosing interval is at least once every week. In some embodiments, the dosing interval is at least once every two weeks.

[0014] In some embodiments, the chimeric polypeptide is administered for prophylactic treatment.

[0015] In some embodiments, the FVIII protein is associated with the VWF fragment by a covalent bond. In some embodiments, the covalent bond is a peptide bond or a disulfide bond.

[0016] In some embodiments, the FVIII protein comprises a FVIII polypeptide and a first half-life extending moiety. In some embodiments, the first half-life extending moiety is fused to the C-terminus or the N-terminus of the FVIII polypeptide. In some embodiments, the first half-life extending moiety is inserted within the FVIII polypeptide. In some embodiments, the first half-life extending moiety is inserted within the B domain of the FVIII polypeptide. In some embodiments, the first half-life extending moiety is inserted within the FVIII polypeptide immediately downstream of an amino acid corresponding to amino acid residue 745 of SEQ ID NO: 65. In some embodiments, the first half-life extending moiety is fused to the FVIII polypeptide by a linker.

[0017] In some embodiments, the VWF fragment comprises a second half-life extending moiety. In some embodiments, the second half-life extending moiety is fused to the C-terminus or the N-terminus of the VWF fragment. In some embodiments, the second half-life extending moiety is inserted within the VWF fragment. In some embodiments, the second half-life extending moiety is fused to the C-terminus of the VWF fragment. In some embodiments, the second half-life extending moiety is fused to the VWF fragment by a linker.

[0018] In some embodiments, the first half-life extending moiety, the second half-life extending moiety, or both is selected from the group consisting of an albumin, an immunoglobulin Fc region, an XTEN sequence, the C-terminal peptide (CTP) of the β subunit of human chorionic gonadotropin, a PAS sequence, a HAP sequence, a transferrin, albumin-binding moieties, or any fragments, derivatives, variants, and any combination thereof.

[0019] In some embodiments, the first half-life extending moiety comprises a first XTEN.

[0020] In some embodiments, the first XTEN is inserted within the FVIII polypeptide immediately downstream of an amino acid corresponding to amino acid residue 745 of SEQ ID NO: 65.

[0021] In some embodiments, the second half-life extending moiety comprises a second XTEN. In some embodiments, the second XTEN is fused to the C-terminus of the VWF fragment.

5 [0022] In some embodiments, the FVIII protein comprises a first immunoglobulin (Ig) constant region or a portion thereof. In some embodiments, the first Ig constant region or the portion thereof is fused to the C-terminus or the N-terminus of the FVIII polypeptide. In some embodiments, the first Ig constant region or the portion thereof is inserted within the FVIII polypeptide. In some embodiments, the first Ig constant region or the portion thereof is fused to the C-terminus of the FVIII polypeptide.
10 In some embodiments, the first Ig constant region or the portion thereof is fused to the FVIII polypeptide by a linker. In some embodiments, the first Ig constant region or the portion thereof comprises a first Fc domain or a portion thereof.

[0023] In some embodiments, the VWF fragment comprises a second Ig constant region or a portion thereof. In some embodiments, the second Ig constant region or the portion thereof is fused to the C-terminus or the N-terminus of the VWF fragment. In some embodiments, the second Ig constant region or the portion thereof is inserted within the VWF fragment. In some embodiments, the second Ig constant region or the portion thereof is fused to the C-terminus of the VWF fragment. In some embodiments, the second Ig constant region or the portion thereof is fused to the VWF fragment by a linker. In some embodiments, the linker is a cleavable linker. In some embodiments,
15 the second Ig constant region or the portion thereof comprises a second Fc domain or a portion thereof.
20

[0024] In some embodiments, the FVIII protein and the VWF fragment are associated with each other through a covalent bond between the first Fc domain and the second Fc domain. In some embodiments, the FVIII protein and the VWF fragment are further associated with each other through
25 a non-covalent interaction between the FVIII protein and the VWF fragment.

[0025] In one aspect, disclosed herein is a method of treating hemophilia A in a human subject comprising administering to the subject in need thereof multiple doses of a chimeric polypeptide at a dosing interval, wherein the chimeric polypeptide comprises: (i) a FVIII protein comprising a first FVIII polypeptide fragment comprising the amino acid sequence of SEQ ID NO: 215; a first XTEN sequence
30 comprising the amino acid sequence of SEQ ID NO: 8 (AE288); a second FVIII polypeptide fragment comprising the amino acid sequence of SEQ ID NO: 216; and a first Fc region comprising the amino

acid sequence of SEQ ID NO: 217; and (ii) a VWF protein comprising: a D' domain of VWF comprising the amino acid sequence of SEQ ID NO: 210; a D3 domain of VWF comprising the amino acid sequence of SEQ ID NO: 214; a second XTEN sequence comprising the amino acid sequence of SEQ ID NO: 58 (AE144_5A); an a2 linker comprising the amino acid sequence of SEQ ID NO: 88; and a second Fc region comprising the amino acid sequence of SEQ ID NO: 217, and wherein the first Fc region is covalently linked to the second Fc region by a disulfide bond.

[0026] In some embodiments, the chimeric polypeptide comprises a FVIII protein comprising a FVIII polypeptide, a first XTEN sequence, a first Fc region, and a VWF protein comprising a D' domain of VWF, a D3 domain of VWF, a second XTEN sequence, an a2 linker of FVIII and a second Fc region, wherein the FVIII polypeptide comprises the amino acid sequence of SEQ ID NO: 215, the first XTEN sequence comprises the amino acid sequence of AE288 (SEQ ID NO: 8) and is fused to the C-terminus of SEQ ID NO: 215, the FVIII polypeptide further comprises the amino acid sequence of SEQ ID NO: 216, the first Fc region comprises the amino acid sequence of SEQ ID NO: 217 and is fused to the C-terminus of SEQ ID NO: 216; the D' domain of VWF comprises the amino acid sequence of SEQ ID NO: 210; the D3 domain of VWF comprises the amino acid sequence of SEQ ID NO: 214, the second XTEN sequence comprises the amino acid sequence of AE144_5A (SEQ ID NO: 58) and is fused to the C-terminus of the D3 domain of VWF; the a2 linker comprises the amino acid sequence of SEQ ID NO: 88 and is fused to the C-terminus of the second XTEN sequence; the second Fc region comprises the amino acid sequence of SEQ ID NO: 217 and is fused to the C-terminus of the a2 linker; and wherein the first Fc region is covalently linked to the second Fc region by a disulfide bond.

[0027] In some embodiments, the chimeric polypeptide comprises a FVIII protein comprising a FVIII signal peptide comprising the amino acid sequence of SEQ ID NO: 64. In some embodiments, the chimeric polypeptide comprises a VWF protein comprising a VWF signal peptide comprising the amino acid sequence of SEQ ID NO: 208. In some embodiments, the chimeric polypeptide comprises a VWF protein comprising a D1D2 domain of VWF comprising the amino acid sequence of SEQ ID NO: 209.

[0028] In some embodiments, the chimeric polypeptide comprises a FVIII protein comprising an amino acid sequence at least about 80%, 90%, 95%, or 100% identical to SEQ ID NO: 201, SEQ ID NO: 203, or SEQ ID NO: 207; and a VWF protein comprising an amino acid sequence at least about 80%, 90%, 95%, or 100% identical to SEQ ID NO: 202 or SEQ ID NO: 205.

[0029] In one embodiment, the chimeric polypeptide comprises a FVIII protein comprising the amino acid sequence of SEQ ID NO: 203 and a VWF protein comprising the amino acid sequence of SEQ ID NO: 205. In another embodiment, the chimeric polypeptide comprises a FVIII protein comprising the amino acid sequence of SEQ ID NO: 201 and a VWF protein comprising the amino acid sequence of SEQ ID NO: 202. In another embodiment, the chimeric polypeptide comprises a FVIII protein comprising the amino acid sequence of SEQ ID NO: 207 and a VWF protein comprising the amino acid sequence of SEQ ID NO: 202.

[0030] In some embodiments, the chimeric polypeptide comprises a FVIII protein comprising an amino acid sequence at least about 80%, 90%, 95%, or 100% identical to a sequence selected from FVIII-161 (SEQ ID NO: 69), FVIII-169 (SEQ ID NO: 70), FVIII-170 (SEQ ID NO: 71), FVIII-173 (SEQ ID NO: 72); FVIII-195 (SEQ ID NO: 73); FVIII-196 (SEQ ID NO: 74), FVIII-199 (SEQ ID NO: 75), FVIII-201 (SEQ ID NO: 76); FVIII-203 (SEQ ID NO: 77), FVIII-204 (SEQ ID NO: 78), FVIII-205 (SEQ ID NO: 79), FVIII-266 (SEQ ID NO: 80), FVIII-267 (SEQ ID NO: 81), FVIII-268 (SEQ ID NO: 82), FVIII-269 (SEQ ID NO: 83), FVIII-271 (SEQ ID NO: 84), FVIII-272 (SEQ ID NO: 85), FVIII-312 (SEQ ID NO: 173), or FVIII-312A (SEQ ID NO: 203); and a VWF protein comprising an amino acid sequence at least about 80%, 90%, 95%, or 100% identical to a sequence selected from VWF031 (SEQ ID NO: 86), VWF034 (SEQ ID NO: 87), VWF059 (SEQ ID NO: 197), VWF059A (SEQ ID NO: 202), or VWF036.

[0031] In some embodiments, the chimeric polypeptide is administered by a route selected from the group consisting of intravenous injection, intravenous infusion, subcutaneous administration, intramuscular administration, oral administration, nasal administration, and pulmonary administration.

[0032] In some embodiments, the chimeric polypeptide after the administration results in a FVIII plasma activity level of at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, or at least about 10%. In some embodiments, the FVIII plasma activity level is at least about 3%. In some embodiments, the FVIII plasma activity level is at least about 5%.

[0033] In some embodiments, the chimeric polypeptide after the administration results in a FVIII plasma activity level of at least about 1 IU/dL, at least about 2 IU/dL, at least about 3 IU/dL, at least about 4 IU/dL, at least about 5 IU/dL, at least about 6 IU/dL, at least about 7 IU/dL, at least about 8 IU/dL, at least about 9 IU/dL, or at least about 10 IU/dL. In some embodiments, the FVIII plasma

activity level is at least about 3 IU/dL. In some embodiments, the FVIII plasma activity level is at least about 5 IU/dL.

[0034] In some embodiments, the FVIII plasma activity level is at least about 10 IU/dL at least about 5 days after the administration of the chimeric polypeptide. In some embodiments, the FVIII plasma activity level is at least about 5 IU/dL at least about 7 days after the administration of the chimeric polypeptide. In some embodiments, the FVIII plasma activity level is at least about 3 IU/dL at least about 8 days after the administration of the chimeric polypeptide. In some embodiments, the FVIII plasma activity level is at least about 1 IU/dL at least about 10 days after the administration of the chimeric polypeptide.

[0035] In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 80 IU/kg. In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 65 IU/kg. In some embodiments, at least one of the multiple doses is from about 65 IU/kg to about 80 IU/kg. In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 80 IU/kg, and the dosing interval is at least about 7 days. In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 65 IU/kg, and the dosing interval is at least about 5 days. In some embodiments, at least one of the multiple doses is from about 65 IU/kg to about 80 IU/kg, and the dosing interval is at least about 5 days.

[0036] In some embodiments, at least one of the multiple doses is about 50 IU/kg. In some embodiments, the multiple doses are about 50 IU/kg, and the dosing interval is about 5 days. In some embodiments, the multiple doses are about 50 IU/kg, and the dosing interval is about 7 days. In some embodiments, the multiple doses are about 50 IU/kg, and the dosing interval is about 14 days.

[0037] In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 80 IU/kg. In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 65 IU/kg. In some embodiments, at least one of the multiple doses is from about 65 IU/kg to about 80 IU/kg. In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 80 IU/kg, and the dosing interval is at least about 7 days. In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 65 IU/kg, and the dosing interval is at least about 7 days. In some embodiments, at least one of the multiple doses is from about 65 IU/kg to about 80 IU/kg, and the dosing interval is at least about 7 days.

[0038] In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 80 IU/kg, and the dosing interval is at least about 10 days. In some embodiments, at least one of the

multiple doses is from about 50 IU/kg to about 65 IU/kg, and the dosing interval is at least about 10 days. In some embodiments, at least one of the multiple doses is from about 65 IU/kg to about 80 IU/kg, and the dosing interval is at least about 10 days.

[0039] In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 80 IU/kg, and the dosing interval is at least about 14 days. In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 65 IU/kg, and the dosing interval is at least about 14 days. In some embodiments, at least one of the multiple doses is from about 65 IU/kg to about 80 IU/kg, and the dosing interval is at least about 14 days.

[0040] In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 80 IU/kg, and the dosing interval is at least about 1 week. In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 65 IU/kg, and the dosing interval is at least about 1 week. In some embodiments, at least one of the multiple doses is from about 65 IU/kg to about 80 IU/kg, and the dosing interval is at least about 1 week.

[0041] In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 80 IU/kg, and the dosing interval is at least about 2 weeks. In some embodiments, at least one of the multiple doses is from about 50 IU/kg to about 65 IU/kg, and the dosing interval is at least about 2 weeks. In some embodiments, at least one of the multiple doses is from about 65 IU/kg to about 80 IU/kg, and the dosing interval is at least about 2 weeks.

[0042] In some embodiments, the dosing interval is at least about 5 days. In some embodiments, the dosing interval is at least about 7 days. In some embodiments, the dosing interval is about 5 days to about 14 days. In some embodiments, the dosing interval is about 7 days to about 14 days. In some embodiments, the dosing interval is at least about 10 days. In some embodiments, the dosing interval is about 10 days to about 21 days. In some embodiments, the dosing interval is about 14 days to about 21 days. In some embodiments, the dosing interval is about 14 days.

[0043] In some embodiments, the human subject is a female. In some embodiments, the human subject is a child. In some embodiments, the human subject is a child less than or equal to about 12 years old, less than about 11 years old, less than about 10 years old, less than about 9 years old, less than about 8 years old, less than about 7 years old, less than about 6 years old, less than about 5 years old, less than about 4 years old, less than about 3 years old, less than about 2 years old, or less than about 1 year old.

[0044] In some embodiments, the administration induces immune tolerance to FVIII in the human subject. In some embodiments, the administration reduces an inhibitory immune response to FVIII in the human subject. In some embodiments, the inhibitory immune response to FVIII comprises a high titer of anti-FVIII antibodies in the human subject.

5 **[0045]** In some embodiments, administration of the chimeric polypeptide induces no FVIII inhibitor after about 7 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 15 days, about 20 days, about 24 days, about 25 days, about 28 days, about 30 days, or about 35 days of the administration. In some embodiments, administration of the chimeric polypeptide induces no FVIII inhibitor after about 28 days of the administration.

10 BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0046] FIG. 1 is a schematic representation of rFVIII₁₋₂Fc-VWF-XTEN. FVIII: factor VIII; VWF: von Willebrand Factor; A1, A2, A3, C1, C2: domains of FVIII; D'D3: domains of VWF; Fc: Fc region of immunoglobulin constant region.

15 **[0047]** FIGS. 2A and 2B show the protocol for testing the safety and efficacy of rFVIII₁₋₂Fc-VWF-XTEN in human patients in a low-dose cohort administered 25 IU/kg rFVIII₁₋₂Fc-VWF-XTEN (FIG. 2A) and a high-dose cohort administered 65 IU/kg rFVIII₁₋₂Fc-VWF-XTEN (FIG. 2B).

20 **[0048]** FIGS. 3A-3B are graphical representations of the baseline-corrected FVIII activity levels based on an activated partial thromboplastin time (aPTT) test in human subjects with severe hemophilia A administered 25 IU/kg rFVIII followed by a washout period and then 25 IU/kg rFVIII₁₋₂Fc-VWF-XTEN (FIG. 3A; low dose cohort) or 65 IU/kg rFVIII followed by a washout period and then 65 IU/kg rFVIII₁₋₂Fc-VWF-XTEN (FIG. 3B; high dose cohort). Horizontal dashed lines indicate 3%, 5%, 10%, and 20% FVIII activity.

25 **[0049]** FIG. 4 is a schematic representation of the design of a clinical study to assess the safety and tolerability of a total of four once-weekly doses of rFVIII₁₋₂Fc-VWF-XTEN at a dose of 50 IU/kg or 65 IU/kg in adult male, previously treated patients (PTPs), 18 to 65 years of age (inclusive), with severe hemophilia A. EOS = End of Study; ET = Early Termination; PK = Pharmacokinetics.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0050] The present disclosure is directed to a method of treating a bleeding disease or condition, e.g., hemophilia A, in a human subject in need thereof comprising administering to the subject multiple doses of a chimeric polypeptide comprising (i) a factor VIII (FVIII) polypeptide and (ii) a von Willebrand factor (VWF) fragment comprising a D' domain of VWF and a D3 domain of VWF at a dosing interval. In some embodiments, at least one of the multiple doses is from about 15 IU/kg to about 100 IU/kg. In some embodiments, the dosing interval is at least about every 5 days. In some embodiments, the dosing interval is at least about every 7 days.

I. Definitions

[0051] It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, "a nucleotide sequence," is understood to represent one or more nucleotide sequences. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

[0052] Furthermore, "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0053] It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0054] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[0055] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. Unless otherwise indicated, amino acid sequences are written left to right in amino to carboxy orientation. The headings

provided herein are not limitations of the various aspects of the disclosure. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.

[0056] The term "about" is used herein to mean approximately, roughly, around, or in the regions of. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" can modify a numerical value above and below the stated value by a variance of, e.g., 10 percent, up or down (higher or lower).

[0057] The term "polynucleotide" or "nucleotide" is intended to encompass a singular nucleic acid as well as plural nucleic acids, and refers to an isolated nucleic acid molecule or construct, e.g., messenger RNA (mRNA) or plasmid DNA (pDNA). In certain embodiments, a polynucleotide comprises a conventional phosphodiester bond or a non-conventional bond (e.g., an amide bond, such as found in peptide nucleic acids (PNA)). The term "nucleic acid" refers to any one or more nucleic acid segments, e.g., DNA or RNA fragments, present in a polynucleotide. By "isolated" nucleic acid or polynucleotide is intended a nucleic acid molecule, DNA or RNA, which has been removed from its native environment. For example, a recombinant polynucleotide encoding a Factor VIII polypeptide contained in a vector is considered isolated for the purposes of the present disclosure. Further examples of an isolated polynucleotide include recombinant polynucleotides maintained in heterologous host cells or purified (partially or substantially) from other polynucleotides in a solution. Isolated RNA molecules include *in vivo* or *in vitro* RNA transcripts of polynucleotides of the present disclosure. Isolated polynucleotides or nucleic acids according to the present disclosure further include such molecules produced synthetically. In addition, a polynucleotide or a nucleic acid can include regulatory elements such as promoters, enhancers, ribosome binding sites, or transcription termination signals.

[0058] Certain proteins secreted by mammalian cells are associated with a secretory signal peptide which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Those of ordinary skill in the art are aware that signal peptides are generally fused to the N-terminus of the polypeptide, and are cleaved from the complete or "full-length" polypeptide to produce a secreted or "mature" form of the polypeptide. In certain embodiments, a native signal peptide or a functional derivative of that sequence that retains the ability to direct the secretion of the polypeptide that is operably associated with it. Alternatively, a heterologous mammalian signal peptide, e.g., a human tissue plasminogen activator (TPA) or mouse β -glucuronidase signal peptide, or a functional derivative thereof, can be used.

[0059] As used herein, the term "polypeptide" is intended to encompass a singular "polypeptide" as well as plural "polypeptides," and refers to a molecule composed of monomers (amino acids) linearly linked by amide bonds (also known as peptide bonds). The term "polypeptide" refers to any chain or chains of two or more amino acids, and does not refer to a specific length of the product. Thus, peptides, dipeptides, tripeptides, oligopeptides, "protein," "amino acid chain," or any other term used to refer to a chain or chains of two or more amino acids, are included within the definition of "polypeptide," and the term "polypeptide" can be used instead of, or interchangeably with any of these terms. The term "polypeptide" is also intended to refer to the products of post-expression modifications of the polypeptide, including without limitation glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, or modification by non-naturally occurring amino acids. A polypeptide can be derived from a natural biological source or produced recombinant technology, but is not necessarily translated from a designated nucleic acid sequence. It can be generated in any manner, including by chemical synthesis.

[0060] An "isolated" polypeptide or a fragment, variant, or derivative thereof refers to a polypeptide that is not in its natural milieu. No particular level of purification is required. For example, an isolated polypeptide can simply be removed from its native or natural environment. Recombinantly produced polypeptides and proteins expressed in host cells are considered isolated for the purpose of the disclosure, as are native or recombinant polypeptides which have been separated, fractionated, or partially or substantially purified by any suitable technique.

[0061] Also included in the present disclosure are fragments or variants of polypeptides, and any combination thereof. The term "fragment" or "variant" when referring to polypeptide binding domains or binding molecules of the present disclosure include any polypeptides which retain at least some of the properties (e.g., FcRn binding affinity for an FcRn binding domain or Fc variant, coagulation activity for an FVIII variant, or FVIII binding activity for the VWF fragment) of the reference polypeptide. Fragments of polypeptides include proteolytic fragments, as well as deletion fragments, in addition to specific antibody fragments discussed elsewhere herein, but do not include the naturally occurring full-length polypeptide (or mature polypeptide). Variants of polypeptide binding domains or binding molecules of the present disclosure include fragments as described above, and also polypeptides with altered amino acid sequences due to amino acid substitutions, deletions, or insertions. Variants can be naturally or non-naturally occurring. Non-naturally occurring variants can

be produced using art-known mutagenesis techniques. Variant polypeptides can comprise conservative or non-conservative amino acid substitutions, deletions or additions.

[0062] The term "VWF protein" or "VWF proteins" used herein means any VWF fragments that interact with FVIII and retain at least one or more properties that are normally provided to FVIII by full-length VWF, *e.g.*, preventing premature activation to FVIIIa, preventing premature proteolysis, preventing association with phospholipid membranes that could lead to premature clearance, preventing binding to FVIII clearance receptors that can bind naked FVIII but not VWF-bound FVIII, and/or stabilizing the FVIII heavy chain and light chain interactions. A VWF fragment referred to herein is a VWF polypeptide that is less than the full-length VWF protein, wherein the VWF fragment retains the ability to interact with and/or bind to FVIII.

[0063] A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, if an amino acid in a polypeptide is replaced with another amino acid from the same side chain family, the substitution is considered to be conservative. In other embodiments, a string of amino acids can be conservatively replaced with a structurally similar string that differs in order and/or composition of side chain family members.

[0064] As known in the art, "sequence identity" between two polypeptides is determined by comparing the amino acid sequence of one polypeptide to the sequence of a second polypeptide. When discussed herein, whether any particular polypeptide is at least about 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or 100% identical to another polypeptide can be determined using methods and computer programs/software known in the art such as, but not limited to, the BESTFIT program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). BESTFIT uses the local homology algorithm of Smith and Waterman, *Advances in Applied Mathematics* 2:482-489 (1981), to find the best segment of homology between two sequences. When using BESTFIT or any other sequence alignment program to determine whether a particular sequence is, for example, 95% identical to a reference sequence according to the present disclosure, the parameters are set, of

course, such that the percentage of identity is calculated over the full-length of the reference polypeptide sequence and that gaps in homology of up to 5% of the total number of amino acids in the reference sequence are allowed.

[0065] As used herein, an "amino acid corresponding to" or an "equivalent amino acid" in a VWF sequence or a FVIII protein sequence is identified by alignment to maximize the identity or similarity between a first VWF or FVIII sequence and a second VWF or FVIII sequence. The number used to identify an equivalent amino acid in a second VWF or FVIII sequence is based on the number used to identify the corresponding amino acid in the first VWF or FVIII sequence.

[0066] As used herein, the term "insertion site" refers to a position in a FVIII polypeptide, or fragment, variant, or derivative thereof, which is immediately downstream of the position at which a half-life extending moiety or heterologous moiety can be inserted. An "insertion site" is specified as a number, the number being the number of the amino acid in mature native FVIII (SEQ ID NO: 65) to which the insertion site corresponds, which is immediately C-terminal to the position of the insertion. For example, the phrase "a3 comprises an XTEN at an insertion site which corresponds to amino acid 1656 of SEQ ID NO: 65" indicates that the heterologous moiety is located between two amino acids corresponding to amino acid 1656 and amino acid 1657 of SEQ ID NO: 65.

[0067] The phrase "immediately downstream of an amino acid" as used herein refers to position right next to the terminal carboxyl group of the amino acid. For example, an insertion site immediately downstream of amino acid 745 corresponding to the mature wild type FVIII protein means that the insertion site is between amino acid 745 and amino acid 746 corresponding to the mature wild type FVIII protein. Similarly, the phrase "immediately upstream of an amino acid" refers to the position right next to the terminal amine group of the amino acid.

[0068] The phrase "between two amino acids of an insertion site" as used herein refers to a position in which an XTEN or any other polypeptide is inserted between two adjacent amino acids. Thus, the phrases "inserted immediately downstream of an amino acid" and "inserted between two amino acids of an insertion site" are used synonymously with "inserted at an insertion site."

[0069] The terms "inserted," "is inserted," "inserted into" or grammatically related terms, as used herein refers to the position of an XTEN in a chimeric polypeptide relative to the analogous position in native mature human FVIII. As used herein the terms refer to the characteristics of the recombinant FVIII polypeptide relative to native mature human FVIII, and do not indicate, imply or infer any methods or process by which the chimeric polypeptide was made. For example, in reference to a

chimeric polypeptide provided herein, the phrase "an XTEN is inserted into immediately downstream of residue 745 of the FVIII polypeptide" means that the chimeric polypeptide comprises an XTEN immediately downstream of an amino acid which corresponds to amino acid 745 in native mature human FVIII, *e.g.*, bounded by amino acids corresponding to amino acids 745 and 746 of native mature human FVIII.

[0070] A "fusion" or "chimeric" protein comprises a first amino acid sequence linked to a second amino acid sequence with which it is not naturally linked in nature. The amino acid sequences which normally exist in separate proteins can be brought together in the fusion polypeptide, or the amino acid sequences which normally exist in the same protein can be placed in a new arrangement in the fusion polypeptide, *e.g.*, fusion of a Factor VIII domain of the disclosure with an Ig Fc domain. A fusion protein is created, for example, by chemical synthesis, or by creating and translating a polynucleotide in which the peptide regions are encoded in the desired relationship. A chimeric polypeptide can further comprise a second amino acid sequence associated with the first amino acid sequence by a covalent, non-peptide bond or a non-covalent bond.

[0071] The term "linked" as used herein refers to a first amino acid sequence or nucleotide sequence covalently or non-covalently joined to a second amino acid sequence or nucleotide sequence, respectively. The first amino acid or nucleotide sequence can be directly joined or juxtaposed to the second amino acid or nucleotide sequence or alternatively an intervening sequence can covalently join the first sequence to the second sequence. The term "linked" means not only a fusion of a first amino acid sequence to a second amino acid sequence at the C-terminus or the N-terminus, but also includes insertion of the whole first amino acid sequence (or the second amino acid sequence) into any two amino acids in the second amino acid sequence (or the first amino acid sequence, respectively). In some embodiments, the first amino acid sequence can be linked to a second amino acid sequence by a peptide bond or a linker. The first nucleotide sequence can be linked to a second nucleotide sequence by a phosphodiester bond or a linker. The linker can be a peptide or a polypeptide (for polypeptide chains) or a nucleotide or a nucleotide chain (for nucleotide chains) or any chemical moiety (for both polypeptide and polynucleotide chains). The term "linked" is also indicated by a hyphen (-).

[0072] As used herein the term "associated with" refers to a covalent or non-covalent bond formed between a first amino acid chain and a second amino acid chain. In some embodiments, the term "associated with" means a covalent, non-peptide bond or a non-covalent bond. This association can be indicated by a colon, *i.e.*, (:). In other embodiments, it means a covalent bond except a peptide

bond. For example, the amino acid cysteine comprises a thiol group that can form a disulfide bond or bridge with a thiol group on a second cysteine residue. In most naturally occurring IgG molecules, the CH1 and CL regions are associated by a disulfide bond and the two heavy chains are associated by two disulfide bonds at positions corresponding to 239 and 242 using the Kabat numbering system (position 226 or 229, EU numbering system). Examples of covalent bonds include, but are not limited to, a peptide bond, a metal bond, a hydrogen bond, a disulfide bond, a sigma bond, a pi bond, a delta bond, a glycosidic bond, an agnostic bond, a bent bond, a dipolar bond, a Pi backbond, a double bond, a triple bond, a quadruple bond, a quintuple bond, a sextuple bond, conjugation, hyperconjugation, aromaticity, hapticity, or antibonding. Non-limiting examples of non-covalent bond include an ionic bond (e.g., cation-pi bond or salt bond), a metal bond, a hydrogen bond (e.g., dihydrogen bond, dihydrogen complex, low-barrier hydrogen bond, or symmetric hydrogen bond), van der Waals force, London dispersion force, a mechanical bond, a halogen bond, aurophilicity, intercalation, stacking, entropic force, or chemical polarity.

[0073] As used herein, the term "cleavage site" or "enzymatic cleavage site" refers to a site recognized by an enzyme. Certain enzymatic cleavage sites comprise an intracellular processing site. In some embodiments, a polypeptide has an enzymatic cleavage site cleaved by an enzyme that is activated during the clotting cascade, such that cleavage of such sites occurs at the site of clot formation. Exemplary such sites include, e.g., those recognized by thrombin, Factor XIa or Factor Xa. Exemplary FXIa cleavage sites include, e.g., TQSFNDFTR (SEQ ID NO: 1) and SVSQTSKLTR (SEQ ID NO: 3). Exemplary thrombin cleavage sites include, e.g., DFLAEGGGVR (SEQ ID NO: 4), TTKIKPR (SEQ ID NO: 5), LVPRG (SEQ ID NO: 6), ALRPR (SEQ ID NO: 7), ISDKNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 106), DKNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 88), and IEPRSFS (SEQ ID NO: 194). Other enzymatic cleavage sites are known in the art and described in elsewhere herein.

[0074] As used herein, the term "processing site" or "intracellular processing site" refers to a type of enzymatic cleavage site in a polypeptide which is a target for enzymes that function after translation of the polypeptide. In some embodiments, such enzymes function during transport from the Golgi lumen to the trans-Golgi compartment. Intracellular processing enzymes cleave polypeptides prior to secretion of the protein from the cell. Examples of such processing sites include, e.g., those targeted by the PACE/furin (where PACE is an acronym for Paired basic Amino acid Cleaving Enzyme) family of endopeptidases. These enzymes are localized to the Golgi membrane and cleave proteins on the carboxyterminal side of the sequence motif Arg-[any residue]-(Lys or Arg)-Arg. As used herein the

"furin" family of enzymes includes, e.g., PCSK1 (also known as PC1/PC3), PCSK2 (also known as PC2), PCSK3 (also known as furin or PACE), PCSK4 (also known as PC4), PCSK5 (also known as PC5 or PC6), PCSK6 (also known as PACE4), or PCSK7 (also known as PC7/LPC, PC8, or SPC7). Other processing sites are known in the art.

5 **[0075]** In constructs that include more than one processing or cleavage site, it will be understood that such sites can be the same or different.

[0076] A "processable linker" as used herein refers to a linker comprising at least one intracellular processing site, which are described elsewhere herein.

[0077] As used herein, the term "half-life" refers to a biological half-life of a particular polypeptide
10 in vivo. Half-life can be represented by the time required for half the quantity administered to a subject to be cleared from the circulation and/or other tissues in the animal. When a clearance curve of a given polypeptide is constructed as a function of time, the curve is usually biphasic with a rapid α -phase and longer β -phase. The α -phase typically represents an equilibration of the administered Fc polypeptide between the intra- and extra-vascular space and is, in part, determined by the size of the
15 polypeptide. The β -phase typically represents the catabolism of the polypeptide in the intravascular space. In some embodiments, FVIII and chimeric polypeptides comprising FVIII are monophasic, and thus do not have an alpha phase, but just the single beta phase. Therefore, in certain embodiments, the term half-life as used herein refers to the half-life of the polypeptide in the β -phase. The typical beta phase half-life of a human antibody in humans is 21 days. In certain embodiments, the half-life
20 is expressed as the half-life of the terminal phase.

[0078] Hemostatic disorder, as used herein, means a genetically inherited or acquired condition characterized by a tendency to hemorrhage, either spontaneously or as a result of trauma, due to an impaired ability or inability to form a fibrin clot. Examples of such disorders include the hemophilias. The three main forms are hemophilia A (factor VIII deficiency), hemophilia B (factor IX deficiency or
25 "Christmas disease") and hemophilia C (factor XI deficiency, mild bleeding tendency). Other hemostatic disorders include, e.g., Von Willebrand disease, Factor XI deficiency (PTA deficiency), Factor XII deficiency, deficiencies or structural abnormalities in fibrinogen, prothrombin, Factor V, Factor VII, Factor X or factor XIII, Bernard-Soulier syndrome, which is a defect or deficiency in GPIb. GPIb, the receptor for VWF, can be defective and lead to lack of primary clot formation (primary
30 hemostasis) and increased bleeding tendency), and thrombasthenia of Glanzman and Naegeli

(Glanzmann thrombasthenia). In liver failure (acute and chronic forms), there is insufficient production of coagulation factors by the liver; this can increase bleeding risk.

[0079] "Administer" or "administering," as used herein refers to delivering to a subject a composition described herein, e.g., a chimeric polypeptide. The composition, e.g., the chimeric polypeptide, can be administered to a subject using methods known in the art. In particular, the composition can be administered intravenously, subcutaneously, intramuscularly, intradermally, or via any mucosal surface, e.g., orally, sublingually, buccally, nasally, rectally, vaginally or via pulmonary route. chimeric polypeptide. In some embodiments, the administration is self-administration. In some embodiments, a parent administers the chimeric polypeptide to a child. In some embodiments, the chimeric polypeptide is administered to a subject by a healthcare practitioner such as a medical doctor, a medic, or a nurse.

[0080] As used herein, the term "dose" refers to a single administration of a composition to a subject. A single dose can be administered all at once, e.g., as a bolus, or over a period of time, e.g., via an intravenous infusion. The term "multiple doses" means more than one dose, e.g., more than one administration.

[0081] When referring to co-administration of more than one composition, a dose of composition A can be administered concurrently with a dose of composition B. Alternatively, a dose of composition A can be administered before or after a dose of composition B. In some embodiments, composition A and composition B are combined into a single formulation.

[0082] As used herein, the term "interval" or "dosing interval" refers to the amount of time that elapses between a first dose of composition A and a subsequent dose of the same composition administered to a subject. A dosing interval can refer to the time that elapses between a first dose and a second dose, or a dosing interval can refer to the amount of time that elapses between multiple doses.

[0083] The term "dosing frequency" as used herein refers to the number of doses administered per a specific dosing interval. For example, a dosing frequency can be written as once a week, once every two weeks, etc. Therefore, a dosing interval of 7 days can be also written as a dosing interval of once in 7 days or once every week, or once a week.

[0084] As used herein the term "prophylactic treatment" refers to the administration of a therapy for the treatment of hemophilia, where such treatment is intended to prevent or reduce the severity of one or more symptoms of hemophilia, e.g., bleeding episodes, e.g., one or more spontaneous

bleeding episodes, and/or joint damage. See Jimenez-Yuste et al., Blood Transfus. 12(3):314-19 (2014). To prevent or reduce the severity of such symptoms, e.g., bleeding episodes and the progression of joint disease, hemophilia A patients may receive regular infusions of clotting factor as part of a prophylactic treatment regimen. The basis of such prophylactic treatment is the observation
5 that hemophilia patients with a clotting factor, e.g., FVIII, level of 1% or more rarely experience spontaneous bleeding episodes and have fewer hemophilia-related comorbidities as compared to patients with severe hemophilia. See, e.g., Coppola A. et al, Semin. Thromb. Hemost. 38(1): 79-94 (2012). . Health care practitioners treating these hemophilia patients surmised that maintaining factor levels at around 1% with regular infusions could potentially reduce the risk of hemophilia symptoms,
10 including bleeding episodes and joint damage. See id. Subsequent research has confirmed these benefits in pediatric hemophilia patients receiving prophylactic treatment with clotting factor, rendering prophylactic treatment the goal for people with severe hemophilia. See id.

[0085] A "prophylactic" treatment can also refer to the preemptive administration of the composition described herein, e.g., a chimeric polypeptide, to a subject in order to control, manage, prevent, or
15 reduce the occurrence or severity of one or more symptoms of hemophilia A, e.g., bleeding episodes. Prophylactic treatment with a clotting factor, e.g., FVIII, is the standard of care for subjects with severe hemophilia A. See, e.g., Oldenburg, Blood 125:2038-44 (2015). In some embodiments, prophylactic treatment refers to administering a composition disclosed herein to a subject in need thereof to reduce the occurrence of one or more symptom of hemophilia A. A prophylactic treatment can include
20 administration of multiple doses. The multiple doses used in prophylactic treatment are typically administered at particular dosing intervals. In certain embodiments, the annualized bleeding rate can be reduced to less than 10, less than 9, less than 8, less than 7, less than 6, less than 5, less than 4, less than 3, less than 2, or less than 1.

[0086] The term "on-demand treatment" or "episodic treatment" refers to the "as needed" administration of a chimeric molecule in response to symptoms of hemophilia A, e.g., a bleeding
25 episode, or before an activity that can cause bleeding. In one aspect, the on-demand treatment can be given to a subject when bleeding starts, such as after an injury, or when bleeding is expected, such as before surgery. In another aspect, the on-demand treatment can be given prior to activities that increase the risk of bleeding, such as contact sports. In some embodiments, the on-demand
30 treatment is given as a single dose. In other embodiments, the on-demand treatment is given as a first dose, followed by one or more additional doses. . When the chimeric polypeptide is administered on-demand, the one or more additional doses can be administered at least about 12 hours, at least

about 24 hours, at least about 36 hours, at least about 48 hours, at least about 60 hours, at least about 72 hours, at least about 84 hours, at least about 96 hours, at least about 108 hours, or at least about 120 hours after the first dose. It should be noted, however, that the dosing interval associated with on-demand treatment is not the same as the dosing interval used for prophylactic treatment.

5 **[0087]** In some embodiments, the subject in need of a general hemostatic agent is undergoing, or is about to undergo, surgery. The chimeric polypeptide of the disclosure can be administered prior to or after surgery. The chimeric polypeptide of the disclosure can also be administered during or after surgery to control an acute bleeding episode. When the chimeric polypeptide is administered prior to surgery, the administration can be at least about 1 hour, at least about 2 hours, at least about 4 hours,
10 at least about 8 hours, at least about 12 hours, at least about 24 hours, at least about 36 hours, at least about 48 hours, or at least about 72 hours prior to surgery. When the chimeric polypeptide is administered to after surgery, the administration can be at least about 1 hour, at least about 2 hours, at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 24 hours, at least about 36 hours, at least about 48 hours, or at least about 72 hours after surgery. The surgery
15 can include, but is not limited to, liver transplantation, liver resection, dental procedures, or stem cell transplantation.

[0088] As used herein the term "acute bleeding" refers to a bleeding episode regardless of the underlying cause. For example, a subject can have trauma, uremia, a hereditary bleeding disorder (e.g., factor VII deficiency) a platelet disorder, or resistance owing to the development of antibodies
20 to clotting factors.

[0089] "Treat", "treatment", "treating", as used herein refers to, e.g., the reduction in severity of a disease or condition; the reduction in the duration of a disease course; the amelioration of one or more symptoms associated with a disease or condition; the provision of beneficial effects to a subject with a disease or condition, without necessarily curing the disease or condition, or the prophylaxis of
25 one or more symptoms associated with a disease or condition. In some embodiments, the term "treating" or "treatment" means maintaining a FVIII trough level at least about 1 IU/dL, 2 IU/dL, 3 IU/dL, 4 IU/dL, 5 IU/dL, 6 IU/dL, 7 IU/dL, 8 IU/dL, 9 IU/dL, 10 IU/dL, 11 IU/dL, 12 IU/dL, 13 IU/dL, 14 IU/dL, 15 IU/dL, 16 IU/dL, 17 IU/dL, 18 IU/dL, 19 IU/dL, or 20 IU/dL in a subject by administering a chimeric polypeptide or a VWF fragment of the disclosure. As used herein, a "trough level" in a
30 hemophilia patient is the measurement of the lowest concentration reached by a factor therapy, e.g., a FVIII therapy, before the next dose is administered. In other embodiments, treating or treatment means maintaining a FVIII trough level of at least about 1 IU/dL between the dosing interval. In other

embodiments, treating or treatment means maintaining a FVIII trough level of at least about 3 IU/dL between the dosing interval. In other embodiments, treating or treatment means maintaining a FVIII trough level of at least about 5 IU/dL between the dosing interval. In other embodiments, treating or treatment means maintaining a FVIII trough level between about 1 and about 20 IU/dL, about 2 and about 20 IU/dL, about 3 and about 20 IU/dL, about 4 and about 20 IU/dL, about 5 and about 20 IU/dL, about 6 and about 20 IU/dL, about 7 and about 20 IU/dL, about 8 and about 20 IU/dL, about 9 and about 20 IU/dL, or about 10 and about 20 IU/dL during the dosing interval.

[0090] "Treatment" or "treating" of a disease or condition can also include maintaining FVIII activity in a subject at a level comparable to at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% of the FVIII activity in a non-hemophiliac subject between the dosing interval. In other embodiments, treating or treatment means maintaining a FVIII activity level of at least about 1% between the dosing interval. In other embodiments, treating or treatment means maintaining a FVIII activity level of at least about 2% between the dosing interval. In other embodiments, treating or treatment means maintaining a FVIII activity level of at least about 3% between the dosing interval. In other embodiments, treating or treatment means maintaining a FVIII activity level of at least about 4% between the dosing interval. In other embodiments, treating or treatment means maintaining a FVIII activity level of at least about 5% between the dosing interval. In other embodiments, treating or treatment means maintaining a FVIII activity level of at least about 6% between the dosing interval. In other embodiments, treating or treatment means maintaining a FVIII activity level of at least about 7% between the dosing interval. In other embodiments, treating or treatment means maintaining a FVIII activity level of at least about 8% between the dosing interval. In other embodiments, treating or treatment means maintaining a FVIII activity level of at least about 9% between the dosing interval. In other embodiments, treating or treatment means maintaining a FVIII activity level of at least about 10% between the dosing interval. The minimum trough level required for treatment can be measured by one or more known methods (for example, the aPTT assays or chromogenic assays described herein) and can be adjusted (increased or decreased) for each person.

II. Methods of the Disclosure

[0091] Certain aspects of the present disclosure are directed to methods of treating hemophilia A in a subject in need thereof, comprising administering to the subject a chimeric polypeptide comprising a FVIII protein and a VWF fragment at a dosing interval. In some embodiments, the

method comprises administering to the subject multiple doses of a chimeric polypeptide, e.g., rFVIII-Fc-VWF-XTEN, comprising (i) a FVIII protein and (ii) a VWF fragment comprising a D' domain of VWF and a D3 domain of VWF at a dosing interval. In other aspects, the present disclosure is directed to methods of treating a bleeding disease or condition, e.g., hemophilia A, in a subject in need thereof, comprising administering to the subject multiple doses of a FVIII protein and multiple doses of a VWF fragment at a dosing interval.

[0092] In some embodiments, the multiple doses comprise at least two doses, at least three doses, at least four doses, at least five doses, at least six doses, at least seven doses, at least eight doses, at least nine doses, at least ten doses, at least eleven doses, at least twelve doses, at least thirteen doses, at least fourteen doses, at least fifteen doses, at least sixteen doses, at least seventeen doses, at least eighteen doses, at least nineteen doses, at least twenty doses, or more. In some embodiments, the multiple doses are administered for at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 12 months, at least about 18 months, at least about 2 years, at least about 3 years, at least about 4 years, at least about 5 years, at least about 10 years, at least about 15 years, at least about 20 years, or for at least about 25 years.

[0093] In certain embodiments, the methods of the present disclosure are directed to treating hemophilia A. In some embodiments, the treatment of hemophilia A comprises preventing a bleeding episode in a human subject in need thereof. In some embodiments, the treatment of hemophilia A comprises treating a bleeding episode in a human subject in need thereof. In some embodiments, the treatment of hemophilia A comprises controlling the incidence or frequency of a bleeding episode in a human subject in need thereof. In some embodiments, the treatment of hemophilia A comprises decreasing the incidence or frequency of a bleeding episode in a human subject in need thereof.

A. Doses

[0094] In some embodiments, the chimeric polypeptide, e.g., rFVIII-Fc-VWF-XTEN, is administered as a single dose or as multiple doses. In some embodiments, the amounts of each of the multiple doses are the same. In other embodiments, one or more of the multiple doses is different from one or more of the other multiple doses. In some embodiments, at least one of the multiple doses of the chimeric polypeptide is from about 5 IU/kg to about 200 IU/kg or from about 10 IU/kg to about 150 IU/kg. In certain embodiments, at least one of the multiple doses is from about 15 IU/kg to about 100 IU/kg. In some embodiments, at least one of the multiple doses is from about 20 IU/kg to about 95

IU/kg, from about 20 IU/kg to about 90 IU/kg, from about 20 IU/kg to about 85 IU/kg, from about 20 IU/kg to about 80 IU/kg, from about 20 IU/kg to about 75 IU/kg, from about 20 IU/kg to about 70 IU/kg, from about 20 IU/kg to about 65 IU/kg, from about 20 IU/kg to about 60 IU/kg, from about 20 IU/kg to about 55 IU/kg, from about 20 IU/kg to about 50 IU/kg, from about 20 IU/kg to about 45 IU/kg, from about 20 IU/kg to about 40 IU/kg, from about 20 IU/kg to about 35 IU/kg, from about 20 IU/kg to about 30 IU/kg, or from about 20 IU/kg to about 25 IU/kg.

[0095] In some embodiments, at least one of the multiple doses is from about 20 IU/kg to about 100 IU/kg, from about 25 IU/kg to about 100 IU/kg, from about 30 IU/kg to about 100 IU/kg, from about 35 IU/kg to about 100 IU/kg, from about 40 IU/kg to about 100 IU/kg, from about 45 IU/kg to about 100 IU/kg, from about 50 IU/kg to about 100 IU/kg, from about 55 IU/kg to about 100 IU/kg, from about 60 IU/kg to about 100 IU/kg, from about 65 IU/kg to about 100 IU/kg, from about 70 IU/kg to about 100 IU/kg, from about 75 IU/kg to about 100 IU/kg, from about 80 IU/kg to about 100 IU/kg, from about 85 IU/kg to about 100 IU/kg, or from about 90 IU/kg to about 100 IU/kg. In some embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg.

[0096] In some embodiments, at least one of the multiple doses of the chimeric polypeptide is from about 50 IU/kg to about 150 IU/kg, from about 50 IU/kg to about 140 IU/kg, from about 50 IU/kg to about 130 IU/kg, from about 50 IU/kg to about 120 IU/kg, from about 50 IU/kg to about 110 IU/kg, or from about 50 IU/kg to about 100 IU/kg. In some embodiments, at least one of the multiple doses of the chimeric polypeptide is from about 50 IU/kg to about 95 IU/kg, from about 50 IU/kg to about 90 IU/kg, from about 50 IU/kg to about 85 IU/kg, from about 50 IU/kg to about 80 IU/kg, from about 50 IU/kg to about 75 IU/kg, from about 50 IU/kg to about 70 IU/kg, from about 50 IU/kg to about 65 IU/kg, from about 50 IU/kg to about 60 IU/kg, from about 50 IU/kg to about 55 IU/kg. In certain embodiments, at least one of the multiple doses of the chimeric polypeptide is from about 50 IU/kg to about 80 IU/kg. In certain embodiments, at least one of the multiple doses of the chimeric polypeptide is from about 50 IU/kg to about 65 IU/kg.

[0097] In some embodiments, at least one of the multiple doses of the chimeric polypeptide is from about 60 IU/kg to about 150 IU/kg, from about 60 IU/kg to about 140 IU/kg, from about 60 IU/kg to about 130 IU/kg, from about 60 IU/kg to about 120 IU/kg, from about 60 IU/kg to about 110 IU/kg, or from about 60 IU/kg to about 100 IU/kg. In some embodiments, at least one of the multiple doses of the chimeric polypeptide is from about 60 IU/kg to about 95 IU/kg, from about 60 IU/kg to about 90 IU/kg, from about 60 IU/kg to about 85 IU/kg, from about 60 IU/kg to about 80 IU/kg, from about 60 IU/kg to about 75 IU/kg, from about 60 IU/kg to about 70 IU/kg, from about 60 IU/kg to about 65 IU/kg, from about 60 IU/kg to about 60 IU/kg.

IU/kg to about 75 IU/kg, from about 60 IU/kg to about 70 IU/kg, or from about 60 IU/kg to about 65 IU/kg.

[0098] In some embodiments, at least one of the multiple doses of the chimeric polypeptide is from about 65 IU/kg to about 150 IU/kg, from about 65 IU/kg to about 140 IU/kg, from about 65 IU/kg to about 130 IU/kg, from about 65 IU/kg to about 120 IU/kg, from about 65 IU/kg to about 110 IU/kg, or from about 65 IU/kg to about 100 IU/kg. In some embodiments, at least one of the multiple doses of the chimeric polypeptide is from about 65 IU/kg to about 95 IU/kg, from about 65 IU/kg to about 90 IU/kg, from about 65 IU/kg to about 85 IU/kg, from about 65 IU/kg to about 80 IU/kg, from about 65 IU/kg to about 75 IU/kg, or from about 65 IU/kg to about 70 IU/kg. In certain embodiments, at least one of the multiple doses of the chimeric polypeptide is from about 65 IU/kg to about 80 IU/kg.

[0099] In some embodiments, at least one of the multiple doses is about 5 IU/kg, about 10 IU/kg, about 15 IU/kg, about 20 IU/kg, about 25 IU/kg, about 30 IU/kg, about 35 IU/kg, about 40 IU/kg, about 45 IU/kg, about 50 IU/kg, about 55 IU/kg, about 60 IU/kg, about 65 IU/kg, about 70 IU/kg, about 75 IU/kg, about 80 IU/kg, about 85 IU/kg, about 90 IU/kg, about 95 IU/kg, about 100 IU/kg, about 125 IU/kg, about 150 IU/kg, about 175 IU/kg, or about 200 IU/kg. In certain embodiments, at least one of the multiple doses is about 25 IU/kg. In certain embodiments, at least one of the multiple doses is about 30 IU/kg. In certain embodiments, at least one of the multiple doses is about 35 IU/kg. In certain embodiments, at least one of the multiple doses is about 40 IU/kg. In certain embodiments, at least one of the multiple doses is about 45 IU/kg. In certain embodiments, at least one of the multiple doses is about 50 IU/kg. In certain embodiments, at least one of the multiple doses is about 55 IU/kg. In certain embodiments, at least one of the multiple doses is about 60 IU/kg. In certain embodiments, at least one of the multiple doses is about 65 IU/kg. In certain embodiments, at least one of the multiple doses is about 70 IU/kg. In certain embodiments, at least one of the multiple doses is about 75 IU/kg. In certain embodiments, at least one of the multiple doses is about 80 IU/kg. In certain embodiments, at least one of the multiple doses is about 85 IU/kg. In certain embodiments, at least one of the multiple doses is about 90 IU/kg. In certain embodiments, at least one of the multiple doses is about 95 IU/kg. In certain embodiments, at least one of the multiple doses is about 100 IU/kg.

[0100] In some embodiments, each dose of the multiple doses is about 25 IU/kg. In some embodiments, each dose of the multiple doses is about 30 IU/kg. In some embodiments, each dose of the multiple doses is about 35 IU/kg. In some embodiments, each dose of the multiple doses is about 40 IU/kg. In some embodiments, each dose of the multiple doses is about 45 IU/kg. In some embodiments, each dose of the multiple doses is about 50 IU/kg. In some embodiments, each dose

of the multiple doses is about 55 IU/kg. In some embodiments, each dose of the multiple doses is about 60 IU/kg. In some embodiments, each dose of the multiple doses is about 65 IU/kg. In some embodiments, each dose of the multiple doses is about 70 IU/kg. In some embodiments, each dose of the multiple doses is about 75 IU/kg. In some embodiments, each dose of the multiple doses is about 80 IU/kg. In some embodiments, each dose of the multiple doses is about 85 IU/kg. In some embodiments, each dose of the multiple doses is about 90 IU/kg. In some embodiments, each dose of the multiple doses is about 95 IU/kg. In some embodiments, each dose of the multiple doses is about 100 IU/kg.

[0101] In some embodiments, the chimeric polypeptide, e.g., rFVIII^hFc-VWF-XTEN, is administered prophylactically. When administered prophylactically, at least one of the multiple doses can be from about 15 IU/kg to about 100 IU/kg. In certain embodiments, at least one of the multiple doses administered prophylactically is about 25 IU/kg, about 30 IU/kg, about 35 IU/kg, about 40 IU/kg, about 45 IU/kg, about 50 IU/kg, about 55 IU/kg, about 60 IU/kg, about 65 IU/kg, about 70 IU/kg, about 75 IU/kg, about 80 IU/kg, about 85 IU/kg, about 90 IU/kg, about 95 IU/kg, or about 100 IU/kg. In some embodiments, at least one of the multiple doses administered prophylactically is about 25 IU/kg. In other embodiments, at least one of the multiple doses administered prophylactically is about 50 IU/kg. In other embodiments, at least one of the multiple doses administered prophylactically is about 65 IU/kg. In other embodiments, at least one of the multiple doses administered prophylactically is about 80 IU/kg.

[0102] In some embodiments, the chimeric polypeptide, e.g., rFVIII^hFc-VWF-XTEN, is administered on-demand. When administered on-demand, the chimeric polypeptide can be administered as a single dose or as multiple doses. In some embodiments, the chimeric polypeptide is administered as one or more doses of from about 15 IU/kg to about 100 IU/kg. In certain embodiments, the chimeric polypeptide is administered on-demand as one or more doses of about 25 IU/kg, about 30 IU/kg, about 35 IU/kg, about 40 IU/kg, about 45 IU/kg, about 50 IU/kg, about 55 IU/kg, about 60 IU/kg, about 65 IU/kg, about 70 IU/kg, about 75 IU/kg, about 80 IU/kg, about 85 IU/kg, about 90 IU/kg, about 95 IU/kg, or about 100 IU/kg. In some embodiments, the chimeric polypeptide is administered on-demand as one or more doses of about 25 IU/kg. In other embodiments, the chimeric polypeptide is administered on-demand as one or more doses of about 50 IU/kg. In other embodiments, the chimeric polypeptide is administered on-demand as one or more doses of about 65 IU/kg. In other embodiments, the chimeric polypeptide is administered on-demand as one or more doses of about 80 IU/kg.

[0103] In some embodiments, the administration of the chimeric polypeptide according to the present methods induces no FVIII inhibitor after about 7 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 15 days, about 20 days, about 24 days, about 25 days, about 28 days, about 30 days, or about 35 days of the administration. In some embodiments, the administration of the chimeric polypeptide induces no FVIII inhibitor after about 28 days of the administration.

B. Dosing Interval

[0104] In certain embodiments, especially for prophylactic treatment, the chimeric polypeptide, e.g., rFVIII-Fc-VWF-XTEN, is administered as multiple doses at a dosing interval. In some embodiments, the dosing interval is at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 7 days, at least about 8 days, at least about 9 days, at least about 10 days, at least about 11 days, at least about 12 days, at least about 13 days, at least about 14 days, at least about 15 days, at least about 16 days, at least about 17 days, at least about 18 days, at least about 19 days, at least about 20 days, at least about 21 days, at least about 22 days, at least about 23 days, at least about 24 days, at least about 25 days, at least about 26 days, at least about 27 days, at least about 28 days, at least about 29 days, at least about 30 days, or at least about 31 days.

[0105] In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 5 days. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 6 days. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 7 days. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 8 days. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 9 days. In certain embodiments, the dosing interval is at least about 10 days. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 11 days. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 12 days. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 13 days. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 14 days. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 21 days. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 27 days. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 30 days.

[0106] In some embodiments, the dosing frequency, e.g., for prophylactic treatment of hemophilia A, is at least twice every week, at least once every week, at least once every 2 weeks, at least once every 3 weeks, at least once every 4 weeks, at least once every 5 weeks, or at least once every 6 weeks. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least once every week. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least 2 weeks. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least 3 weeks. In certain embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least 4 weeks.

[0107] In some embodiments, the dosing frequency, e.g., for prophylactic treatment of hemophilia A, is about 2 times every three months, about 1 time every month, about 2 times every month, about 3 times every month, about 4 times every month, about 5 times every month, about 6 times every month, about 7 times every month, or about 8 times every month. In certain embodiments, the dosing frequency is about 1 time every month. In certain embodiments, the dosing frequency is about 2 times every month. In certain embodiments, the dosing frequency is about 3 times every month. In certain embodiments, the dosing frequency is about 4 times every month. In certain embodiments, the dosing frequency is about 5 times every month. In certain embodiments, the dosing frequency is about 6 times every month.

[0108] In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 3 to 5 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 4 to 6 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 4 to 7 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 4 to 8 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 4 to 9 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 4 to 10 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 5 to 7 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 5 to 8 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 5 to 9 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 5 to 10 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 6 to 8 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 6 to 9 days. In some embodiments, the

dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 6 to 10 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 7 to 9 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 7 to 10 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 7 to 11 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 7 to 12 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 7 to 13 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 7 to 14 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 8 to 14 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 9 to 14 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 10 to 14 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 11 to 14 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 10 to 21 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 12 to 14 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 12 to 15 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 13 to 15 days. In some embodiments, the dosing interval, e.g., for prophylactic treatment of hemophilia A, is at least about 14 to 21 days.

[0109] In some embodiments, at least one of the multiple doses is administered according to a dose and dosing frequency described in Table 1.

Table 1A: Dosing amounts and corresponding dosing frequency, e.g., for prophylactic treatment of hemophilia.

	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
5 days	5 IU/kg Every 5 days	10 IU/kg Every 5 days	15 IU/kg Every 5 days	20 IU/kg Every 5 days	25 IU/kg Every 5 days	30 IU/kg Every 5 days	35 IU/kg Every 5 days	40 IU/kg Every 5 days	45 IU/kg Every 5 days	50 IU/kg Every 5 days
6 days	5 IU/kg Every	10 IU/kg Every	15 IU/kg Every	20 IU/kg Every	25 IU/kg Every	30 IU/kg Every	35 IU/kg Every	40 IU/kg Every	45 IU/kg Every	50 IU/kg Every

	6 days	6 days	6 days	6 days	6 days	6 days	6 days	6 days	6 days	6 days
7 days	5 IU/kg Every 7 days	10 IU/kg Every 7 days	15 IU/kg Every 7 days	20 IU/kg Every 7 days	25 IU/kg Every 7 days	30 IU/kg Every 7 days	35 IU/kg Every 7 days	40 IU/kg Every 7 days	45 IU/kg Every 7 days	50 IU/kg Every 7 days
8 days	5 IU/kg Every 8 days	10 IU/kg Every 8 days	15 IU/kg Every 8 days	20 IU/kg Every 8 days	25 IU/kg Every 8 days	30 IU/kg Every 8 days	35 IU/kg Every 8 days	40 IU/kg Every 8 days	45 IU/kg Every 8 days	50 IU/kg Every 8 days
9 days	5 IU/kg Every 9 days	10 IU/kg Every 9 days	15 IU/kg Every 9 days	20 IU/kg Every 9 days	25 IU/kg Every 9 days	30 IU/kg Every 9 days	35 IU/kg Every 9 days	40 IU/kg Every 9 days	45 IU/kg Every 9 days	50 IU/kg Every 9 days
10 days	5 IU/kg Every 10 days	10 IU/kg Every 10 days	15 IU/kg Every 10 days	20 IU/kg Every 10 days	25 IU/kg Every 10 days	30 IU/kg Every 10 days	35 IU/kg Every 10 days	40 IU/kg Every 10 days	45 IU/kg Every 10 days	50 IU/kg Every 10 days
11 days	5 IU/kg Every 11 days	10 IU/kg Every 11 days	15 IU/kg Every 11 days	20 IU/kg Every 11 days	25 IU/kg Every 11 days	30 IU/kg Every 11 days	35 IU/kg Every 11 days	40 IU/kg Every 11 days	45 IU/kg Every 11 days	50 IU/kg Every 11 days
12 days	5 IU/kg Every 12 days	10 IU/kg Every 12 days	15 IU/kg Every 12 days	20 IU/kg Every 12 days	25 IU/kg Every 12 days	30 IU/kg Every 12 days	35 IU/kg Every 12 days	40 IU/kg Every 12 days	45 IU/kg Every 12 days	50 IU/kg Every 12 days
13 days	5 IU/kg Every 13 days	10 IU/kg Every 13 days	15 IU/kg Every 13 days	20 IU/kg Every 13 days	25 IU/kg Every 13 days	30 IU/kg Every 13 days	35 IU/kg Every 13 days	40 IU/kg Every 13 days	45 IU/kg Every 13 days	50 IU/kg Every 13 days
14 days	5 IU/kg Every 14 days	10 IU/kg Every 14 days	15 IU/kg Every 14 days	20 IU/kg Every 14 days	25 IU/kg Every 14 days	30 IU/kg Every 14 days	35 IU/kg Every 14 days	40 IU/kg Every 14 days	45 IU/kg Every 14 days	50 IU/kg Every 14 days
15 days	5 IU/kg Every 15 days	10 IU/kg Every 15 days	15 IU/kg Every 15 days	20 IU/kg Every 15 days	25 IU/kg Every 15 days	30 IU/kg Every 15 days	35 IU/kg Every 15 days	40 IU/kg Every 15 days	45 IU/kg Every 15 days	50 IU/kg Every 15 days
16 days	5 IU/kg Every 16 days	10 IU/kg Every 16 days	15 IU/kg Every 16 days	20 IU/kg Every 16 days	25 IU/kg Every 16 days	30 IU/kg Every 16 days	35 IU/kg Every 16 days	40 IU/kg Every 16 days	45 IU/kg Every 16 days	50 IU/kg Every 16 days

17 days	5 IU/kg Every 17 days	10 IU/kg Every 17 days	15 IU/kg Every 17 days	20 IU/kg Every 17 days	25 IU/kg Every 17 days	30 IU/kg Every 17 days	35 IU/kg Every 17 days	40 IU/kg Every 17 days	45 IU/kg Every 17 days	50 IU/kg Every 17 days
18 days	5 IU/kg Every 18 days	10 IU/kg Every 18 days	15 IU/kg Every 18 days	20 IU/kg Every 18 days	25 IU/kg Every 18 days	30 IU/kg Every 18 days	35 IU/kg Every 18 days	40 IU/kg Every 18 days	45 IU/kg Every 18 days	50 IU/kg Every 18 days
19 days	5 IU/kg Every 19 days	10 IU/kg Every 19 days	15 IU/kg Every 19 days	20 IU/kg Every 19 days	25 IU/kg Every 19 days	30 IU/kg Every 19 days	35 IU/kg Every 19 days	40 IU/kg Every 19 days	45 IU/kg Every 19 days	50 IU/kg Every 19 days
20 days	5 IU/kg Every 20 days	10 IU/kg Every 20 days	15 IU/kg Every 20 days	20 IU/kg Every 20 days	25 IU/kg Every 20 days	30 IU/kg Every 20 days	35 IU/kg Every 20 days	40 IU/kg Every 20 days	45 IU/kg Every 20 days	50 IU/kg Every 20 days
21 days	5 IU/kg Every 21 days	10 IU/kg Every 21 days	15 IU/kg Every 21 days	20 IU/kg Every 21 days	25 IU/kg Every 21 days	30 IU/kg Every 21 days	35 IU/kg Every 21 days	40 IU/kg Every 21 days	45 IU/kg Every 21 days	50 IU/kg Every 21 days
	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
5 days	55 IU/kg Every 5 days	60 IU/kg Every 5 days	65 IU/kg Every 5 days	70 IU/kg Every 5 days	75 IU/kg Every 5 days	80 IU/kg Every 5 days	85 IU/kg Every 5 days	90 IU/kg Every 5 days	95 IU/kg Every 5 days	100 IU/kg Every 5 days
6 days	55 IU/kg Every 6 days	60 IU/kg Every 6 days	65 IU/kg Every 6 days	70 IU/kg Every 6 days	75 IU/kg Every 6 days	80 IU/kg Every 6 days	85 IU/kg Every 6 days	90 IU/kg Every 6 days	95 IU/kg Every 6 days	100 IU/kg Every 6 days
7 days	55 IU/kg Every 7 days	60 IU/kg Every 7 days	65 IU/kg Every 7 days	70 IU/kg Every 7 days	75 IU/kg Every 7 days	80 IU/kg Every 7 days	85 IU/kg Every 7 days	90 IU/kg Every 7 days	95 IU/kg Every 7 days	100 IU/kg Every 7 days
8 days	55 IU/kg Every 8 days	60 IU/kg Every 8 days	65 IU/kg Every 8 days	70 IU/kg Every 8 days	75 IU/kg Every 8 days	80 IU/kg Every 8 days	85 IU/kg Every 8 days	90 IU/kg Every 8 days	95 IU/kg Every 8 days	100 IU/kg Every 8 days
9 days	55 IU/kg Every 9 days	60 IU/kg Every 9 days	65 IU/kg Every 9 days	70 IU/kg Every 9 days	75 IU/kg Every 9 days	80 IU/kg Every 9 days	85 IU/kg Every 9 days	90 IU/kg Every 9 days	95 IU/kg Every 9 days	100 IU/kg Every 9 days

10 days	55 IU/kg Every 10 days	60 IU/kg Every 10 days	65 IU/kg Every 10 days	70 IU/kg Every 10 days	75 IU/kg Every 10 days	80 IU/kg Every 10 days	85 IU/kg Every 10 days	90 IU/kg Every 10 days	95 IU/kg Every 10 days	100 IU/kg Every 10 days
11 days	55 IU/kg Every 11 days	60 IU/kg Every 11 days	65 IU/kg Every 11 days	70 IU/kg Every 11 days	75 IU/kg Every 11 days	80 IU/kg Every 11 days	85 IU/kg Every 11 days	90 IU/kg Every 11 days	95 IU/kg Every 11 days	100 IU/kg Every 11 days
12 days	55 IU/kg Every 12 days	60 IU/kg Every 12 days	65 IU/kg Every 12 days	70 IU/kg Every 12 days	75 IU/kg Every 12 days	80 IU/kg Every 12 days	85 IU/kg Every 12 days	90 IU/kg Every 12 days	95 IU/kg Every 12 days	100 IU/kg Every 12 days
13 days	55 IU/kg Every 13 days	60 IU/kg Every 13 days	65 IU/kg Every 13 days	70 IU/kg Every 13 days	75 IU/kg Every 13 days	80 IU/kg Every 13 days	85 IU/kg Every 13 days	90 IU/kg Every 13 days	95 IU/kg Every 13 days	100 IU/kg Every 13 days
14 days	55 IU/kg Every 14 days	60 IU/kg Every 14 days	65 IU/kg Every 14 days	70 IU/kg Every 14 days	75 IU/kg Every 14 days	80 IU/kg Every 14 days	85 IU/kg Every 14 days	90 IU/kg Every 14 days	95 IU/kg Every 14 days	100 IU/kg Every 14 days
15 days	55 IU/kg Every 15 days	60 IU/kg Every 15 days	65 IU/kg Every 15 days	70 IU/kg Every 15 days	75 IU/kg Every 15 days	80 IU/kg Every 15 days	85 IU/kg Every 15 days	90 IU/kg Every 15 days	95 IU/kg Every 15 days	100 IU/kg Every 15 days
16 days	55 IU/kg Every 16 days	60 IU/kg Every 16 days	65 IU/kg Every 16 days	70 IU/kg Every 16 days	75 IU/kg Every 16 days	80 IU/kg Every 16 days	85 IU/kg Every 16 days	90 IU/kg Every 16 days	95 IU/kg Every 16 days	100 IU/kg Every 16 days
17 days	55 IU/kg Every 17 days	60 IU/kg Every 17 days	65 IU/kg Every 17 days	70 IU/kg Every 17 days	75 IU/kg Every 17 days	80 IU/kg Every 17 days	85 IU/kg Every 17 days	90 IU/kg Every 17 days	95 IU/kg Every 17 days	100 IU/kg Every 17 days
18 days	55 IU/kg Every 18 days	60 IU/kg Every 18 days	65 IU/kg Every 18 days	70 IU/kg Every 18 days	75 IU/kg Every 18 days	80 IU/kg Every 18 days	85 IU/kg Every 18 days	90 IU/kg Every 18 days	95 IU/kg Every 18 days	100 IU/kg Every 18 days
19 days	55 IU/kg Every	60 IU/kg Every	65 IU/kg Every	70 IU/kg Every	75 IU/kg Every	80 IU/kg Every	85 IU/kg Every	90 IU/kg Every	95 IU/kg Every	100 IU/kg Every

	19 days	19 days	19 days	19 days	19 days	19 days	19 days	19 days	19 days	19 days
20 days	55 IU/kg Every 20 days	60 IU/kg Every 20 days	65 IU/kg Every 20 days	70 IU/kg Every 20 days	75 IU/kg Every 20 days	80 IU/kg Every 20 days	85 IU/kg Every 20 days	90 IU/kg Every 20 days	95 IU/kg Every 20 days	100 IU/kg Every 20 days
21 days	55 IU/kg Every 21 days	60 IU/kg Every 21 days	65 IU/kg Every 21 days	70 IU/kg Every 21 days	75 IU/kg Every 21 days	80 IU/kg Every 21 days	85 IU/kg Every 21 days	90 IU/kg Every 21 days	95 IU/kg Every 21 days	100 IU/kg Every 21 days

Table 1B: Dosing amounts and corresponding dosing intervals, e.g., for prophylactic treatment of hemophilia.

	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
5 days	55 IU/kg Every 5 days	60 IU/kg Every 5 days	65 IU/kg Every 5 days	70 IU/kg Every 5 days	75 IU/kg Every 5 days	80 IU/kg Every 5 days	85 IU/kg Every 5 days	90 IU/kg Every 5 days	95 IU/kg Every 5 days	100 IU/kg Every 5 days
6 days	55 IU/kg Every 6 days	60 IU/kg Every 6 days	65 IU/kg Every 6 days	70 IU/kg Every 6 days	75 IU/kg Every 6 days	80 IU/kg Every 6 days	85 IU/kg Every 6 days	90 IU/kg Every 6 days	95 IU/kg Every 6 days	100 IU/kg Every 6 days
7 days	55 IU/kg Every 7 days	60 IU/kg Every 7 days	65 IU/kg Every 7 days	70 IU/kg Every 7 days	75 IU/kg Every 7 days	80 IU/kg Every 7 days	85 IU/kg Every 7 days	90 IU/kg Every 7 days	95 IU/kg Every 7 days	100 IU/kg Every 7 days
8 days	55 IU/kg Every 8 days	60 IU/kg Every 8 days	65 IU/kg Every 8 days	70 IU/kg Every 8 days	75 IU/kg Every 8 days	80 IU/kg Every 8 days	85 IU/kg Every 8 days	90 IU/kg Every 8 days	95 IU/kg Every 8 days	100 IU/kg Every 8 days
9 days	55 IU/kg Every 9 days	60 IU/kg Every 9 days	65 IU/kg Every 9 days	70 IU/kg Every 9 days	75 IU/kg Every 9 days	80 IU/kg Every 9 days	85 IU/kg Every 9 days	90 IU/kg Every 9 days	95 IU/kg Every 9 days	100 IU/kg Every 9 days
10 days	55 IU/kg Every 10 days	60 IU/kg Every 10 days	65 IU/kg Every 10 days	70 IU/kg Every 10 days	75 IU/kg Every 10 days	80 IU/kg Every 10 days	85 IU/kg Every 10 days	90 IU/kg Every 10 days	95 IU/kg Every 10 days	100 IU/kg Every 10 days
11 days	55 IU/kg Every	60 IU/kg Every	65 IU/kg Every	70 IU/kg Every	75 IU/kg Every	80 IU/kg Every	85 IU/kg Every	90 IU/kg Every	95 IU/kg Every	100 IU/kg Every

	11 days	11 days	11 days	11 days	11 days	11 days	11 days	11 days	11 days	11 days
12 days	55 IU/kg Every 12 days	60 IU/kg Every 12 days	65 IU/kg Every 12 days	70 IU/kg Every 12 days	75 IU/kg Every 12 days	80 IU/kg Every 12 days	85 IU/kg Every 12 days	90 IU/kg Every 12 days	95 IU/kg Every 12 days	100 IU/kg Every 12 days
13 days	55 IU/kg Every 13 days	60 IU/kg Every 13 days	65 IU/kg Every 13 days	70 IU/kg Every 13 days	75 IU/kg Every 13 days	80 IU/kg Every 13 days	85 IU/kg Every 13 days	90 IU/kg Every 13 days	95 IU/kg Every 13 days	100 IU/kg Every 13 days
14 days	55 IU/kg Every 14 days	60 IU/kg Every 14 days	65 IU/kg Every 14 days	70 IU/kg Every 14 days	75 IU/kg Every 14 days	80 IU/kg Every 14 days	85 IU/kg Every 14 days	90 IU/kg Every 14 days	95 IU/kg Every 14 days	100 IU/kg Every 14 days
15 days	55 IU/kg Every 15 days	60 IU/kg Every 15 days	65 IU/kg Every 15 days	70 IU/kg Every 15 days	75 IU/kg Every 15 days	80 IU/kg Every 15 days	85 IU/kg Every 15 days	90 IU/kg Every 15 days	95 IU/kg Every 15 days	100 IU/kg Every 15 days
16 days	55 IU/kg Every 16 days	60 IU/kg Every 16 days	65 IU/kg Every 16 days	70 IU/kg Every 16 days	75 IU/kg Every 16 days	80 IU/kg Every 16 days	85 IU/kg Every 16 days	90 IU/kg Every 16 days	95 IU/kg Every 16 days	100 IU/kg Every 16 days
17 days	55 IU/kg Every 17 days	60 IU/kg Every 17 days	65 IU/kg Every 17 days	70 IU/kg Every 17 days	75 IU/kg Every 17 days	80 IU/kg Every 17 days	85 IU/kg Every 17 days	90 IU/kg Every 17 days	95 IU/kg Every 17 days	100 IU/kg Every 17 days
18 days	55 IU/kg Every 18 days	60 IU/kg Every 18 days	65 IU/kg Every 18 days	70 IU/kg Every 18 days	75 IU/kg Every 18 days	80 IU/kg Every 18 days	85 IU/kg Every 18 days	90 IU/kg Every 18 days	95 IU/kg Every 18 days	100 IU/kg Every 18 days
19 days	55 IU/kg Every 19 days	60 IU/kg Every 19 days	65 IU/kg Every 19 days	70 IU/kg Every 19 days	75 IU/kg Every 19 days	80 IU/kg Every 19 days	85 IU/kg Every 19 days	90 IU/kg Every 19 days	95 IU/kg Every 19 days	100 IU/kg Every 19 days
20 days	55 IU/kg Every 20 days	60 IU/kg Every 20 days	65 IU/kg Every 20 days	70 IU/kg Every 20 days	75 IU/kg Every 20 days	80 IU/kg Every 20 days	85 IU/kg Every 20 days	90 IU/kg Every 20 days	95 IU/kg Every 20 days	100 IU/kg Every 20 days
21 days	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

	Every 21 days	Every 21 days	Every 21 days	Every 21 days	Every 21 days	Every 21 days	Every 21 days	Every 21 days	Every 21 days	Every 21 days
	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
5 days	55 IU/kg Every 5 days	60 IU/kg Every 5 days	65 IU/kg Every 5 days	70 IU/kg Every 5 days	75 IU/kg Every 5 days	80 IU/kg Every 5 days	85 IU/kg Every 5 days	90 IU/kg Every 5 days	95 IU/kg Every 5 days	100 IU/kg Every 5 days
6 days	55 IU/kg Every 6 days	60 IU/kg Every 6 days	65 IU/kg Every 6 days	70 IU/kg Every 6 days	75 IU/kg Every 6 days	80 IU/kg Every 6 days	85 IU/kg Every 6 days	90 IU/kg Every 6 days	95 IU/kg Every 6 days	100 IU/kg Every 6 days
7 days	55 IU/kg Every 7 days	60 IU/kg Every 7 days	65 IU/kg Every 7 days	70 IU/kg Every 7 days	75 IU/kg Every 7 days	80 IU/kg Every 7 days	85 IU/kg Every 7 days	90 IU/kg Every 7 days	95 IU/kg Every 7 days	100 IU/kg Every 7 days
8 days	55 IU/kg Every 8 days	60 IU/kg Every 8 days	65 IU/kg Every 8 days	70 IU/kg Every 8 days	75 IU/kg Every 8 days	80 IU/kg Every 8 days	85 IU/kg Every 8 days	90 IU/kg Every 8 days	95 IU/kg Every 8 days	100 IU/kg Every 8 days
9 days	55 IU/kg Every 9 days	60 IU/kg Every 9 days	65 IU/kg Every 9 days	70 IU/kg Every 9 days	75 IU/kg Every 9 days	80 IU/kg Every 9 days	85 IU/kg Every 9 days	90 IU/kg Every 9 days	95 IU/kg Every 9 days	100 IU/kg Every 9 days
10 days	55 IU/kg Every 10 days	60 IU/kg Every 10 days	65 IU/kg Every 10 days	70 IU/kg Every 10 days	75 IU/kg Every 10 days	80 IU/kg Every 10 days	85 IU/kg Every 10 days	90 IU/kg Every 10 days	95 IU/kg Every 10 days	100 IU/kg Every 10 days
11 days	55 IU/kg Every 11 days	60 IU/kg Every 11 days	65 IU/kg Every 11 days	70 IU/kg Every 11 days	75 IU/kg Every 11 days	80 IU/kg Every 11 days	85 IU/kg Every 11 days	90 IU/kg Every 11 days	95 IU/kg Every 11 days	100 IU/kg Every 11 days
12 days	55 IU/kg Every 12 days	60 IU/kg Every 12 days	65 IU/kg Every 12 days	70 IU/kg Every 12 days	75 IU/kg Every 12 days	80 IU/kg Every 12 days	85 IU/kg Every 12 days	90 IU/kg Every 12 days	95 IU/kg Every 12 days	100 IU/kg Every 12 days
13 days	55 IU/kg Every 13 days	60 IU/kg Every 13 days	65 IU/kg Every 13 days	70 IU/kg Every 13 days	75 IU/kg Every 13 days	80 IU/kg Every 13 days	85 IU/kg Every 13 days	90 IU/kg Every 13 days	95 IU/kg Every 13 days	100 IU/kg Every 13 days
14 days	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

	Every 14 days	Every 14 days	Every 14 days	Every 14 days	Every 14 days	Every 14 days	Every 14 days	Every 14 days	Every 14 days	Every 14 days
15 days	55 IU/kg Every 15 days	60 IU/kg Every 15 days	65 IU/kg Every 15 days	70 IU/kg Every 15 days	75 IU/kg Every 15 days	80 IU/kg Every 15 days	85 IU/kg Every 15 days	90 IU/kg Every 15 days	95 IU/kg Every 15 days	100 IU/kg Every 15 days
16 days	55 IU/kg Every 16 days	60 IU/kg Every 16 days	65 IU/kg Every 16 days	70 IU/kg Every 16 days	75 IU/kg Every 16 days	80 IU/kg Every 16 days	85 IU/kg Every 16 days	90 IU/kg Every 16 days	95 IU/kg Every 16 days	100 IU/kg Every 16 days
17 days	55 IU/kg Every 17 days	60 IU/kg Every 17 days	65 IU/kg Every 17 days	70 IU/kg Every 17 days	75 IU/kg Every 17 days	80 IU/kg Every 17 days	85 IU/kg Every 17 days	90 IU/kg Every 17 days	95 IU/kg Every 17 days	100 IU/kg Every 17 days
18 days	55 IU/kg Every 18 days	60 IU/kg Every 18 days	65 IU/kg Every 18 days	70 IU/kg Every 18 days	75 IU/kg Every 18 days	80 IU/kg Every 18 days	85 IU/kg Every 18 days	90 IU/kg Every 18 days	95 IU/kg Every 18 days	100 IU/kg Every 18 days
19 days	55 IU/kg Every 19 days	60 IU/kg Every 19 days	65 IU/kg Every 19 days	70 IU/kg Every 19 days	75 IU/kg Every 19 days	80 IU/kg Every 19 days	85 IU/kg Every 19 days	90 IU/kg Every 19 days	95 IU/kg Every 19 days	100 IU/kg Every 19 days
20 days	55 IU/kg Every 20 days	60 IU/kg Every 20 days	65 IU/kg Every 20 days	70 IU/kg Every 20 days	75 IU/kg Every 20 days	80 IU/kg Every 20 days	85 IU/kg Every 20 days	90 IU/kg Every 20 days	95 IU/kg Every 20 days	100 IU/kg Every 20 days
21 days	55 IU/kg Every 21 days	60 IU/kg Every 21 days	65 IU/kg Every 21 days	70 IU/kg Every 21 days	75 IU/kg Every 21 days	80 IU/kg Every 21 days	85 IU/kg Every 21 days	90 IU/kg Every 21 days	95 IU/kg Every 21 days	100 IU/kg Every 21 days

[0110] In some embodiments, such as for prophylactic treatment of hemophilia A, at least one of the multiple doses is administered at a dose of about 25 IU/kg to about 65 IU/kg at a dosing interval of at least about 5 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg to about 65 IU/kg at a dosing interval of at least about 6 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg to about 65 IU/kg at a dosing interval of at least about 6 to 10 days. In some embodiments, at least one

30

doses is administered at a dose of about 25 IU/kg to about 65 IU/kg at a dosing interval of at least about 14 to 21 days.

[0111] In some embodiments, such as for prophylactic treatment of hemophilia A, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 5 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 6 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 6 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 6 to 8 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 6 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 6 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 6 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 6 to 13 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 7 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 7 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 7 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 7 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 7 to 13 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 7 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 8 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 9 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 10 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 10 to 21 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 11 to 14 days. In some embodiments, at least one of the multiple doses is administered at a

dose of about 25 IU/kg at a dosing interval of at least about 12 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 12 to 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 13 to 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 25 IU/kg at a dosing interval of at least about 14 to 21 days.

[0112] In some embodiments, such as for prophylactic treatment of hemophilia A, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 5 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 6 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 6 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 6 to 8 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 6 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 6 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 6 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 6 to 13 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 7 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 7 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 7 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 7 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 7 to 13 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 7 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 8 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 9 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 10 to

14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 10 to 21 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 11 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 12 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 12 to 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 13 to 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg at a dosing interval of at least about 14 to 21 days.

[0113] In some embodiments, such as for prophylactic treatment of hemophilia A, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 5 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 6 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 6 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 6 to 8 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 6 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 6 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 6 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 6 to 13 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 7 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 7 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 7 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 7 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 7 to 13 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 7 to 14 days. In some embodiments, at least one

of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 8 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 9 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 10 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 10 to 21 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 11 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 12 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 12 to 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 13 to 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg at a dosing interval of at least about 14 to 21 days.

[0114] In some embodiments, such as for prophylactic treatment of hemophilia A, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 5 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 6 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 6 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 6 to 8 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 6 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 6 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 6 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 6 to 13 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 7 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 7 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 7 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of

about 80 IU/kg at a dosing interval of at least about 7 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 7 to 13 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 7 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 8 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 9 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 10 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 10 to 21 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 11 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 12 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 12 to 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 13 to 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 80 IU/kg at a dosing interval of at least about 14 to 21 days.

[0115] In some embodiments, such as for prophylactic treatment of hemophilia A, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 5 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 8 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 13 days. In

some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 to 13 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 8 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 9 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 10 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 10 to 21 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 11 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 12 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 12 to 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 13 to 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 80 IU/kg at a dosing interval of at least about 14 to 21 days.

[0116] In some embodiments, such as for prophylactic treatment of hemophilia A, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 65 IU/kg at a dosing interval of at least about 5 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 65 IU/kg at a dosing interval of at least about 6 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 50 IU/kg to about 65 IU/kg at a dosing interval of at least about 6 to 10 days. In some embodiments, at least one

[illegible]

doses is administered at a dose of about 50 IU/kg to about 65 IU/kg at a dosing interval of at least about 14 to 21 days.

[0117] In some embodiments, such as for prophylactic treatment of hemophilia A, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 5 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 8 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 13 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 to 13 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 8 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 9 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 10 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to

about 80 IU/kg at a dosing interval of at least about 10 to 21 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 11 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 12 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 12 to 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 13 to 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 14 to 21 days.

[0118] In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 2 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 2 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 2 to 8 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 2 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 2 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 2 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 2 to 13 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 4 to 9 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 4 to 10 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 4 to 11 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 4 to 12 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 4 to 13 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about

80 IU/kg at a dosing interval of at least about 4 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 5 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 5 to 14 days. In some
5 embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 to 14 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 8 to 14 days. In some
10 embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 10 to 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 10 to 21 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 13 to
15 15 days. In some embodiments, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 14 to 21 days.

[0119] In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 5 days. In some embodiments, such as for prophylactic
20 treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 7 days. In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 6 days. In some embodiments, such as for prophylactic treatment of hemophilia A in
25 a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 5 days. In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 4 days. In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject,
30 at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 3 days. In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of

about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 2 days. In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 8 days. In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 9 days. In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 10 days. In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 11 days. In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 12 days. In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 13 days. In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 14 days. In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 21 days.

[0120] In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing interval of at least about 1 week. In some embodiments, such as for prophylactic treatment of hemophilia A in a pediatric subject, at least one of the multiple doses is administered at a dose of about 65 IU/kg to about 80 IU/kg at a dosing frequency of at least twice about every 1 week.

[0121] In certain embodiments, such as for prophylactic treatment of hemophilia A, the method comprises administering to the subject multiple doses of a chimeric polypeptide comprising (i) a FVIII protein and (ii) a VWF fragment comprising a D' domain of VWF and a D3 domain of VWF, e.g., rFVIII-Fc-VWF-XTEN, at a dosing interval, wherein at least one of the multiple doses is from about 15 IU/kg to about 100 IU/kg and the dosing interval is at least about 5 days. In certain embodiments, such as for prophylactic treatment of hemophilia A, the method comprises administering to the subject multiple doses of a chimeric polypeptide comprising (i) a FVIII protein and (ii) a VWF fragment

comprising a D' domain of VWF and a D3 domain of VWF at a dosing interval, wherein at least one of the multiple doses is from about 15 IU/kg to about 100 IU/kg and the dosing interval is at least about 7 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 8 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 9 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 10 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 11 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 12 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 13 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 14 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 15 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 16 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 17 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 18 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 19 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 20 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg to about 65 IU/kg and the dosing interval is at least about 21 days.

[0122] In certain embodiments, the method comprises administering to the subject multiple doses of a chimeric polypeptide comprising (i) a FVIII protein and (ii) a VWF fragment comprising a D' domain of VWF and a D3 domain of VWF, e.g., rFVIII-Fc-VWF-XTEN, at a dosing interval, wherein at least one of the multiple doses is about 25 IU/kg and the dosing interval is at least about 5 days. In certain embodiments, the method comprises administering to the subject multiple doses of a chimeric polypeptide comprising (i) a FVIII protein and (ii) a VWF fragment comprising a D' domain of VWF and a D3 domain of VWF at a dosing interval, wherein at least one of the multiple doses is about 25 IU/kg and the dosing interval is at least about 6 days. In some embodiments, the method is

for the prophylactic treatment of hemophilia A. In certain embodiments, at least one of the multiple doses is about 25 IU/kg and the dosing interval is at least about 7 days. In certain embodiments, at least one of the multiple doses is about 25 IU/kg and the dosing interval is at least about 8 days. In certain embodiments, at least one of the multiple doses is about 25 IU/kg and the dosing interval is at least about 9 days. In certain embodiments, at least one of the multiple doses is about 25 IU/kg and the dosing interval is at least about 10 days. In certain embodiments, at least one of the multiple doses is about 25 IU/kg and the dosing interval is at least about 11 days. In certain embodiments, at least one of the multiple doses is about 25 IU/kg and the dosing interval is at least about 12 days. In certain embodiments, at least one of the multiple doses is about 25 IU/kg and the dosing interval is at least about 13 days. In certain embodiments, at least one of the multiple doses is about 25 IU/kg and the dosing interval is at least about 14 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg and the dosing interval is at least about 15 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg and the dosing interval is at least about 16 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg and the dosing interval is at least about 17 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg and the dosing interval is at least about 18 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg and the dosing interval is at least about 19 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg and the dosing interval is at least about 20 days. In certain embodiments, at least one of the multiple doses is from about 25 IU/kg and the dosing interval is at least about 21 days.

[0123] In certain embodiments, the method comprises administering to the subject multiple doses of a chimeric polypeptide comprising (i) a FVIII protein and (ii) a VWF fragment comprising a D' domain of VWF and a D3 domain of VWF, e.g., rFVIII-Fc-VWF-XTEN, at a dosing interval, wherein at least one of the multiple doses is about 50 IU/kg and the dosing interval is at least about 5 days. In certain embodiments, the method comprises administering to the subject multiple doses of a chimeric polypeptide comprising (i) a FVIII protein and (ii) a VWF fragment comprising a D' domain of VWF and a D3 domain of VWF at a dosing interval, wherein at least one of the multiple doses is about 50 IU/kg and the dosing interval is at least about 6 days. In some embodiments, the method is for the prophylactic treatment of hemophilia A. In certain embodiments, at least one of the multiple doses is about 50 IU/kg and the dosing interval is at least about 7 days. In certain embodiments, at least one of the multiple doses is about 50 IU/kg and the dosing interval is at least about 8 days. In certain embodiments, at least one of the multiple doses is about 50 IU/kg and the dosing interval is at least

about 9 days. In certain embodiments, at least one of the multiple doses is about 50 IU/kg and the dosing interval is at least about 10 days. In certain embodiments, at least one of the multiple doses is about 50 IU/kg and the dosing interval is at least about 11 days. In certain embodiments, at least one of the multiple doses is about 50 IU/kg and the dosing interval is at least about 12 days. In certain
5 embodiments, at least one of the multiple doses is about 50 IU/kg and the dosing interval is at least about 13 days. In certain embodiments, at least one of the multiple doses is about 50 IU/kg and the dosing interval is at least about 14 days. In certain embodiments, at least one of the multiple doses is from about 50 IU/kg and the dosing interval is at least about 15 days. In certain embodiments, at least one of the multiple doses is from about 50 IU/kg and the dosing interval is at least about 16
10 days. In certain embodiments, at least one of the multiple doses is from about 50 IU/kg and the dosing interval is at least about 17 days. In certain embodiments, at least one of the multiple doses is from about 50 IU/kg and the dosing interval is at least about 18 days. In certain embodiments, at least one of the multiple doses is from about 50 IU/kg and the dosing interval is at least about 19 days. In certain embodiments, at least one of the multiple doses is from about 50 IU/kg and the dosing interval is at
15 least about 20 days. In certain embodiments, at least one of the multiple doses is from about 50 IU/kg and the dosing interval is at least about 21 days.

[0124] In certain embodiments, the method comprises administering to the subject multiple doses of a chimeric polypeptide comprising (i) a FVIII protein and (ii) a VWF fragment comprising a D' domain of VWF and a D3 domain of VWF, e.g., rFVIII-Fc-VWF-XTEN, at a dosing interval, wherein
20 at least one of the multiple doses is about 65 IU/kg and the dosing interval is at least about 5 days. In certain embodiments, the method comprises administering to the subject multiple doses of a chimeric polypeptide comprising (i) a FVIII protein and (ii) a VWF fragment comprising a D' domain of VWF and a D3 domain of VWF at a dosing interval, wherein at least one of the multiple doses is about 65 IU/kg and the dosing interval is at least about 6 days. In some embodiments, the method is
25 for the prophylactic treatment of hemophilia A. In certain embodiments, at least one of the multiple doses is about 65 IU/kg and the dosing interval is at least about 7 days. In certain embodiments, at least one of the multiple doses is about 65 IU/kg and the dosing interval is at least about 8 days. In certain embodiments, at least one of the multiple doses is about 65 IU/kg and the dosing interval is at least about 9 days. In certain embodiments, at least one of the multiple doses is about 65 IU/kg
30 and the dosing interval is at least about 10 days. In certain embodiments, at least one of the multiple doses is about 65 IU/kg and the dosing interval is at least about 11 days. In certain embodiments, at least one of the multiple doses is about 65 IU/kg and the dosing interval is at least about 12 days. In

certain embodiments, at least one of the multiple doses is about 65 IU/kg and the dosing interval is at least about 13 days. In certain embodiments, at least one of the multiple doses is about 65 IU/kg and the dosing interval is at least about 14 days. In certain embodiments, at least one of the multiple doses is from about 65 IU/kg and the dosing interval is at least about 15 days. In certain embodiments, at least one of the multiple doses is from about 65 IU/kg and the dosing interval is at least about 16 days. In certain embodiments, at least one of the multiple doses is from about 65 IU/kg and the dosing interval is at least about 17 days. In certain embodiments, at least one of the multiple doses is from about 65 IU/kg and the dosing interval is at least about 18 days. In certain embodiments, at least one of the multiple doses is from about 65 IU/kg and the dosing interval is at least about 19 days. In certain embodiments, at least one of the multiple doses is from about 65 IU/kg and the dosing interval is at least about 20 days. In certain embodiments, at least one of the multiple doses is from about 65 IU/kg and the dosing interval is at least about 21 days.

[0125] In certain embodiments, the method comprises administering to the subject multiple doses of a chimeric polypeptide comprising (i) a FVIII protein and (ii) a VWF fragment comprising a D' domain of VWF and a D3 domain of VWF, e.g., rFVIII-Fc-VWF-XTEN, at a dosing interval, wherein at least one of the multiple doses is about 80 IU/kg and the dosing interval is at least about 5 days. In certain embodiments, the method comprises administering to the subject multiple doses of a chimeric polypeptide comprising (i) a FVIII protein and (ii) a VWF fragment comprising a D' domain of VWF and a D3 domain of VWF at a dosing interval, wherein at least one of the multiple doses is about 80 IU/kg and the dosing interval is at least about 6 days. In some embodiments, the method is for the prophylactic treatment of hemophilia A. In certain embodiments, at least one of the multiple doses is about 80 IU/kg and the dosing interval is at least about 7 days. In certain embodiments, at least one of the multiple doses is about 80 IU/kg and the dosing interval is at least about 8 days. In certain embodiments, at least one of the multiple doses is about 80 IU/kg and the dosing interval is at least about 9 days. In certain embodiments, at least one of the multiple doses is about 80 IU/kg and the dosing interval is at least about 10 days. In certain embodiments, at least one of the multiple doses is about 80 IU/kg and the dosing interval is at least about 11 days. In certain embodiments, at least one of the multiple doses is about 80 IU/kg and the dosing interval is at least about 12 days. In certain embodiments, at least one of the multiple doses is about 80 IU/kg and the dosing interval is at least about 13 days. In certain embodiments, at least one of the multiple doses is about 80 IU/kg and the dosing interval is at least about 14 days. In certain embodiments, at least one of the multiple doses is from about 80 IU/kg and the dosing interval is at least about 15 days. In certain embodiments,

at least one of the multiple doses is from about 80 IU/kg and the dosing interval is at least about 16 days. In certain embodiments, at least one of the multiple doses is from about 80 IU/kg and the dosing interval is at least about 17 days. In certain embodiments, at least one of the multiple doses is from about 80 IU/kg and the dosing interval is at least about 18 days. In certain embodiments, at least one of the multiple doses is from about 80 IU/kg and the dosing interval is at least about 19 days. In certain embodiments, at least one of the multiple doses is from about 80 IU/kg and the dosing interval is at least about 20 days. In certain embodiments, at least one of the multiple doses is from about 80 IU/kg and the dosing interval is at least about 21 days.

[0126] In some embodiments, the chimeric polypeptide is administered for prophylactic treatment of hemophilia A. Prophylactic treatment of hemophilia A includes alleviating or reducing the severity of the symptoms of hemophilia A on a continuous or nearly continuous basis. In some embodiments, the prophylactic treatment is administered before the occurrence of a symptom of hemophilia A, e.g., before a bleeding incident. In other embodiments, the prophylactic treatment is administered on a regular basis, e.g., at a dosing interval described herein, to prevent the onset of or to lessen the severity of a symptom prior to the onset of the symptom. Any dosing interval disclosed herein can be used in a prophylactic treatment of hemophilia A.

[0127] In other embodiments, the chimeric polypeptide is administered before an activity that can bring on one or more symptom of hemophilia A, e.g., as an on-demand treatment. For example, a chimeric polypeptide of the present disclosure can be administered to a subject suffering from hemophilia A before the subject undergoes a surgery or engages in an activity that otherwise increases the risk of physical trauma and/or a bleeding incident. When administered on-demand, the chimeric polypeptide can be administered as a single dose or as multiple doses. In some embodiments, the on-demand treatment comprises administering multiple doses of the chimeric polypeptide at a dosing interval of at least about 12 hours, at least about 24 hours, at least about 36 hours, at least about 48 hours, at least about 60 hours, at least about 72 hours, at least about 84 hours, at least about 96 hours, at least about 108 hours or at least about 120 hours. In certain embodiments, the on-demand treatment comprises administering at least 2 doses, at least 3 doses, at least 4 doses or at least 5 doses of the chimeric polypeptide.

[0128] In some embodiments, the subject has previously been treated with one or more FVIII replacement therapy. In certain embodiments, the subject failed to respond to a previous FVIII replacement therapy. In certain embodiments, the FVIII replacement therapy is ELOCTATE® or ADVATE®. In some embodiments, the subject is an adult. In some embodiments, the subject is an

adult male. In other embodiments, the subject is an adult female. In other embodiments, the subject is a child, e.g., less than or equal to about 12 years old, less than or equal to about 11 years old, less than or equal to about 10 years old, less than or equal to about 9 years old, less than or equal to about 8 years old, less than or equal to about 7 years old, less than or equal to about 6 years old, less than or equal to about 5 years old, less than or equal to about 4 years old, less than or equal to about 3 years old, less than or equal to about 2 years old, or less than or equal to about 1 year old). In some embodiments, the subject is a female. In some embodiments, the subject is a male. In some embodiments, the subject is a female less than or equal to about 12 years old. In some embodiments, the subject is a female less than or equal to about 11 years old. In some embodiments, the subject is a female less than or equal to about 10 years old.

[0129] A chimeric polypeptide described herein can be administered by any means known in the art. In some embodiments, the chimeric polypeptide is administered by a route selected from the group consisting of intravenous injection, intravenous infusion, subcutaneous administration, intramuscular administration, oral administration, nasal administration, and pulmonary administration. In some embodiments, the chimeric polypeptide is administered intravenously. In other embodiments, the chimeric polypeptide is administered subcutaneously.

[0130] In some embodiments, the chimeric polypeptide, e.g., rFVIII_h-VWF-XTEN, after the administration results in a FVIII plasma activity level of at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, or at least about 10%. In certain embodiments, the FVIII plasma activity level is at least about 3%. In some embodiments, the FVIII plasma activity level is at least about 4%. In some embodiments, the FVIII plasma activity level is at least about 5%. In some embodiments, the FVIII plasma activity level is at least about 4%. In some embodiments, the FVIII plasma activity level is at least about 5%. In some embodiments, the FVIII plasma activity level is at least about 5.6%. In some embodiments, the FVIII plasma activity level is at least about 7%. In some embodiments, the FVIII plasma activity level is at least about 10%. In some embodiments, the FVIII plasma activity level is at least about 12%. In some embodiments, the FVIII plasma activity level is at least about 12.95%. As used herein, plasma activity level is expressed as a percent (%). Alternatively, plasma activity can be expressed in IU/dL units, wherein 1% is equal to 1 IU/dL.

[0131] In some embodiments, the FVIII plasma activity level is at least about 10% at least about 5 days after the administration of the chimeric polypeptide, e.g., at a dose of 25 IU/kg. In some embodiments, the FVIII plasma activity level is at least about 12% at least about 5 days after the

administration of the chimeric polypeptide, e.g., at a dose of 25 IU/kg. In some embodiments, the FVIII plasma activity level is at least about 12.95% at least about 5 days after the administration of the chimeric polypeptide, e.g., at a dose of 25 IU/kg. In some embodiments, the FVIII plasma activity level is at least about 5% at least about 7 days after the administration of the chimeric polypeptide, e.g., at a dose of 25 IU/kg. In some embodiments, the FVIII plasma activity level is at least about 5.6% at least about 7 days after the administration of the chimeric polypeptide, e.g., at a dose of 25 IU/kg. In some embodiments, the FVIII plasma activity level is at least about 3% at least about 8 days after the administration of the chimeric polypeptide, e.g., at a dose of 25 IU/kg. In some embodiments, the FVIII plasma activity level is at least about 1% at least about 10 days after the administration of the chimeric polypeptide, e.g., at a dose of 25 IU/kg.

[0132] The present disclosure also includes a method of treating hemophilia A comprising administering to a subject a composition comprising (i) a FVIII protein and (ii) a VWF fragment. In some embodiments, the FVIII protein is present in a first formulation and the VWF fragment is present in a second formulation. In other embodiments, the FVIII protein and the VWF fragment are present in the same formulation. In particular embodiments, the FVIII protein and the VWF fragment are separate components of a single formulation. In certain embodiments, the FVIII protein, e.g., single chain FVIII, FVIII-Fc, pegylated FVIII, full length mature FVIII, or B domain deleted FVIII, is administered at a dose disclosed herein, e.g., 25 IU/kg, 30 IU/kg, 35 IU/kg, 40 IU/kg, 45 IU/kg, 50 IU/kg, 55 IU/kg, 60 IU/kg, or 65 IU/kg, and at a doing interval of at least 6 days, at least 7 days, at least 8 days, at least 9 days, at least 10 days, at least 11 days, at least 12 days, at least 13 days, or at least 14 days, and the VWF fragment is administered at a dose of at least about 0.25:1, 0.5:1, 1:1, 2:1, 3:1, 4:1, 5:1, 10:1, 15:1, 20:1, 25:1, 30:1, 35:1, 40:1, 45:1, 50:1, 100:1, 200:1, 300:1, 400:1, 500:1, 1000:1, 2000:1, 3000:1, 4000:1, 5000:1, 10,000:1, 50,000:1, 100,000:1, or 500,000:1 VWF fragment to FVIII molecule administered. In other embodiments, the VWF fragment is administered to the subject concurrently with, right after, or right before the FVIII protein. In certain embodiments, the VWF fragment is administered about 0.5 hours, about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 3 hours, about 3.5 hours, about 4 hours, about 4.5 hours, about 5 hours, about 5.5 hours, or about 6 hours before the FVIII protein. In other embodiments, the FVIII protein is administered about 0.5 hours, about 1 hour, about 1.5 hours, about 2 hours, about 2.5 hours, about 3 hours, about 3.5 hours, about 4 hours, about 4.5 hours, about 5 hours, about 5.5 hours, or about 6 hours before the VWF fragment.

C. Immune Tolerance Induction

[0133] Certain aspects of the present disclosure are directed to methods of treating hemophilia A in a subject in need thereof, comprising administering to the subject a chimeric polypeptide comprising a FVIII protein and a VWF fragment at a dosing interval, wherein the chimeric polypeptide induces immune tolerance to FVIII in the subject. Some aspects of the present disclosure are directed to methods of treating hemophilia A in a subject in need thereof, comprising administering to the subject a chimeric polypeptide comprising a FVIII protein and a VWF fragment at a dosing interval, wherein the chimeric polypeptide reduces an inhibitory response to FVIII in the subject. Some aspects of the present disclosure are directed to methods of treating hemophilia A in a subject in need thereof, comprising administering to the subject a chimeric polypeptide comprising a FVIII protein and a VWF fragment at a dosing interval, wherein the chimeric polypeptide does not induce an immune response to the chimeric polypeptide following the administration. Another aspect of the present disclosure is directed to a method of inducing immune tolerance in a human with hemophilia, comprising (1) administering to the human an effective amount of a chimeric polypeptide described herein, e.g., rFVIII-Fc-VWF-XTEN, wherein the effective amount of the chimeric polypeptide induces immune tolerance in the human. Various methods of immune tolerance induction using chimeric polypeptides comprising a FVIII and an Fc are disclosed in International Publication No. WO 2018/102760 A1, which is incorporated by reference herein in its entirety.

[0134] In certain embodiments, the method further comprises (2) following induction of immune tolerance, administering to the human a tapering regimen of the composition or the chimeric polypeptide. In certain embodiments, induction of immune tolerance occurs when the titer of the inhibitory antibodies in the human is less than about 0.6 BU. In certain embodiments, induction of immune tolerance occurs when the titer of the inhibitory antibodies in the human is less than about 0.6 BU, and 60% recovery of clotting factor activity as monitored in plasma. In some embodiments of the present disclosure, the method further comprises (3) following the tapering regimen, administering to the human a prophylactic dose of the clotting factor, e.g., a chimeric polypeptide described herein, e.g., rFVIII-Fc-VWF-XTEN.

[0135] In certain aspects, the human has not been treated with a previous immune tolerance therapy against the clotting factor, e.g., against a FVIII. The chimeric polypeptide, e.g., rFVIII-Fc-VWF-XTEN, can be administered to the human at any time it has been determined that the human has developed an inhibitor immune response, e.g., after measuring the level of an inhibitory immune response in the human. In other embodiments, the chimeric polypeptide, e.g., rFVIII-Fc-VWF-XTEN,

can be administered to the human who has not yet developed one or more inhibitor immune response to prevent development of an inhibitor immune response. In some embodiments, the chimeric polypeptide, e.g., rFVIII^hFc-VWF-XTEN, is administered to the human who has a high likelihood (e.g., family history, genetic predisposition, or showing of a biomarker) of developing an inhibitor immune response. In some embodiments, the method further comprises measuring the level of an inhibitory immune response or the likelihood of developing an inhibitor immune response before the administration.

[0136] In some embodiments, the chimeric polypeptide, e.g., rFVIII^hFc-VWF-XTEN, is administered to the human less than about 1 day, less than about 2 days, less than about 3 days, less than about 4 days, less than about 5 days, less than about 6 days, less than about 7 days, less than about 2 weeks, less than about 3 weeks, less than about 4 weeks, less than about 2 months, less than about 3 months, less than about 4 months, less than about 5 months, less than about 6 months, less than about 1 year, less than about 2 years, less than about 3 years, less than about 4 years, or less than about 5 years after it has been determined that the human has developed an inhibitor immune response or that the human has a likelihood of developing an inhibitor immune response, e.g., after measuring the level of an inhibitory immune response or the likelihood of developing an inhibitor immune response in the human. In certain embodiments, the chimeric polypeptide, e.g., rFVIII^hFc-VWF-XTEN, is administered to the human immediately after it has been determined that the human has developed an inhibitor immune response or that the human has a likelihood of developing an inhibitor immune response, e.g., after measuring the level of an inhibitory immune response or the likelihood of developing an inhibitor immune response in the human. In particular embodiments, the chimeric polypeptide, e.g., rFVIII^hFc-VWF-XTEN, is administered to the human less than about 5 minutes, less than about 10 minutes, less than about 15 minutes, less than about 20 minutes, less than about 30 minutes, less than about 45 minutes, less than about 1 hour, less than about 2 hours, less than about 3 hours, less than about 4 hours, less than about 5 hours, less than about 6 hours, less than about 7 hours, less than about 8 hours, less than about 9 hours, less than about 10 hours, less than about 11 hours, less than about 12 hours, about 18 hours, or less than about 24 hours after it has been determined that the human has developed an inhibitor immune response or that the human has a likelihood of developing an inhibitor immune response, e.g., after measuring the level of an inhibitory immune response or the likelihood of developing an inhibitor immune response in the human. In particular embodiments, the chimeric polypeptide, e.g., rFVIII^hFc-VWF-XTEN, is administered to the human about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes,

about 30 minutes, about 45 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 18 hours, or about 24 hours after it has been determined that the human has developed an inhibitor immune response or that the human has a likelihood of developing an inhibitor immune response, e.g., after measuring the level of an inhibitory immune response or the likelihood of developing an inhibitor immune response in the human. In certain embodiments, the chimeric polypeptide, e.g., rFVIII^hFc-VWF-XTEN, is administered to the human less than about 1 day after it has been determined that the human has developed an inhibitor immune response or that the human has a likelihood of developing an inhibitor immune response, e.g., after measuring the level of an inhibitory immune response or the likelihood of developing an inhibitor immune response in the human.

[0137] Induction of an immune response can be continued until the level of inhibitor is lower than a certain level or until inhibitors are not detectable. In certain embodiments, the induction period can continue for at least about 24 weeks, at least about 26 weeks, at least about 28 weeks, at least about 30 weeks, at least about 32 weeks, at least about 34 weeks, at least about 36 weeks, at least about 38 weeks, at least about 40 weeks, at least about 42 weeks, at least about 44 weeks, at least about 46 weeks, at least about 48 weeks, at least about 50 weeks, at least about 52 weeks, at least about 54 weeks, at least about 56 weeks, at least about 58 weeks, at least about 60 weeks, at least about 62 weeks, at least about 64 weeks, at least about 66 weeks, at least about 68 weeks, at least about 70 weeks. In a particular embodiment, the induction period is less than 60 weeks.

[0138] The inhibitory immune response treated by the methods of the present invention can include any response within the human that negatively impacts one or more effects of a clotting factor treatment. In some embodiments, the inhibitory immune response comprises production of inhibitory antibodies against the clotting factor, e.g., inhibitory anti-FVIII antibodies. In certain embodiments, the method of the present disclosure further comprises measuring the titer of one or more inhibitory antibodies in the human before (e.g., at baseline) and after administering an effective amount of a chimeric polypeptide described herein, e.g., rFVIII^hFc-VWF-XTEN, or a polynucleotide encoding the same. In some embodiments, titer of the inhibitory antibodies prior to the administration (e.g., at baseline) is at least about 0.6 Bethesda Units (BU). In certain embodiments, the titer of the inhibitory antibodies prior to the administration (e.g., at baseline) is at least about 1 BU, at least about 2 BU, at least about 3 BU, at least about 4 BU, at least about 5 BU, at least about 6 BU, at least about 7 BU, at least about 10 BU, at least about 20 BU, at least about 30 BU, at least about 40 BU, at least about

50 BU, at least about 100 BU, at least about 150 BU, or at least about 200 BU. In one particular embodiment, the titer of the inhibitory antibodies prior to the administration (e.g., at baseline) is at least about 5 BU.

[0139] In some embodiments, the methods of the present invention reduce the titer of inhibitory antibodies in a human subject relative to the titer of the inhibitory antibodies prior to the administration. In certain embodiments, the titer of the inhibitory antibodies after the administration is less than about 0.6 BU. In some embodiments, the titer of the inhibitory antibodies after the administration is less than about 0.5 BU, less than about 0.4 BU, less than about 0.3 BU, less than about 0.2 BU, or less than about 0.1 BU. In one particular embodiment, the titer of the inhibitory antibodies after the administration is 0 BU. In other embodiments, the titer of the inhibitory antibodies after the administration is less than 5 BU, less than 4 BU, less than 3 BU, less than 2 BU, less than 1 BU, less than 0.9 BU, less than 0.8 BU, less than 0.7 BU, or less than 0.6 BU.

[0140] In some embodiments, the administration of a chimeric polypeptide described herein, e.g., rFVIII-Fc-VWF-XTEN, increases the differentiation of macrophages in the human towards an M2-like phenotype, as compared to macrophage differentiation in untreated controls and humans treated with the clotting factor alone. In some embodiments, the M2-like phenotype comprises upregulation of the NRF2 pathway, the PPAR gamma pathway, or both the NRF2 pathway and the PPAR gamma pathway. In some embodiments, the M2-like phenotype comprises upregulation of CD206 (MRC1). In some embodiments, the M2-like phenotype comprises upregulation of ARG1. In some embodiments, the M2-like phenotype comprises upregulation of CD206 (MRC1) and ARG1.

[0141] In some embodiments, the administration of a chimeric polypeptide described herein, e.g., rFVIII-Fc-VWF-XTEN, results in greater expression of one or more genes in the human, relative to the expression of the one or more genes in an untreated subject or in a subject treated with the clotting factor alone. In some embodiments, the administration results in greater expression of one or more genes selected from the group consisting of Hmox1, PPAR gamma, LPL, EGR2, SLCO4A1, heme oxygenase 1 (HO-1), oxidative stress induced growth inhibitor 1 (OSGIN1), superoxide dismutase 1 (SOD1), glutathione-disulfide reductase (GSR), glutamate-cysteine ligase catalytic subunit (GCLC), glutamate-cysteine ligase modifier subunit (GCLM), NAD(P)H quinone dehydrogenase 1 (NQO1), fatty acid binding protein 5 (FABP5), B7-H3 (CD276), SLAM family member 3 (SLAMF3; lymphocyte antigen 9; LY9), SLAM family member 7 (SLAMF7), mannose receptor C-type 1 (MRC1), solute carrier family 12 member 4 (SLC12A), neuropilin 1 (NRP1), and any combination thereof. In some embodiments, the administration results in greater expression of one or more genes of the NRF2

pathway. In certain embodiments, the one or more genes of the NRF2 pathway are selected from the group consisting of HO-1, OSGIN1, SOD1, GSR, GCLC, GCLM, NQO1, and any combination thereof. In some embodiments, the administration results in greater expression of one or more genes of the PPAR gamma pathway. In some embodiments, the one or more genes of the PPAR gamma pathway are selected from the group consisting of PPAR gamma, LPL, FABP5, EGR2, and any combination thereof. In some embodiments, the administration results in greater expression of one or more genes selected from the group consisting of B7-H3 (CD276), SLAMF3, SLAMF7, MRC1, SLC12A, NRP1, and any combination thereof. In particular embodiments, the administration results in greater expression of the one or more genes relative to the expression of the one or more genes in an untreated human or a human administered the clotting factor alone, wherein the expression is at least about 1.5 fold greater, at least about 2 fold greater, at least about 2.5 fold greater, at least about 3 fold greater, at least about 3.5 fold greater, at least about 4 fold greater, at least about 4.5 fold greater, or at least about 5 fold greater.

[0142] In some embodiments, the differential expression of the one or more genes is observed less than 6 hours after the administration of a chimeric polypeptide described herein, e.g., rFVIII-Fc-VWF-XTEN. In some embodiments, the differential expression is observed less than 12 hours after administration. In some embodiments, the differential expression is observed less than 18 hours after administration. In some embodiments, the differential expression is observed less than 24 hours after administration.

[0143] In some embodiments, the inhibitory immune response comprises a cell-mediated immune response. In certain embodiments, the cell-mediated immune response comprises the release of a cytokine. In some embodiments, the cytokine is any cytokine associated with an increased immune response. In some embodiments, the cytokine selected from the group consisting of IL-1, IL-6, IL-16, IL-12, IL-4, IL-17, tumor necrosis factor α (TNF- α), interferon α , interferon γ and any combination thereof. In one embodiment, the cell-mediated immune response comprises increased serum levels of IL-12. In another embodiment, the cell-mediated immune response comprises increased serum levels of IL-4. In another embodiment, the cell-mediated immune response comprises increased serum levels of IL-17. In another embodiment, the cell-mediated immune response comprises increased serum levels of TNF- α .

[0144] Various gene mutations have been linked with an increased risk of developing an inhibitory immune response. For example, the TNF- α -308G>A polymorphism within Hap2, which is associated with increased constitutive and inducible transcription levels of TNF has been linked with an increased

risk of developing an inhibitory immune response. See Astermark et al., Blood 108: 3739-3745 (2006), which is herein incorporated by reference in its entirety. Thus, in some embodiments, the human has a genetic polymorphism associated with increased TNF- α . In some embodiments, the polymorphism is the TNF- α -308G>A polymorphism. In some embodiments, the human has a polymorphism in an IL10 gene, e.g. a polymorphism associated with increased secretion of IL10. In some embodiments, FVIII-Fc is administered to a subject with the allele 134 of the IL10G microsatellite in the promote region of the IL10 gene. See Astermark et al. Hemostasis, Thrombosis, and Vascular Biology 108: 3739-3745 (2006), which is herein incorporated by reference in its entirety.

[0145] In some embodiments, the human has a genetic polymorphism associated with decreased CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4) expression. In some embodiments, the human has a mutation in DR15 (HLA-DR15) or DQB0602 MHC (Major histocompatibility complex) Class II molecules. Other MHC Class II molecules associated with the development of an inhibitory immune response in subjects with hemophilia are A3, B7, C7, DQA0102, C2, DQA0103, DQB0603, and DR13 (see Inhibitors in Patients with Hemophilia, E.C. Rodriguez-Merchan & C.A. Lee, Eds., Blackwell Science, Ltd., 2002).

[0146] In some embodiments, the methods of the present disclosure reduce the level of one or more cytokine in the subject compared to the level of the one or more cytokines in the subject after a previous treatment with a polypeptide consisting of a FVIII protein. In another embodiment, the methods of the present disclosure reduce the level of one or more cytokine in the subject compared to the level of the one or more cytokines in the subject prior to the administration. In other embodiments, the expression of one or more tolerogenic molecules is increased after the administration of the methods of the present disclosure relative to the expression level of the one or more tolerogenic molecules prior to the administration. In certain embodiments, the one or more tolerogenic molecules is selected from IL-10, TGF- β , IL-35, IDO-1, and any combination thereof.

[0147] In other embodiments, the immune response comprises a clinical symptom selected from the group consisting of: increased bleeding tendency, high clotting factor consumption, lack of response to clotting factor therapy, decreased efficacy of clotting factor therapy, shortened half-life of the clotting factor, and any combination thereof. In certain embodiments, the immune response comprises a clinical symptom selected from the group consisting of: increased bleeding tendency, high clotting factor consumption, lack of response to clotting factor therapy, decreased efficacy of clotting factor therapy, decreased recovery of clotting factor activity as monitored in the plasma, shortened half-life of the clotting factor, and any combination thereof.

[0148] In certain embodiments, the human was previously diagnosed as having an inhibitory immune response. Such a diagnosis can be made using any methods known in the art. For example, a human can be characterized as having an immune response to a clotting factor, e.g., a FVIII, if the human has one or more the following: (a) a titer of inhibitory antibodies to the clotting factor greater than or equal to 0.6 BU; (b) increased serum levels of one or more cytokine selected from the group consisting of IL-12, IL-4, IL-17, and TNF- α ; (c) increased bleeding tendency; (d) high clotting factor consumption; (e) a lack of response to clotting factor therapy; (f) decreased efficacy of clotting factor therapy; (g) shortened half-life of the clotting factor, and any combination thereof. In one particular embodiment, the human is characterized as having an immune response to a clotting factor if the human has a titer of inhibitory antibodies to the clotting factor greater than or equal to 0.6 BU.

[0149] In some embodiments, the human was previously diagnosed as having developed an inhibitory immune response to the clotting factor at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about 13 months, at least about 14 months, at least about 15 months, at least about 16 months, at least about 17 months, at least about 18 months, at least about 19 months, at least about 20 months, at least about 21 months, at least about 22 months, at least about 23 months, at least about 24 months, at least about 27 months, at least about 30 months, at least about 33 months, at least about 36 months, at least about 39 months, at least about 42 months, at least about 45 months, at least about 48 years, at least about 51 months, at least about 54 months, at least about 57 months, at least about 60 months, at least about 6 years, at least about 7 years, at least about 8 years, at least about 10 years, at least about 15 years, or at least about 20 years prior to the administration. In one embodiment, the human was previously diagnosed as having developed an inhibitory immune response to the clotting factor at least about 5 years prior to the administration.

[0150] In some embodiments, the methods of the present disclosure provide an improved time to tolerance as compared to standard of care methods of inducing immune tolerance. The term "time to tolerance," as used herein refers to the amount of time between the administration of the first dose of the composition or the chimeric protein comprising a clotting factor and an Fc region and the development of immune tolerance in the human. Decreasing the time to tolerance can have significant benefits for the human, including but not limited to reducing the total financial burden required to achieve tolerance. In some embodiments, the time to tolerance is about 1 to about 24 weeks, about

1 to about 23 weeks, about 1 to about 22 weeks, about 1 to about 21 weeks, about 2 to about 20 weeks, about 2 to about 19 weeks, about 2 to about 18 weeks, about 2 to about 17 weeks, about 3 to about 16 weeks, about 3 to about 15 weeks, about 3 to about 14 weeks, about 3 to about 13 weeks, about 4 to about 12 weeks, about 4 to about 11 weeks, about 4 to about 10 weeks, about 4 to about 9 weeks, about 5 to about 8 weeks, about 5 to about 7 weeks, about 5 to about 6 weeks, about 1 to about 12 weeks, about 1 to about 11 weeks, about 1 to about 10 weeks, about 1 to about 9 weeks, about 1 to about 8 weeks, about 1 to about 7 weeks, about 1 to about 6 weeks, about 1 to about 5 weeks, or about 1 to about 4 weeks. In some embodiments, the time to tolerance is less than about 70 weeks, less than about 65 weeks, less than about 60 weeks, less than about 58 weeks, less than about 56 weeks, less than about 54 weeks, less than about 52 weeks, less than about 50 weeks, less than about 48 weeks, less than about 46 weeks, less than about 44 weeks, less than about 42 weeks, less than about 40 weeks, less than about 38 weeks, less than about 36 weeks, less than about 34 weeks, less than about 32 weeks, less than about 30 weeks, less than about 28 weeks, less than about 26 weeks, less than about 24 weeks, less than about 23 weeks, less than about 22 weeks, less than about 21 weeks, less than about 20 weeks, less than about 19 weeks, less than about 18 weeks, less than about 17 weeks, less than about 16 weeks, less than about 15 weeks, less than about 14 weeks, less than about 13 weeks, less than about 12 weeks, less than about 11 weeks, less than about 10 weeks, less than about 9 weeks, less than about 8 weeks, less than about 7 weeks, less than about 6 weeks, less than about 5 weeks, less than about 4 weeks, less than about 3 weeks, less than about 2 weeks, or less than about 1 week. In certain embodiments, the time to tolerance is about 4 to about 12 weeks. In one embodiment, the time to tolerance is about 4 weeks. In another embodiment, the time to tolerance is about 12 weeks. In some embodiments, the time to tolerance is less than about 10 months. In some embodiments, the time to tolerance is less than about 9 months. In some embodiments, the time to tolerance is less than about 8 months. In some embodiments, the time to tolerance is less than about 7 months. In some embodiments, the time to tolerance is less than about 6 months. In some embodiments, the time to tolerance is less than about 5 months. In some embodiments, the time to tolerance is less than about 4 months. In some embodiments, the methods of the present disclosure result in a shorter time to tolerance in the human following treatment with a composition or the chimeric protein comprising a clotting factor and an Fc region as compared to the time to tolerance following treatment with the clotting factor alone.

[0151] In some embodiments, development of immune tolerance is characterized by a titer of an inhibitory antibody to the clotting factor of less than about 0.6 BU. In some embodiments,

development of immune tolerance is characterized by a titer of an inhibitory antibody to the clotting factor of than about 0.5 BU. In some embodiments, development of immune tolerance is characterized by a titer of an inhibitory antibody to the clotting factor of less than about 0.4 BU. In some embodiments, development of immune tolerance is characterized by a titer of an inhibitory antibody to the clotting factor of less than about 0.3 BU. In some embodiments, development of immune tolerance is characterized by a titer of an inhibitory antibody to the clotting factor of less than about 0.2 BU. In some embodiments, development of immune tolerance is characterized by a titer of an inhibitory antibody to the clotting factor of less than about 0.1 BU. In some embodiments, development of immune tolerance is characterized by a titer of an inhibitory antibody to the clotting factor of 0.0 BU. In certain embodiments, the titer of inhibitory immune antibodies is observed at two consecutive measurements, e.g., in two consecutive weeks within a four-week period.

[0152] In some embodiments, the development of immune tolerance is characterized by incremental recovery >66% (e.g., incremental recovery of about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%). As used herein, "incremental recovery" refers to peak FVIII levels 15 -30 minutes after infusion.

[0153] After the induction period and tapering period are completed, the subject can then be on prophylactic treatment of the chimeric protein. The prophylactic dosing regimen can be any dosing regimen disclosed herein.

[0154] In some embodiments, the human treated using the methods of the present disclosure is receiving or has recently received an immunostimulatory therapy. For example, inhibitors have also been reported in HCV positive hemophilia A patients undergoing treatment with interferon as well as in HIV positive hemophilia A patients having an immune reconstitution inflammatory syndrome associated with anti-retroviral therapy. See Report of Expert Meeting on FVIII Products and Inhibitor Development, European Medicines Agency (February 28, 2006-March 2, 2006). Thus, in some embodiments, the human is receiving interferon therapy. In some embodiments, the human is receiving anti-viral therapy. In some embodiments, the human is receiving an anti-retroviral therapy and having an immune reconstitution inflammatory syndrome.

[0155] In certain embodiments, the human has had less than 150 exposure days (ED) to the clotting factor, e.g. FVIII. In one embodiment, the human has had less than 50 ED. In another embodiment, the human has had less than 20 ED.

[0156] Some aspects of the present disclosure are directed to methods of reducing the severity or occurrence of an allergic or anaphylactic reaction to a clotting factor in a subject in need thereof, comprising administering to the subject a composition or a chimeric protein comprising the clotting factor and an Fc region. In some embodiments, the administration of the composition or the chimeric protein reduces the severity of an anaphylactoid reaction to the clotting factor. In some embodiments, the administration of the composition or the chimeric protein reduces the severity of an allergic reaction to the clotting factor.

III. Chimeric Polypeptides

[0157] Chimeric polypeptides useful for the present disclosure comprise a FVIII protein comprising a FVIII polypeptide and a VWF fragment comprising a D' domain and a D3 domain of VWF. The VWF fragment is used to prevent or block the FVIII protein from interacting with endogenous VWF, thereby preventing the FVIII protein from being cleared through a VWF clearance pathway. In order to prevent dissociation of the FVIII protein from the VWF fragment, in some embodiments, the FVIII protein and the VWF fragment are associated directly or indirectly with each other through an association stronger than the natural interaction between FVIII and VWF.

[0158] In certain embodiments, the FVIII protein is associated with the VWF fragment by a covalent bond. The covalent bond can be any covalent bond known in the art. In some embodiments, the covalent bond is a disulfide bond. In some embodiments, the covalent bond is a peptide bond. In other embodiments, the FVIII protein is modified to increase the strength of the interaction between the FVIII protein and the VWF fragment. In other embodiments, the VWF fragment is modified to increase the strength of the interaction between the FVIII protein and the VWF fragment. In still other embodiments, the FVIII protein and the VWF protein both are modified to increase the strength of the interaction between the FVIII protein and the VWF fragment.

[0159] In particular embodiments, the FVIII protein comprising a FVIII polypeptide and the VWF fragment comprising a D' domain and a D3 domain of VWF associate directly through at least one covalent bond between at least one amino acid in the FVIII polypeptide sequence and at least one amino acid in the D' and D3 domains of VWF. In other embodiments, the FVIII protein and the VWF fragment associate indirectly through at least one covalent bond between at least one amino acid in

the FVIII polypeptide sequence and at least one amino acid in a heterologous sequence fused directly or indirectly with the D' and D3 domains of VWF. In other embodiments, the FVIII protein and the VWF fragment associate indirectly through at least one covalent bond between at least one amino acid in the VWF fragment sequence and at least one amino acid in a heterologous sequence fused
5 directly or indirectly with the FVIII polypeptide. In still other embodiments, the FVIII protein and the VWF fragment associate indirectly through at least one covalent bond between at least one amino acid in a heterologous sequence fused directly or indirectly with the D' and D3 domains of VWF and at least one amino acid in a heterologous sequence fused directly or indirectly with the FVIII polypeptide.

10 **[0160]** The FVIII protein of the present disclosure can comprise a FVIII polypeptide and one or more heterologous moieties, e.g., half-life extending moieties, fused directly or indirectly with the FVIII polypeptide. The VWF fragment of the present disclosure can also comprise a D' domain and a D3 domain of VWF and one or more heterologous moieties, e.g., half-life extending moieties, fused directly or indirectly with the D' and D3 domains of VWF. In some embodiments, the FVIII protein
15 useful for the present disclosure consists essentially of or consists of a FVIII polypeptide and the VWF fragment useful for the disclosure comprises a D' domain and a D3 domain of VWF and one or more heterologous moieties, e.g., half-life extending moieties, fused directly or indirectly with the D' and D3 domains of VWF. In some embodiments, the FVIII protein comprises a FVIII polypeptide and one or more heterologous moieties, e.g., half-life extending moieties, fused directly or indirectly with the FVIII
20 polypeptide and the VWF fragment useful for the present disclosure consists essentially of or consists of a D' domain and a D3 domain of VWF. In some embodiments, the chimeric polypeptide comprises a FVIII protein consists essentially of or consists of a FVIII polypeptide and a VWF fragment consists essentially of or consists of a D' domain and a D3 domain of VWF.

[0161] In some embodiments, the chimeric polypeptide or protein disclosed herein is a FVIII-XTEN-Fc/D'D3-XTEN-Fc heterodimer. In one embodiment, the FVIII-XTEN-Fc/D'D3-XTEN-Fc heterodimer
25 chimeric polypeptide comprises: (i) a FVIII protein comprising a FVIII polypeptide, an XTEN inserted within the B domain of the FVIII polypeptide, and a first Fc region; and (ii) a VWF protein comprising a VWF fragment, a second XTEN sequence, an $\alpha 2$ linker, and a second Fc region. A schematic representation of an exemplary FVIII-XTEN-Fc/D'D3-XTEN-Fc heterodimer, rFVIII-Fc-VWF-XTEN, is
30 presented in FIG. 1.

[0162] In a specific embodiment, the chimeric polypeptide is rFVIII-Fc-VWF-XTEN. In another specific embodiment, rFVIII-Fc-VWF-XTEN comprises (i) a FVIII protein comprising the amino acid

sequence of SEQ ID NO: 203 and (ii) a VWF protein comprising the amino acid sequence of SEQ ID NO: 205. In yet another specific embodiment, rFVIII-Fc-VWF-XTEN comprises (i) a FVIII protein and (ii) a VWF protein that are covalently linked via a disulfide bond.

III.A. Factor VIII Polypeptides

[0163] "Factor VIII," abbreviated throughout the instant application as "FVIII," as used herein, means functional FVIII polypeptide in its normal role in coagulation, unless otherwise specified. Thus, the term FVIII includes variant polypeptides that are functional. "A FVIII protein" is used to refer to a FVIII polypeptide (or protein) alone, a FVIII polypeptide fused to additional polypeptides, and a FVIII polypeptide associated with one or more additional polypeptides as long as the FVIII protein exhibits a FVIII function/activity. The terms "FVIII polypeptide," "FVIII portion," and "FVIII" refer to the FVIII polypeptide sequence alone. Examples of the FVIII functions/activities include, but are not limited to, an ability to activate coagulation, an ability to act as a cofactor for factor IX, or an ability to form a tenase complex with factor IX in the presence of Ca^{2+} and phospholipids, which then converts Factor X to the activated form Xa. The FVIII polypeptide can be the human, porcine, canine, rat, or murine FVIII polypeptide. In addition, comparisons between FVIII from humans and other species have identified conserved residues that are likely to be required for function (Cameron et al., *Thromb. Haemost.* 79:317-22 (1998); US 6,251,632). The full-length polypeptide and polynucleotide sequences are known, as are many functional fragments, mutants and modified versions. Various FVIII amino acid and nucleotide sequences are disclosed in, e.g., US Publication Nos. 2015/0158929 A1, 2014/0308280 A1, and 2014/0370035 A1 and International Publication No. WO 2015/106052 A1. FVIII polypeptides include, e.g., full-length FVIII, full-length FVIII minus Met at the N-terminus, mature FVIII polypeptide (minus the signal sequence), mature FVIII polypeptide with an additional Met at the N-terminus, and/or FVIII polypeptide with a full or partial deletion of the B domain. FVIII variants include B domain deletions, whether partial or full deletions.

[0164] The FVIII polypeptide of the chimeric polypeptide used herein has FVIII activity in the plasma. FVIII activity can be measured by any known methods in the art. A number of tests are available to assess the function of the coagulation system: activated partial thromboplastin time (aPTT) test, chromogenic assay, ROTEM assay, prothrombin time (PT) test (also used to determine INR), fibrinogen testing (often by the Clauss method), platelet count, platelet function testing (often by PFA-100), TCT, bleeding time, mixing test (whether an abnormality corrects if the patient's plasma

is mixed with normal plasma), coagulation factor assays, antiphospholipid antibodies, D-dimer, genetic tests (e.g., factor V Leiden, prothrombin mutation G20210A), dilute Russell's viper venom time (dRVVT), miscellaneous platelet function tests, thromboelastography (TEG or Sonoclot), thromboelastometry (TEM®, e.g., ROTEM®), or euglobulin lysis time (ELT).

5 **[0165]** The aPTT test is a performance indicator measuring the efficacy of both the "intrinsic" (also referred to the contact activation pathway) and the common coagulation pathways. This test is commonly used to measure clotting activity of commercially available recombinant clotting factors, e.g., FVIII. It is typically used in conjunction with prothrombin time (PT), which measures the extrinsic pathway. (See, e.g., Kamal et al., Mayo Clin Proc., 82(7):864-873 (2007)). In one embodiment, aPTT
10 is tested using an assay where FVIII activity is measured using the Dade® Actin® FSL Activated PTT Reagent (Siemens Health Care Diagnostics) on a BCS® XP analyzer (Siemens Healthcare Diagnostics). In certain embodiments, the chimeric polypeptide has a plasma FVIII activity of at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%,
15 at least about 12 %, at least about 13%, at least about 14%, at least about 15%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, or at least about 20% as measured by aPTT test.

[0166] The aPTT assay may also be used for assessing the potency of a chimeric polypeptide prior to administration to a patient or subject. (Hubbard AR, et al. J Thromb Haemost 11: 988–9 (2013)).
20 The aPTT assay may further be used in conjunction with any of the assays described herein, either prior to administration or following administration to a patient or subject.

[0167] ROTEM analysis provides information on the whole kinetics of haemostasis: clotting time, clot formation, clot stability and lysis. The different parameters in thromboelastometry are dependent on the activity of the plasmatic coagulation system, platelet function, fibrinolysis, or many factors
25 which influence these interactions. This assay can provide a complete view of secondary haemostasis.

[0168] The chromogenic assay mechanism is based on the principles of the blood coagulation cascade, where activated FVIII accelerates the conversion of Factor X into Factor Xa in the presence of activated Factor IX, phospholipids and calcium ions. The Factor Xa activity is assessed by
30 hydrolysis of a p-nitroanilide (pNA) substrate specific to Factor Xa. The initial rate of release of p-nitroaniline measured at 405 nM is directly proportional to the Factor Xa activity and thus to the FVIII

activity in the sample. In one embodiment, the chromogenic assay is the BIOPHEN FVIII:C assay (Hyphen Biomed, Neurville sur Oise, France)

[0169] The chromogenic assay is recommended by the FVIII and Factor IX Subcommittee of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Hemostasis (ISTH). Since 1994, the chromogenic assay has also been the reference method of the European Pharmacopoeia for the assignment of FVIII concentrate potency. Thus, in some embodiments, the chimeric polypeptide comprising a FVIII polypeptide has FVIII activity comparable to a chimeric polypeptide comprising mature FVIII polypeptide or a BDD FVIII polypeptide (e.g., RECOMBIMATE[®], KOGENATE FS[®], HELIXATE FS[®], XYNTHA/REFACTO AB[®], HEMOFIL-M[®], MONARC-M[®], MONOCLATE-P[®], HUMATE-P[®], ALPHANATE[®], KOATE-DVI[®], AFSTYLA[®], AND HYATE:C[®]).

[0170] The chromogenic assay may also be used for assessing the potency of a chimeric polypeptide prior to administration to a patient or subject. (Hubbard AR, et al. J Thromb Haemost 11: 988–9 (2013)). The chromogenic assay may further be used in conjunction with any of the assays described herein, either prior to administration or following administration to a patient or subject.

[0171] In other embodiments, the chimeric polypeptide comprising a FVIII polypeptide of this disclosure has a Factor Xa generation rate comparable to a chimeric polypeptide comprising a mature FVIII polypeptide or a BDD FVIII polypeptide (e.g., ADVATE[®], REFACTO[®], or ELOCTATE[®]).

[0172] In order to activate Factor X to Factor Xa, activated Factor IX (Factor IXa) hydrolyzes one arginine-isoleucine bond in Factor X to form Factor Xa in the presence of Ca²⁺, membrane phospholipids, and a FVIII cofactor. Therefore, the interaction of FVIII with Factor IX is critical in coagulation pathway. In certain embodiments, the chimeric polypeptide comprising a FVIII polypeptide can interact with Factor IXa at a rate comparable to a chimeric polypeptide comprising a mature FVIII polypeptide sequence or a BDD FVIII polypeptide (e.g., ADVATE[®], REFACTO[®], or ELOCTATE[®]).

[0173] In addition, FVIII is bound to von Willebrand Factor while inactive in circulation. FVIII degrades rapidly when not bound to VWF and is released from VWF by the action of thrombin. In some embodiments, the chimeric polypeptide comprising a FVIII polypeptide binds to von Willebrand Factor, e.g., a VWF fragment disclosed herein, at a level comparable to a chimeric polypeptide comprising a mature FVIII polypeptide sequence or a BDD FVIII polypeptide (e.g., ADVATE[®], REFACTO[®], or ELOCTATE[®]).

[0174] FVIII can be inactivated by activated protein C in the presence of calcium and phospholipids. Activated protein C cleaves FVIII heavy chain after Arginine 336 in the A1 domain, which disrupts a Factor X substrate interaction site, and cleaves after Arginine 562 in the A2 domain, which enhances the dissociation of the A2 domain as well as disrupts an interaction site with the Factor IXa. This cleavage also bisects the A2 domain (43 kDa) and generates A2-N (18 kDa) and A2-C (25 kDa) domains. Thus, activated protein C can catalyze multiple cleavage sites in the heavy chain. In some embodiments, the chimeric polypeptide comprising a FVIII polypeptide is inactivated by activated Protein C at a level comparable to a chimeric polypeptide comprising a mature FVIII polypeptide sequence or a BDD FVIII polypeptide (e.g., ADVATE®, REFACTO®, or ELOCTATE®).

[0175] In other embodiments, the chimeric polypeptide comprising a FVIII polypeptide has FVIII activity in vivo comparable to a chimeric polypeptide comprising a mature FVIII polypeptide sequence or a BDD FVIII polypeptide (e.g., ADVATE®, REFACTO®, or ELOCTATE®). In a particular embodiment, the chimeric polypeptide comprising a FVIII polypeptide is capable of protecting a HemA mouse at a level comparable to a chimeric polypeptide comprising a mature FVIII polypeptide sequence or a BDD FVIII polypeptide (e.g., ADVATE®, REFACTO®, or ELOCTATE®) in a HemA mouse tail vein transection model.

[0176] Examples of human FVIII sequences (full-length) are shown below.

Table 2: Amino Acid Sequence of Full-length Human Factor VIII

(Full-length FVIII: FVIII signal peptide underlined; FVIII heavy chain is double underlined; B domain is italicized; and FVIII light chain is in plain text)

Signal Peptide: (SEQ ID NO: 64)

MQIELSTCFFLCLLRFCFS

Mature Factor VIII (SEQ ID NO: 65)*

ATRRYYLGAVELSWDYMOSDLGELPVDARFP RPVPKSEPFNTSVVYKKT LFVEFTDHLFNIAKPRPPWMGLL
GPTIQAEVYD TVVITLKNMASHPVSLH AVGVSYWKASEGA EYDDOTSQREKEDDKVFP GGSHTYVWQVLK
ENGPMASDPLCLTYSYLSHVDLVKDLNSGLIGALLVCREGSLAKEKTQTLHKFILLFAVDEGKSWHSETKN
SLMQRDAASARAWPKMHTVNGYVNRSLPGLIGCHRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQA
SLEISPITFLTAQTLLMDLGOFLLFCHISSHQHDGMEAYVKVDSCPEEPQLRMKNNEEAEDYDDDLTDSEMD
VVRFDDDNPSFQIRSVAKKHPKTWVHYIAAEEEDWDYAPLV LAPDDRSYKSOYLNNGPORIGRKYKKVR
FMAYTDETFKTREAIQHESGILGPLLYGEVGD TLLIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDF
PILPGEIFKYKWTVTVEDGPTKSDPRCLTRYYSFVNMERDLASGLIGPLLCYKESVDORGNQIMSDKRNVL
FSVFDENRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFD SLQLSVCLHEVAYWYILSIGAQTDF
LSVFFSGYTFKHKMVYEDTLTLFPFSGETVFM SMENPGLWILGCHNSDFRNRGMTALLKVSSCDKNTGDYY

EDSYEDISAYLLSKNNAIEPRSFSQNSRHPSTRQKQFNATTIPENDIEKTDPWFFAHRTPMPKIQNVSSDLLMLLRQ
SPTPHGLSLSDLQEAKYETFSDDPSPGAIDSNNLSSEMTHFRPQLHHSGDMVFTPESGLQLRLNEKLGTTAATELKK
LDFKVSSTNNLISTIPSDNLAAGTDNTSSLGPPSMPVHYDSQLDTTLFGKKSSPLTESGGPLSLSEENNDSKLLESGL
MNSQESSWGKNVSSTESGRLFKGKRAHGPALLTKDNALFKVSISLLKTNKTSNNSATNRKTHIDGPSLLIENSPSVWQ
NILESDTEFKKVTPLIHDRMLMDKNATALRLNHMSNKTTSSKNMEMVQQKKEGPIPPDAQNPDMSFFKMLFLPES
ARWIQRTHGKNSLNSGQGSPKQLVSLGPEKSVEQNFLSEKNKVVGKGEFTKDVGLKEMVFPSSRNFLTNLD
NLHENNTHNQEKKIQEEIEKKETLIQENVVLPQIHTVTGTNFMKNLFLSTRQNVEGSYDGAYAPVLQDFRSLND
TNRTKKHTAHFSKKGEEENLEGLGNQTKQIVEKYACTTRISPNTSQQNFVTQRSKALKQFRLPLEETELEKRIIVD
DTSTQWSKNMKHLTPSTLTQIDYNEKEKGAITQSPLSDCLTRSHSIPQANRSPLIAKVSSFPSIRPIYLTRVLFQDNSS
HLPAASYRKKDSGVQESSHFLQGAKKNNLSLAILTLEMTGDQREVGSLGTSATNSVTYKKVENTVLPKPDLPKTSSGK
VELLPKVHIYQKDLFPTETSNGSPGHLDLVEGSLLOGTEGAIKWNEANRPGKVPFLRVATESSAKTPSKLLDPLAWD
NHYGTQIPKEEWKSQEKSPEKTAFKKKDTILSLNACESNHAIAINEGQNKPEIEVTWAKQGRTERLCSQNPPVLKR
HQREITRTTLQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSPRSFQKKTRHYFIAAVERLWDYGMSSSPHVL
RNRAQSGSVPQFKKVVFQEFTDGSFTQPLYRGELNEHLGLPYIRAEVEDNIMVTRNQASRPYSFYSSLIS
YEEDQRQGAEPRKNFVKPNETKTYFWKVQHHMAPTKDEFDCKAWAYFSDVDLEKDVHSGLIGPLLVCHTN
TLNPAHGRQVTVQEFALFFTIFDETKSWYFTENMERNCRAPCNIQMEDPTFKENYRFHAINGYIMDTLPGLV
MAQDQRIRWYLLSMGSNENIHSIHFSGHVFTVRKKEEYKMALYNLYPGVFETVEMLPSKAGIWRVECLIGE
HLHAGMSTLFLVYSNKCQTPLGMASGHIRDFQITASGQYGQWAPKLARLHYSGSINAWSTKEPFSWIKVDL
LAPMIIHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGNVDSSGIKHNIFNPPIIARYIR
LHPTHYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSYFTNMFATWSPSKARLHLQGRSNAWRPQ
VNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTSMYVKEFLISSQDGHQWTLFFQNGKVKVFQGNQDSFTP
VVNSLDPPLLTRYLRIHPQSWVHQIALRMEVLGCEAQDLY

TABLE 3. Nucleotide Sequence Encoding Full-Length FVIII (SEQ ID NO: 66)*

*The underlined nucleic acids encode a signal peptide.

661	<u>ATG CAAATAGAGC TCTCCACCTG</u>
721	<u>CTTCTTTCTG TGCCTTTTCG GATTCTGCTT TAGTGCCACC</u> AGAAGATACT ACCTGGGTGC
781	AGTGGAAGCTG TCATGGGACT ATATGCAAAG TGATCTCGGT GAGCTGCCTG TGGACGCAAG
841	ATTTCTCCT AGAGTGCCAA AATCTTTTCC ATTCAACACC TCAGTCGTGT AAAAAAGAC
901	TCTGTTTGTA GAATTCACGG ATCACCTTTT CAACATCGCT AAGCCAAGGC CACCCTGGAT
961	GGGTCTGCTA GGTCTACCA TCCAGGCTGA GGTTTATGAT ACAGTGGTCA TTACACTTAA
1021	GAACATGGCT TCCCATCCTG TCAGTCTTCA TGCTGTTGGT GTATCCTACT GGAAAGCTTC
1081	TGAGGGAGCT GAATATGATG ATCAGACCAG TCAAAGGGAG AAAGAAGATG ATAAAGTCTT
1141	CCCTGGTGGA AGCCATACAT ATGTCTGGCA GGTCCTGAAA GAGAATGGTC CAATGGCCTC
1201	TGACCCACTG TGCCTTACCT ACTCATATCT TTCTCATGTG GACCTGGTAA AAGACTTGAA
1261	TTCAGGCCTC ATTGGAGCCC TACTAGTATG TAGAGAAGGG AGTCTGGCCA AGGAAAAGAC
1321	ACAGACCTTG CACAAATTTA TACTACTTTT TGCTGTATTT GATGAAGGGA AAAGTTGGCA
1381	CTCAGAAACA AAGAACTCCT TGATGCAGGA TAGGGATGCT GCATCTGCTC GGGCCTGGCC
1441	TAAATGCAC ACAGTCAATG GTTATGTAAA CAGGTCTCTG CCAGGTCTGA TTGGATGCCA
1501	CAGGAAATCA GTCTATTGGC ATGTGATTGG AATGGGCACC ACTCCTGAAG TGCACTCAAT
1561	ATTCTCGAA GGTCACACAT TTCTTGTTGAG GAACCATCGC CAGGCGTCTT TGGAAATCTC
1621	GCCAAATACT TTCCTTACTG CTCAAACACT CTTGATGGAC CTTGGACAGT TTCTACTGTT
1681	TTGTCATATC TCTTCCCACC AACATGATGG CATGGAAGCT TATGTCAAAG TAGACAGCTG
1741	TCCAGAGGAA CCCCAACTAC GAATGAAAAA TAATGAAGAA GCGGAAGACT ATGATGATGA
1801	TCTTACTGAT TCTGAAATGG ATGTGGTCAG GTTTGATGAT GACAACTCTC CTTCTTTTAT
1861	CCAAATTCGC TCAGTTGCCA AGAAGCATCC TAAAACTTGG GTACATTACA TTGCTGCTGA
1921	AGAGGAGGAC TGGGACTATG CTCCCTTAGT CTCGCCCCC GATGACAGAA GTTATAAAAG

1981	TCAATATTTG AACAATGGCC CTCAGCGGAT TGGTAGGAAG TACAAAAAAG TCCGATTTAT
2041	GGCATACACA GATGAAACCT TTAAGACTCG TGAAGCTATT CAGCATGAAT CAGGAATCTT
2101	GGGACCTTTA CTTTATGGGG AAGTTGGAGA CACACTGTTG ATTATATTTA AGAATCAAGC
2161	AAGCAGACCA TATAACATCT ACCCTCACGG AATCACTGAT GTCCGTCCTT TGTATTCAAG
2221	GAGATTACCA AAAGGTGTAA AACATTTGAA GGATTTTCCA ATTCTGCCAG GAGAAATATT
2281	CAAATATAAA TGGACAGTGA CTGTAGAAGA TGGGCCAACT AAATCAGATC CTCGGTGCCT
2341	GACCCGCTAT TACTCTAGTT TCGTTAATAT GGAGAGAGAT CTAGCTTCAG GACTCATTGG
2401	CCCTCTCCTC ATCTGCTACA AAGAATCTGT AGATCAAAGA GGAAACCAGA TAATGTCAGA
2461	CAAGAGGAAT GTCATCCTGT TTTCTGTATT TGATGAGAAC CGAAGCTGGT ACCTCACAGA
2521	GAATATACAA CGCTTCTCC CCAATCCAGC TGGAGTGCAG CTTGAGGATC CAGAGTTCCA
2581	AGCCTCCAAC ATCATGCACA GCATCAATGG CTATGTTTTT GATAGTTTGC AGTTGTCAGT
2641	TTGTTTGCAT GAGGTGGCAT ACTGGTACAT TCTAAGCATT GGAGCACAGA CTGACTTCCT
2701	TTCTGTCTTC TTCTCTGGAT ATACCTTCAA ACACAAAATG GTCTATGAAG ACACACTCAC
2761	CCTATTCCCA TTCTCAGGAG AAACCTGTCTT CATGTCGATG GAAAACCCAG GTCTATGGAT
2821	TCTGGGGTGC CACAACCTCAG ACTTTCGGAA CAGAGGCATG ACCGCCTTAC TGAAGGTTTT
2881	TAGTTGTGAC AAGAACACTG GTGATTATTA CGAGGACAGT TATGAAGATA TTTCAGCATA
2941	CTTGCTGAGT AAAAAAATG CCATTGAACC AAGAAGCTTC TCCCAGAATT CAAGACACCC
3001	TAGCACTAGG CAAAAGCAAT TTAATGCCAC CACAATTCCA GAAATGACA TAGAGAAGAC
3061	TGACCCTTGG TTTGCACACA GAACACCTAT GCCTAAAATA CAAAATGTCT CCTCTAGTGA
3121	TTTGTGATG CTCTTGCGAC AGAGTCCTAC TCCACATGGG CTATCCTTAT CTGATCTCCA
3181	AGAAGCCAAA TATGAGACTT TTTCTGATGA TCCATCACCT GGAGCAATAG ACAGTAATAA
3241	CAGCCTGTCT GAAATGACAC ACTTCAGGCC ACAGCTCCAT CACAGTGGGG ACATGGTATT
3301	TACCCCTGAG TCAGGCCTCC AATTAAGATT AAATGAGAAA CTGGGGACAA CTGCAGCAAC
3361	AGAGTTGAAG AAACCTTGATT TCAAAGTTTC TAGTACATCA AATAATCTGA TTTCAACAAT
3421	TCCATCAGAC AATTTGGCAG CAGGTACTGA TAATACAAGT TCCTTAGGAC CCCCAGTAT
3481	GCCAGTTCAT TATGATAGTC AATTAGATAC CACTCTATTT GGCAAAAAGT CATCTCCCCT
3541	TACTGAGTCT GGTGGACCTC TGAGCTTGAG TGAAGAAAAT AATGATTCAA AGTTGTTAGA
3601	ATCAGGTTTA ATGAATAGCC AAGAAAGTTC ATGGGGAAAA AATGTATCGT CAACAGAGAG
3661	TGGTAGGTTA TTAAAGGGA AAAGAGCTCA TGGACCTGCT TTGTTGACTA AAGATAATGC
3721	CTTATTCAAA GTTAGCATCT CTTTGTTAAA GACAAACAAA ACTTCCAATA ATTCAGCAAC
3781	TAATAGAAAAG ACTCACATTG ATGGCCCATC ATTATTAATT GAGAATAGTC CATCAGTCTG
3841	GCAAAATATA TTAGAAAGTG ACACTGAGTT TAAAAAAGTG ACACCTTTGA TTCATGACAG
3901	AATGCTTATG GACAAAAATG CTACAGCTTT GAGGCTAAAT CATATGTCAA ATAAACTAC
3961	TTCATCAAAA AACATGGAAA TGGTCCAACA GAAAAAAGAG GGCCCCATTC CACCATGTC
4021	ACAAAATCCA GATATGTCGT TCTTTAAGAT GCTATTCTTG CCAGAATCAG CAAGGTGGAT
4081	ACAAAGGACT CATGGAAAGA ACTCTCTGAA CTCTGGGCAA GGCCCCAGTC CAAAGCAATT
4141	AGTATCCTTA GGACCAGAAA AATCTGTGGA AGGTCAGAAT TTCTTGTCTG AGAAAAACAA
4201	AGTGGTAGTA GGAAAGGGTG AATTTACAAA GGACGTAGGA CTCAAAGAGA TGGTTTTTCC
4261	AAGCAGCAGA AACCTATTTT TACTAACTT GGATAATTTA CATGAAAATA ATACACACAA
4321	TCAAGAAAAA AAAATTCAGG AAGAAATAGA AAAGAAGGAA ACATTAATCC AAGAGAATGT
4381	AGTTTTGCCT CAGATACATA CAGTGACTGG CACTAAGAAT TTCATGAAGA ACCTTTTCTT
4441	ACTGAGCACT AGGCAAAATG TAGAAGGTTC ATATGACGGG GCATATGCTC CAGTACTTCA
4501	AGATTTTAGG TCATTAAATG ATTCAACAAA TAGAACAAAG AAACACACAG CTCATTTCTC
4561	AAAAAAAGGG GAGGAAGAAA ACTTGGAAGG CTTGGGAAAT CAAACCAAGC AAATTGTAGA
4621	GAAATATGCA TGCACCACAA GGATATCTCC TAATACAAGC CAGCAGAATT TTGTCACGCA
4681	ACGTAGTAAG AGAGCTTTGA AACAAATCAG ACTCCCACTA GAAGAAACAG AACTTGAAAA
4741	AAGGATAATT GTGGATGACA CCTCAACCCA GTGGTCCAAA AACATGAAAC ATTTGACCCC
4801	GAGCACCTC ACACAGATAG ACTACAATGA GAAGGAGAAA GGGGCCATTA CTCAGTCTCC
4861	CTTATCAGAT TGCCTTACGA GGAGTCATAG CATCCCTCAA GCAAATAGAT CTCCATTACC
4921	CATTGCAAAG GTATCATCAT TTCCATCTAT TAGACCTATA TATCTGACCA GGGTCCTATT
4981	CCAAGACAAC TCTTCTCATC TTCCAGCAGC ATCTTATAGA AAGAAAGATT CTGGGGTCCA
5041	AGAAAGCAGT CATTTCTTAC AAGGAGCCAA AAAAAATAAC CTTTCTTTAG CCATTCTAAC
5101	CTTGAGATG ACTGGTGATC AAAGAGAGGT TGGCTCCCTG GGGACAAGTG CCACAAATTC

```

5161 AGTCACATAC AAGAAAGTTG AGAACACTGT TCTCCCGAAA CCAGACTTGC CAAAAACATC
5221 TGGCAAAGTT GAATTGCTTC CAAAAGTTCA CATTATCAG AAGGACCTAT TCCCTACGGA
5281 AACTAGCAAT GGGTCTCCTG GCCATCTGGA TCTCGTGGA GGGAGCCTTC TTCAGGGAAC
5341 AGAGGGAGCG ATTAAGTGGA ATGAAGCAAA CAGACCTGGA AAAGTTCCCT TTCTGAGAGT
5401 AGCAACAGAA AGCTCTGCAA AGACTCCCTC CAAGCTATTG GATCCTCTTG CTTGGGATAA
5461 CCACTATGGT ACTCAGATAC CAAAAGAAGA GTGGAAATCC CAAGAGAAGT CACCAGAAAA
5521 AACAGCTTTT AAGAAAAAGG ATACCATTTT GTCCCTGAAC GCTTGTGAAA GCAATCATGC
5581 AATAGCAGCA ATAAATGAGG GACAAAATAA GCCCCGAAATA GAAGTCACCT GGGCAAAGCA
5641 AGGTAGGACT GAAAGGCTGT GCTCTCAAAA CCCACCAGTC TTGAAACGCC ATCAACGGGA
5701 AATAACTCGT ACTACTCTTC AGTCAGATCA AGAGGAAATT GACTATGATG ATACCATATC
5761 AGTTGAAATG AAGAAGGAAG ATTTTGACAT TTATGATGAG GATGAAAATC AGAGCCCCCG
5821 CAGCTTTCAA AAGAAAACAC GACACTATTT TATTGCTGCA GTGGAGAGGC TCTGGGATTA
5881 TGGGATGAGT AGCTCCCCAC ATGTTCTAAG AAACAGGGCT CAGAGTGGCA GTGTCCCTCA
5941 GTTCAAGAAA GTTGTTTTCC AGGAATTTAC TGATGGCTCC TTTACTCAGC CCTTATACCG
6001 TGGAGAACTA AATGAACATT TGGGACTCCT GGGGCCATAT ATAAGAGCAG AAGTTGAAGA
6061 TAATATCATG GTAACTTTCA GAAATCAGGC CTCTCGTCCC TATTCCTTCT ATTCTAGCCT
6121 TATTTCTTAT GAGGAAGATC AGAGGCAAGG AGCAGAACCT AGAAAAAACT TTGTCAAGCC
6181 TAATGAAACC AAAACTTACT TTTGGAAAGT GCAACATCAT ATGGCACCCA CTAAAGATGA
6241 GTTTGACTGC AAAGCCTGGG CTTATTTCTC TGATGTTGAC CTGGAAAAAG ATGTGCACTC
6301 AGGCCTGATT GGACCCCTTC TGGTCTGCCA CACTAACACA CTGAACCCTG CTCATGGGAG
6361 ACAAGTGACA GTACAGGAAT TTGCTCTGTT TTTCACCATC TTTGATGAGA CAAAAGCTG
6421 GTACTTCACT GAAAATATGG AAAGAACTG CAGGGCTCCC TGCAATATCC AGATGGAAGA
6481 TCCCACTTTT AAAGAGAATT ATCGTTCCA TGCAATCAAT GGCTACATAA TGGATACACT
6541 ACCTGGCTTA GTAATGGCTC AGGATCAAAG GATTTCGATGG TATCTGCTCA GCATGGGCAG
6601 CAATGAAAAC ATCCATTCTA TTCATTTTCA TGGACATGTG TTTACTGTAC GAAAAAAGA
6661 GGAGTATAAA ATGGCACTGT ACAATCTCTA TCCAGGTGTT TTTGAGACAG TGGAAATGTT
6721 ACCATCCAAA GCTGGAATTT GGCGGGTGGA ATGCCTTATT GGCGAGCATC TACATGCTGG
6781 GATGAGCACA CTTTTTCTGG TGTACAGCAA TAAGTGTCAG ACTCCCCTGG GAATGGCTTC
6841 TGGACACATT AGAGATTTTC AGATTACAGC TTCAGGACAA TATGGACAGT GGGCCCCAAA
6901 GCTGGCCAGA CTTTATTATT CCGGATCAAT CAATGCCTGG AGCACCAAGG AGCCCTTTTC
6961 TTGGATCAAG GTGGATCTGT TGGCACCAAT GATTATTCAC GGCATCAAGA CCCAGGGTGC
7021 CCGTCAGAAG TTCTCCAGCC TCTACATCTC TCAGTTTATC ATCATGTATA GTCTTGATGG
7081 GAAGAAGTGG CAGACTTATC GAGGAAATTC CACTGGAACC TTAATGGTCT TCTTTGGCAA
7141 TGTGGATTCA TCTGGGATAA AACACAATAT TTTTAACCCT CCAATTATTG CTCGATACAT
7201 CCGTTTGCAC CCAACTCATT ATAGCATTCT CAGCACTCTT CGCATGGAGT TGATGGGCTG
7261 TGATTTAAAT AGTTGCAGCA TGCCATTGGG AATGGAGAGT AAAGCAATAT CAGATGCACA
7321 GATTACTGCT TCATCCTACT TTACCAATAT GTTTGCCACC TGGTCTCCTT CAAAAGCTCG
7381 ACTTCACCTC CAAGGGAGGA GTAATGCCTG GAGACCTCAG GTGAATAATC CAAAAGAGTG
7441 GCTGCAAGTG GACTTCCAGA AGACAATGAA AGTCACAGGA GTAATACTC AGGGAGTAAA
7501 ATCTCTGCTT ACCAGCATGT ATGTGAAGGA GTTCCTCATC TCCAGCAGTC AAGATGGCCA
7561 TCAGTGGACT CTCTTTTTTC AGAATGGCAA AGTAAAGGTT TTTAGGGGAA ATCAAGACTC
7621 CTTACACACT GTGGTGAACCT CTCTAGACCC ACCGTTACTG ACTCGCTACC TTCGAATTCA
7681 CCCCCAGAGT TGGGTGCACC AGATTGCCCT GAGGATGGAG GTTCTGGGCT GCGAGGCACA
7741 GGACCTCTAC

```

[0177] FVIII polypeptides include full-length FVIII, full-length FVIII minus Met at the N-terminus, mature FVIII (minus the signal sequence), mature FVIII with an additional Met at the N-terminus,

and/or FVIII with a full or partial deletion of the B domain. In certain embodiments, FVIII variants include B domain deletions, whether partial or full deletions.

[0178] The sequence of native mature human FVIII polypeptide is presented as SEQ ID NO: 65. A native FVIII polypeptide has the following formula: A1-a1-A2-a2-B-a3-A3-C1-C2, where A1, A2, and A3 are the structurally-related "A domains," B is the "B domain," C1 and C2 are the structurally-related "C domains," and a1, a2 and a3 are acidic spacer regions. Referring to the primary amino acid sequence position in SEQ ID NO:65, the A1 domain of human FVIII extends from Ala1 to about Arg336, the a1 spacer region extends from about Met337 to about Val374, the A2 domain extends from about Ala375 to about Tyr719, the a2 spacer region extends from about Glu720 to about Arg740, the B domain extends from about Ser741 to about Arg 1648, the a3 spacer region extends from about Glu1649 to about Arg1689, the A3 domain extends from about Ser1690 to about Leu2025, the C1 domain extends from about Gly2026 to about Asn2072, and the C2 domain extends from about Ser2073 to Tyr2332. Other than specific proteolytic cleavage sites, designation of the locations of the boundaries between the domains and regions of FVIII can vary in different literature references. The boundaries noted herein are therefore designated as approximate by use of the term "about."

[0179] The human FVIII gene was isolated and expressed in mammalian cells (Toole, J. J., et al., Nature 312:342-347 (1984); Gitschier, J., et al., Nature 312:326-330 (1984); Wood, W. I., et al., Nature 312:330-337 (1984); Vehar, G. A., et al., Nature 312:337-342 (1984); WO 87/04187; WO 88/08035; WO 88/03558; and U.S. Pat. No. 4,757,006). The FVIII amino acid sequence was deduced from cDNA as shown in U.S. Pat. No. 4,965,199. In addition, partially or fully B-domain deleted FVIII is shown in U.S. Pat. Nos. 4,994,371 and 4,868,112. In some embodiments, the human FVIII B-domain is replaced with the human Factor V B-domain as shown in U.S. Pat. No. 5,004,803. The cDNA sequence encoding human Factor VIII and amino acid sequence are shown in SEQ ID NOs: 1 and 2, respectively, of US Application Publ. No. 2005/0100990.

[0180] The porcine FVIII sequence is published in Toole, J. J., et al., Proc. Natl. Acad. Sci. USA 83:5939-5942 (1986). Further, the complete porcine cDNA sequence obtained from PCR amplification of FVIII sequences from a pig spleen cDNA library has been reported in Healey, J. F., et al., Blood 88:4209-4214 (1996). Hybrid human/porcine FVIII having substitutions of all domains, all subunits, and specific amino acid sequences were disclosed in U.S. Pat. No. 5,364,771 by Lollar and Runge, and in WO 93/20093. More recently, the nucleotide and corresponding amino acid sequences of the A1 and A2 domains of porcine FVIII and a chimeric FVIII with porcine A1 and/or A2 domains substituted for the corresponding human domains were reported in WO 94/11503. U.S. Pat.

No. 5,859,204, Lollar, J. S., also discloses the porcine cDNA and deduced amino acid sequences. U.S. Pat. No. 6,458,563 discloses a B-domain-deleted porcine FVIII.

[0181] U.S. Pat. No. 5,859,204 to Lollar, J. S. reports functional mutants of FVIII having reduced antigenicity and reduced immunoreactivity. U.S. Pat. No. 6,376,463 to Lollar, J. S. also reports mutants of FVIII having reduced immunoreactivity. US Appl. Publ. No. 2005/0100990 to Saenko et al. reports functional mutations in the A2 domain of FVIII.

[0182] In some embodiments, the FVIII polypeptide (or FVIII portion of a chimeric polypeptide) can be at least 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to a FVIII amino acid sequence of amino acids 1 to 1438 of SEQ ID NO: 67 or amino acids 1 to 2332 of SEQ ID NO: 65 (without a signal sequence) or a FVIII amino acid sequence of amino acids 1 to 19 of SEQ ID NO: 64 and 1 to 1438 of SEQ ID NO: 67 or amino acids 1 to 19 of SEQ ID NO: 64 and amino acids 1 to 2332 of SEQ ID NO: 65 (with a signal sequence), wherein the FVIII has a clotting activity, e.g., activates Factor IX as a cofactor to convert Factor X to activated Factor X. The FVIII polypeptide (or FVIII portion of a chimeric polypeptide) can be identical to a FVIII amino acid sequence of amino acids 1 to 1438 of SEQ ID NO: 67 or amino acids 1 to 2332 of SEQ ID NO: 65 (without a signal sequence). The FVIII polypeptide can further comprise a signal sequence.

[0183] The "B-domain" of FVIII, as used herein, is the same as the B-domain known in the art that is defined by internal amino acid sequence identity and sites of proteolytic cleavage, e.g., residues Ser741-Arg1648 of full-length human FVIII. The other human FVIII domains are defined by the following amino acid residues: A1, residues Ala1-Arg372; A2, residues Ser373-Arg740; A3, residues Ser1690-Asn2019; C1, residues Lys2020-Asn2172; C2, residues Ser2173-Tyr2332. The A3-C1-C2 sequence includes residues Ser1690-Tyr2332. The remaining sequence, residues Glu1649-Arg1689, is usually referred to as the a3 acidic region. The locations of the boundaries for all of the domains, including the B-domains, for porcine, mouse and canine FVIII are also known in the art. In some embodiments, the B domain of FVIII is deleted ("B-domain-deleted factor VIII" or "BDD FVIII"). An example of a BDD FVIII is REFACTO® (recombinant BDD FVIII), which has the same sequence as the Factor VIII portion of the sequence in Table 4. (BDD FVIII heavy chain is double underlined; B domain is italicized; and BDD FVIII light chain is in plain text). In some embodiments, the B domain FVIII has a deletion of the full B domain except 5 amino acids, as shown in Table 5 (SEQ ID NO: 68) (B domain is italicized).

TABLE 4. Amino Acid Sequence of B-domain Deleted Factor VIII (B-domain deletion except 14 amino acid residues) (SEQ ID NO: 67)

ATRRYYLGAVELSWDYMOSDLGELPVDARFPFPRVPKSPFNTSVVYKKTLFVEFTDHLFNIAPRPPWMGLL
 GPTIQAEVYDVTVITLKNMASHPVSLHAGVGSYWKASEGAEYDDQTSQREKEDDKVFPGGSHTYVWQVLK
 ENGPMSADPLCLTYSYLSHVDLVKDLNSGLIGALLVCREGLAKEKTQTLHKFILLFAVFEDEGKSWHSETKN
 SLMQDRDAASARAWPKMHTVNGYVNRSLPGLIGCHRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQA
 SLEISPITFLTAOTLLMDLGQFLLFCHISSHQHDGMEAYVKVDSCEEPQLRMKNNEEAEDYDDDLTDSEMD
 VVRFDDDNPSFQIRSVAKKHPKWTWVHYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQRIGRKYKKVR
 FMAYTDETFKTREAIQHESGILGPLLYGEVGDTLIIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDF
 PILPGEIFKYKWTVTVEDGPTKSDPRCLTRYSSSFVNMERDLASGLIGPLLYCYKESVDQRGNOIMSDKRNVL
 FSVFDENRSWYL TENIQRFLPNPAGVQLEDPEFOASNIMHSINGYVFDLSLQSVCLHEVAYWYILSIGAQTD
 FLSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSENPGLWILGCHNSDFRNRGMTALLKVSSCDKNTGDY
 EDSYEDISAYLLSKNNAIEPRSFQNEITRTTLQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSP
 RSFQKKTRHYFIAAVERLWDYGMSSSPHVLNRNAQSGSVPOFKKVVFEFTDGSFTQPLYRGELNEHLGLL
 PYIRAEVEDNIMVTFRNQASRPYSFYSSLISYEEDQRQGAEPKRFVKNPNETKTYFWKVQHMAPTKDEFDC
 KAWAYFSDVDLEKDVHSGLIGPLLVCHTNTLNPAHGRQVTVQEFALFFTIFDETKSWYFTENMERNCRAPC
 NIQMEDPTFKENYRFHAINGYIMDTLPLGLVMAQDQIRWYLLSMGNSNENIHSIHFSGHVFTVRKKEEYKMA
 LYNLYPGVFETVEMLPSKAGIWRVECLIGEHLHAGMSTLFLVYSNKCQTPGLMASGHIRDFQITASGQYQGW
 APKLARLHYSGSINAWSTKEPFSWIKVDLLAPMIIHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNST
 GTLMVFFGNVDSSGIKHNFNPPIARYIRLHPHTHSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSY
 FTNMFATWSPSKARLHLQGRSNAWRPQVNNPKEWLQVDFQKTMKVTGVTTOGVKSLTSMYVKEFLISS
 QDGHQWTLFFQNGKVKVFQGNQDSFTPVVNSLDPPLTRYLRIHPQSWVHQIALRMEVLGCEAQDLY

TABLE 5. Amino Acid Sequence of B-domain Deleted Factor VIII (B-domain deletion except 5 amino acid residues) (SEQ ID NO: 68)

ATRRYYLGAVELSWDYMOSDLGELPVDARFPFPRVPKSPFNTSVVYKKTLFVEFTDHLFNIAPRPPWMGLL
 GPTIQAEVYDVTVITLKNMASHPVSLHAGVGSYWKASEGAEYDDQTSQREKEDDKVFPGGSHTYVWQVLK
 ENGPMSADPLCLTYSYLSHVDLVKDLNSGLIGALLVCREGLAKEKTQTLHKFILLFAVFEDEGKSWHSETKN
 SLMQDRDAASARAWPKMHTVNGYVNRSLPGLIGCHRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQA
 SLEISPITFLTAOTLLMDLGQFLLFCHISSHQHDGMEAYVKVDSCEEPQLRMKNNEEAEDYDDDLTDSEMD
 VVRFDDDNPSFQIRSVAKKHPKWTWVHYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQRIGRKYKKVR
 FMAYTDETFKTREAIQHESGILGPLLYGEVGDTLIIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDF
 PILPGEIFKYKWTVTVEDGPTKSDPRCLTRYSSSFVNMERDLASGLIGPLLYCYKESVDQRGNOIMSDKRNVL
 FSVFDENRSWYL TENIQRFLPNPAGVQLEDPEFOASNIMHSINGYVFDLSLQSVCLHEVAYWYILSIGAQTD
 FLSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSENPGLWILGCHNSDFRNRGMTALLKVSSCDKNTGDY
 EDSYEDISAYLLSKNNAIEPRSFQNEITRTTLQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSPRSFQKKTRH
 YFIAAVERLWDYGMSSSPHVLNRNAQSGSVPOFKKVVFEFTDGSFTQPLYRGELNEHLGLLGPYIRAEVED
 NIMVTFRNQASRPYSFYSSLISYEEDQRQGAEPKRFVKNPNETKTYFWKVQHMAPTKDEFDC
 KAWAYFSDVDLEKDVHSGLIGPLLVCHTNTLNPAHGRQVTVQEFALFFTIFDETKSWYFTENMERNCRAPC
 NIQMEDPTFKENYRFHAINGYIMDTLPLGLVMAQDQIRWYLLSMGNSNENIHSIHFSGHVFTVRKKEEYKMA
 LYNLYPGVFETVEMLPSKAGIWRVECLIGEHLHAGMSTLFLVYSNKCQTPGLMASGHIRDFQITASGQYQGW
 APKLARLHYSGSINAWSTKEPFSWIKVDLLAPMIIHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNST
 GTLMVFFGNVDSSGIKHNFNPPIARYIRLHPHTHSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSY

GNVDSSGIKHNIFNPPIIARYIRLHPHTHSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSYFTNMFAT
 WSPSKARLHLQGRSNAWRPQVNNPKEWLQVDFQKTMKVTGVTQGVKSLTSMYVKEFLISSSQDGHQW
 TLFFQNGKVKVFQGNQDSFTPVVNSLDPPLLTRYLRIHPQSWVHQIALRMEVLGCEAQDLY

[0184] A "B-domain-deleted FVIII" can have the full or partial deletions disclosed in U.S. Pat. Nos. 6,316,226, 6,346,513, 7,041,635, 5,789,203, 6,060,447, 5,595,886, 6,228,620, 5,972,885, 6,048,720, 5,543,502, 5,610,278, 5,171,844, 5,112,950, 4,868,112, and 6,458,563, U.S. Publ. Nos. US 2017/0073393 A1 and US 2012/308641 A1, and Int'l Publ. Nos. WO 2011/041770 A1, WO 2015/106052 A1 (PCT/US2015/010738), and WO 2016/025764. In some embodiments, a B-domain-deleted FVIII sequence used in the methods of the present disclosure comprises any one of the deletions disclosed at col. 4, line 4 to col. 5, line 28 and Examples 1-5 of U.S. Pat. No. 6,316,226 (also in US 6,346,513). In other embodiments, a B-domain deleted Factor VIII is the S743/Q1638 B-domain deleted Factor VIII (SQ BDD FVIII) (e.g., Factor VIII having a deletion from amino acid 744 to amino acid 1637, e.g., Factor VIII having amino acids 1-743 and amino acids 1638-2332 of mature FVIII). In some embodiments, a B-domain-deleted FVIII used in the methods of the present disclosure has a deletion disclosed at col. 2, lines 26-51 and examples 5-8 of U.S. Patent No. 5,789,203 (also US 6,060,447, US 5,595,886, and US 6,228,620). In some embodiments, a B-domain-deleted Factor VIII has a deletion described in col. 1, lines 25 to col. 2, line 40 of US Patent No. 5,972,885; col. 6, lines 1-22 and example 1 of U.S. Patent no. 6,048,720; col. 2, lines 17-46 of U.S. Patent No. 5,543,502; col. 4, line 22 to col. 5, line 36 of U.S. Patent no. 5,171,844; col. 2, lines 55-68, figure 2, and example 1 of U.S. Patent No. 5,112,950; col. 2, line 2 to col. 19, line 21 and table 2 of U.S. Patent No. 4,868,112; col. 2, line 1 to col. 3, line 19, col. 3, line 40 to col. 4, line 67, col. 7, line 43 to col. 8, line 26, and col. 11, line 5 to col. 13, line 39 of U.S. Patent no. 7,041,635; or col. 4, lines 25-53, of U.S. Patent No. 6,458,563. In some embodiments, a B-domain-deleted FVIII polypeptide has a deletion of most of the B domain, but still contains amino-terminal sequences of the B domain that are essential for in vivo proteolytic processing of the primary translation product into two polypeptide chains, as disclosed in WO 91/09122. In some embodiments, a B-domain-deleted FVIII polypeptide is constructed with a deletion of amino acids 747-1638, i.e., virtually a complete deletion of the B domain. Hoebe R.C., et al. J. Biol. Chem. 265 (13): 7318-7323 (1990). A B-domain-deleted Factor VIII polypeptide can also contain a deletion of amino acids 771-1666 or amino acids 868-1562 of FVIII. Meulien P., et al. Protein Eng. 2(4): 301-6 (1988). Additional B domain deletions that are part of the disclosure include: deletion of amino acids 982 through 1562 or 760 through 1639 (Toole et

al., Proc. Natl. Acad. Sci. U.S.A. (1986) 83, 5939-5942)), 797 through 1562 (Eaton, et al. Biochemistry (1986) 25:8343-8347)), 741 through 1646 (Kaufman (PCT published application No. WO 87/04187)), 747-1560 (Sarver, et al., DNA (1987) 6:553-564)), 741 through 1648 (Pasek (PCT application No.88/00831)), or 816 through 1598 or 741 through 1648 (Lagner (Behring Inst. Mitt. (1988) No 82:16-25, EP 295597)). In particular embodiments, the B-domain-deleted FVIII polypeptide comprises a deletion of amino acid residues 746 to 1648 of mature FVIII (corresponding to a deletion of 765 to 1665 of full length FVIII). In other embodiments, the B-domain-deleted FVIII polypeptide comprises a deletion of amino acid residues 745 to 1648 of mature FVIII (corresponding to a deletion of 764 to 1665 of full length FVIII).

[0185] In other embodiments, BDD FVIII includes a FVIII polypeptide containing fragments of the B-domain that retain one or more N-linked glycosylation sites, e.g., residues 757, 784, 828, 900, 963, or optionally 943, which correspond to the amino acid sequence of the full-length FVIII sequence. Examples of the B-domain fragments include 226 amino acids or 163 amino acids of the B-domain as disclosed in Miao, H.Z., et al., Blood 103(a): 3412-3419 (2004), Kasuda, A, et al., J. Thromb. Haemost. 6: 1352-1359 (2008), and Pipe, S.W., et al., J. Thromb. Haemost. 9: 2235-2242 (2011) (i.e., the first 226 amino acids or 163 amino acids of the B domain are retained). In still other embodiments, BDD FVIII further comprises a point mutation at residue 309 (from Phe to Ser) to improve expression of the BDD FVIII polypeptide. See Miao, H.Z., et al., Blood 103(a): 3412-3419 (2004). In still other embodiments, the BDD FVIII includes a FVIII polypeptide containing a portion of the B-domain, but not containing one or more furin cleavage sites (e.g., Arg1313 and Arg 1648). See Pipe, S.W., et al., J. Thromb. Haemost. 9: 2235-2242 (2011). In some embodiments, the BDD FVIII comprises single chain FVIII that contains a deletion in amino acids 765 to 1652 corresponding to the mature full length FVIII (also known as rFVIII-SingleChain and AFSTYLA®). See US Patent No. 7,041,635. Each of the foregoing deletions can be made in any FVIII sequence.

[0186] In some embodiments, the FVIII has a partial B-domain. In some embodiments, the FVIII polypeptide with a partial B-domain is FVIII198. FVIII198 is a partial B-domain containing single chain FVIII-Fc molecule-226N6. Number 226 represents the N-terminus 226 amino acid of the FVIII B-domain, and N6 represents six N-glycosylation sites in the B-domain.

[0187] In certain embodiments, the FVIII polypeptide is selected from a FVIII polypeptide disclosed in Publication Nos. WO 2017/117630 A1, WO 2018/087271 A1, US 9,878,017 B2, US 8,575,104 B2, US 8,754,194 B2, US 7,939,632 B2, US 2018/0161402 A1, US 9,956,269 B2, US 9,107,902 B2, US 2017/209546 A1,

[0188] In some embodiments, FVIII is cleaved right after Arginine at amino acid 1648 (in full-length Factor VIII or SEQ ID NO: 65), amino acid 754 (in the S743/Q1638 B-domain deleted Factor VIII or SEQ ID NO: 67), or the corresponding Arginine residue (in other variants), thereby resulting in a heavy chain and a light chain. In other embodiments, a FVIII polypeptide comprises a heavy chain and a light chain, which are linked or associated by a metal ion-mediated non-covalent bond.

[0189] In other embodiments, FVIII is a single chain FVIII that has not been cleaved right after Arginine at amino acid 1648 (in full-length FVIII or SEQ ID NO: 65), amino acid 754 (in the S743/Q1638 B-domain-deleted FVIII or SEQ ID NO: 67), or the corresponding Arginine residue (in other variants). A single chain FVIII can comprise one or more amino acid substitutions. In some embodiments, the amino acid substitution is at a residue corresponding to residue 1648, residue 1645, or both of full-length mature Factor VIII polypeptide (SEQ ID NO: 65) or residue 754, residue 751, or both of SQ BDD Factor VIII (SEQ ID NO: 67). The amino acid substitution can be any amino acids other than Arginine, e.g., isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, alanine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, proline, selenocysteine, serine, tyrosine, histidine, ornithine, pyrrolysine, or taurine.

[0190] FVIII can further be cleaved by thrombin and then activated as FVIIIa, serving as a cofactor for activated Factor IX (FIXa). And the activated FIX together with activated FVIII forms a Xase complex and converts Factor X to activated Factor X (FXa). For activation, FVIII is cleaved by thrombin after three Arginine residues, at amino acids 372, 740, and 1689 (corresponding to amino acids 372, 740, and 795 in the B-domain deleted FVIII sequence), the cleavage generating FVIIIa having the 50kDa A1, 43kDa A2, and 73kDa A3-C1-C2 chains. In some embodiments, the FVIII polypeptide useful for the present disclosure is non-active FVIII. In other embodiments, the FVIII polypeptide is an activated FVIII.

[0191] The protein having FVIII polypeptide linked to or associated with the VWF protein can comprise a sequence at least 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 65 or 67, wherein the sequence has the FVIII clotting activity, e.g., activating Factor IX as a cofactor to convert Factor X to activated Factor X (FXa).

[0192] "Hybrid" or "chimeric" polypeptides and proteins, as used herein, includes a combination of a first polypeptide and a second polypeptide. In some embodiments, the hybrid or chimeric polypeptide comprises a single polypeptide chain, e.g., a chimeric polypeptide comprising a FVIII polypeptide and an XTEN. See, e.g., US 2015/0158929 A1, which is incorporated by reference herein

in its entirety. In some embodiments, the hybrid or chimeric polypeptide comprises a combination of a first polypeptide chain, e.g., a VWF fragment fused to an XTEN sequence and a first Ig constant region or a portion thereof, with a second polypeptide chain, e.g., a FVIII polypeptide fused to a second Ig constant region or a portion thereof, thereby forming a heterodimer. See, e.g., US 2015/0266943 A1, US 2016/0251408 A1, US 2017/0073393 A1, each of which is incorporated by reference herein in its entirety. In some embodiments, the first polypeptide and the second polypeptide in a hybrid are associated with each other via protein-protein interactions, such as charge-charge or hydrophobic interactions. In other embodiments, a first polypeptide comprises a VWF protein-XTEN-Fc fusion protein, and a second polypeptide comprises FVIII-Fc fusion protein, making the hybrid a heterodimer, wherein the XTEN contains less than 288 amino acids. In other embodiments, the first polypeptide comprises a VWF protein-XTEN-Fc fusion protein, and the second polypeptide comprises FVIII(X)-Fc fusion protein, making the hybrid a heterodimer, wherein the XTEN contains less than 288 amino acids. The first polypeptide and the second polypeptide can be associated through a covalent bond, e.g., a disulfide bond, between the first Fc region and the second Fc region. The first polypeptide and the second polypeptide can further be associated with each other by binding between the VWF fragment and the FVIII polypeptide.

[0193] In certain embodiments, the chimeric polypeptide disclosed herein comprises a FVIII protein comprising a first FVIII polypeptide fragment, an XTEN sequence, a second FVIII polypeptide fragment, and a Fc region. In some embodiments, the FVIII protein comprises, as ordered from N-terminal to C-terminal, a first FVIII polypeptide fragment, fused to an XTEN sequence, fused to a second FVIII polypeptide fragment, fused to a Fc region. In a specific embodiment, the FVIII protein comprises a first FVIII polypeptide fragment comprising the amino acid sequence of SEQ ID NO: 215, an XTEN sequence comprising the amino acid sequence of SEQ ID NO: 8, a second FVIII polypeptide comprising the amino acid sequence of SEQ ID NO: 216, and/or a first Fc region comprising the amino acid sequence of SEQ ID NO: 217.

[0194] In one specific embodiment, the chimeric polypeptide is rFVIII-Fc-VWF-XTEN and comprises a FVIII protein comprising the amino acid sequence of SEQ ID NO: 201. In another specific embodiment, rFVIII-Fc-VWF-XTEN comprises the amino acid sequence of SEQ ID NO: 207.

[0195] In some embodiments, the FVIII protein further comprises a FVIII signal peptide sequence. In one specific embodiment, the FVIII protein comprises a FVIII signal peptide comprising the amino acid sequence of SEQ ID NO: 64, a first FVIII polypeptide fragment comprising the amino acid sequence of SEQ ID NO: 215, an XTEN sequence comprising the amino acid sequence of SEQ ID

NO: 8, a second FVIII polypeptide comprising the amino acid sequence of SEQ ID NO: 216, and/or a first Fc region comprising the amino acid sequence of SEQ ID NO: 217.

[0196] In one specific embodiment, the chimeric polypeptide is rFVIII-Fc-VWF-XTEN and comprises a FVIII protein comprising the amino acid sequence of SEQ ID NO: 203. In another specific embodiment, rFVIII-Fc-VWF-XTEN comprises a FVIII protein encoded by the nucleic acid sequence of SEQ ID NO: 204 or a fragment thereof. Additional exemplary polypeptide sequences relating to the FVIII proteins of the chimeric polypeptides disclosed herein are provided in Tables 18-19.

[0197] A great many functional FVIII variants are known, as is discussed above and below. In addition, hundreds of nonfunctional mutations in FVIII have been identified in hemophilia patients, and it has been determined that the effect of these mutations on FVIII function is due more to where they lie within the 3-dimensional structure of FVIII than on the nature of the substitution (Cutler et al., Hum. Mutat. 19:274-8 (2002)), incorporated herein by reference in its entirety. In addition, comparisons between FVIII from humans and other species have identified conserved residues that are likely to be required for function (Cameron et al., Thromb. Haemost. 79:317-22 (1998); US 6,251,632), incorporated herein by reference in its entirety.

III.B. Von Willebrand Factor (VWF) Fragments

[0198] VWF (also known as F8VWF) is a large multimeric glycoprotein present in blood plasma and produced constitutively in endothelium (in the Weibel-Palade bodies), megakaryocytes (α -granules of platelets), and subendothelial connective tissue. The basic VWF monomer is a 2813 amino acid protein. Every monomer contains a number of specific domains with a specific function, the D'/D3 domain (which binds to Factor VIII), the A1 domain (which binds to platelet GPIIb-receptor, heparin, and/or possibly collagen), the A3 domain (which binds to collagen), the C1 domain (in which the RGD domain binds to platelet integrin α IIb β 3 when this is activated), and the "cysteine knot" domain at the C-terminal end of the protein (which VWF shares with platelet-derived growth factor (PDGF), transforming growth factor- β (TGF β) and β -human chorionic gonadotropin (β HCG)).

[0199] The term "a VWF fragment" as used herein includes, but is not limited to, functional VWF fragments comprising a D' domain and a D3 domain, which are capable of inhibiting binding of endogenous VWF to FVIII. In some embodiments, the VWF fragment binds to the FVIII protein. In other embodiments, the VWF fragment blocks the VWF binding site on the FVIII protein, thereby inhibiting interaction of the FVIII protein with endogenous VWF. In other embodiments, the VWF fragment blocks the binding of FVIII to endogenous VWF, thereby preventing clearance of the FVIII

protein through a VWF-clearance pathway. The VWF fragments include derivatives, variants, mutants, or analogues that retain these activities of VWF.

[0200] The 2813 monomer amino acid sequence for human VWF is reported as Accession Number NP000543.2 in Genbank. The nucleotide sequence encoding the human VWF is reported as Accession Number NM000552.3 in Genbank. A nucleotide sequence of human VWF is designated as SEQ ID NO: 20. SEQ ID NO: 21 is the amino acid sequence of full-length VWF. Each domain of VWF is listed in Table 6.

TABLE 6. VWF Sequences (human)

VWF domains	Amino acid Sequence		
VWF Signal Peptide	1	<u>MIPARFAGVL LALALILPGT LC</u>	22
SEQ ID NO: 208			
(Amino acids 1 to 22 of SEQ ID NO: 21)			
VWF D1D2 Domain	23	AEGTRGRS STARCSLFGS DFVNTFDGSM	
	51	YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG	
	101	TVTQGDQRVSPYASKGLYL ETEAGYYKLS GEAYGFVARI DGSGNFQVLL	
	151	SDRYFNKTCG LCGNFNIFAE DDFMTQEGTL TSDPYDFANS WALSSGEQWC	
SEQ ID NO: 209	201	ERASPPSSSC NISSGEMQKG LWEQCQLLKS TSVFARCHPL VDPEPFVALC	
	251	EKTLCECAGG LECACPALLE YARTCAQEGM VLYGWTDHSA CSPVCPAGME	
	301	YRQCVSPCAR TCQSLHINEM CQERCVDGCS CPEGQLLDEG LCVESTCPC	
	351	VHSGKRYPPG TSLSRDCNTC ICRNSQWICS NEECPGECLV TGQSHFKSFD	
	401	NRYFTFSGIC QYLLARDCQD HSFSIVIETV QCADDRDAVC TRSVTVRLPG	
(Amino acids 23 to 763 of SEQ ID NO: 21)	451	LHNSLVKLKH GAGVAMDGQD IQLPLLKGD LRIQHTVTASV RLSYGEDLQM	
	501	DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG	
	551	NAWKLHGDCQ DLQKQHSDPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS	
	601	PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCCL	
	651	NCPKGQVYLQ CGTPCNLTCT SLSYPDEECN EACLEGCFCP PGLYMDERGD	
	701	CVPKAQCPCY YDGEIFQPED IFSDHHTMCY CEDGFMHCTM SGVPGSLLPD	
	751	AVLSSPLSHR SKR	763
VWF D' Domain	764	<u>SLSCRPP MVKLVC PADN LRAEGLECTK TCONYDLECM</u>	
	801	<u>SMGCVSGCLC PPGMVRHENR CVALERCPCF HQGKEYAPGE TVKIGCNTCV</u>	
	851	<u>CRDRKWNCTD HVCDAT</u>	866

SEQ ID NO: 210 (Amino acids 764 to 866 of SEQ ID NO: 21)	
VWF D3 Domain SEQ ID NO: 211 (Amino acids 867 to 1240 of SEQ ID NO: 21)	867 CSTI GMAHYLTFDG LKYLFPGEQ YVLVQDYCGS 901 NPGTFRILVG NKGCSHPSVK CKKRVTILVE GGEIELFDGE VNVKRPMKDE 951 THFEVVESGR YIILLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD 1001 GIONNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI 1051 MKQTMVDSSC RILTSDVFQD CNKLVDPEPY LDVCIYDTCS CESIGDCACF 1101 CDTIAAYAHV CAQHKG VVTW RTATLCQOSC EERNLRENGY ECEWRYNSCA 1151 PACQVTCQHP EPLACPVOCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE 1201 VAGR RFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP 1240
VWF A1 Domain SEQ ID NO: 212 (Amino acids 1241 to 1479 of SEQ ID NO: 21)	1241 GGLVVPPTDA 1251 PVSPTTLYVE DISEPPLHDF YCSRLLDLVF LLDGSSRLSE AEFEVLKAFV 1301 VDMMERLRIS QKWVRVAVVE YHDGSHAYIG LKDRKRPESEL RRIASQVKYA 1351 GSQVASTSEV LKYTLFQIFS KIDRPEASRI ALLLMASQEP QRMSRNFRVRY 1401 VQGLKKKKVI VIPVGIGPHA NLKQIRLIEK QAPENKAFVL SSVDELEQQR 1451 DEIVSYLCDL APEAPPPTLP PDMAQVTVG 1479
VWF A2 Domain to C-terminus SEQ ID NO: 213 (Amino acids 1480 to 2813 of SEQ ID NO: 21)	1480 PGLLGVSTLGP KRNSMVLDVA 1501 FVLEGSDKIG EADFNRSKEF MEEVIQRMDV GQDSIHVTVL QYSYMTVEY 1551 PFSEAQSKGD ILQRVREIRY QGGNRTNTGL ALRYLSDHSF LVSQGDREQA 1601 PNLVYMTGN PASDEIKRLP GDIQVPIGV GPNANVQELE RIGWPNAPIL 1651 IQDFETLPRE APDLVLQRCC SGEGLQIPTL SPAPDCSQPL DVILLLDGSS 1701 SFPASYFDEM KSFAKAFISK ANIGPRLTQV SVLQYGSITT IDVPWNVVPE 1751 KAHLLSLVDV MQREGGPSQI GDALGFAVRY LTSEMHGARP GASKAVVILV 1801 TDVSVDSVDA AADAARSNRV TVFPIGIGDR YDAAQLRILA GPAGDSNVVK 1851 LQRIEDLPTM VTLGNSFLHK LSCGFVRICM DEDGNEKRPG DVWTLPDQCH 1901 TVTCQPDGQT LLKSHRVNCD RGLRPSCPNs QSPVKVEETC GCRWTCPCVC 1951 TGSSTRHIVT FDGQNFKL TG SCSYVLFQNK EQDLEVILHN GACSPGARQG 2001 CMKSIEVKHS ALSVEXHSDM EVTVNGRLVS VPYVGGNMEV NVYGAIMHEV 2051 RFNHLGHIFT FTPQNNEFQL QLSPKTFASK TYGLCGICDE NGANDFMLRD 2101 GTVTTDWKTL VQEWTVQRPQ QTCQPILEEQ CLVPDSSHQC VLLLPLFAEC 2151 HKV LAPATFY AICQQDSCHQ EQVCEVIASV AHLCRTNGVC VDWRTPDFCA 2201 MSCPPSLVYN HCEHGCPRHC DGNVSSCGDH PSEGCFPPD KVMLEGSCVP 2251 EEACTQCIGE DGVQHQFLEA WVPDHQPCQI CTCLSGRKVN CTTQPCPTAK

2301	APTCGLCEVA RLRQNADQCC PEYECVCDPV SCDLPPVPHC ERGLQPTLTN
2351	PGECPNFTC ACRKEECKRV SPPSCPPHRL PTLRKTQCCD EYECACNCVN
2401	STVSCPLGYL ASTATNDCGC TTTTCLPDKV CVHRSTIYPV GQFWEEGCDV
2451	CTCTDMEDAV MGLRVAQCSQ KPCEDSCRSQ FTYVLHEGEC CGRCLPSACE
2501	VVTGSPRGDS QSSWKSQSG WASPENPCLI NECVRVKEEV FIQQRNVSCP
2551	QLEVPVCPSP FQLSCKTSAC CPSCRCERME ACMLNGTVIG PGKTVMIDVC
2601	TTCRCMVQVG VISGFKLECR KTTCNPCPLG YKEENNTGEC CGRCLPTACT
2651	IQLRGGQIMT LKRDETLQDG CDTHFCKVNE RGEYFWEKRV TGCPPFDEHK
2701	CLAEKGKIMK IPGTCCDTCE EPECNDITAR LQYVKVGSCK SEVEVDIHYC
2751	QGKCASKAMY SIDINDVQDQ CSCCSPTRTE PMQVALHCTN GSVVYHEVLN
2801	AMECKCSPRK CSK 2813

[0201] The VWF protein as used herein can be a VWF fragment comprising a D' domain and a D3 domain of VWF, wherein the VWF fragment binds to Factor VIII (FVIII) and inhibits binding of endogenous VWF (full-length VWF) to FVIII. The VWF fragment comprising the D' domain and the D3 domain can further comprise a VWF domain selected from the group consisting of an A1 domain, an A2 domain, an A3 domain, a D1 domain, a D2 domain, a D4 domain, a B1 domain, a B2 domain, a B3 domain, a C1 domain, a C2 domain, a CK domain, one or more fragments thereof, and any combinations thereof. In some embodiments, a VWF fragment comprises, consists essentially of, or consists of: (1) the D' and D3 domains of VWF or fragments thereof; (2) the D1, D', and D3 domains of VWF or fragments thereof; (3) the D2, D', and D3 domains of VWF or fragments thereof; (4) the D1, D2, D', and D3 domains of VWF or fragments thereof; or (5) the D1, D2, D', D3, and A1 domains of VWF or fragments thereof. The VWF fragment described herein does not contain a site binding to a VWF clearance receptor. In other embodiments, the VWF fragment described herein is not amino acids 764 to 1274 of SEQ ID NO: 21. The VWF fragment of the present disclosure can comprise any other sequences linked to or fused to the VWF fragment. For example, a VWF fragment described herein can further comprise a signal peptide.

[0202] In some embodiments, the VWF fragment comprising a D' domain and a D3 domain binds to or is associated with a FVIII protein. See, e.g., US 2015/0023959 A1, US 2015/0266943 A1, US 2016/0251408 A1, US 2017/0073393 A1, US 2018/185455 A1, US 2018/0051067 A1, US 2017/0152300 A1, US 9,878,017 B2, US 9,458,223 B2, US 8,575,104 B2, WO 2017/117630 A1, US 2018/0161402 A1, WO 2017/117631 A1, WO 2018/087271 A1, US 9,107,902 B2, WO 2017/222337 A1, WO 2015/185758 A1, each of which is incorporated by reference herein in its entirety. By binding to or associating with a FVIII protein, a VWF fragment of the disclosure protects FVIII from protease cleavage and FVIII activation, stabilizes the heavy chain and light chain of FVIII, and prevents

clearance of FVIII by scavenger receptors. In other embodiments, the VWF fragment binds to or associates with a FVIII protein and blocks or prevents binding of the FVIII protein to phospholipid and activated Protein C. By preventing or inhibiting binding of the FVIII protein with endogenous, full-length VWF, the VWF fragment of the disclosure reduces the clearance of FVIII by VWF clearance
5 receptors and thus extends half-life of the chimeric polypeptide. The half-life extension of a chimeric polypeptide is thus due to the binding of or associating with the VWF fragment lacking a VWF clearance receptor binding site to the FVIII protein and shielding or protecting of the FVIII protein by the VWF fragment from endogenous VWF which contains the VWF clearance receptor binding site. The FVIII protein bound to or protected by the VWF fragment can also allow recycling of a FVIII
10 protein. By eliminating the VWF clearance pathway receptor binding sites contained in the full length VWF molecule, the FVIII/VWF heterodimers of the disclosure are shielded from the VWF clearance pathway, further extending FVIII half-life.

[0203] In some embodiments, a VWF protein useful for the present disclosure comprises a D' domain and a D3 domain of VWF, wherein the D' domain is at least 60%, 70%, 80%, 85%, 90%,
15 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acids 764 to 866 of SEQ ID NO: 21, wherein the VWF protein prevents or inhibits binding of endogenous VWF to FVIII. In other embodiments, a VWF protein comprises the D' domain and the D3 domain of VWF, wherein the D3 domain is at least 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acids 867 to 1240 of SEQ ID NO: 21, wherein the VWF protein prevents or inhibits binding of endogenous VWF
20 to FVIII. In some embodiments, a VWF protein described herein comprises, consists essentially of, or consists of the D' domain and D3 domain of VWF, which are at least 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acids 764 to 1240 of SEQ ID NO: 21, wherein the VWF protein prevents or inhibits binding of endogenous VWF to FVIII. In other embodiments, a VWF protein comprises, consists essentially of, or consists of the D1, D2, D', and D3 domains at least
25 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acids 23 to 1240 of SEQ ID NO: 21, wherein the VWF protein prevents or inhibits binding of endogenous VWF to FVIII. In still other embodiments, the VWF protein further comprises a signal peptide operably linked thereto.

[0204] In some embodiments, a VWF protein useful for the disclosure consists essentially of or consists of (1) the D'D3 domain, the D1D'D3 domain, D2D'D3 domain, or D1D2D'D3 domain and (2)
30 an additional VWF sequence up to about 10 amino acids (e.g., any sequences from amino acids 764 to 1240 of SEQ ID NO: 21 to amino acids 764 to 1250 of SEQ ID NO: 21), up to about 15 amino acids (e.g., any sequences from amino acids 764 to 1240 of SEQ ID NO: 21 to amino acids 764 to 1255 of

SEQ ID NO: 21), up to about 20 amino acids (e.g., any sequences from amino acids 764 to 1240 of SEQ ID NO: 21 to amino acids 764 to 1260 of SEQ ID NO: 21), up to about 25 amino acids (e.g., any sequences from amino acids 764 to 1240 of SEQ ID NO: 21 to amino acids 764 to 1265 of SEQ ID NO: 21), or up to about 30 amino acids (e.g., any sequences from amino acids 764 to 1240 of SEQ ID NO: 21 to amino acids 764 to 1260 of SEQ ID NO: 21). In some embodiments, the VWF protein comprising or consisting essentially of the D' domain and the D3 domain is neither amino acids 764 to 1274 of SEQ ID NO: 21 nor the full-length mature VWF. In some embodiments, the D1D2 domain is expressed in trans with the D'D3 domain. In some embodiments, the D1D2 domain is expressed in cis with the D'D3 domain.

[0205] In other embodiments, the VWF protein comprising the D'D3 domains linked to the D1D2 domains further comprises an intracellular cleavage site, e.g., (a cleavage site by PACE (furin) or PC5), allowing cleavage of the D1D2 domains from the D'D3 domains upon expression. Non-limiting examples of the intracellular cleavage site are disclosed elsewhere herein.

[0206] In yet other embodiments, a VWF protein comprises a D' domain and a D3 domain, but does not comprise an amino acid sequence selected from the group consisting of (1) amino acids 1241 to 2813 corresponding to SEQ ID NO: 21, (2) amino acids 1270 to amino acids 2813 corresponding to SEQ ID NO: 21, (3) amino acids 1271 to amino acids 2813 corresponding to SEQ ID NO: 21, (4) amino acids 1272 to amino acids 2813 corresponding to SEQ ID NO: 21, (5) amino acids 1273 to amino acids 2813 corresponding to SEQ ID NO: 21, (6) amino acids 1274 to amino acids 2813 corresponding to SEQ ID NO: 21, and any combinations thereof.

[0207] In still other embodiments, a VWF protein of the present disclosure comprises, consists essentially of, or consists of an amino acid sequence corresponding to the D' domain, D3 domain, and A1 domain, wherein the amino acid sequence is at least 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acid 764 to 1479 of SEQ ID NO: 21, wherein the VWF protein prevents binding of endogenous VWF to FVIII. In particular embodiments, the VWF protein is not amino acids 764 to 1274 of SEQ ID NO: 21.

[0208] In some embodiments, a VWF protein of the disclosure comprises a D' domain and a D3 domain, but does not comprise at least one VWF domain selected from the group consisting of (1) an A1 domain, (2) an A2 domain, (3) an A3 domain, (4) a D4 domain, (5) a B1 domain, (6) a B2 domain, (7) a B3 domain, (8) a C1 domain, (9) a C2 domain, (10) a CK domain, (11) a CK domain and C2 domain, (12) a CK domain, a C2 domain, and a C1 domain, (13) a CK domain, a C2 domain,

a C1 domain, a B3 domain, (14) a CK domain, a C2 domain, a C1 domain, a B3 domain, a B2 domain, (15) a CK domain, a C2 domain, a C1 domain, a B3 domain, a B2 domain, and a B1 domain, (16) a CK domain, a C2 domain, a C1 domain, a B3 domain, a B2 domain, a B1 domain, and a D4 domain, (17) a CK domain, a C2 domain, a C1 domain, a B3 domain, a B2 domain, a B1 domain, a D4 domain, and an A3 domain, (18) a CK domain, a C2 domain, a C1 domain, a B3 domain, a B2 domain, a B1 domain, a D4 domain, an A3 domain, and an A2 domain, (19) a CK domain, a C2 domain, a C1 domain, a B3 domain, a B2 domain, a B1 domain, a D4 domain, an A3 domain, an A2 domain, and an A1 domain, and (20) any combinations thereof.

[0209] In yet other embodiments, the VWF protein comprises the D'D3 domains and one or more domains or modules. Examples of such domains or modules include, but are not limited to, the domains and modules disclosed in Zhou et al., Blood published online April 6, 2012: DOI 10.1182/blood-2012-01-405134, which is incorporated herein by reference in its entirety. For example, the VWF protein can comprise the D'D3 domain and one or more domains or modules selected from the group consisting of A1 domain, A2 domain, A3 domain, D4N module, VWD4 module, C8-4 module, TIL-4 module, C1 module, C2 module, C3 module, C4 module, C5 module, C5 module, C6 module, and any combinations thereof.

[0210] In still other embodiments, the VWF protein is linked to a heterologous moiety, wherein the heterologous moiety is linked to the N-terminus or the C-terminus of the VWF protein or inserted immediately downstream of one or more amino acids (e.g., one or more XTEN insertion sites) in the VWF protein. For example, the insertion sites for the heterologous moiety in the VWF protein can be in the D' domain, the D3 domain, or both. The heterologous moiety can be a half-life extender.

[0211] In certain embodiments, a VWF protein useful for the disclosure forms a multimer, e.g., dimer, trimer, tetramer, pentamer, hexamer, heptamer, or the higher order multimers. In other embodiments, the VWF protein is a monomer having only one VWF protein. In some embodiments, the VWF protein of the present disclosure can have one or more amino acid substitutions, deletions, additions, or modifications. In some embodiments, the VWF protein can include amino acid substitutions, deletions, additions, or modifications such that the VWF protein is not capable of forming a disulfide bond or forming a dimer or a multimer. In other embodiments, the amino acid substitution is within the D' domain and the D3 domain. In a particular embodiment, a VWF protein useful for the disclosure contains at least one amino acid substitution at a residue corresponding to residue 1099, residue 1142, or both residues 1099 and 1142 corresponding to SEQ ID NO: 21. The at least one amino acid substitution can be any amino acids that are not occurring naturally in the

wild type VWF. For example, the amino acid substitution can be any amino acids other than cysteine, e.g., Isoleucine, Alanine, Leucine, Asparagine, Lysine, Aspartic acid, Methionine, Phenylalanine, Glutamic acid, Threonine, Glutamine, Tryptophan, Glycine, Valine, Proline, Serine, Tyrosine, Arginine, or Histidine. In another example, the amino acid substitution has one or more amino acids
5 that prevent or inhibit the VWF proteins from forming multimers.

[0212] In certain embodiments, the VWF protein useful herein can be further modified to improve its interaction with FVIII, e.g., to improve binding affinity to FVIII. As a non-limiting example, the VWF protein comprises a serine residue at the residue corresponding to amino acid 764 of SEQ ID NO: 21 and a lysine residue at the residue corresponding to amino acid 773 of SEQ ID NO: 21. Residues
10 764 and/or 773 can contribute to the binding affinity of the VWF proteins to FVIII. In other embodiments, The VWF proteins useful for the disclosure can have other modifications, e.g., the protein can be pegylated, glycosylated, hesylated, or polysialylated.

[0213] In certain embodiments, the chimeric polypeptide disclosed herein comprises a VWF protein comprising a VWF fragment, an XTEN sequence, an $\alpha 2$ linker of FVIII, and a Fc region. In some
15 embodiments, the VWF protein comprises, as ordered from N-terminal to C-terminal, a VWF fragment, fused to an XTEN sequence, fused to an $\alpha 2$ linker, fused to a Fc region. In certain embodiments, the VWF protein comprises a D' domain of VWF comprising the amino acid sequence of SEQ ID NO: 210, a D3 domain of VWF comprising the amino acid sequence of SEQ ID NO: 214, an XTEN sequence comprising the amino acid sequence of SEQ ID NO: 58 (AE144_5A), an $\alpha 2$ linker
20 comprising the amino acid sequence of SEQ ID NO: 88, and/or a Fc region comprising the amino acid sequence of SEQ ID NO: 217.

[0214] In one specific embodiment, the chimeric polypeptide is rFVIII-Fc-VWF-XTEN and comprises a VWF protein comprising the amino acid sequence of SEQ ID NO: 202.

[0215] In some embodiments, the VWF protein comprises a VWF fragment comprising a D1, D2, D', and/or D3 domain of VWF. In one embodiment, the VWF fragment comprises a D1D2 domain of
25 VWF comprising the amino acid sequence of SEQ ID NO: 209. In some embodiments, the VWF protein further comprises a VWF signal peptide sequence. In one embodiment, the VWF signal peptide comprises the amino acid sequence of SEQ ID NO: 208. In one specific embodiment, the VWF protein comprises a VWF signal peptide comprising the amino acid sequence of SEQ ID NO:
30 208, a D1D2 region of VWF comprising the amino acid sequence of SEQ ID NO: 209, a D' domain of VWF comprising the amino acid sequence of SEQ ID NO: 210, a D3 domain of VWF comprising

the amino acid sequence of SEQ ID NO: 214, an XTEN sequence comprising the amino acid sequence of SEQ ID NO: 58 (AE144_5A), an a2 linker comprising the amino acid sequence of SEQ ID NO: 88, and/or a Fc region comprising the amino acid sequence of SEQ ID NO: 217.

[0216] In one specific embodiment, the chimeric polypeptide is rFVIII^hFc-VWF-XTEN and comprises a VWF protein comprising the amino acid sequence of SEQ ID NO: 205. In another specific embodiment, rFVIII^hFc-VWF-XTEN comprises a VWF protein encoded by the nucleic acid sequence of SEQ ID NO: 206 or a fragment thereof. Additional exemplary polypeptide sequences relating to the VWF proteins of the chimeric polypeptides disclosed herein are provided in Tables 18-19.

III.C. Half-Life Extending Moieties

[0217] In some embodiments, the chimeric polypeptide of the disclosure comprises one or more half-life extending moieties. In some embodiments, the FVIII polypeptide of the chimeric polypeptide is fused to or associated with one or more half-life extending moieties (i.e., FVIII protein). In other embodiments, the chimeric polypeptide comprises at least two half-life extending moieties, a first half-life extending moiety fused to a FVIII polypeptide and a second half-life extending moiety fused to D'D3 domains of VWF. In some embodiments, the first half-life extending moiety is fused to the C-terminus or the N-terminus of the FVIII polypeptide. In some embodiments, the first half-life extending moiety is inserted within the FVIII polypeptide. In some embodiments, the first half-life extending moiety is inserted within the B domain of the FVIII polypeptide. In some embodiments, the first half-life extending moiety is inserted within the FVIII polypeptide immediately downstream of an amino acid corresponding to amino acid residue 745 of SEQ ID NO: 65. In some embodiments, the first heterologous moiety is fused to the FVIII polypeptide by a linker.

[0218] In certain embodiments, the D'D3 domains of VWF in the VWF fragment can be fused to or associated with a second half-life extending moiety. In some embodiments, the second half-life extending moiety is fused to the C-terminus or the N-terminus of the VWF fragment. In some embodiments, the second half-life extending moiety is inserted within the VWF fragment. In some embodiments, the second half-life extending moiety is fused to the C-terminus of the VWF fragment. In certain embodiments, wherein the second half-life extending moiety is fused to the VWF fragment by a linker.

[0219] In other embodiments, the chimeric polypeptide comprises a FVIII polypeptide and a VWF fragment comprising a D' domain and a D3 domain of VWF, wherein the D'D3 domain of VWF is fused to one or more half-life extending moieties and wherein the D'D3 domain of VWF and the FVIII polypeptide are associated with a bond stronger than naturally occurring bond between FVIII and VWF.

[0220] In some embodiments, the chimeric polypeptide comprises a FVIII polypeptide and a VWF fragment comprising a D' domain and a D3 domain of VWF, wherein the D'D3 domain of VWF is fused to the FVIII polypeptide by a linker. In some embodiments, the linker is a cleavable linker. In some embodiments, the D' domain and D3 domain of VWF are further associated with the FVIII polypeptide by at least one non-covalent bond. In certain embodiments, the D' domain and the D3 domain of VWF are further fused to an Fc. In some embodiments, the D' domain and D3 domain of VWF are fused to an Fc by a linker. In some embodiments, the Fc is fused to a second Fc by an additional linker. In certain embodiments, the Fc and the second Fc are associated with each other by a covalent bond, e.g., a disulphide bond. In particular embodiments, the chimeric polypeptide comprises a FVIII polypeptide and a VWF fragment comprising a D' domain and a D3 domain of VWF as disclosed in International Publication No. WO 2017/222337 A1, which is incorporated by reference herein in its entirety.

[0221] The first half-life extending moiety, the second half-life extending moiety, or both can be selected from the group consisting of an FcRn binding partner, e.g., an albumin or an immunoglobulin Fc region, an XTEN sequence, the C-terminal peptide (CTP) of the β subunit of human chorionic gonadotropin, a PAS sequence, a HAP sequence, a transferrin, albumin-binding moieties, or any fragments, derivatives, variants, and any combination thereof.

III.C.1. Ig Constant Region or a portion thereof

[0222] In some embodiments, the chimeric polypeptide of the disclosure also includes a first Ig constant region or a portion thereof fused to a FVIII polypeptide by an optional linker. The first Ig constant region or the portion thereof can be inserted within the FVIII polypeptide or fused to the C-terminus or the N-terminus of the FVIII polypeptide. In some embodiments, the chimeric polypeptide further includes a second Ig constant region or a portion thereof fused to a VWF protein. The first Ig constant region or the portion thereof can be inserted within the VWF fragment or fused to the C-terminus or the N-terminus of the VWF fragment. In particular embodiments, the first Ig constant

region is linked to or associated with the second Ig constant region by a covalent bond, e.g., a disulfide bond.

[0223] The Ig constant region or a portion thereof can improve pharmacokinetic or pharmacodynamic properties of the chimeric polypeptide in combination with an additional heterologous moiety, e.g., an XTEN sequence, and the VWF protein. In certain embodiments, the Ig constant region or a portion thereof extends a half-life of a molecule fused to the Ig constant region or a portion thereof.

[0224] An Ig constant region is comprised of domains denoted CH (constant heavy) domains (CH1, CH2, etc.). Depending on the isotype, (i.e. IgG, IgM, IgA, IgD, or IgE), the constant region can be comprised of three or four CH domains. Some isotypes (e.g. IgG) constant regions also contain a hinge region. See Janeway et al. 2001, Immunobiology, Garland Publishing, N.Y., N.Y.

[0225] An Ig constant region or a portion thereof for producing the chimeric polypeptide of the present disclosure can be obtained from a number of different sources. In some embodiments, an Ig constant region or a portion thereof is derived from a human Ig. It is understood, however, that the Ig constant region or a portion thereof can be derived from an Ig of another mammalian species, including for example, a rodent (e.g. a mouse, rat, rabbit, guinea pig) or non-human primate (e.g. chimpanzee, macaque) species. Moreover, the Ig constant region or a portion thereof can be derived from any Ig class, including IgM, IgG, IgD, IgA, and IgE, and any Ig isotype, including IgG1, IgG2, IgG3, and IgG4. In some embodiments, the human isotype IgG1 is used.

[0226] A variety of the Ig constant region gene sequences (e.g., human constant region gene sequences) are available in the form of publicly accessible deposits. Constant region domains sequence can be selected having a particular effector function (or lacking a particular effector function) or with a particular modification to reduce immunogenicity. Many sequences of antibodies and antibody-encoding genes have been published and suitable Ig constant region sequences (e.g., hinge, CH2, and/or CH3 sequences, or portions thereof) can be derived from these sequences using art recognized techniques. The genetic material obtained using any of the foregoing methods can then be altered or synthesized to obtain polypeptides of the present disclosure. It will further be appreciated that the scope of this disclosure encompasses alleles, variants and mutations of constant region DNA sequences.

[0227] The sequences of the Ig constant region or a portion thereof can be cloned, e.g., using the polymerase chain reaction and primers which are selected to amplify the domain of interest. To clone

a sequence of the Ig constant region or a portion thereof from an antibody, mRNA can be isolated from hybridoma, spleen, or lymph cells, reverse transcribed into DNA, and antibody genes amplified by PCR. PCR amplification methods are described in detail in U.S. Pat. Nos. 4,683,195; 4,683,202; 4,800,159; 4,965,188; and in, e.g., "PCR Protocols: A Guide to Methods and Applications" Innis et al. eds., Academic Press, San Diego, CA (1990); Ho et al. 1989. Gene 77:51; Horton et al. 1993. Methods Enzymol. 217:270). PCR can be initiated by consensus constant region primers or by more specific primers based on the published heavy and light chain DNA and amino acid sequences. As discussed above, PCR also can be used to isolate DNA clones encoding the antibody light and heavy chains. In this case the libraries can be screened by consensus primers or larger homologous probes, such as mouse constant region probes. Numerous primer sets suitable for amplification of antibody genes are known in the art (e.g., 5' primers based on the N-terminal sequence of purified antibodies (Benhar and Pastan. 1994. Protein Engineering 7:1509); rapid amplification of cDNA ends (Ruberti, F. et al. 1994. J. Immunol. Methods 173:33); antibody leader sequences (Larrick et al. 1989 Biochem. Biophys. Res. Commun. 160:1250)). The cloning of antibody sequences is further described in Newman et al., U.S. Pat. No. 5,658,570, filed January 25, 1995, which is incorporated by reference herein.

[0228] An Ig constant region used herein can include all domains and the hinge region or portions thereof. In some embodiments, the Ig constant region or a portion thereof comprises CH2 domain, CH3 domain, and a hinge region, i.e., an Fc region or an FcRn binding partner.

[0229] As used herein, the term "Fc region" is defined as the portion of a polypeptide which corresponds to the Fc region of native Ig, i.e., as formed by the dimeric association of the respective Fc domains of its two heavy chains. A native Fc region forms a homodimer with another Fc region. In contrast, the term "genetically-fused Fc region" or "single-chain Fc region" (scFc region), as used herein, refers to a synthetic dimeric Fc region comprised of Fc domains genetically linked within a single polypeptide chain (i.e., encoded in a single contiguous genetic sequence).

[0230] In some embodiments, the "Fc region" refers to the portion of a single Ig heavy chain beginning in the hinge region just upstream of the papain cleavage site (i.e. residue 216 in IgG, taking the first residue of heavy chain constant region to be 114) and ending at the C-terminus of the antibody. Accordingly, a complete Fc domain comprises at least a hinge domain, a CH2 domain, and a CH3 domain.

[0231] The Fc region of an Ig constant region, depending on the Ig isotype can include the CH2, CH3, and CH4 domains, as well as the hinge region. Chimeric polypeptides comprising an Fc region of an Ig bestow several desirable properties on a chimeric polypeptide including increased stability, increased serum half-life (see Capon et al., 1989, Nature 337:525) as well as binding to Fc receptors
5 such as the neonatal Fc receptor (FcRn) (U.S. Pat. Nos. 6,086,875, 6,485,726, 6,030,613; WO 03/077834; US2003-0235536A1), which are incorporated herein by reference in their entireties.

[0232] An Ig constant region or a portion thereof can be an FcRn binding partner. FcRn is active in adult epithelial tissues and expressed in the lumen of the intestines, pulmonary airways, nasal surfaces, vaginal surfaces, colon and rectal surfaces (U.S. Pat. No. 6,485,726). An FcRn binding
10 partner is a portion of an Ig that binds to FcRn. Another example of an FcRn binding partner is albumin, further described below.

[0233] The FcRn receptor has been isolated from several mammalian species including humans. The sequences of the human FcRn, monkey FcRn, rat FcRn, and mouse FcRn are known (Story et al. 1994, J. Exp. Med. 180:2377). The FcRn receptor binds IgG (but not other Ig classes such as IgA,
15 IgM, IgD, and IgE) at relatively low pH, actively transports the IgG transcellularly in a luminal to serosal direction, and then releases the IgG at relatively higher pH found in the interstitial fluids. It is expressed in adult epithelial tissue (U.S. Pat. Nos. 6,485,726, 6,030,613, 6,086,875; WO 03/077834; US2003-0235536A1) including lung and intestinal epithelium (Israel et al. 1997, Immunology 92:69) renal proximal tubular epithelium (Kobayashi et al. 2002, Am. J. Physiol. Renal Physiol. 282:F358)
20 as well as nasal epithelium, vaginal surfaces, and biliary tree surfaces.

[0234] FcRn binding partners useful in the present disclosure encompass molecules that can be specifically bound by the FcRn receptor including whole IgG, the Fc fragment of IgG, and other fragments that include the complete binding region of the FcRn receptor. The region of the Fc portion of IgG that binds to the FcRn receptor has been described based on X-ray crystallography
25 (Burmeister et al. 1994, Nature 372:379). The major contact area of the Fc with the FcRn is near the junction of the CH2 and CH3 domains. Fc-FcRn contacts are all within a single Ig heavy chain. The FcRn binding partners include whole IgG, the Fc fragment of IgG, and other fragments of IgG that include the complete binding region of FcRn. The major contact sites include amino acid residues 248, 250-257, 272, 285, 288, 290-291, 308-311, and 314 of the CH2 domain and amino acid residues
30 385-387, 428, and 433-436 of the CH3 domain. References made to amino acid numbering of Igs or Ig fragments, or regions, are all based on Kabat et al. 1991, Sequences of Proteins of Immunological Interest, U.S. Department of Public Health, Bethesda, Md.

[0235] Fc regions or FcRn binding partners bound to FcRn can be effectively shuttled across epithelial barriers by FcRn, thus providing a non-invasive means to systemically administer a desired therapeutic molecule. Additionally, fusion proteins comprising an Fc region or an FcRn binding partner are endocytosed by cells expressing the FcRn. But instead of being marked for degradation, these fusion proteins are recycled out into circulation again, thus increasing the in vivo half-life of these proteins. In certain embodiments, the portions of Ig constant regions are an Fc region or an FcRn binding partner that typically associates, via disulfide bonds and other non-specific interactions, with another Fc region or another FcRn binding partner to form dimers and higher order multimers.

[0236] Two FcRn receptors can bind a single Fc molecule. Crystallographic data suggest that each FcRn molecule binds a single polypeptide of the Fc homodimer. In some embodiments, linking the FcRn binding partner, e.g., an Fc fragment of an IgG, to a biologically active molecule provides a means of delivering the biologically active molecule orally, buccally, sublingually, rectally, vaginally, as an aerosol administered nasally or via a pulmonary route, or via an ocular route. In other embodiments, the chimeric polypeptide can be administered invasively, e.g., subcutaneously, intravenously.

[0237] An FcRn binding partner region is a molecule or a portion thereof that can be specifically bound by the FcRn receptor with consequent active transport by the FcRn receptor of the Fc region. Specifically bound refers to two molecules forming a complex that is relatively stable under physiologic conditions. Specific binding is characterized by a high affinity and a low to moderate capacity as distinguished from nonspecific binding which usually has a low affinity with a moderate to high capacity. Typically, binding is considered specific when the affinity constant K_A is higher than 10^6 M^{-1} , or higher than 10^8 M^{-1} . If necessary, non-specific binding can be reduced without substantially affecting specific binding by varying the binding conditions. The appropriate binding conditions such as concentration of the molecules, ionic strength of the solution, temperature, time allowed for binding, concentration of a blocking agent (e.g. serum albumin, milk casein), etc., can be optimized by a skilled artisan using routine techniques.

[0238] In certain embodiments, a chimeric polypeptide of the disclosure comprises one or more truncated Fc regions that are nonetheless sufficient to confer Fc receptor (FcR) binding properties to the Fc region. For example, the portion of an Fc region that binds to FcRn (i.e., the FcRn binding portion) comprises from about amino acids 282-438 of IgG1, EU numbering (with the primary contact sites being amino acids 248, 250-257, 272, 285, 288, 290-291, 308-311, and 314 of the CH2 domain and amino acid residues 385-387, 428, and 433-436 of the CH3 domain. Thus, an Fc region of the

disclosure can comprise or consist of an FcRn binding portion. FcRn binding portions can be derived from heavy chains of any isotype, including IgG1, IgG2, IgG3 and IgG4. In some embodiments, an FcRn binding portion from an antibody of the human isotype IgG1 is used. In other embodiments, an FcRn binding portion from an antibody of the human isotype IgG4 is used.

5 **[0239]** In other embodiments, the "Fc region" includes an amino acid sequence of an Fc domain or derived from an Fc domain. In certain embodiments, an Fc region comprises at least one of: a hinge (e.g., upper, middle, and/or lower hinge region) domain (about amino acids 216-230 of an antibody Fc region according to EU numbering), a CH2 domain (about amino acids 231-340 of an antibody Fc region according to EU numbering), a CH3 domain (about amino acids 341-438 of an antibody Fc region according to EU numbering), a CH4 domain, or a variant, portion, or fragment thereof. In other
10 embodiments, an Fc region comprises a complete Fc domain (i.e., a hinge domain, a CH2 domain, and a CH3 domain). In some embodiments, an Fc region comprises, consists essentially of, or consists of a hinge domain (or a portion thereof) fused to a CH3 domain (or a portion thereof), a hinge domain (or a portion thereof) fused to a CH2 domain (or a portion thereof), a CH2 domain (or a portion thereof) fused to a CH3 domain (or a portion thereof), a CH2 domain (or a portion thereof) fused to
15 both a hinge domain (or a portion thereof) and a CH3 domain (or a portion thereof). In still other embodiments, an Fc region lacks at least a portion of a CH2 domain (e.g., all or part of a CH2 domain). In a particular embodiment, an Fc region comprises or consists of amino acids corresponding to EU numbers 221 to 447.

20 **[0240]** The Fc regions denoted as F, F1, or F2 herein can be obtained from a number of different sources. In some embodiments, an Fc region of the polypeptide is derived from a human Ig. It is understood, however, that an Fc region can be derived from an Ig of another mammalian species, including for example, a rodent (e.g. a mouse, rat, rabbit, or guinea pig) or non-human primate (e.g. chimpanzee, macaque) species. Moreover, the polypeptide of the Fc domains or portions thereof can
25 be derived from any Ig class, including IgM, IgG, IgD, IgA and IgE, and any Ig isotype, including IgG1, IgG2, IgG3 and IgG4. In other embodiments, the human isotype IgG1 is used.

[0241] In certain embodiments, the Fc variant confers a change in at least one effector function imparted by an Fc region comprising said wild-type Fc domain (e.g., an improvement or reduction in the ability of the Fc region to bind to Fc receptors (e.g. FcγRI, FcγRII, or FcγRIII) or complement
30 proteins (e.g. C1q), or to trigger antibody-dependent cytotoxicity (ADCC), phagocytosis, or complement-dependent cytotoxicity (CDCC)). In other embodiments, the Fc variant provides an engineered cysteine residue.

[0242] The Fc regions of the disclosure can employ art-recognized Fc variants which are known to impart a change (e.g., an enhancement or reduction) in effector function and/or FcR or FcRn binding. Specifically, a binding molecule of the disclosure can include, for example, a change (e.g., a substitution) at one or more of the amino acid positions disclosed in International PCT Publications

5 WO88/07089A1, WO96/14339A1, WO98/05787A1, WO98/23289A1, WO99/51642A1, WO99/58572A1, WO00/09560A2, WO00/32767A1, WO00/42072A2, WO02/44215A2, WO02/060919A2, WO03/074569A2, WO04/016750A2, WO04/029207A2, WO04/035752A2, WO04/063351A2, WO04/074455A2, WO04/099249A2, WO05/040217A2, WO04/044859, WO05/070963A1, WO05/077981A2, WO05/092925A2, WO05/123780A2, WO06/019447A1,

10 WO06/047350A2, and WO06/085967A2; US Patent Publication Nos. US2007/0231329, US2007/0231329, US2007/0237765, US2007/0237766, US2007/0237767, US2007/0243188, US20070248603, US20070286859, US20080057056 ; or US Patent Nos. 5,648,260; 5,739,277; 5,834,250; 5,869,046; 6,096,871; 6,121,022; 6,194,551; 6,242,195; 6,277,375; 6,528,624; 6,538,124; 6,737,056; 6,821,505; 6,998,253; 7,083,784; 7,404,956, and 7,317,091, each of which is

15 incorporated by reference herein. In some embodiments, the specific change (e.g., the specific substitution of one or more amino acids disclosed in the art) can be made at one or more of the disclosed amino acid positions. In other embodiments, a different change at one or more of the disclosed amino acid positions (e.g., the different substitution of one or more amino acid position disclosed in the art) can be made.

20 **[0243]** The Fc region or FcRn binding partner of IgG can be modified according to well recognized procedures such as site directed mutagenesis and the like to yield modified IgG or Fc fragments or portions thereof that will be bound by FcRn. Such modifications include modifications remote from the FcRn contact sites as well as modifications within the contact sites that preserve or even enhance binding to the FcRn. For example, the following single amino acid residues in human IgG1 Fc (Fc □1)

25 can be substituted without significant loss of Fc binding affinity for FcRn: P238A, S239A, K246A, K248A, D249A, M252A, T256A, E258A, T260A, D265A, S267A, H268A, E269A, D270A, E272A, L274A, N276A, Y278A, D280A, V282A, E283A, H285A, N286A, T289A, K290A, R292A, E293A, E294A, Q295A, Y296F, N297A, S298A, Y300F, R301A, V303A, V305A, T307A, L309A, Q311A, D312A, N315A, K317A, E318A, K320A, K322A, S324A, K326A, A327Q, P329A, A330Q, P331A,

30 E333A, K334A, T335A, S337A, K338A, K340A, Q342A, R344A, E345A, Q347A, R355A, E356A, M358A, T359A, K360A, N361A, Q362A, Y373A, S375A, D376A, A378Q, E380A, E382A, S383A, N384A, Q386A, E388A, N389A, N390A, Y391F, K392A, L398A, S400A, D401A, D413A, K414A,

R416A, Q418A, Q419A, N421A, V422A, S424A, E430A, N434A, T437A, Q438A, K439A, S440A, S444A, and K447A, where for example P238A represents wild type proline substituted by alanine at position number 238. As an example, some embodiments incorporate the N297A mutation, removing a highly conserved N-glycosylation site. In addition to alanine other amino acids can be substituted for the wild type amino acids at the positions specified above. Mutations can be introduced singly into Fc giving rise to more than one hundred Fc regions distinct from the native Fc. Additionally, combinations of two, three, or more of these individual mutations can be introduced together, giving rise to hundreds more Fc regions. Moreover, one of the Fc region of a construct of the disclosure can be mutated and the other Fc region of the construct not mutated at all, or they both can be mutated but with different mutations.

[0244] Certain of the above mutations can confer new functionality upon the Fc region or FcRn binding partner. For example, some embodiments incorporate N297A, removing a highly conserved N-glycosylation site. The effect of this mutation is to reduce immunogenicity, thereby enhancing circulating half-life of the Fc region, and to render the Fc region incapable of binding to FcγRI, FcγRIIA, FcγRIIB, and FcγRIIIA, without compromising affinity for FcRn (Routledge et al. 1995, Transplantation 60:847; Friend et al. 1999, Transplantation 68:1632; Shields et al. 1995, J. Biol. Chem. 276:6591). As a further example of new functionality arising from mutations described above affinity for FcRn can be increased beyond that of wild type in some instances. This increased affinity can reflect an increased "on" rate, a decreased "off" rate or both an increased "on" rate and a decreased "off" rate. Examples of mutations believed to impart an increased affinity for FcRn include, but not limited to, T256A, T307A, E380A, and N434A (Shields et al. 2001, J. Biol. Chem. 276:6591).

[0245] Additionally, at least three human Fc gamma receptors appear to recognize a binding site on IgG within the lower hinge region, generally amino acids 234-237. Therefore, another example of new functionality and potential decreased immunogenicity can arise from mutations of this region, as for example by replacing amino acids 233-236 of human IgG1 "ELLG" to the corresponding sequence from IgG2 "PVA" (with one amino acid deletion). It has been shown that FcγRI, FcγRII, and FcγRIII, which mediate various effector functions will not bind to IgG1 when such mutations have been introduced. Ward and Ghetie 1995, Therapeutic Immunology 2:77 and Armour et al. 1999, Eur. J. Immunol. 29:2613.

[0246] In some embodiments, the Ig constant region or a portion thereof, e.g., an Fc region, is a polypeptide including the sequence PKNSSMISNTP (SEQ ID NO: 89 or SEQ ID NO: 3 of U.S. Pat.

No. 5,739,277) and optionally further including a sequence selected from HQSLGTQ (SEQ ID NO: 90), HQNLSDGK (SEQ ID NO: 91), HQNISDGK (SEQ ID NO: 92), or VISSHLGQ (SEQ ID NO: 93) (or SEQ ID NOs: 11, 1, 2, and 31, respectively of U.S. Pat. No. 5,739,277).

[0247] In other embodiments, the immunoglobulin constant region or a portion thereof comprises an amino acid sequence in the hinge region or a portion thereof that forms one or more disulfide bonds with another immunoglobulin constant region or a portion thereof. The disulfide bond by the immunoglobulin constant region or a portion thereof places the first polypeptide comprising a FVIII polypeptide and the second polypeptide comprising the VWF fragment together so that endogenous VWF does not replace the VWF fragment and does not bind to the FVIII polypeptide. Therefore, the disulfide bond between the first immunoglobulin constant region or a portion thereof and a second immunoglobulin constant region or a portion thereof prevents interaction between endogenous VWF and the FVIII polypeptide. This inhibition of interaction between the VWF and the FVIII polypeptide allows the half-life of the chimeric polypeptide to go beyond the two fold limit. The hinge region or a portion thereof can further be linked to one or more domains of CH1, CH2, CH3, a fragment thereof, and any combinations thereof. In a particular embodiment, the immunoglobulin constant region or a portion thereof is a hinge region and CH2.

[0248] In certain embodiments, the Ig constant region or a portion thereof is hemi-glycosylated. For example, the chimeric polypeptide comprising two Fc regions or FcRn binding partners can contain a first, glycosylated, Fc region (e.g., a glycosylated CH2 region) or FcRn binding partner and a second, aglycosylated, Fc region (e.g., an aglycosylated CH2 region) or FcRn binding partner. In some embodiments, a linker can be interposed between the glycosylated and aglycosylated Fc regions. In other embodiments, the Fc region or FcRn binding partner is fully glycosylated, i.e., all of the Fc regions are glycosylated. In other embodiments, the Fc region can be aglycosylated, i.e., none of the Fc moieties are glycosylated.

[0249] In certain embodiments, a chimeric polypeptide of the disclosure comprises an amino acid substitution to an Ig constant region or a portion thereof (e.g., Fc variants), which alters the antigen-independent effector functions of the Ig constant region, in particular the circulating half-life of the protein.

[0250] Such proteins exhibit either increased or decreased binding to FcRn when compared to proteins lacking these substitutions and, therefore, have an increased or decreased half-life in serum, respectively. Fc variants with improved affinity for FcRn are anticipated to have longer serum half-

lives, and such molecules have useful applications in methods of treating mammals where long half-life of the administered polypeptide is desired, e.g., to treat a chronic disease or disorder (see, e.g., US Patents 7,348,004, 7,404,956, and 7,862,820). In contrast, Fc variants with decreased FcRn binding affinity are expected to have shorter half-lives, and such molecules are also useful, for example, for administration to a mammal where a shortened circulation time can be advantageous, e.g. for in vivo diagnostic imaging or in situations where the starting polypeptide has toxic side effects when present in the circulation for prolonged periods. Fc variants with decreased FcRn binding affinity are also less likely to cross the placenta and, thus, are also useful in the treatment of diseases or disorders in pregnant women. In addition, other applications in which reduced FcRn binding affinity can be desired include those applications in which localization the brain, kidney, and/or liver is desired. In one exemplary embodiment, the chimeric polypeptides of the disclosure exhibit reduced transport across the epithelium of kidney glomeruli from the vasculature. In other embodiments, the chimeric polypeptides of the disclosure exhibit reduced transport across the blood brain barrier (BBB) from the brain, into the vascular space. In some embodiments, a protein with altered FcRn binding comprises at least one Fc region or FcRn binding partner (e.g, one or two Fc regions or FcRn binding partners) having one or more amino acid substitutions within the "FcRn binding loop" of an Ig constant region. The FcRn binding loop is comprised of amino acid residues 280-299 (according to EU numbering) of a wild-type, full-length, Fc region. In other embodiments, an Ig constant region or a portion thereof in a chimeric polypeptide of the disclosure having altered FcRn binding affinity comprises at least one Fc region or FcRn binding partner having one or more amino acid substitutions within the 15 Å FcRn "contact zone." As used herein, the term 15 Å FcRn "contact zone" includes residues at the following positions of a wild-type, full-length Fc moiety: 243-261, 275-280, 282-293, 302-319, 336- 348, 367, 369, 372-389, 391, 393, 408, 424, 425-440 (EU numbering). In other embodiments, a Ig constant region or a portion thereof of the disclosure having altered FcRn binding affinity comprises at least one Fc region or FcRn binding partner having one or more amino acid substitutions at an amino acid position corresponding to any one of the following EU positions: 256, 277-281, 283-288, 303-309, 313, 338, 342, 376, 381, 384, 385, 387, 434 (e.g., N434A or N434K), and 438. Exemplary amino acid substitutions which altered FcRn binding activity are disclosed in International PCT Publication No. WO05/047327 which is incorporated by reference herein.

[0251] An Fc region or FcRn binding partner used in the disclosure can also comprise an art recognized amino acid substitution which alters the glycosylation of the chimeric polypeptide. For example, the Fc region or FcRn binding partner of the chimeric polypeptide linked to the D'D3 domain

of VWF or a FVIII polypeptide can comprise an Fc region having a mutation leading to reduced glycosylation (e.g., N- or O-linked glycosylation) or can comprise an altered glycoform of the wild-type Fc moiety (e.g., a low fucose or fucose-free glycan).

[0252] In some embodiments, an unprocessed chimeric polypeptide of the disclosure can comprise a genetically fused Fc region (i.e., scFc region) having two or more of its constituent Ig constant region or a portion thereof independently selected from the Ig constant region or a portion thereof described herein. In some embodiments, the Fc regions of a dimeric Fc region are the same. In other embodiments, at least two of the Fc regions are different. For example, the Fc regions or FcRn binding partners of the proteins of the disclosure comprise the same number of amino acid residues or they can differ in length by one or more amino acid residues (e.g., by about 5 amino acid residues (e.g., 1, 2, 3, 4, or 5 amino acid residues), about 10 residues, about 15 residues, about 20 residues, about 30 residues, about 40 residues, or about 50 residues). In yet other embodiments, the Fc regions or FcRn binding partners of the protein of the disclosure can differ in sequence at one or more amino acid positions. For example, at least two of the Fc regions or FcRn binding partners can differ at about 5 amino acid positions (e.g., 1, 2, 3, 4, or 5 amino acid positions), about 10 positions, about 15 positions, about 20 positions, about 30 positions, about 40 positions, or about 50 positions).

III.C.2. XTEN Sequences

[0253] As used herein "XTEN sequence" refers to extended length polypeptides with non-naturally occurring, substantially non-repetitive sequences that are composed mainly of small hydrophilic amino acids, with the sequence having a low degree or no secondary or tertiary structure under physiologic conditions. As a chimeric polypeptide partner, XTENs can serve as a carrier, conferring certain desirable pharmacokinetic, physicochemical and pharmaceutical properties when linked to a VWF protein or a FVIII sequence of the disclosure to create a chimeric polypeptide. Such desirable properties include but are not limited to enhanced pharmacokinetic parameters and solubility characteristics. As used herein, "XTEN" specifically excludes antibodies or antibody fragments such as single-chain antibodies or Fc fragments of a light chain or a heavy chain.

[0254] In some embodiments, a shorter XTEN sequence provides an improved half-life extending property compared to a longer XTEN sequence when the XTEN sequence is fused to a VWF protein and/or a second Ig constant region or a portion thereof. Therefore, in some embodiments, the XTEN sequence fused to a VWF protein and/or the second Ig constant region or a portion thereof contains less than 288 amino acids in length, i.e., is shorter than 288 amino acids. In some embodiments, the

XTEN sequence fused to a VWF protein and/or the second Ig constant region or a portion thereof consists of an amino acid sequence having a length of between 12 amino acids and 287 amino acids. In other embodiments, the XTEN sequence fused to a VWF protein and/or the second Ig constant region or a portion thereof comprise at least about 36 amino acids, at least about 42 amino acids, at least about 72 amino acids, or at least about 144 amino acids, but less than 288 amino acids. In other embodiments, the XTEN sequence fused to a VWF protein and/or the second Ig constant region or a portion thereof is selected from AE36, AG36, AE42, AG42, AE72, AG72, AE144, or AG144. In some embodiments, the XTEN sequence fused to a VWF protein and/or the second Ig constant region or a portion thereof is an amino acid sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 14, wherein the chimeric polypeptide exhibits an improved half-life compared to a chimeric polypeptide without the XTEN sequence.

[0255] The chimeric polypeptide of the disclosure can further comprise an additional (second, third, or more) XTEN sequences. The additional XTEN sequence can further be fused to the FVIII polypeptide or the first Ig constant region or a portion thereof. The additional XTEN sequences can be any length. For example, the additional XTEN sequence fused to the FVIII polypeptide or the first Ig constant region or a portion thereof is a peptide or a polypeptide having greater than about 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1200, 1400, 1600, 1800, or 2000 amino acid residues. In certain embodiments, the additional XTEN sequence is a peptide or a polypeptide having greater than about 20 to about 3000 amino acid residues, greater than about 30 to about 2500 residues, greater than about 40 to about 2000 residues, greater than about 50 to about 1500 residues, greater than about 60 to about 1000 residues, greater than about 70 to about 900 residues, greater than about 80 to about 800 residues, greater than about 90 to about 700 residues, greater than about 100 to about 600 residues, greater than about 110 to about 500 residues, or greater than about 120 to about 400 residues. In certain embodiments, the additional XTEN that is fused to the FVIII polypeptide comprises at least about 288 amino acids. In particular embodiments, the additional XTEN that is fused to the FVIII polypeptide comprises about 288 amino acids. In particular embodiments, the additional XTEN that is fused to the FVIII polypeptide comprises an amino acid sequence at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence of AE288 (SEQ ID NO: 8).

[0256] The XTEN sequences (i.e., the XTEN sequence fused to the VWF protein and/or the second Ig constant region or a portion thereof or the XTEN sequence fused to the FVIII polypeptide and/or the first Ig constant region or a portion thereof or inserted at one or more insertion sites within the FVIII polypeptide) can comprise one or more sequence motif of 9 to 14 amino acid residues or an amino acid sequence at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the sequence motif, wherein the motif comprises, consists essentially of, or consists of 4 to 6 types of amino acids selected from the group consisting of glycine (G), alanine (A), serine (S), threonine (T), glutamate (E) and proline (P). See US 2010-0239554 A1.

[0257] In some embodiments, the XTEN sequence comprises non-overlapping sequence motifs in which at least about 80%, or at least about 85%, or at least about 90%, or at least about 91%, or at least about 92%, or at least about 93%, or at least about 94%, or at least about 95%, or at least about 96%, or at least about 97%, or at least about 98%, or at least about 99% or about 100% of the sequence consists of multiple units of non-overlapping sequences selected from a single motif family selected from Table 7, resulting in a family sequence. As used herein, "family" means that the XTEN has motifs selected only from a single motif category from Table 7; i.e., AD, AE, AF, AG, AM, AQ, BC, or BD XTEN, and that any other amino acids in the XTEN not from a family motif are selected to achieve a needed property, such as to permit incorporation of a restriction site by the encoding nucleotides, incorporation of a cleavage sequence, or to achieve a better linkage to FVIII or VWF. In some embodiments of XTEN families, an XTEN sequence comprises multiple units of non-overlapping sequence motifs of the AD motif family, or of the AE motif family, or of the AF motif family, or of the AG motif family, or of the AM motif family, or of the AQ motif family, or of the BC family, or of the BD family, with the resulting XTEN exhibiting the range of homology described above. In other embodiments, the XTEN comprises multiple units of motif sequences from two or more of the motif families of Table 7. These sequences can be selected to achieve desired physical/chemical characteristics, including such properties as net charge, hydrophilicity, lack of secondary structure, or lack of repetitiveness that are conferred by the amino acid composition of the motifs, described more fully below. In the embodiments hereinabove described in this paragraph, the motifs incorporated into the XTEN can be selected and assembled using the methods described herein to achieve an XTEN of about 36 to about 3000 amino acid residues.

Table 7. XTEN Sequence Motifs of 12 Amino Acids and Motif Families

Motif Family*	MOTIF SEQUENCE
AD	GESPGGSSGSES (SEQ ID NO: 24)
AD	GSEGSSGPGESE (SEQ ID NO: 25)
AD	GSSESGSSEGGP (SEQ ID NO: 26)
AD	GSGGEPSESGSS (SEQ ID NO: 27)
AE, AM	GSPAGSPTSTEE (SEQ ID NO: 28)
AE, AM, AQ	GSEPATSGSETP (SEQ ID NO: 29)
AE, AM, AQ	GTSESATPESGP (SEQ ID NO: 30)
AE, AM, AQ	GTSTEPSEGSAP (SEQ ID NO: 31)
AF, AM	GSTSESPSGTAP (SEQ ID NO: 32)
AF, AM	GTSTPESGSASP (SEQ ID NO: 33)
AF, AM	GTSPSGESSTAP (SEQ ID NO: 34)
AF, AM	GSTSSTAESPGP (SEQ ID NO: 35)
AG, AM	GTPGSGTASSSP (SEQ ID NO: 36)
AG, AM	GSSTPSGATGSP (SEQ ID NO: 37)
AG, AM	GSSPSASTGTGP (SEQ ID NO: 38)
AG, AM	GASPGTSSTGSP (SEQ ID NO: 39)
AQ	GEPAGSPTSTSE (SEQ ID NO: 40)
AQ	GTGEPSTPASE (SEQ ID NO: 41)
AQ	GSGPSTESAPTE (SEQ ID NO: 42)
AQ	GSETPSGPSETA (SEQ ID NO: 43)
AQ	GPSETSTSEPGA (SEQ ID NO: 44)
AQ	GSPSEPTEGTSA (SEQ ID NO: 45)
BC	GSGASEPTSTEP (SEQ ID NO: 46)
BC	GSEPATSGTEPS (SEQ ID NO: 47)
BC	GTSEPSTSEPGA (SEQ ID NO: 48)
BC	GTSTEPSEPGSA (SEQ ID NO: 49)
BD	GSTAGSETSTEA (SEQ ID NO: 50)
BD	GSETATSGSETA (SEQ ID NO: 51)
BD	GTSESATSESGA (SEQ ID NO: 52)
BD	GTSTEASEGSAS (SEQ ID NO: 53)

*Denotes individual motif sequences that, when used together in various permutations, results in a "family sequence"

[0258] In some embodiments, the XTEN sequence used in the disclosure is at least 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to a sequence selected from the group consisting of AE42, AG42, AE48, AM48, AE72, AG72, AE108, AG108, AE144, AF144, AG144, AE180, AG180, AE216, AG216, AE252, AG252, AE288, AG288, AE324, AG324, AE360, AG360, AE396, AG396, AE432, AG432, AE468, AG468, AE504, AG504, AF504, AE540, AG540, AF540, AD576, AE576, AF576, AG576, AE612, AG612, AE624, AE648, AG648,

AG684, AE720, AG720, AE756, AG756, AE792, AG792, AE828, AG828, AD836, AE864, AF864, AG864, AM875, AE912, AM923, AM1318, BC864, BD864, AE948, AE1044, AE1140, AE1236, AE1332, AE1428, AE1524, AE1620, AE1716, AE1812, AE1908, AE2004A, AG948, AG1044, AG1140, AG1236, AG1332, AG1428, AG1524, AG1620, AG1716, AG1812, AG1908, and AG2004.

5 See US 2010-0239554 A1.

[0259] In some embodiments, the XTEN sequence is at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to an amino acid sequence selected from the group consisting of AE42 (SEQ ID NO: 9), AE72 (SEQ ID NO: 10), AE144_2A (SEQ IDNO: 55), AE144_3B (SEQ ID NO: 56), AE144_4A (SEQ ID NO: 57), AE144_5A (SEQ ID NO: 58), AE144_6B (SEQ ID NO: 59),
 10 AG144_A (SEQ ID NO: 60), AG144_B (SEQ ID NO: 61), AG144_C (SEQ ID NO: 62), AG144_F (SEQ IDNO: 63), AE864 (SEQ ID NO: 15), AE576 (SEQ ID NO: 16), AE288 (SEQ ID NO: 8), AE288_2 (SEQ ID NO: 54), AE144 (SEQ ID NO: 11), AG864 (SEQ ID NO: 17), AG576 (SEQ ID NO: 18), AG288 (SEQ ID NO: 19), AG144 (SEQ ID NO: 14), and any combinations thereof. In other embodiments, the XTEN sequence is selected from the group consisting of AE42 (SEQ ID NO: 9),
 15 AE72 (SEQ ID NO: 10), AE144_2A (SEQ IDNO: 55), AE144_3B (SEQ ID NO: 56), AE144_4A (SEQ ID NO: 57), AE144_5A (SEQ IDNO: 58), AE144_6B (SEQ ID NO: 59), AG144_A (SEQ ID NO: 60), AG144_B (SEQ ID NO: 61), AG144_C (SEQ ID NO: 62), AG144_F (SEQ IDNO: 63), AE864 (SEQ ID NO: 15), AE576 (SEQ ID NO: 16), AE288 (SEQ ID NO: 8), AE288_2 (SEQ ID NO: 54), AE144 (SEQ ID NO: 11), AG864 (SEQ ID NO: 17), AG576 (SEQ ID NO: 18), AG288 (SEQ ID NO: 19),
 20 AG144 (SEQ ID NO: 14), and any combinations thereof. In some embodiments, the XTEN sequence is AE288. The amino acid sequences for certain XTEN sequences of the disclosure are shown in Table 8.

TABLE 8. XTEN Sequences

XTEN	Amino Acid Sequence
AE42 SEQ ID NO: 9	GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS
AE72 (SEQ ID NO: 10)	GAP TSESATPESG PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG TSTEPSEGSAPGASS
AE144 (SEQ ID NO:11)	GSEPATSGSETPGTSESATPESGPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEG SAPGSEPATSGSETPGSEPATSGSETPGSEPATSGSETPGTSTEPSEGSAPGTSESA PESGPGSEPATSGSETPGTSTEPSEGSAP

AE144_2A (SEQ ID NO: 55)	TSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGTSESATPESGPGTSTEPS EGSAPGTSESATPESGPGSEPATSGSETPGTSTEPSEGSAPGTSTEPSEGSAPGTSESATPESGP GTSESATPESGPG
AE144_3B (SEQ ID NO: 56)	SPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEPS EGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEE GTSTEPSEGSAPG
AE144_4A (SEQ ID NO: 57)	TSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPS EGSAPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGSPAGSPTSTEEGTSESATPESGP GTSTEPSEGSAPG
AE144_5A (SEQ ID NO: 58)	TSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPS EGSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEE GSPAGSPTSTEEG
AE144_6B (SEQ ID NO: 59)	TSTEPSEGSAPGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSG GSETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPG TSTEPSEGSAPG
AG144 SEQ ID NO:14	GTPGSGTASSSPGSSTPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGASPGTSST GSPGASPGTSSTGSPGSSTPSGATGSPGSSPSASTGTGPGASPGTSSTGSPGSSPSA STGTGPGTTPGSGTASSSPGSSTPSGATGSP
AG144_A (SEQ ID NO: 60)	GASPGTSSTGSPGSSPSASTGTGPGSSPSASTGTGPGTTPGSGTASSSPGSSTPSGATGSPGSSPS ASTGTGPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGTPGSGTASSSPGASPGTSSTG SPGASPGTSSTGSP
AG144_B (SEQ ID NO: 61)	GTPGSGTASSSPGSSTPSGATGSPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGSSPS ASTGTGPGSSPSASTGTGPGSSTPSGATGSPGSSTPSGATGSPGASPGTSSTGSPGASPGTSSTG SPGASPGTSSTGSP
AG144_C (SEQ ID NO: 62)	GTPGSGTASSSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGSSPSASTGTGPGTPGS GTASSSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGSSTPSGATGSPGSSTPSGATG SPGASPGTSSTGSP
AG144_F (SEQ ID NO: 63)	GSSPSASTGTGPGSSPSASTGTGPGASPGTSSTGSPGASPGTSSTGSPGSSTPSGATGSPGSSPS ASTGTGPGASPGTSSTGSPGSSPSASTGTGPGTPGSGTASSSPGSSTPSGATGSPGSSTPSGATG SPGASPGTSSTGSP
AE288 SEQ ID NO: 8	GTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESG PGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPES GPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSESATPE SGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSE GSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAP
AE288_2	GSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEP SEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEE GTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESA

(SEQ ID NO: 54)	TPESGPGTSTEPSEGSAPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAP
AG288 SEQ ID NO:19	PGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGTPGSGTASSSPGSSTPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGASPGTSSTGSPGASPGTSSTGSPGSSTPSGATGSPGSSPSASTGTGPGASPGTSSTGSPGSSPSASTGTGPGTPGSGTASSSPGSSTPSGATGS
AE576 SEQ ID NO:16	GSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSA PGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTST EEGTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEG SAPGTSTEPSEGSAPGTSESATPESGPGTSTEPSEGSAPGTSESATPESGPGSEPATSG SETPGTSTEPSEGSAPGTSTEPSEGSAPGTSESATPESGPGTSTEPSEGSAPGTSTEP TSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEP SEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAG SPTSTEEGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSE ATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSESATPESGPGSPAGSPTSTEEGSP AGSPTSTEEGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAP
AG576 SEQ ID NO:18	PGTPGSGTASSSPGSSTPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGSSTPSGATG SPGSSTPSGATGSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGTPGSGTAS SSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGSSPSASTGTGPGTPGSGTA SSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGSSPSASTGTGPGTPGSGTA ATGSPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGSSTPSGATGSPGSSTPS GATGSPGSSPSASTGTGPGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASSSPGASPG TSSTGSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASSSPGSST PSGATGSPGTPGSGTASSSPGSSTPSGATGSPGTPGSGTASSSPGSSTPSGATGSPGSS TPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGASPGTSSTGSPGTPGSGTASSSPGS STPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGASPGTSSTGS
AE864 SEQ ID NO:15	GSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSA PGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTST EEGTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEG SAPGTSTEPSEGSAPGTSESATPESGPGTSTEPSEGSAPGTSESATPESGPGSEPATSG SETPGTSTEPSEGSAPGTSTEPSEGSAPGTSESATPESGPGTSTEPSEGSAPGTSTEP TSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEP SEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAG SPTSTEEGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSE ATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSESATPESGPGSPAGSPTSTEEGSP AGSPTSTEEGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGTSESATPESGPGS EPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPG SPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEE GSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSTEPSEGSAPGTSESATPESG PGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGS APGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAP
AG864 SEQ ID NO:17	GASPGTSSTGSPGSSPSASTGTGPGSSPSASTGTGPGTPGSGTASSSPGSSTPSGATGS PGSSPSASTGTGPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGTPGSGTASS SPGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGASPGTSST GSPGTPGSGTASSSPGSSTPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGSSTPSGA TGSPGSSTPSGATGSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGTPGSGT

ASSSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGSSPSASTGTGPGTPGSG TASSSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGSSTPSGATGSPGSSTP SGATGSPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGSSTPSGATGSPGSST PSGATGSPGSSPSASTGTGPGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASSSPGAS PGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASSSPGS STPSGATGSPGTPGSGTASSSPGSSTPSGATGSPGTPGSGTASSSPGSSTPSGATGSPG SSTPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGASPGTSSTGSPGTPGSGTASSSP GSSTPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGASPGTSSTGSPGASPGTSSTGS PGSSTPSGATGSPGSSPSASTGTGPGASPGTSSTGSPGSSPSASTGTGPGTPGSGTASS SPGSSTPSGATGSPGSSTPSGATGSPGASPGTSSTGSP

[0260] In those embodiments wherein the XTEN component(s) have less than 100% of its amino acids consisting of 4, 5, or 6 types of amino acid selected from glycine (G), alanine (A), serine (S), threonine (T), glutamate (E) and proline (P), or less than 100% of the sequence consisting of the sequence motifs from Table 7 or the XTEN sequences of Table 8, the other amino acid residues of the XTEN are selected from any of the other 14 natural L-amino acids, but are preferentially selected from hydrophilic amino acids such that the XTEN sequence contains at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or at least about 99% hydrophilic amino acids. The XTEN amino acids that are not glycine (G), alanine (A), serine (S), threonine (T), glutamate (E) and proline (P) are either interspersed throughout the XTEN sequence, are located within or between the sequence motifs, or are concentrated in one or more short stretches of the XTEN sequence, e.g., to create a linker between the XTEN and the FVIII or VWF components. In such cases where the XTEN component comprises amino acids other than glycine (G), alanine (A), serine (S), threonine (T), glutamate (E) and proline (P), it is preferred that less than about 2% or less than about 1% of the amino acids be hydrophobic residues such that the resulting sequences generally lack secondary structure, e.g., not having more than 2% alpha helices or 2% beta-sheets, as determined by the methods disclosed herein. Hydrophobic residues that are less favored in construction of XTEN include tryptophan, phenylalanine, tyrosine, leucine, isoleucine, valine, and methionine. Additionally, one can design the XTEN sequences to contain less than 5% or less than 4% or less than 3% or less than 2% or less than 1% or none of the following amino acids: cysteine (to avoid disulfide formation and oxidation), methionine (to avoid oxidation), asparagine and glutamine (to avoid desamidation). Thus, in some embodiments, the XTEN component comprising other amino acids in addition to glycine (G), alanine (A), serine (S), threonine (T), glutamate (E) and proline (P) have a sequence with less than 5% of the residues contributing to alpha-helices and beta-sheets as measured by the Chou-Fasman algorithm and have at least 90%, or at least about 95% or more random coil formation as measured by the GOR algorithm.

[0261] In further embodiments, the XTEN sequence used in the disclosure affects the physical or chemical property, e.g., pharmacokinetics, of the chimeric polypeptide of the present disclosure. The XTEN sequence used in the present disclosure can exhibit one or more of the following advantageous properties: conformational flexibility, enhanced aqueous solubility, high degree of protease resistance, low immunogenicity, low binding to mammalian receptors, or increased hydrodynamic (or Stokes) radii. In some embodiments, the XTEN sequence linked to a FVIII protein in this disclosure increases pharmacokinetic properties such as longer terminal half-life or increased area under the curve (AUC), so that the chimeric polypeptide described herein stays in vivo for an increased period of time compared to wild type FVIII. In further embodiments, the XTEN sequence used in this disclosure increases pharmacokinetic properties such as longer terminal half-life or increased area under the curve (AUC), so that FVIII protein stays in vivo for an increased period of time compared to wild type FVIII.

[0262] A variety of methods and assays can be employed to determine the physical/chemical properties of proteins comprising the XTEN sequence. Such methods include, but are not limited to analytical centrifugation, EPR, HPLC-ion exchange, HPLC-size exclusion, HPLC-reverse phase, light scattering, capillary electrophoresis, circular dichroism, differential scanning calorimetry, fluorescence, HPLC-ion exchange, HPLC-size exclusion, IR, NMR, Raman spectroscopy, refractometry, and UV/Visible spectroscopy. Additional methods are disclosed in Amau et al., *Prot Expr and Purif* 48, 1-13 (2006).

[0263] Additional examples of XTEN sequences that can be used according to the present disclosure and are disclosed in US Patent Publication Nos. 2010/0239554 A1, 2010/0323956 A1, 2011/0046060 A1, 2011/0046061 A1, 2011/0077199 A1, or 2011/0172146 A1, or International Patent Publication Nos. WO 2010091122 A1, WO 2010144502 A2, WO 2010144508 A1, WO 2011028228 A1, WO 2011028229 A1, WO 2011028344 A2, or WO 20130122617 A1.

III.C.2. Albumins

[0264] An albumin or a portion thereof can be an FcRn binding partner. In certain aspects, a chimeric polypeptide used in the methods of the present disclosure comprises at least one albumin polypeptide or fragment, variant, or derivative thereof. Human serum albumin (HSA, or HA), a protein of 609 amino acids in its full-length form, is responsible for a significant proportion of the osmotic pressure of serum and also functions as a carrier of endogenous and exogenous ligands. The term "albumin" as used herein includes full-length albumin or a functional fragment, variant, derivative, or

analog thereof. Examples of albumin or the fragments or variants thereof are disclosed in US Pat. Publ. Nos. 2008/0194481A1, 2008/0004206 A1, 2008/0161243 A1, 2008/0261877 A1, or 2008/0153751 A1 or PCT Appl. Publ. Nos. 2008/033413 A2, 2009/058322 A1, or 2007/021494 A2, which are incorporated herein by reference in their entireties.

5 **[0265]** The albumin-binding polypeptides (ABPs) can comprise, without limitation, bacterial albumin-binding domains, albumin-binding peptides, or albumin-binding antibody fragments that can bind to albumin. Domain 3 from streptococcal protein G, as disclosed by Kraulis et al., FEBS Lett. 378:190-194 (1996) and Linhult et al., Protein Sci. 11:206-213 (2002) is an example of a bacterial albumin-binding domain. Examples of albumin-binding peptides are disclosed in Dennis et al., J. Biol.
10 Chem. 2002, 277: 35035-35043 (2002). Examples of albumin-binding antibody fragments are disclosed in Muller and Kontermann, Curr. Opin. Mol. Ther. 9:319-326 (2007); Roovers et al., Cancer Immunol. Immunother. 56:303-317 (2007), and Holt et al., Prot. Eng. Design Sci., 21:283-288 (2008), which are incorporated herein by reference in their entireties.

[0266] In certain aspects, a chimeric polypeptide used in the methods of the present disclosure
15 comprises at least one attachment site for a non-polypeptide small molecule, variant, or derivative that can bind to albumin thereof. For example, the chimeric polypeptide can include one or more organic albumin-binding moieties. An example of such albumin-binding moieties is 2-(3-maleimidopropanamido)-6-(4-(4-iodophenyl)butanamido)hexanoate ("Albu" tag) as disclosed by Trussel et al., Bioconjugate Chem. 20:2286-2292 (2009).

20 **[0267]** In certain embodiments, the a VWF fragment described herein is fused to an albumin. In some embodiments, the VWF fragment-albumin constructs form homodimers. In some embodiments, the D'D3 domain of VWF that is fused to the albumin associates with a FVIII polypeptide. In certain embodiments, the D'D3 domain of VWF fused to the albumin associated with the FVIII polypeptide by an interaction stronger than the natural non-covalent interactions between wild-type FVIII and
25 VWF. In particular embodiments, the D'D3 domain of VWF and/or the FVIII polypeptide comprises one or more mutation that increases the affinity between the D'D3 domain of VWF and the FVIII polypeptide. In certain embodiments, the D'D3 domain of VWF and/or the FVIII polypeptide comprises one or more mutation that allows for a disulfide bond to form between the D'D3 domain of VWF and/or the FVIII polypeptide.

III.C.3. CTP

[0268] In certain aspects, a chimeric polypeptide used in the methods of the present disclosure comprises at least one C-terminal peptide (CTP) of the β subunit of human chorionic gonadotropin or fragment, variant, or derivative thereof. CTP peptides are known to increase the half-life of that protein. See, e.g., U.S. Patent No. 5,712,122, incorporated by reference herein in its entirety. Non-limiting exemplary CTP peptides are disclosed in U.S. Patent Application Publication No. US 2009/0087411 A1, incorporated by reference.

III.C.4. PAS

[0269] In certain aspects, a chimeric polypeptide used in the methods of the present disclosure comprises at least one PAS peptide or fragment, variant, or derivative thereof. A PAS peptide or PAS sequence, as used herein, means an amino acid sequence comprising mainly alanine and serine residues or comprising mainly alanine, serine, and proline residues, the amino acid sequence forming random coil conformation under physiological conditions. Accordingly, the PAS sequence is a building block, an amino acid polymer, or a sequence cassette comprising, consisting essentially of, or consisting of alanine, serine, and proline which can be used as a part of the heterologous moiety in the chimeric polypeptide. An amino acid polymer also can form random coil conformation when residues other than alanine, serine, and proline are added as a minor constituent in the PAS sequence. By "minor constituent" is meant that that amino acids other than alanine, serine, and proline can be added in the PAS sequence to a certain degree, e.g., up to about 12%, i.e., about 12 of 100 amino acids of the PAS sequence, up to about 10%, up to about 9%, up to about 8%, about 6%, about 5%, about 4%, about 3%, i.e. about 2%, or about 1%, of the amino acids. The amino acids different from alanine, serine and proline can be selected from the group consisting of Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Tyr, and Val. Under physiological conditions, a PAS peptide forms a random coil conformation and thereby can mediate an increased in vivo and/or in vitro stability to a recombinant protein of the disclosure, and has procoagulant activity.

[0270] Non-limiting examples of the PAS peptides are disclosed in, e.g., US Pat. Publ. No. 2010/0292130 A1; PCT Appl. Publ. No. WO 2008/155134 A1; and European issued patent EP2173890.

III.C.5. HAP

[0271] In certain aspects, a chimeric polypeptide used in the methods of the present disclosure comprises at least one homo-amino acid polymer (HAP) peptide or fragment, variant, or derivative thereof. A HAP peptide can comprise a repetitive sequence of glycine, which has at least 50 amino acids, at least 100 amino acids, 120 amino acids, 140 amino acids, 160 amino acids, 180 amino acids, 200 amino acids, 250 amino acids, 300 amino acids, 350 amino acids, 400 amino acids, 450 amino acids, or 500 amino acids in length. A HAP sequence is capable of extending half-life of a moiety fused to or linked to the HAP sequence. Non-limiting examples of the HAP sequence includes, but are not limited to (Gly)*n*, (Gly4Ser)*n* or S(Gly4Ser)*n*, wherein *n* is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20. In some embodiments, *n* is 20, 21, 22, 23, 24, 25, 26, 26, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40. In other embodiments, *n* is 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200. See, e.g., Schlapschy M et al., Protein Eng. Design Selection, 20: 273-284 (2007).

III.C.6. Transferrin

[0272] In certain aspects, a chimeric polypeptide used in the methods of the present disclosure comprises at least one transferrin peptide or fragment, variant, or derivative thereof. Any transferrin can fuse with the chimeric polypeptide used in the methods of the present disclosure. As an example, wild-type human Tf (Tf) is a 679 amino acid protein, of approximately 75 kDa (not accounting for glycosylation), with two main domains, N (about 330 amino acids) and C (about 340 amino acids), which appear to originate from a gene duplication. See GenBank accession numbers NM001063, XM002793, M12530, XM039845, XM 039847 and S95936 (www.ncbi.nlm.nih.gov), all of which are herein incorporated by reference in their entirety.

[0273] Transferrin transports iron through transferrin receptor (TfR)-mediated endocytosis. After the iron is released into an endosomal compartment and Tf-TfR complex is recycled to cell surface, the Tf is released back extracellular space for next cycle of iron transporting. Tf possesses a long half-life that is in excess of 14-17 days (Li et al., Trends Pharmacol. Sci. 23:206-209 (2002)). Transferrin fusion proteins have been studied for half-life extension, targeted deliver for cancer therapies, oral delivery and sustained activation of proinsulin (Brandsma et al., Biotechnol. Adv., 29: 230-238 (2011); Bai et al., Proc. Natl. Acad. Sci. USA 102:7292-7296 (2005); Kim et al., J. Pharmacol. Exp. Ther., 334:682-692 (2010); Wang et al., J. Controlled Release 155:386-392 (2011)).

III.C.7. PEG

[0274] In certain aspects, a chimeric polypeptide used in the methods of the present disclosure comprises at least one attachment site for a non-polypeptide heterologous moiety or fragment, variant, or derivative thereof. For example, a chimeric polypeptide used in the methods of the present disclosure can include one or more polyethylene glycol (PEG) moieties attached to one or more amino acid residues in the clotting factor and/or the Fc region.

[0275] PEGylation of a protein can refer to a conjugate formed between the protein and at least one polyethylene glycol (PEG) molecule. PEG is commercially available in a large variety of molecular weights and average molecular weight ranges. Typical examples of PEG average molecular weight ranges include, but are not limited to, about 200, about 300, about 400, about 600, about 1000, about 1300-1600, about 1450, about 2000, about 3000, about 3000-3750, about 3350, about 3000-7000, about 3500-4500, about 5000-7000, about 7000-9000, about 8000, about 10000, about 8500-11500, about 16000-24000, about 35000, about 40000, about 60000, and about 80000 Daltons. These average molecular weights are provided merely as examples and are not meant to be limiting in any way.

[0276] A chimeric polypeptide used in the methods of the present disclosure can be PEGylated to include mono- or poly-(e.g., 2-4) PEG moieties. PEGylation can be carried out by any of the PEGylation reactions known in the art. Methods for preparing a PEGylated protein product will generally include (i) reacting a polypeptide with polyethylene glycol (such as a reactive ester or aldehyde derivative of PEG) under conditions whereby the peptide of the disclosure becomes attached to one or more PEG groups; and (ii) obtaining the reaction product(s). In general, the optimal reaction conditions for the reactions will be determined case by case based on known parameters and the desired result.

[0277] There are a number of PEG attachment methods available to those skilled in the art, for example Malik F et al., Exp. Hematol. 20:1028-35 (1992); Francis, Focus on Growth Factors 3(2):4-10 (1992); European Pat. Pub. Nos. EP0401384, EP0154316, and EP0401384; and International Pat. Appl. Pub. Nos. WO92/16221 and WO95/34326. As a non-limiting example, FVIII variants can contain cysteine substitutions, and the cysteines can be further conjugated to PEG polymer. See Mei et al., Blood 116:270-279 (2010) and U.S. Patent No. 7,632,921, which are incorporated herein by reference in their entireties.

[0278] In certain embodiments, the chimeric polypeptide comprises a single chain FVIII polypeptide covalently linked to a VWF fragment comprising a D' domain and a D3 domain of VWF, wherein the FVIII polypeptide comprises a deletion of all or a portion of the B domain, wherein the FVIII polypeptide is pegylated, and wherein the VWF fragment is fused directly or indirectly to the N-terminus of the FVIII polypeptide (e.g., PEG-scFVIII-D'D3, "MG1121," or LAFATE). In other embodiments, the chimeric polypeptide comprises a single chain FVIII polypeptide covalently linked to a VWF fragment comprising a D' domain and a D3 domain of VWF, wherein the FVIII polypeptide comprises a deletion of all or a portion of the B domain, wherein the VWF fragment is pegylated, and wherein the VWF fragment is fused directly or indirectly to the N-terminus of the FVIII polypeptide (e.g., scFVIII-D'D3-PEG). In other embodiments, the chimeric polypeptide comprises a single chain FVIII polypeptide covalently linked to a VWF fragment comprising a D' domain and a D3 domain of VWF, wherein the FVIII polypeptide comprises a deletion of all or a portion of the B domain, wherein FVIII polypeptide and the VWF fragment are pegylated, and wherein the VWF fragment is fused directly or indirectly to the N-terminus of the FVIII polypeptide (e.g., scFVIII-D'D3-PEG).

III.C.8. HES

[0279] In certain aspects, a chimeric polypeptide used in the methods of the present disclosure comprises at least one hydroxyethyl starch (HES) polymer. HES is a derivative of naturally occurring amylopectin and is degraded by alpha-amylase in the body. HES exhibits advantageous biological properties and is used as a blood volume replacement agent and in hemodilution therapy in the clinics. See, e.g., Sommermeyer et al., *Krankenhauspharmazie* 8:271-278 (1987); and Weidler et al., *Arzneim.-Forschung/Drug Res.* 41: 494-498 (1991).

[0280] HES is mainly characterized by the molecular weight distribution and the degree of substitution. HES has a mean molecular weight (weight mean) of from 1 to 300 kD, from 2 to 200kD, from 3 to 100 kD, or from 4 to 70kD. Hydroxyethyl starch can further exhibit a molar degree of substitution of from 0.1 to 3, from 0.1 to 2, from 0.1 to 0.9, or from 0.1 to 0.8, and a ratio between C2:C6 substitution in the range of from 2 to 20 with respect to the hydroxyethyl groups. HES with a mean molecular weight of about 130 kD is VOLUVEN® from Fresenius. VOLUVEN® is an artificial colloid, employed, e.g., for volume replacement used in the therapeutic indication for therapy and prophylaxis of hypovolaemia. There are a number of HES attachment methods available to those skilled in the art, e.g., the same PEG attachment methods described above.

III.C.9. PSA

[0281] In certain aspects, a chimeric polypeptide used in the methods of the present disclosure comprises at least one polysialic acid (PSA) polymer. PSAs are naturally occurring unbranched polymers of sialic acid produced by certain bacterial strains and in mammals in certain cells. See, e.g., Roth J. et al. (1993) in *Polysialic Acid: From Microbes to Man*, eds. Roth J., Rutishauser U., Troy F. A. (BirkhäuserVerlag, Basel, Switzerland), pp. 335–348. PSAs can be produced in various degrees of polymerization from n=about 80 or more sialic acid residues down to n=2 by limited acid hydrolysis or by digestion with neuraminidases, or by fractionation of the natural, bacterially derived forms of the polymer. There are a number of PSA attachment methods available to those skilled in the art, e.g., the same PEG attachment methods described above. In certain aspects, an activated PSA can also be attached to a cysteine amino acid residue within the clotting factor, e.g., on FVIII, or within the Fc region. See, e.g., U.S. Patent No. 5846951.

III.C.10. Clearance Receptors

[0282] In certain aspects, the half-life of a chimeric polypeptide used in the methods of the present disclosure can be extended where the clotting factor of the chimeric polypeptide comprises a FVIII polypeptide and at least one fragment of a FVIII clearance receptor or FVIII-binding fragment, variant, or derivative thereof. Insertion of soluble forms of clearance receptors, such as the low-density lipoprotein-related protein receptor LRP1, or fragments thereof, can block binding of FVIII to clearance receptors and thereby extend its half-life, e.g., in vivo half-life. LRP1 is a 600 kDa integral membrane protein that is implicated in the receptor-mediate clearance of a variety of proteins, including FVIII. See, e.g., Lenting et al., *Haemophilia* 16:6-16 (2010). Other suitable FVIII clearance receptors are, e.g., LDLR (low-density lipoprotein receptor), VLDLR (very low-density lipoprotein receptor), and megalin (LRP-2), or fragments thereof. See, e.g., Bovenschen et al., *Blood* 106:906-912 (2005); Bovenschen, *Blood* 116:5439-5440 (2010); Martinelli et al., *Blood* 116:5688-5697 (2010).

III.D. Insertion Sites

[0283] In some aspects, the insertion site in the FVIII polypeptide is located in one or more domains of the FVIII polypeptide, which is the N-terminus, the A1 domain, the A2 domain, the A3 domain, the B domain, the C1 domain, the C2 domain, the C-terminus, or two or more combinations thereof or between two domains of the FVIII polypeptide, which are the A1 domain and a1 acidic region, and the a1 acidic region and A2 domain, the A2 domain and a2 acidic region, the a2 acidic region and B

domain, the B domain and A3 domain, and the A3 domain and C1 domain, the C1 domain and C2 domain, or any combinations thereof. For example, the insertion sites in which the XTEN sequence can be inserted are selected from the group consisting of the N-terminus and A1 domain, the N-terminus and A2 domain, the N-terminus and A3 domain, the N-terminus and B domain, the N-terminus and C1 domain, the N-terminus and C2 domain, the N-terminus and the C-terminus, the A1 and A2 domains, the A1 and A3 domains, the A1 and B domains, the A1 and C1 domains, the A1 and C2 domains, the A1 domain and the C-terminus, the A2 and A3 domains, the A2 and B domains, the A2 and C1 domains, the A2 and C2 domains, the A2 domain and the C-terminus, the A3 and B domains, the A3 and C1 domains, the A3 and C2 domains, the A3 domain and the C-terminus, the B and C1 domains, the B and C2 domains, the B domain and the C-terminus, the C1 and C2 domains, the C1 and the C-terminus, the C2 domain, and the C-terminus, and two or more combinations thereof.

[0284] The FVIII polypeptide, in which the XTEN sequence is inserted immediately downstream of one or more amino acids (e.g., one or more XTEN insertion sites) in the FVIII polypeptide or linked at the C-terminus or the N-terminus, retains the FVIII activity after linkage to or insertion by the XTEN sequence. The XTEN sequence can be inserted in the FVIII polypeptide once or more than once, twice, three times, four times, five times, or six times such that the insertions do not affect the FVIII activity (i.e., the FVIII protein still retains the coagulation property).

[0285] The FVIII polypeptide useful in the present disclosure can be linked to one or more XTEN polypeptides at the N-terminus or C-terminus of the FVIII polypeptide by an optional linker or inserted immediately downstream of one or more amino acids (e.g., one or more XTEN insertion sites) in the FVIII polypeptide by one or more optional linkers.

[0286] In yet other embodiments, one or more XTENs are inserted in the B domain of FVIII. In one example, an XTEN is inserted between amino acids 740 and 1640 corresponding to SEQ ID NO: 65, wherein the FVIII sequence between amino acids 740 and 1640 is optionally not present. In another example, an XTEN is inserted between amino acids 741 and 1690 corresponding to SEQ ID NO: 65, wherein the FVIII sequence between amino acids 740 and 1690 is optionally not present. In other examples, an XTEN is inserted between amino acids 741 and 1648 corresponding to SEQ ID NO: 65, wherein the FVIII sequence between amino acids 741 and 1648 is optionally not present. In yet other examples, an XTEN is inserted between amino acids 743 and 1638 corresponding to SEQ ID NO: 65, wherein the FVIII sequence between amino acids 743 and 1638 is optionally not present. In still other examples, an XTEN is inserted between amino acids 745 and 1656 corresponding to SEQ

ID NO: 65, wherein the FVIII sequence between amino acids 745 and 1656 is optionally not present. In some examples, an XTEN is inserted between amino acids 745 and 1657 corresponding to SEQ ID NO: 65, wherein the FVIII sequence between amino acids 745 and 1657 is optionally not present. In certain examples, an XTEN is inserted between amino acids 745 and 1667 corresponding to SEQ ID NO: 65, wherein the FVIII sequence between amino acids 745 and 1667 is optionally not present. In still other examples, an XTEN is inserted between amino acids 745 and 1686 corresponding to SEQ ID NO: 65, wherein the FVIII sequence between amino acids 745 and 1686 is optionally not present. In some other examples, an XTEN is inserted between amino acids 747 and 1642 corresponding to SEQ ID NO: 65, wherein the FVIII sequence between amino acids 747 and 1642 is optionally not present. In still other examples, an XTEN is inserted between amino acids 751 and 1667 corresponding to SEQ ID NO: 65, wherein the FVIII sequence between amino acids 751 and 1667 is optionally not present. In some embodiments, an XTEN sequence is inserted between amino acids 745 and 746 of a mature FVIII polypeptide or the corresponding insertion site of the B-domain deleted FVIII polypeptide. In a particular embodiment, an XTEN sequence comprising an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of AE288 (SEQ ID NO: 8) is inserted between amino acids 745 and 746 of a mature FVIII, wherein the mature FVIII has a deletion of amino acid residues 746-1648. In particular embodiments, the XTEN is inserted immediately downstream of amino acid 745 of the B domain deleted FVIII of Table 5 (SEQ ID NO: 68).

III.E. Linkers

[0287] In certain embodiments, the chimeric polypeptide of the present disclosure further comprises one or more linkers in the FVIII protein and/or in the VWF fragment. One type of the linkers is a cleavable linker, which can be cleaved by various proteases when administered to a subject in vivo, e.g., at a site of coagulation. In some embodiments, the cleavable linker allows cleavage of moiety, e.g., a VWF protein, from the XTEN sequence, thus from the chimeric polypeptide at the site of the coagulation cascade, thereby allowing activated FVIII (FVIIIa) to have its FVIIIa activity. Another type of the linkers is a processable linker, which contains an intracellular cleavage site and thus can be cleaved by an intracellular processing enzyme in a host cell, allowing convenient expression of a polypeptide and formation of a chimeric polypeptide.

[0288] One or more linkers can be present between any two proteins in the chimeric polypeptide. In some embodiments, a chimeric polypeptide comprises a first polypeptide which comprises (i) a FVIII polypeptide and (ii) a first Ig constant region or a portion thereof and a second polypeptide which comprises (iii) a VWF protein, (iv) a linker (e.g., a cleavable linker), (v) an XTEN sequence, and (vi) a second Ig constant region or a portion thereof. In other embodiments, a chimeric polypeptide comprises a first polypeptide which comprises (i) a FVIII polypeptide and (ii) a first Ig constant region or a portion thereof and a second polypeptide which comprises (iii) a VWF protein, (iv) an XTEN sequence, (v) a linker (e.g., a cleavable linker), and (vi) a second Ig constant region or a portion thereof. In other embodiments, a chimeric polypeptide comprises a first polypeptide which comprises (i) a FVIII polypeptide and (ii) a first Ig constant region or a portion thereof and a second polypeptide which comprises (iii) a VWF protein, (iv) a first linker (e.g., a cleavable linker), (v) an XTEN sequence, (vi) a second linker (e.g., a cleavable linker), and (vii) a second Ig constant region or a portion thereof. In some embodiments, the first polypeptide further comprises a linker, e.g., a cleavable linker between the FVIII polypeptide and the first Ig constant region.

[0289] In certain embodiments, a chimeric polypeptide comprises a single chain comprising (i) a FVIII polypeptide, (ii) a first Ig constant region or a portion thereof, (iii) a linker (e.g., a processable linker), (iv) a VWF protein, (v) an XTEN sequence, and (vi) a second Ig constant region or a portion thereof. In other embodiments, a chimeric polypeptide comprises a single chain comprising (i) a FVIII polypeptide, (ii) a first Ig constant region or a portion thereof, (iii) a first linker (e.g., a processable linker), (iv) a VWF protein, (v) a second linker (e.g., a cleavable linker), (vi) an XTEN sequence, and (vii) a second Ig constant region or a portion thereof. The processable linker can be processed after the chimeric polypeptide is expressed in the host cell; thus the chimeric polypeptide produced in the host cell can be in the final form comprising two or three polypeptide chains.

[0290] The linker useful in the present disclosure can comprise any organic molecule. Example of linkers that can be used in the chimeric polypeptides of the present disclosure are disclosed, for example, in US 2011/0183907 A1, US 2016/0229903 A1, and US 2016/0251408 A1, each of which is incorporated by reference herein in its entirety. In some embodiments, the linker comprises a polymer, e.g., polyethylene glycol (PEG) or hydroxyethyl starch (HES). In other embodiments, the linker comprises an amino acids sequence. The linker can comprise at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 amino acids. The linker can comprise 1-5 amino acids, 1-10 amino acids, 1-20 amino acids, 10-50 amino acids, 50-100 amino acids, 100-200 amino acids, 200-

300 amino acids, 300-400 amino acids, 400-500 amino acids, 500-600 amino acids, 600-700 amino acids, 700-800 amino acids, 800-900 amino acids, or 900-1000 amino acids. In some embodiments, the linker comprises an XTEN sequence. Additional examples of XTEN can be used according to the present disclosure and are disclosed in US Patent Publication Nos. 2010/0239554 A1, 2010/0323956 A1, 2011/0046060 A1, 2011/0046061 A1, 2011/0077199 A1, or 2011/0172146 A1, or International Patent Publication Nos. WO 2010091122 A1, WO 2010144502 A2, WO 2010144508 A1, WO 2011028228 A1, WO 2011028229 A1, or WO 2011028344 A2. In other embodiments, the linker is a PAS sequence.

[0291] In certain embodiments, the linker is a polymer, e.g., polyethylene glycol (PEG) or hydroxyethyl starch (HES). In other embodiments, the linker is an amino acid sequence. The linker can comprise at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 amino acids. The linker can comprise 1-5 amino acids, 1-10 amino acids, 1-20 amino acids, 10-50 amino acids, 50-100 amino acids, 100-200 amino acids, 200-300 amino acids, 300-400 amino acids, 400-500 amino acids, 500-600 amino acids, 600-700 amino acids, 700-800 amino acids, 800-900 amino acids, or 900-1000 amino acids.

[0292] Examples of linkers are well known in the art. In certain embodiments, the linker comprises the sequence G_n . The linker can comprise the sequence $(GA)_n$. The linker can comprise the sequence $(GGS)_n$. In other embodiments, the linker comprises $(GGGS)_n$ (SEQ ID NO: 101). In still other embodiments, the linker comprises the sequence $(GGS)_n(GGGGS)_n$ (SEQ ID NO: 95). In these instances, n can be an integer from 1-100. In other instances, n can be an integer from 1-20, i.e., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20. Examples of linkers include, but are not limited to, GGG, SGGSGGS (SEQ ID NO: 96), GGSGGSGGSGGSGGG (SEQ ID NO: 97), GGSGGSGGGGSGGGGS (SEQ ID NO: 98), GGSGGSGGSGGSGGSGGGS (SEQ ID NO: 99), or GGGGSGGGGSGGGGS (SEQ ID NO: 100). The linker does not eliminate or diminish the VWF protein activity or the clotting activity of Factor VIII. Optionally, the linker enhances the VWF protein activity or the clotting activity of Factor VIII protein, e.g., by further diminishing the effects of steric hindrance and making the VWF protein or Factor VIII portion more accessible to its target binding site.

[0293] In certain embodiments, the linker useful for the chimeric polypeptide is 15-25 amino acids long. In other embodiments, the linker useful for the chimeric polypeptide is 15-20 amino acids long. In some embodiments, the linker for the chimeric polypeptide is 10-25 amino acids long. In other

embodiments, the linker for the chimeric polypeptide is 15 amino acids long. In still other embodiments, the linker for the chimeric polypeptide is (GGGGS)_n (SEQ ID NO: 94) where G represents glycine, S represents serine and n is an integer from 1-20.

III.F. Cleavage Sites

5 **[0294]** A cleavable linker can incorporate a moiety capable of being cleaved either chemically (e.g., hydrolysis of an ester bond), enzymatically (i.e., incorporation of a protease cleavage sequence), or photolytically (e.g., a chromophore such as 3-amino-3-(2-nitrophenyl) propionic acid (ANP)) in order to release one molecule from another. Examples of cleavable linkers suitable for the chimeric polypeptide of the present disclosure can be found, for example, in US 2016/0229903 A1 and US
10 2016/0251408 A1, each of which is incorporated by reference herein in its entirety.

[0295] In certain embodiments, a cleavable linker comprises one or more cleavage sites at the N-terminus or C-terminus or both. In other embodiments, the cleavable linker consists essentially of or consists of one or more cleavable sites. In other embodiments, the cleavable linker comprises heterologous amino acid linker sequences described herein or polymers and one or more cleavable
15 sites.

[0296] In certain embodiments, a cleavable linker comprises one or more cleavage sites that can be cleaved in a host cell (i.e., intracellular processing sites). Non limiting examples of the cleavage site include RRRR (SEQ ID NO: 102), RKRRKR (SEQ ID NO: 103), and RRRRS (SEQ ID NO: 104).

[0297] In some embodiments, a cleavable linker comprises an a1 region from FVIII, an a2 region from FVIII, an a3 region from FVIII, a thrombin cleavable site which comprises X-V-P-R (SEQ ID NO: 105) and a PAR1 exosite interaction motif, wherein X is an aliphatic amino acid, or any combinations thereof. comprises the a2 region which comprises an amino acid sequence at least about 80%, about 85%, about 90%, about 95%, or 100% identical to Glu720 to Arg740 corresponding to full-length FVIII, wherein the a2 region is capable of being cleaved by thrombin. In particular embodiments, a cleavable
20 linker useful for the disclosure comprises an a2 region which comprises ISDKNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 106) or DKNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 88). In other embodiments, a cleavable linker for the disclosure comprises the a1 region which comprises an amino acid sequence at least about 80%, about 85%, about 90%, about 95%, or 100% identical to Met337 to Arg372 corresponding
25 to full-length FVIII, wherein the a1 region is capable of being cleaved by thrombin. In particular embodiments, the a1 region comprises ISMKNNEEAEDYDDDLTDSEMDVVRFDDDNSPSFIQIRSV
30

(SEQ ID NO: 107). In some embodiments, a cleavable linker of the disclosure comprises the a3 region which comprises an amino acid sequence at least about 80%, about 85%, about 90%, about 95%, or 100% identical to Glu1649 to Arg1689 corresponding to full-length FVIII, wherein the a3 region is capable of being cleaved by thrombin. In certain embodiments, a cleavable linker for the disclosure
 5 comprises an a3 region comprising ISEITRTTLQSDQEEIDYDDTISVEMKKEDFDIYDEDEN QSPRSFQ (SEQ ID NO: 108).

[0298] In other embodiments, a cleavable linker comprises the thrombin cleavage site which comprises X-V-P-R (SEQ ID NO: 105) and the PAR1 exosite interaction motif and wherein the PAR1 exosite interaction motif comprises S-F-L-L-R-N (SEQ ID NO: 109). The PAR1 exosite interaction
 10 motif can further comprise an amino acid sequence selected from P, P-N, P-N-D, P-N-D-K (SEQ ID NO: 110), P-N-D-K-Y (SEQ ID NO: 111), P-N-D-K-Y-E (SEQ ID NO: 112), P-N-D-K-Y-E-P (SEQ ID NO: 113), P-N-D-K-Y-E-P-F (SEQ ID NO: 114), P-N-D-K-Y-E-P-F-W (SEQ ID NO: 115), P-N-D-K-Y-E-P-F-W-E (SEQ ID NO: 116), P-N-D-K-Y-E-P-F-W-E-D (SEQ ID NO: 117), P-N-D-K-Y-E-P-F-W-E-D-E (SEQ ID NO: 118), P-N-D-K-Y-E-P-F-W-E-D-E-E (SEQ ID NO: 119), P-N-D-K-Y-E-P-F-W-E-D-E-E-S (SEQ ID NO: 120), or any combination thereof. In some embodiments, the aliphatic amino
 15 acid is selected from Glycine, Alanine, Valine, Leucine, or Isoleucine.

[0299] In other embodiments, a cleavable linker comprises one or more cleavage sites that are cleaved by a protease after a chimeric polypeptide comprising the cleavable linker is administered to a subject. In some embodiments, the cleavage site is cleaved by a protease selected from the group
 20 consisting of factor XIa, factor XIIa, kallikrein, factor VIIa, factor IXa, factor Xa, factor IIa (thrombin), Elastase-2, MMP-12, MMP-13, MMP-17, and MMP-20. In other embodiments, the cleavage site is selected from the group consisting of a FXIa cleavage site (e.g., KLTR↓AET (SEQ ID NO: 121)), a FXIa cleavage site (e.g., DFTR↓VVG (SEQ ID NO: 122)), a FXIIa cleavage site (e.g., TMTR↓IVGG (SEQ ID NO: 123)), a Kallikrein cleavage site (e.g., SPFR↓STGG (SEQ ID NO: 124)), a FVIIa
 25 cleavage site (e.g., LQVR↓IVGG (SEQ ID NO: 125)), a FIXa cleavage site (e.g., PLGR↓IVGG (SEQ ID NO: 126)), a FXa cleavage site (e.g., IEGR↓TVGG (SEQ ID NO: 127)), a FIIa (thrombin) cleavage site (e.g., LTPR↓SLLV (SEQ ID NO: 128)), a Elastase-2 cleavage site (e.g., LGPV↓SGVP (SEQ ID NO: 129)), a Granzyme-B cleavage (e.g., VAGD↓SLEE (SEQ ID NO: 130)), a MMP-12 cleavage site (e.g., GPAG↓LGGA (SEQ ID NO: 131)), a MMP-13 cleavage site (e.g., GPAG↓LRGA (SEQ ID NO: 132)), a MMP-17 cleavage site (e.g., APLG↓LRLR (SEQ ID NO: 133)), a MMP-20 cleavage site (e.g., PALP↓LVAQ (SEQ ID NO: 134)), a TEV cleavage site (e.g., ENLYFQ↓G (SEQ ID NO: 135)), a
 30 Enterokinase cleavage site (e.g., DDDK↓IVGG (SEQ ID NO: 136)), a Protease 3C

(PRESCISSION™) cleavage site (e.g., LEVLFQ↓GP (SEQ ID NO: 137)), and a Sortase A cleavage site (e.g., LPKT↓GSES) (SEQ ID NO: 138). In certain embodiments, the FXIa cleavage sites include, but are not limited to, e.g., TQSFNDFTR (SEQ ID NO: 1) and SVSQTSKLTR (SEQ ID NO: 3). Non-limiting exemplary thrombin cleavage sites include, e.g., DFLAEGGGVR (SEQ ID NO: 4), TTKIKPR (SEQ ID NO: 5), LVPRG (SEQ ID NO: 6), DKNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 88), or IEPRSFS (SEQ ID NO: 194), and a sequence comprising, consisting essentially of, or consisting of ALRPR (SEQ ID NO: 7) (e.g., ALRPRVVGGA (SEQ ID NO: 145)).

[0300] In some embodiments, the cleavage site is TLDPRSFLLRNPNDKYEPFWEDEEK (SEQ ID NO: 146). In other embodiments, the cleavage site comprises DKNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 88) or a fragment thereof. In particular embodiments, the cleavage site comprises IEPRSFS (SEQ ID NO: 194). In other embodiments, the cleavage site comprises EPRSFS (SEQ ID NO: 195), wherein the cleavage site is not the full-length a2 region of FVIII. In still other embodiments, the cleavage site comprises IEPR (SEQ ID NO: 200). In yet other embodiments, the cleavage site comprises IEPR (SEQ ID NO: 200), wherein the cleavage site is not the full-length a2 region of FVIII or does not comprise the full-length a2 region of FVIII. In other embodiments, the cleavage site comprises DKNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 88), KNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 139), NTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 140), TGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 141), GDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 142), DYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 143), YYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 144), YEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 176), EDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 177), DSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 178), SYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 179), YEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 180), EDISAYLLSKNNAIEPRSFS (SEQ ID NO: 181), DISAYLLSKNNAIEPRSFS (SEQ ID NO: 182), ISAYLLSKNNAIEPRSFS (SEQ ID NO: 183), SAYLLSKNNAIEPRSFS (SEQ ID NO: 184), AYLLSKNNAIEPRSFS (SEQ ID NO: 185), YLLSKNNAIEPRSFS (SEQ ID NO: 186), LLSKNNAIEPRSFS (SEQ ID NO: 187), LSKNNAIEPRSFS (SEQ ID NO: 188), SKNNAIEPRSFS (SEQ ID NO: 189), KNNNAIEPRSFS (SEQ ID NO: 190), NNAIEPRSFS (SEQ ID NO: 191), NAIIEPRSFS (SEQ ID NO: 192), AIEPRSFS (SEQ ID NO: 193), or IEPRSFS (SEQ ID NO: 194). In other embodiments, the cleavage site comprises DKNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 88), KNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 139),

NTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 140),
 TGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 141),
 GDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 142), DYYEDSYEDISAYLLSKNNAIEPRSFS
 (SEQ ID NO: 143), YYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 144),
 5 YEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 176), EDSYEDISAYLLSKNNAIEPRSFS (SEQ ID
 NO: 177), DSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 178), SYEDISAYLLSKNNAIEPRSFS (SEQ
 ID NO: 179), YEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 180), EDISAYLLSKNNAIEPRSFS (SEQ ID
 NO: 181), DISAYLLSKNNAIEPRSFS (SEQ ID NO: 182), ISAYLLSKNNAIEPRSFS (SEQ ID NO:
 183), SAYLLSKNNAIEPRSFS (SEQ ID NO: 184), AYLLSKNNAIEPRSFS (SEQ ID NO: 185),
 10 YLLSKNNAIEPRSFS (SEQ ID NO: 186), LLSKNNAIEPRSFS (SEQ ID NO: 187), LSKNNAIEPRSFS
 (SEQ ID NO: 188), SKNNAIEPRSFS (SEQ ID NO: 189), KNNNAIEPRSFS (SEQ ID NO: 190),
 NNAIEPRSFS (SEQ ID NO: 191), NAEPRSFS (SEQ ID NO: 192), AIEPRSFS (SEQ ID NO: 193), or
 IEPRSFS (SEQ ID NO: 194), wherein the cleavage site is not the full-length FVIII a2 region. In certain
 embodiments the cleavable linker is cleavable in a thrombin cleavage assay as provided herein or as
 15 known in the art.

[0301] In particular embodiments, the chimeric polypeptide of the present disclosure comprises: (i)
 a FVIII protein comprising a FVIII polypeptide, a first XTEN sequence, and a first Fc region; and (ii) a
 VWF fragment comprising a D' domain of VWF and a D3 domain of VWF, a second XTEN sequence,
 an a2 linker of FVIII, and a second Fc region; wherein:

- 20 (a) the FVIII protein has a deletion of amino acids 746 to 1648 corresponding to mature FVIII;
- (b) the first XTEN sequence is inserted within the FVIII polypeptide immediately downstream of
 amino acid 745 corresponding to mature FVIII;
- (c) the first XTEN sequence comprises an amino acid sequence having at least about 70%, at
 least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at
 25 least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence
 identity to the amino acid sequence of AE288 (SEQ ID NO: 8);
- (d) the first Fc region is fused to the C-terminus of the FVIII polypeptide;
- (e) the second XTEN sequence is fused to the C-terminus of the VWF fragment;
- (f) the second XTEN sequence comprises an amino acid sequence having at least about 70%,
 30 at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%,

at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of AE144_5A (SEQ ID NO: 58);

(g) the a2 linker is fused to the C-terminus of the XTEN;

(h) the a2 linker comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to the amino acid sequence of SEQ ID NO: 88;

(i) the second Fc region is fused to the C-terminus of the a2 linker; and

(j) the first Fc region is covalently linked to the second Fc region by a disulfide bond.

10 **[0302]** In particular embodiments, a chimeric polypeptide of the disclosure comprises two polypeptide sequences, a first polypeptide sequence comprising an amino acid sequence at least about 80%, 90%, 95%, or 100% identical to a sequence selected from FVIII-161 (SEQ ID NO: 69), FVIII-169 (SEQ ID NO: 70), FVIII-170 (SEQ ID NO: 71), FVIII-173 (SEQ ID NO: 72); FVIII-195 (SEQ ID NO: 73); FVIII-196 (SEQ ID NO: 74), FVIII-199 (SEQ ID NO: 75), FVIII-201 (SEQ ID NO: 76); FVIII-203 (SEQ ID NO: 77), FVIII-204 (SEQ ID NO: 78), FVIII-205 (SEQ ID NO: 79), FVIII-266 (SEQ ID NO: 80), FVIII-267 (SEQ ID NO: 81), FVIII-268 (SEQ ID NO: 82), FVIII-269 (SEQ ID NO: 83), FVIII-271 (SEQ ID NO: 84) or FVIII-272 (SEQ ID NO: 85) and a second polypeptide sequence comprising an amino acid sequence at least about 80%, 90%, 95%, or 100% identical to a sequence selected from VWF031 (SEQ ID NO: 86), VWF034 (SEQ ID NO: 87), or VWF-036.

20 **[0303]** In some embodiments, the chimeric polypeptide of the disclosure comprises two polypeptide sequences, a first polypeptide sequence comprising an amino acid sequence at least about 80%, 90%, 95%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 201; and a second polypeptide sequence comprising a VWF fragment comprising a D' domain of VWF and a D3 domain of VWF and an Fc region. In some embodiments, the chimeric polypeptide of the disclosure comprises two polypeptide sequences, a first polypeptide sequence comprising FVIII polypeptide and an Fc region; and a second polypeptide sequence comprising an amino acid sequence at least about 80%, 90%, 95%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 202. In certain embodiments, the chimeric polypeptide of the disclosure comprises two polypeptide sequences, a first polypeptide sequence comprising an amino acid sequence at least about 80%, 90%, 95%, or 100% identical to the amino acid sequence set forth in SEQ ID NO: 201 and a second polypeptide sequence comprising an amino acid sequence at least about 80%, 90%, 95%, or 100% identical to

the amino acid sequence set forth in SEQ ID NO: 202. In particular embodiments, the chimeric polypeptide of the disclosure comprises two polypeptide sequences, a first polypeptide sequence comprising the amino acid sequence set forth in SEQ ID NO: 201 and a second polypeptide sequence comprising the amino acid sequence set forth in SEQ ID NO: 202. In other particular embodiments, the chimeric polypeptide of the disclosure comprises two polypeptide sequences, a first polypeptide sequence comprising the amino acid sequence set forth in SEQ ID NO: 201 and a second polypeptide sequence comprising the amino acid sequence set forth in SEQ ID NO: 202, wherein the first polypeptide sequence and the second polypeptide sequence are linked to each other by a disulphide bond.

IV. Pharmaceutical Compositions

[0304] Compositions containing the chimeric polypeptide of the present disclosure can contain a suitable pharmaceutically acceptable carrier. For example, they can contain excipients and/or auxiliaries that facilitate processing of the active compounds into preparations designed for delivery to the site of action.

[0305] The pharmaceutical composition can be formulated for parenteral administration (i.e. intravenous, subcutaneous, or intramuscular) by bolus injection. Formulations for injection can be presented in unit dosage form, e.g., in ampoules or in multidose containers with an added preservative. The compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, e.g., pyrogen free water.

[0306] Suitable formulations for parenteral administration also include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts. In addition, suspensions of the active compounds as appropriate oily injection suspensions can be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides. Aqueous injection suspensions can contain substances, which increase the viscosity of the suspension, including, for example, sodium carboxymethyl cellulose, sorbitol and dextran. Optionally, the suspension can also contain stabilizers. Liposomes also can be used to encapsulate the molecules of the disclosure for delivery into cells or interstitial spaces. Exemplary pharmaceutically acceptable carriers are physiologically compatible solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying

agents, water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like. In some embodiments, the composition comprises isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride. In other embodiments, the compositions comprise pharmaceutically acceptable substances such as wetting agents or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the active ingredients.

[0307] Compositions of the disclosure can be in a variety of forms, including, for example, liquid (e.g., injectable and infusible solutions), dispersions, suspensions, semi-solid and solid dosage forms. The preferred form depends on the mode of administration and therapeutic application.

[0308] The composition can be formulated as a solution, micro emulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration. Sterile injectable solutions can be prepared by incorporating the active ingredient in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active ingredient into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

[0309] The active ingredient can be formulated with a controlled-release formulation or device. Examples of such formulations and devices include implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, for example, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for the preparation of such formulations and devices are known in the art. See e.g., Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

[0310] Injectable depot formulations can be made by forming microencapsulated matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to

polymer, and the nature of the polymer employed, the rate of drug release can be controlled. Other exemplary biodegradable polymers are polyorthoesters and polyanhydrides. Depot injectable formulations also can be prepared by entrapping the drug in liposomes or microemulsions.

[0311] Supplementary active compounds can be incorporated into the compositions. In some embodiments, the chimeric polypeptide of the disclosure is formulated with another clotting factor, or a variant, fragment, analogue, or derivative thereof. For example, the clotting factor includes, but is not limited to, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, factor XII, factor XIII, prothrombin, fibrinogen, von Willebrand factor or recombinant soluble tissue factor (rsTF) or activated forms of any of the preceding. The clotting factor of hemostatic agent can also include anti-fibrinolytic drugs, e.g., epsilon-amino-caproic acid, tranexamic acid.

[0312] Dosage regimens can be adjusted to provide the optimum desired response. For example, a single bolus can be administered, several divided doses can be administered over time, or the dose can be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. See, e.g., Remington's Pharmaceutical Sciences (Mack Pub. Co., Easton, Pa. 1980).

[0313] In addition to the active compound, the liquid dosage form can contain inert ingredients such as water, ethyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols, and fatty acid esters of sorbitan.

[0314] Non-limiting examples of suitable pharmaceutical carriers are also described in Remington's Pharmaceutical Sciences by E. W. Martin. Some examples of excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol, and the like. The composition can also contain pH buffering reagents, and wetting or emulsifying agents.

[0315] In some embodiments, a pharmaceutical composition comprises a chimeric polypeptide and a pharmaceutically acceptable carrier. The FVIII protein in a chimeric polypeptide has extended half-life compared to wild type FVIII protein or the corresponding FVIII protein without the VWF fragment. In some embodiments, wherein the half-life of the chimeric polypeptide is extended at least about 1.5 times, at least about 2 times, at least about 2.5 times, at least about 3 times, at least about 4 times, at least about 5 times, at least about 6 times, at least about 7 times, at least about 8 times, at least

about 9 times, at least about 10 times, at least about 11 times, or at least about 12 times longer than wild type FVIII. In other embodiments, the half-life of Factor VIII is at least about 17 hours, at least about 18 hours, at least about 19 hours, at least about 20 hours, at least about 21 hours, at least about 22 hours, at least about 23 hours, at least about 24 hours, at least about 25 hours, at least about 26 hours, at least about 27 hours, at least about 28 hours, at least about 29 hours, at least about 30 hours, at least about 31 hours, at least about 32 hours, at least about 33 hours, at least about 34 hours, at least about 35 hours, at least about 36 hours, at least about 48 hours, at least about 60 hours, at least about 72 hours, at least about 84 hours, at least about 96 hours, or at least about 108 hours. In some embodiments, the half-life of the chimeric polypeptide is extended about 3 times compared to wild type FVIII.

[0316] In some embodiments, the composition is administered by parenteral administration, which can be intravenous or subcutaneous administration.

[0317] In other embodiments, the composition is used to treat a bleeding disease or condition in a subject in need thereof. The bleeding disease or condition is selected from the group consisting of a bleeding coagulation disorder, hemarthrosis, muscle bleed, oral bleed, hemorrhage, hemorrhage into muscles, oral hemorrhage, trauma, trauma capitis, gastrointestinal bleeding, intracranial hemorrhage, intra-abdominal hemorrhage, intrathoracic hemorrhage, bone fracture, central nervous system bleeding, bleeding in the retropharyngeal space, bleeding in the retroperitoneal space, bleeding in the iliopsoas sheath and any combinations thereof. In still other embodiments, the subject is scheduled to undergo a surgery. In yet other embodiments, the treatment is prophylactic or on-demand.

[0318] Having now described the present disclosure in detail, the same will be more clearly understood by reference to the following examples, which are included herewith for purposes of illustration only and are not intended to be limiting of the disclosure. All patents, publications, and articles referred to herein are expressly and specifically incorporated herein by reference.

EXAMPLES

Example 1: First in human study of FVIII-XTEN-Fc/D'D3-XTEN-Fc heterodimers

[0319] Factor-based replacement therapy is the cornerstone of hemophilia care. Conventional recombinant FVIII (rFVIII) products have a short half-life, requiring frequent administration. Significant

advances to patient care have been brought by rFVIII Fc (Eloctate®), including the longest dosing interval for hemophilia A; adequate bleed control, including prophylactically, in acute, perioperative, and emergency situations; protection beyond bleed control, including joint protection and improved quality of life; and long-term consistent and well-characterized safety profile. However, weekly or longer factor VIII prophylactic dosing still remains an unmet need for the majority of people with hemophilia A.

[0320] The present study investigates the safety and pharmacokinetics (PK) of rFVIII Fc-VWF-XTEN, a chimeric polypeptide comprising a (i) a FVIII polypeptide, an XTEN inserted within the B domain of the FVIII polypeptide, and a first Fc region; and (ii) a VWF fragment, a second XTEN sequence, an a2 linker, and a second Fc region (FIG. 1).

[0321] Study Design

[0322] The object of the present study was to assess the safety, tolerability, and FVIII activity (PK) of a single dose of rFVIII Fc-VWF-XTEN compared with rFVIII. The patient population included previously treated adult males with severe hemophilia A (<1 IU/dL [$<1\%$] endogenous FVIII activity level) with at least 150 exposure days to FVIII products, and with no history of positive inhibitor test or clinical signs of decreased response to FVIII administration. The primary endpoints were adverse events and clinical abnormalities in laboratory tests, including development of inhibitors. Key secondary endpoints included pharmacokinetics parameters, including but not limited to elimination half-life ($t_{1/2}$), clearance (CL), area under the curve from 0 to infinity ($AUC_{0-\infty}$), mean residence time (MRT), and incremental recovery (IR).

[0323] Patients were enrolled into a low-dose cohort (7 patients; FIG. 2A) or a high-dose cohort (9 patients; FIG. 2B). Each patient was dosed with rFVIII (ADVATE®) followed by a PK sampling period. Following a brief washout period (≥ 3 days for the low dose cohort (FIG. 2A) and ≥ 4 days for the high-dose cohort (FIG. 2B)), each subject was then administered rFVIII Fc-VWF-XTEN followed by a PK sampling period. Subjects underwent safety observation for 28 days following the injection of rFVIII Fc-VWF-XTEN, including sample collection for inhibitor assessments at 14 and 28 days after the injection of rFVIII Fc-VWF-XTEN. Patients in the low-dose cohort received 25 IU/kg of rFVIII and 25 IU/kg of rFVIII Fc-VWF-XTEN. Patients in the high-dose cohort received 65 IU/kg of rFVIII and 65 IU/kg of rFVIII Fc-VWF-XTEN.

[0324] Methods

[0325] Pharmacokinetic parameters were measured by a modified activated partial thromboplastin time (aPTT) clotting assay ("one stage" assay). Briefly, FVIII activity is measured in a modified aPTT assay using the Dade® Actin® FSL Activated PTT Reagent (Siemens Health Care Diagnostics) on a BCS® XP analyzer (Siemens Healthcare Diagnostics). 7-point calibration curves (High: 1.500-0.050 IU/mL; Low: 0.150-0.0025 IU/mL) were prepared using a rFVIII-Fc-VWF-XTEN specific calibrator. For the high calibration curve, the rFVIII-Fc-VWF-XTEN calibrator [1.000 IU/mL] is diluted into Tris/BSA buffer (50 mM, 150 mM sodium chloride, pH 7.4 +/- 0.2, containing 1% BSA). This dilution is carried out by the BCS® XP analyzer to generate pre-selected calibration FVIII activity levels. These are then tested at the 1:2 working dilution prepared in Tris/BSA buffer. For the low calibration curve, the rFVIII-Fc-VWF-XTEN calibrator [1.000 IU/mL] is diluted in immuno-depleted FVIII deficient plasma (Siemens Healthcare Diagnostics) by the BCS® XP analyzer, and tested neat (in the absence of a working dilution). Calibration is performed in duplicate. Curves are plotted by FVIII activity in IU/mL (x-axis) and clotting time in seconds (y-axis). Both high and low calibration curves use a linear log-lin regression curve fit.

[0326] Samples are tested in duplicate using the high calibration curve metatest (1:2, 1:4, and 1:8 working dilutions in Tris/BSA) or the low calibration curve metatest (neat, 1:2, and 1:4 working dilutions in immuno-depleted FVIII deficient plasma). After the appropriate working dilution, all calibrators, patient samples and quality control samples are mixed 1:1 with immuno-depleted FVIII deficient plasma, containing less than or equal to 0.010 IU/mL FVIII activity and at least 0.400 IU/mL of the other clotting factors. After the samples are mixed with this plasma, the APTT reagent is added and the mixture is incubated. Following incubation, calcium chloride is added and the time to clot formation is measured optically. An algorithm then examines whether the individual working dilution results fall within +/- 15.0% of the mean to determine reported FVIII activity. Minimum of two metatest working dilution results are necessary to determine the reported FVIII activity, except near the Lower Limit of Quantification (LLOQ).

[0327] Results: Low Dose Cohort

[0328] Seven subjects enrolled in the low dose cohort; one subject withdrew for reasons unrelated to the study prior to receiving rFVIII-Fc-VWF-XTEN. Six subjects received a single, low dose of rFVIII-Fc-VWF-XTEN (25 IU/kg). Characteristics of the first four subjects treated in the low dose cohort included: previously treated adult male subjects with severe hemophilia A (<1 IU/dL [$<1\%$] endogenous FVIII activity level); all subjects were Caucasian; the age of the subjects ranged from

19-60 years, with an average age of 33; and the average weight was 85 kg (ranging from 67.2-100.6 kg).

[0329] In all patients, rFVIII^hFc-VWF-XTEN was generally well tolerated, and no inhibitors were observed at Day 14 or Day 28 following dosing.

- 5 **[0330]** The average FVIII activity post-infusion for the first six subjects receiving a single low dose of rFVIII^hFc-VWF-XTEN (25 IU/kg) at 5 days was about 12.0% and at 7 days was about 5.3% (FIG. 3A). Average FVIII activity remained above 1% through 10 days (FIG. 3A). Pharmacokinetic parameters, measured by activated partial thromboplastin time (aPTT) measurement, for rFVIII^hFc-VWF-XTEN (25 IU/kg) and rFVIII (25 IU/kg) are shown in **Table 9**. rFVIII^hFc-VWF-XTEN was observed
- 10 to have an average half-life of about 37.6 hours in the human subjects, which was over 4-fold higher than the average half-life for rFVIII (about 9.12 hours) administered at the same dose.

Table 9: Pharmacokinetic (PK) Parameters for the Low-Dose Cohort

PK Parameter	rFVIII-Fc-VWF-XTEN Geometric Mean [Range] (N=6)	rFVIII Geometric Mean [Range] (N=7)	Mean Ratio [95% CI]
Half-life, h	37.61 [33.28–42.50]	9.12 [6.24–13.33]	4.13 [2.94, 5.79] P < 0.001
C _{max} (IU/dL)	70.1 [49.7–98.9]	51.80 [43.3–61.9]	1.35 [1.04, 1.77] P = 0.032
AUC _∞ , h x IU/dL	4470 [3280–6080]	638 [495–822]	7.00 [5.78, 8.48] P < 0.001
MRT, h	56.93 [49.19–65.89]	12.54 [9.82–16.10]	4.54 [3.64, 5.66] P < 0.001
CL, mL/h/kg	0.56 [0.41–0.76]	3.91 [3.05–5.02]	0.14 [0.12, 0.17] P < 0.001
IR, IU/dL per IU/kg	2.72 [1.95–3.80]	2.00 [1.60–2.50]	1.36 [0.98, 1.89] P = 0.063

[0331] Results: High Dose Cohort

[0332] Nine subjects were enrolled in the high dose cohort. The subjects were administered a single, high dose of rFVIII-Fc-VWF-XTEN (65 IU/kg). One subject could not be tested for PK parameters due to reasons unrelated to the study. Characteristics of the subjects treated in the high dose cohort included: previously treated adult male subjects with severe hemophilia A (<1 IU/dL [$<1\%$] endogenous FVIII activity level); 7 of 9 subjects were Caucasian; the age of the subjects ranged from 32–63 years, with an average age of 44; and the average weight was 81.1 kg (ranging from 61.5–100.7 kg).

[0333] The average FVIII activity post-infusion for the eight evaluated subjects receiving a single high dose of rFVIII-Fc-VWF-XTEN (65 IU/kg) at 5 days was about 38.0% and at 7 days was about 17% (FIG. 3B). Average FVIII activity remained above 1% through 14 days (FIG. 3B). Pharmacokinetic parameters, measured activated partial thromboplastin time (aPTT) measurement, for rFVIII-Fc-VWF-XTEN (65 IU/kg) and rFVIII (65 IU/kg) are shown in **Table 10**. rFVIII-Fc-VWF-XTEN was observed to have an average half-life of about 42.5 hours in the human subjects, which was over 3-fold higher than the average half-life for rFVIII (about 13 hours) administered at the same dose.

Table 10: Pharmacokinetic (PK) Parameters for the High-Dose Cohort

PK parameter	rFVIII-Fc-VWF-XTEN Geometric Mean [Range] (N=8)	rFVIII Geometric Mean [Range] (N=9)	Mean Ratio [95% CI]
Half-life (h)	42.54 [39.72-45.56]	13.15 [10.89-15.87]	3.24 [2.76, 3.79] P < 0.001
C _{max} (IU/dL)	161 [142-183]	138 [117-162]	1.17 [1.09-1.25] P < 0.001
AUC _{0-inf} (h x IU/dL)	12,800 [11,100-14,900]	1960 [1670-2310]	6.54 [5.89-7.27] P < 0.001
MRT (h)	67.66 [62.59-73.14]	15.66 [14.06-17.45]	4.32 [3.96-4.72] P < 0.001
CL (mL/h/kg)	0.51 [0.44-0.59]	3.31 [2.81-3.88]	0.15 [0.14-0.17] P < 0.001
IR (IU/dL per IU/kg)	2.48 [2.18-2.82]	2.11 [1.79-2.49]	1.18 [1.10-1.26] P < 0.001

[0334] Conclusions:

[0335] rFVIII-Fc-VWF-XTEN was well tolerated in all patients with severe hemophilia A who were treated with either a single low dose (25 IU/kg) or a single high dose (65 IU/kg). No patient developed an inhibitor to FVIII. rFVIII-Fc-VWF-XTEN demonstrated a half-life that was 3-fold to 4-fold higher than rFVIII, suggesting a breakthrough in the VWF-imposed half-life ceiling. Sustained, high FVIII activity has the potential to provide extended protection against all bleed types.

Example 2: Repeat Dose Study of FVIII-XTEN-Fc/D'D3-XTEN-Fc heterodimers

[0336] rFVIII-Fc-VWF-XTEN was well-tolerated and provided sustained FVIII levels in a cohort of subjects who received a single dose of rFVIII-Fc-VWF-XTEN. (Example 1). The present study will evaluate the safety and tolerability and characterize the pharmacokinetics of repeat doses of rFVIII-Fc-VWF-XTEN (FIG. 1).

[0337] Study Design

[0338] A total of 4 once-weekly doses of rFVIII-Fc-VWF-XTEN will be administered to adult male patients with severe hemophilia A who have been previously treated with FVIII treatment and received at least 150 exposure days of such FVIII treatment. Two cohorts, each consisting of approximately

ten adult males 18 to 65 years of age will be enrolled. Each subject in Cohort 1 will receive a total of four once-weekly doses of 50 IU/kg rFVIII Fc-VWF-XTEN on Days 1, 8, 15, and 22. Each subject in Cohort 2 will receive a total of four once-weekly doses of 65 IU/kg rFVIII Fc-VWF-XTEN on Days 1, 8, 15, and 22.

5 **[0339]** A schematic representation of the design of the clinical study is depicted as FIG. 4. A pre-dose pharmacokinetic sample will be taken on Day 1. In addition, there will be multiple PK samples taken after dosing on Days 1 and 22, and a trough (168h) sample occurring prior to dosing on Days 8, 15, and 22. Subjects will undergo a safety observation period for 28 days after the last dose of rFVIII Fc-VWF-XTEN, including inhibitor assessments at 14 and 28 days after the last dose of
10 rFVIII Fc-VWF-XTEN. For subjects who complete all four once-weekly doses of rFVIII Fc-VWF-XTEN, the safety observation period will end with the end-of-study (EOS) visit at Day 50 (+3 days). For subjects who discontinue treatment early, the safety observation period will end with the early termination (ET) visit 28 days after the last dose of rFVIII Fc-VWF-XTEN.

[0340] The primary objective of the study is to assess the safety and tolerability of a total of four
15 once-weekly doses of intravenous (IV) rFVIII Fc-VWF-XTEN. The primary endpoints are the occurrence of adverse events (AEs) and the occurrence of clinically significant abnormalities in laboratory tests, including development of inhibitors (neutralizing antibodies directed against FVIII) as determined via the Nijmegen-modified Bethesda assay. (Verbruggen et al, Thrombosis and Haemostasis, 73: 247–251 (1995)).

20 **[0341]** The secondary objective of the study is the characterization of the pharmacokinetics of rFVIII Fc-VWF-XTEN after a total of four once-weekly IV doses, with FVIII activity determined by the one-stage activated partial thromboplastin time (aPTT) clotting assay, as described in Example 1. The secondary endpoints are pharmacokinetics assessed via the estimation of parameters, including but not limited to maximum activity (C_{max}), half-life (t_{1/2}), total clearance at steady state (CL_{ss}),
25 accumulating index (AI), area under the activity-time curve from hour 0 over the dosing interval (AUC_{0-tau}), volume of distribution at steady state (V_{ss}), mean residence time (MRT), IR, lowest (trough) concentration that a drug reaches before the next dose is administered (C_{trough}), and time to 1% above baseline for FVIII activity.

[0342] The exploratory objective of the study is to characterize the pharmacokinetics of rFVIII Fc-VWF-XTEN after a total of four once-weekly IV doses, with FVIII activity determined by the two-stage
30 chromogenic coagulation assay. The exploratory endpoints are PK assessed via the estimation of

parameters, including but not limited to the C_{max}, t_{1/2}, CL_{ss}, A_I, AUC_{0-tau}, V_{ss}, MRT, IR, C_{trough}, and time to 1% above baseline for FVIII activity.

[0343] Methods

[0344] FVIII activity was determined by the modified activated partial thromboplastin time (aPTT) clotting assay ("one stage" assay), as detailed above in Example 1.

[0345] The two-stage chromogenic coagulation assay measures FVIII activity using the BIOPHEN FVIII:C assay (Hyphen Biomed 221402-RUO) on the BCS® XP analyzer (Siemens Healthcare Diagnostics). Briefly, phospholipids, calcium and thrombin activated FVIII:C form an enzymatic complex in the presence of a constant amount of Factor IXa. This enzymatic complex in turn activates Factor X (FX), which is supplied at a constant concentration and in excess to Factor Xa (FXa). The activation of FX to FXa is directly related to the amount of FVIII:C, which is the limiting factor in the assay in the presence of a constant and in an excess amount of Factor IXa. The activity of the generated FXa is then measured using a specific chromogenic FXa substrate, Sxa-11 (Hyphen Biomed). Factor Xa cleaves Sxa-11 and releases paranitroaniline (pNA). The amount of pNA released is directly proportional to the amount of FXa generated. There is a direct relationship between the amount of FVIII:C in the sample, the amount of FXa generated, and the amount of pNA released. The release of pNA is determined by color development at a wavelength of 405 nm.

[0346] 8-point calibration curves (High: 1.500 – 0.150 IU/mL; Low: 0.200 – 0.008 IU/mL) are prepared using a rFVIII_{FC}-VWF-XTEN specific calibrator. For the high calibration curve, rFVIII_{FC}-VWF-XTEN at 1IU/mL is diluted in Tris/BSA buffer to generate pre-selected calibration levels of FVIII activity. This dilution is carried out by the BCS® XP analyzer. The pre-selected calibration levels of FVIII activity are tested at a 1:4 working dilution in Tris/BSA buffer. For the low calibration curve, rFVIII_{FC}-VWF-XTEN at 1 IU/mL is pre-diluted 1:4 in congenital FVIII deficient plasma (Helena Laboratories) and then further diluted by the BCS® XP analyzer in Tris/BSA buffer to generate pre-selected calibration levels of FVIII activity which are tested in the absence of further dilution in the reaction setup.

[0347] Calibration is performed in duplicate. Curves are plotted for FVIII activity in IU/mL (x-axis) and change in absorbance/min (y-axis). For the high calibration curve, a linear log-log regression curve fit is used. For the low calibration curve, a linear lin-lin regression curve fit is used. Samples are tested in duplicate on either the high calibration curve at a 1:4 working dilution or the low

calibration curve using the 1:4 dilution in congenital FVIII deficient plasma or neat (in the absence of a working dilution).

[0348] Results

[0349] Demographics and Baseline Characteristics

5 **[0350]** 10 adult male subjects 18 to 65 years of age (inclusive) enrolled in Cohort 1 (50 IU/kg) and 5 adult male subjects 18 to 65 years of age (inclusive) enrolled in Cohort 2 (65 IU/kg). All 10 subjects in the 50 IU/kg dosing cohort received 4 doses of rFVIII Fc-VWF-XTEN. Three of the 5 subjects enrolled in the 65 IU/kg dosing cohort received at least one dose of rFVIII Fc-VWF-XTEN. All 15 subjects enrolled were from a single site in Sofia, Bulgaria. Of the 15 subjects enrolled, 13 subjects
10 received at least one dose of BIVV001 and were included in the summary of demographic and baseline characteristics. All subjects were male. The median age was 35 years (range: 25 to 55 years) and all subjects were white. The median weight was 86.7 kg (range: 51.0 to 130.9 kg) and the median body mass index was 25.9 kg/m² (range: 16.4 to 40.9 kg/m²).

[0351] Safety Analysis

15 **[0352]** For the interim analysis a total of 13 subjects were included in the Safety Analysis Set (n=10 from the 50 IU/kg cohort and n=3 from the 65 IU/kg cohort). All safety analyses were performed based on the Safety Analysis Set and included all subjects who received at least one dose of rFVIII Fc-VWF-XTEN.

[0353] A treatment-emergent AE (TEAE) is defined as any adverse event that began on or after
20 the first rFVIII Fc-VWF-XTEN administration and within 28 days after the final rFVIII Fc-VWF-XTEN administration. AEs with missing start dates are assumed to be treatment-emergent, unless the stop date was before the dosing date. In general, AEs were summarized by subject incidence by cohort and overall as well as presented in a data listing by cohort and subject. Treatment-emergent serious adverse events (TESAEs) were also also evaluated for each subject, but none were observed in
25 treated subjects (**Table 11**).

[0354] Of the 15 subjects enrolled, 13 subjects received at least one dose of rFVIII Fc-VWF-XTEN and were included in the safety analysis. 19 TEAEs were reported in 8 of the 13 subjects (61.5%) (**Table 11**). There were no serious or related TEAEs reported and no subject discontinued the study due to a TEAE. The most common TEAEs were arthralgia, upper respiratory tract infection,
30 headache, and rhinitis (2/13 subjects each; 15.4%). No inhibitor development to FVIII was detected

and there were no reports of serious hypersensitivity or anaphylaxis. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages reported in Table 11 are based on the number of subjects who received at least one dose of rFVIII-Fc-VWF-XTEN in each cohort and overall.

5

TABLE 11. Summary of Treatment Emergent Adverse Events (TEAEs) in Safety Analysis Set

	rFVIII-Fc-VWF-XTEN 50 IU/kg	rFVIII-Fc-VWF-XTEN 65 IU/kg	Major Surgical Period (N=0)	rFVIII-Fc-VWF-XTEN Total treated
Number of Subjects treated with rFVIII-Fc-VWF-XTEN	10	3	0	13
Total number of TEAEs	17	2	0	19
Subjects with at least one TEAE	7 (70.0%)	1 (33.3%)	0	8 (61.5%)
Subjects with at least one related TEAE	0	0	0	0
Subjects who discontinued study due to TEAE	0	0	0	0
Total Number of TESAEs	0	0	0	0
Subjects with at least one TESA	0	0	0	0
Subjects with at least one related TESA	0	0	0	0

[0355] Immunogenicity Analysis

[0356] All subjects were assessed for inhibitor development and anti-rFVIII-Fc-VWF-XTEN antibodies at Screening, Day 1, Day 8, Day 15, Day 22, Day 36, and Day 50 (EOS or ET visit). Testing for inhibitors was performed by the central laboratory using the Nijmegen-modified Bethesda assay.

5 If a Nijmegen-modified Bethesda assay result returned as ≥ 0.6 BU/mL, a separate sample was collected and tested for confirmation of inhibitor development within 2 to 4 weeks. Testing for potential antibody formation was performed at a central laboratory using a validated rFVIII-Fc-VWF-XTEN-specific anti-drug antibody (ADA) assay. Confirmed positive samples were further characterized for antibodies specific to FVIII, D'D3, or XTEN. The number and percentage of subjects who tested
10 positive for inhibitor development and the number and percentage of subjects who tested positive for anti-rFVIII-Fc-VWF-XTEN antibodies were summarized by cohort using the Safety Analysis Set.

[0357] No subject developed a positive anti-drug antibody assay result following rFVIII-Fc-VWF-XTEN administration.

[0358] Pharmacokinetic Analysis and Results

15 **[0359]** In general, safety and PK data were summarized using standard summary statistics for continuous and categorical data. Data was summarized by cohort. Continuous variables were summarized using descriptive statistics including the number of non-missing values (n), mean, standard deviation (SD), median, minimum, and maximum. Pharmacokinetic parameters were also summarized using geometric mean and percent coefficient of variation (%CV). Categorical variables
20 were summarized by counts and percentages.

[0360] All PK analyses were performed based on the PK analysis set (PKAS) and included 9 subjects from the 50 IU/kg dosing cohort who had adequate blood sample collections following rFVIII-Fc-VWF-XTEN administration.

[0361] **FVIII Activity**

25 **[0362]** To characterize the pharmacokinetics of rFVIII-Fc-VWF-XTEN after a total of four once-weekly IV doses, FVIII activity was determined in each subject at the prespecified time points. FVIII activity was summarized by cohort, scheduled PK visit, and timepoint for both the one-stage (activated partial thromboplastin time [aPTT]) clotting assay and the chromogenic coagulation assay. FVIII activity versus time profiles were plotted in both original and log scale for both FVIII activity

assays. Individual FVIII activity was listed for each subject by cohort, scheduled PK visit and timepoint for both FVIII activity assays. Results for FVIII activity according to the one-stage [aPTT] assay are depicted in Table 12. Results for FVIII activity according to the chromogenic assay are depicted in Table 13.

5 [0363] Briefly, following Day 1 dosing, mean FVIII activities based on one-stage and chromogenic assay at 72 h were 45.53% and 29.37%, at 120 h were 21.56% and 13.49%, and at 168 h were 7.91% and 5.97%, respectively. Following Day 22 dosing, mean FVIII activities based on one stage and chromogenic assay at 72 h were 46.28% and 30.46%, at 120 h were 22.30% and 14.48%, and at 168 h were 9.83% and 6.74%, respectively. Generally across all patients, time points, and with both
10 assays, the Ctrough for rFVIIIIFc-VWF-XTEN at 50 IU/kg QW in this interim analysis ranged between 7-10%.

[0364] PK Parameters

[0365] Individual PK parameter estimates were listed for each subject and summarized descriptively by cohort, scheduled PK visit, and time point for both FVIII activity assays.

15 [0366] The geometric mean elimination half-life ($t_{1/2}$) for all subjects receiving rFVIIIIFc-VWF-XTEN at 50 IU/kg QW in this interim analysis was 41.24 hours according to the one stage assay (Table 16B) and 43.87 hours according to the chromogenic assay (Table 17B).

[0367] Following Day 1 dosing, the geometric mean maximum FVIII activity (C_{max}) was 113 IU/dL with the one stage assay (Table 14) and 108 IU/dL with the chromogenic assay (Table 15). Following
20 Day 22 dosing, the geometric mean FVIII activity at steady state (C_{maxss}) was 127 IU/dL according to the one stage assay (Table 16A) and 115 IU/dL according to the chromogenic assay (Table 17A).

[0368] Following Day 1 dosing, the geometric mean cumulative FVIII activity (AUC_{0-tau}) was 7650 hr*IU/dL according to the one stage assay (Table 14) and 5630 hr*IU/dL according to the chromogenic assay (Table 15). Following Day 22 dosing, the geometric mean AUC_{0-tau} was 8270
25 hr*IU/dL according to the one stage assay (Table 16A) and 5880 hr*IU/dL according to the chromogenic assay (Table 17A).

[0369] C_{max} and AUC_{0-tau} data on Day 1 and Day 22 dosing indicated minimal accumulation supported by accumulation index (AI) of 1.07 (one-stage assay, Table 16B) and 1.08 (chromogenic assay, Table 17B). For all of the PK parameter data presented in Tables 12-17, values below the
30 limit of quantification (BLQ) were treated as 0 for the purpose of analysis. Where necessary for

calculation of PK parameters, as infusion end time was not captured, infusion duration was imputed as 8 minutes for each subject in line with administration guidance in the study's Directions for Handling and Administration document.

5 **TABLE 12. Summary of Baseline-Corrected FVIII Activity Levels (IU/dL) based on one-stage aPTT clotting assay: PK Analysis Set (Dose Level: 50 IU/kg)**

Dosing Day	Timepoint	n	Mean (SD)	Median	Geo. Mean	%CV	Min, Max
Day1	Pre-injection	9	0.00 (0.000)	0.00	0.00	-----	0.0, 0.0
	30 mins from SOI	9	113.17 (20.214)	118.10	111.51	17.862	82.0, 140.2
	3 hrs from SOI	9	109.07 (19.243)	109.90	107.49	17.643	77.4, 135.5
	24 hrs from SOI	9	91.04 (15.231)	92.80	89.88	16.730	68.9, 115.8
	48 hrs from SOI	9	66.38 (12.231)	65.90	65.30	18.426	46.7, 80.3
	72 hrs from SOI	9	45.53 (6.742)	45.60	45.08	14.807	36.7, 53.9
	120 hrs from SOI	9	21.56 (4.473)	22.20	21.11	20.750	14.2, 27.1
Day8	Pre injection	9	7.91 (2.869)	7.40	7.48	36.265	4.0, 13.1
Day 15	Pre injection	9	8.94 (3.322)	7.80	8.34	37.140	3.9, 13.5
Day 22	Pre injection	9	9.91 (2.838)	11.61	9.49	28.633	5.0, 12.9
	30 mins from SOI	9	132.77 (31.741)	131.80	129.56	23.907	96.0, 190.7
	3 hrs from SOI	9	120.94 (22.168)	126.60	119.03	18.329	85.2, 152.0
	24 hrs from SOI	9	103.79 (18.513)	110.20	102.21	17.838	74.0, 126.3
	48 hrs from SOI	9	69.89 (12.812)	68.10	68.84	18.332	49.8, 91.7
	72 hrs from SOI	9	46.28 (7.720)	47.90	45.68	16.682	33.4, 58.3
	120 hrs from SOI	9	22.30 (4.979)	21.70	21.77	22.329	13.7, 29.8
	168 hrs from SOI	9	9.83 (3.847)	9.60	9.16	39.120	4.9, 15.5
	240 hrs from SOI	9	2.84 (0.999)	2.80	2.68	35.117	1.4, 4.4
	336 hrs from SOI	9	1.28 (2.651)	0.00	0.00	207.494	0.0, 8.2

Abbreviations: SD = standard deviation, Geo. Mean = geometric mean, %CV = percent coefficient of variation, Min = minimum value, Max = maximum value, SOI = start of injection

TABLE 13. Summary of Baseline-Corrected FVIII Activity Levels (IU/dL) based on chromogenic assay: PK Analysis Set (Dose Level: 50 IU/kg)

Dosing Day	Timepoint	n	Mean (SD)	Median	Geo. Mean	%CV	Min, Max
Day1	Pre-injection	9	0.00 (0.000)	0.00	0.00	-----	0.0, 0.0
	30 mins from SOI	9	108.94 (15.126)	113.00	107.99	13.884	87.4, 129.9
	3 hrs from SOI	9	101.86 (13.782)	102.50	100.99	13.531	79.1, 118.3
	24 hrs from SOI	9	71.68 (14.654)	73.50	70.24	20.445	47.8, 93.5
	48 hrs from SOI	9	43.84 (7.086)	43.40	43.32	16.163	32.5, 54.0
	72 hrs from SOI	9	29.37 (5.319)	30.10	28.93	18.112	22.3, 37.2
	120 hrs from SOI	9	13.49 (2.680)	13.80	13.24	19.870	9.4, 17.2
Day8	Pre injection	9	5.97 (1.764)	6.20	5.74	29.568	3.6, 9.4
Day 15	Pre injection	9	6.93 (1.736)	6.70	6.74	25.044	4.8, 10.0
Day 22	Pre injection	9	7.13 (1.817)	7.50	6.93	25.466	5.0, 10.4
	30 mins from SOI	9	113.58 (14.920)	113.25	112.72	13.137	91.3, 137.6
	3 hrs from SOI	9	109.08 (16.394)	112.50	107.96	15.029	85.4, 132.6
	24 hrs from SOI	9	72.13 (14.985)	71.40	70.78	20.774	56.6, 95.8
	48 hrs from SOI	9	45.23 (4.907)	46.10	44.99	10.847	37.4, 52.3
	72 hrs from SOI	9	30.46 (5.247)	31.20	30.04	17.230	21.4, 39.6
	120 hrs from SOI	9	14.48 (2.862)	13.70	14.23	19.769	10.5, 18.7
	168 hrs from SOI	9	6.74 (1.911)	6.20	6.51	28.328	4.4, 9.7
	240 hrs from SOI	9	2.20 (1.025)	2.20	0.00	46.577	0.0, 3.7
	336 hrs from SOI	9	0.46 (1.021)	0.00	0.00	224.158	0.0, 3.0

Abbreviations: SD = standard deviation, Geo. Mean = geometric mean, %CV = percent coefficient of variation, Min = minimum value, Max = maximum value, SOI = start of injection

TABLE 14. Day 1 Dosing Summary of Pharmacokinetic Parameters for Baseline-Corrected FVIII Activity based on one-stage aPTT clotting assay: PK Analysis Set

Subject No.	Actual Dose (IU/kg)	C _{MAX} (IU/dL)	T _{MAX} (hr)	AUC ₀ -tau (hr*IU/dL)	Dose-normalized AUC ₀ -tau (hr*kg*IU/dL/IU)	IVR (%)	IR (IU/dL per IU/kg)
Cohort 1 (50 IU/kg): BIVV001 Day 1 Dosing							
170-001	50.0	91.7	3.13	7940	159	52.5	1.83
170-002	49.9	140	0.50	8310	166	97.4	2.81
170-003	50.2	82.0	0.50	6000	119	53.1	1.63
170-004	50.1	131	3.00	9300	186	95.9	2.61
170-006	50.0	139	0.50	7960	159	89.4	2.78
170-007	49.8	109	0.50	7480	150	71.1	2.19
170-009	50.0	121	2.85	8170	163	85	2.42
170-010	50.2	99.1	0.50	5750	115	61.3	1.97
170-011	49.8	118	0.50	8740	176	64.2	2.37
n	9	9	9	9	9	9	9
Mean	50.00	115	1.33	7740	155	74.4	2.29
Median	50.00	118	0.5	7960	159	71.1	2.37
Std. Dev	0.150	20.7	1.25	1180	23.8	17.9	0.42
%CV	0	18	94	15	15	24	18
Geo. Mean	50.00	113	0.91	7650	153	72.5	2.26
(95% CI)	(49.88, 50.12)	(97.6, 130)	(0.46, 1.81)	(6750, 8670)	(135, 174)	(60.1, 87.5)	(1.95, 2.61)
Minimum	49.8	82.0	0.50	5750	115	52.5	1.63
Maximum	50.2	140	3.13	9300	186	97.4	2.81

Abbreviations: Std Dev = standard deviation, Geo. Mean = geometric mean, %CV = percent coefficient of variation, C_{MAX} = maximum concentration at steady state, T_{MAX} = time to reach maximum concentration, C_{MAXSS} = maximum concentration at steady state, IVR = in vivo recovery, AUC₀-inf = area under the activity-time curve from time 0 to infinity, AUC₀-tau = area under the activity-time curve from hour 0 over the dosing interval, MRT_{INF} = mean residence time extrapolated to infinity, A_I = accumulating index, IR = incremental recovery, C_{trough} = lowest concentration that a drug reaches before the next dose is administered, C_{avg} = average concentration after reaching steady state, t_{1/2} = elimination half-life, CL_{ss} = clearance at steady state, V_{ss} = volume of distribution at steady state.

TABLE 15: Day 1 Summary of Pharmacokinetic Parameters for Baseline-Corrected FVIII Activity based on chromogenic assay: PK Analysis Set

Subject No.	Actual Dose (IU/kg)	C _{MAX} (IU/dL)	T _{MAX} (hr)	AUC _{0-tau} (hr*IU/dL)	Dose-normalized AUC _{0-tau} (hr*kg*IU/dL/IU)	IVR (%)	IR (IU/dL per IU/kg)
Cohort 1 (50 IU/kg): BIVV001 Day 1 Dosing							
170-001	50	90.8	0.63	5850	117	52	1.82
170-002	49.9	130	0.5	6160	123	90.2	2.6
170-003	50.2	87.4	0.5	4290	85.4	56.6	1.74
170-004	50.1	124	0.5	7030	140	90.5	2.47
170-006	50	117	0.5	5530	111	74.9	2.33
170-007	49.8	105	0.5	5580	112	68.3	2.1
170-009	50	119	0.5	6500	130	84	2.39
170-010	50.2	95.4	0.5	4360	86.9	59	1.9
170-011	49.8	113	0.5	5970	120	61.4	2.27
n	9	9	9	9	9	9	9
Mean	50	109	0.51	5700	114	70.8	2.18
Median	50	113	0.5	5850	117	68.3	2.27
Std. Dev	0.15	15.1	0.04	905	18.2	14.8	0.3
%CV	0	14	9	16	16	21	14
Geo. Mean	50	108	0.51	5630	113	69.4	2.16
(95% CI)	(49.88, 50.12)	(96.8, 120)	(0.48, 0.55)	(4950, 6400)	(98.9, 128)	(59.1, 81.5)	(1.93, 2.41)
Minimum	49.8	87.4	0.5	4290	85.4	52	1.74
Maximum	50.2	130	0.63	7030	140	90.5	2.6

Abbreviations: Std Dev = standard deviation, Geo. Mean = geometric mean, %CV = percent coefficient of variation, C_{MAX} = maximum concentration at steady state, T_{MAX} = time to reach maximum concentration, C_{MAXSS} = maximum concentration at steady state, IVR = in vivo recovery, AUC_{0-inf} = area under the activity-time curve from time 0 to infinity, AUC_{0-tau} = area under the activity-time curve from hour 0 over the dosing interval, MRT_{INF} = mean residence time extrapolated to infinity, AI = accumulating index, IR = incremental recovery, C_{trough} = lowest concentration that a drug reaches before the next dose is administered, C_{avg} = average concentration after reaching steady state, t_{1/2} = elimination half-life, CL_{ss} = clearance at steady state, V_{ss} = volume of distribution at steady state.

TABLE 16A. Day 22 - Summary of Pharmacokinetic Parameters for Baseline-Corrected FVIII Activity based on one-stage aPTT clotting assay: PK Analysis Set (Part 1)

Subject No.	Actual Dose (IU/kg)	C _{MAX} SS (IU/dL)	AUC _{0-inf} (hr*IU/dL)	Dose-normalized AUC _{0-inf} (hr*kg*IU/dL/IU)	AUC _{0-tau} (hr*IU/dL)	Dose-normalized AUC _{0-tau} (hr*kg*IU/dL/IU)
Cohort 1 (50 IU/kg): BIVV001 Day 22 Dosing						
170-001	50.1	106	9230	184	8240	165
170-002	49.9	135	8690	174	8310	167
170-003	50	104	7520	150	6950	139
170-004	50	143	11000	219	10100	201
170-006	50	165	9480	190	9210	184
170-007	49.9	132	9300	186	8550	171
170-009	49.8	154	8980	180	8580	172
170-010	49.8	96	6130	123	5810	117
170-011	49.9	129	10200	205	9560	192
n	9	9	9	9	9	9
Mean	49.93	129	8940	179	8370	168
Median	49.9	132	9230	184	8550	171
Std. Dev	0.1	23.2	1420	28.4	1310	26.1
%CV	0	18	16	16	16	16
Geo. Mean	49.93	127	8830	177	8270	166
(95% CI)	(49.86, 50.01)	(110, 147)	(7740, 10100)	(155, 202)	(7260, 9410)	(145, 188)
Minimum	49.8	96	6130	123	5810	117
Maximum	50.1	165	11000	219	10100	201

Abbreviations: Std Dev = standard deviation, Geo. Mean = geometric mean, %CV = percent coefficient of variation, C_{MAX} = maximum concentration at steady state, T_{MAX} = time to reach maximum concentration, C_{MAX}SS = maximum concentration at steady state, I_{VR} = in vivo recovery, AUC_{0-inf} = area under the activity-time curve from time 0 to infinity, AUC_{0-tau} = area under the activity-time curve from hour 0 over the dosing interval, MRT_{INF} = mean residence time extrapolated to infinity, AI = accumulating index, I_R = incremental recovery, C_{trough} = lowest concentration that a drug reaches before the next dose is administered, C_{avg} = average concentration after reaching steady state, t_{1/2} = elimination half-life, CL_{ss} = clearance at steady state, V_{ss} = volume of distribution at steady state.

TABLE 16B: Day 22 - Summary of Pharmacokinetic Parameters for Baseline-Corrected FVIII Activity based on one-stage aPTT clotting assay: PK Analysis Set (Part 2)

Subject No.	t _{1/2} (hr)	MRTINF (hr)	CL _{ss} (mL/hr/kg)	V _{ss} (mL/kg)	AI	C _{trough} (IU/dL)	C _{avg} (IU/dL)
Cohort 1 (50 IU/kg): BIVV001 Day 22 Dosing							
170-001	50.05	78.56	0.61	47.8	1.11	15.2	49.1
170-002	36.86	57.13	0.6	34.3	1.04	7	49.5
170-003	43.86	66.35	0.72	47.8	1.08	9.6	41.4
170-004	45.45	69.54	0.5	34.5	1.08	15.5	60
170-006	34.21	49.79	0.54	27	1.03	4.9	54.8
170-007	48.87	67.08	0.58	39.1	1.1	11.5	50.9
170-009	34.63	56.19	0.58	32.6	1.04	7.8	51.1
170-010	38.29	58.71	0.86	50.3	1.05	5.8	34.6
170-011	42.34	63.41	0.52	33.1	1.07	11.2	56.9
n	9	9	9	9	9	9	9
Mean	41.62	62.97	0.61	38.5	1.07	9.83	49.8
Median	42.34	63.41	0.58	34.5	1.07	9.6	50.9
Std. Dev	5.93	8.57	0.11	8.21	0.03	3.85	7.79
%CV	14	14	18	21	3	39	16
Geo. Mean	41.24	62.46	0.6	37.7	1.07	9.16	49.2
(95% CI)	(36.95, 46.04)	(56.27, 69.33)	(0.531, 0.688)	(32.0, 44.4)	(1.05, 1.09)	(6.70, 12.5)	(43.2, 56.0)
Minimum	34.21	49.79	0.5	27	1.03	4.9	34.6
Maximum	50.05	78.56	0.86	50.3	1.11	15.5	60

Abbreviations: Std Dev = standard deviation, Geo. Mean = geometric mean, %CV = percent coefficient of variation, C_{MAX} = maximum concentration at steady state, T_{MAX} = time to reach maximum concentration, C_{MAXSS} = maximum concentration at steady state, IVR = in vivo recovery, AUC_{0-inf} = area under the activity-time curve from time 0 to infinity, AUC_{0-tau} = area under the activity-time curve from hour 0 over the dosing interval, MRTINF = mean residence time extrapolated to infinity, AI = accumulating index, IR = incremental recovery, C_{trough} = lowest concentration that a drug reaches before the next dose is administered, C_{avg} = average concentration after reaching steady state, t_{1/2} = elimination half-life, CL_{ss} = clearance at steady state, V_{ss} = volume of distribution at steady state.

TABLE 17A. Day 22 - Summary of Pharmacokinetic Parameters for Baseline-Corrected FVIII Activity based on chromogenic assay: PK Analysis Set (Part 1)

Subject No.	Actual Dose (IU/kg)	C _{MAX} SS (IU/dL)	AUC _{0-inf} (hr*IU/dL)	Dose-normalized AUC _{0-inf} (hr*kg*IU/dL/IU)	AUC _{0-tau} (hr*IU/dL)	Dose-normalized AUC _{0-tau} (hr*kg*IU/dL/IU)
Cohort 1 (50 IU/kg): BIVV001 Day 22 Dosing						
170-001	50.1	103	6560	131	5810	116
170-002	49.9	124	6830	137	6430	129
170-003	50.0	91.3	5210	104	4780	95.5
170-004	50.0	126	7050	141	6410	128
170-006	50.0	138	6520	130	6300	126
170-007	49.9	117	6460	129	5990	120
170-009	49.8	123	6620	133	6290	126
170-010	49.8	103	5080	102	4800	96.5
170-011	49.9	113	6910	138	6450	129
n	9	9	9	9	9	9
Mean	49.93	115	6360	127	5920	119
Median	49.9	117	6560	131	6290	126
Std. Dev	0.100	14.5	718	14.3	674	13.5
%CV	0	13	11	11	11	11
Geo. Mean	49.93	115	6320	127	5880	118
(95% CI)	(49.86, 50.01)	(104, 126)	(5760, 6940)	(115, 139)	(5360, 6460)	(107, 129)
Minimum	49.8	91.3	5080	102	4780	95.5

Abbreviations: Std Dev = standard deviation, Geo. Mean = geometric mean, %CV = percent coefficient of variation, C_{MAX} = maximum concentration at steady state, T_{MAX} = time to reach maximum concentration, C_{MAXSS} = maximum concentration at steady state, I_{VR} = in vivo recovery, AUC_{0-inf} = area under the activity-time curve from time 0 to infinity, AUC_{0-tau} = area under the activity-time curve from hour 0 over the dosing interval, MRT_{INF} = mean residence time extrapolated to infinity, A_I = accumulating index, I_R = incremental recovery, C_{trough} = lowest concentration that a drug reaches before the next dose is administered, C_{avg} = average concentration after reaching steady state, t_{1/2} = elimination half-life, CL_{ss} = clearance at steady state, V_{ss} = volume of distribution at steady state.

TABLE 17B. Day 22 - Summary of Pharmacokinetic Parameters for Baseline-Corrected FVIII Activity based on chromogenic assay: PK Analysis Set (Part 2)

Subject No.	t _{1/2} (hr)	MRTINF (hr)	CL _{ss} (mL/hr/kg)	V _{ss} (mL/kg)	AI	C _{trough} (IU/dL)	C _{avg} (IU/dL)
Cohort 1 (50 IU/kg): BIVV001 Day 22 Dosing							
170-001	53.31	76.94	0.86	66.3	1.13	9.6	34.6
170-002	44.73	55.57	0.78	43.1	1.08	6	38.3
170-003	48.29	64.39	1.05	67.4	1.1	6.2	28.4
170-004	46.03	71.12	0.78	55.5	1.09	9.7	38.2
170-006	35.59	47.89	0.79	38	1.04	4.4	37.5
170-007	45.35	62.51	0.83	52	1.08	7	35.7
170-009	40.09	54.93	0.79	43.5	1.06	5.5	37.4
170-010	40.2	56.26	1.04	58.3	1.06	4.8	28.6
170-011	43.61	60.71	0.77	47	1.07	7.5	38.4
n	9	9	9	9	9	9	9
Mean	44.13	61.15	0.85	52.4	1.08	6.74	35.2
Median	44.73	60.71	0.79	52	1.08	6.2	37.4
Std. Dev	5.15	8.88	0.11	10.4	0.03	1.91	4.01
%CV	12	15	13	20	2	28	11
Geo. Mean	43.87	60.59	0.85	51.4	1.08	6.51	35
(95% CI)	(40.08, 48.01)	(54.25, 67.67)	(0.773, 0.932)	(44.1, 60.0)	(1.06, 1.10)	(5.26, 8.07)	(31.9, 38.4)
Minimum	35.59	47.89	0.77	38	1.04	4.4	28.4
Maximum	53.31	76.94	1.05	67.4	1.13	9.7	38.4

- 5 Abbreviations: Std Dev = standard deviation, Geo. Mean = geometric mean, %CV = percent coefficient of variation, C_{MAX} = maximum concentration at steady state, T_{MAX} = time to reach maximum concentration, C_{MAXSS} = maximum concentration at steady state, IVR = in vivo recovery, AUC_{0-inf} = area under the activity-time curve from time 0 to infinity, AUC_{0-tau} = area under the activity-time curve from hour 0 over the dosing interval, MRTINF = mean residence time extrapolated to infinity, AI = accumulating index, IR = incremental recovery, C_{trough} = lowest concentration that a drug reaches before the next dose is administered, C_{avg} = average concentration after reaching steady state, t_{1/2} = elimination half-life, CL_{ss} = clearance at steady state, V_{ss} = volume of distribution at steady state.
- 10

[0370] Conclusions

[0371] Consistent with the results observed in the single dose study (Example 1), the weekly dosing of rFVIII Fc-VWF-XTEN was generally well tolerated and no inhibitors were detected through 28 days following the final rFVIII Fc-VWF-XTEN administration. rFVIII Fc-VWF-XTEN at a dose of 50 IU/kg exhibited mean elimination half-life ($t_{1/2}$) of 41.24 and 43.87 hours with the one stage and chromogenic assays, respectively. These interim results demonstrate that the enhanced half-life observed in single dosing of rFVIII Fc-VWF-XTEN is maintained with repeat dosing QW, strongly signaling that the advantages of rFVIII Fc-VWF-XTEN can be realized by hemophilia A patients receiving treatment according to a prophylactic FVIII dosing schedule.

Example 3: Phase 3 Study of rFVIII Fc-VWF-XTEN in Previously Treated Patients With Severe Hemophilia A

[0372] The present study will evaluate the safety and tolerability and characterize the pharmacokinetics of once weekly administration of 50 IU/kg rFVIII Fc-VWF-XTEN (FIG. 1). The primary objective of the study is to evaluate the efficacy of rFVIII Fc-VWF-XTEN prophylactic treatment compared with rFVIII Fc-VWF-XTEN on-demand treatment. The secondary objective of the study is to evaluate rFVIII Fc-VWF-XTEN as a prophylactic treatment, its effect on bleeding episodes and consumption of rFVIII Fc-VWF-XTEN, joint health, and quality of life as measured by Patient-Reported Outcomes (PROs), and evaluate rFVIII Fc-VWF-XTEN for on-demand treatment.

[0373] In addition, the pharmacokinetic (PK) objective is to characterize the PK of rFVIII Fc-VWF-XTEN prophylaxis at baseline for all subjects and repeated at three months for a predefined subset of subjects, based on the aPTT FVIII activity assay. Additional objectives are to evaluate the efficacy of rFVIII Fc-VWF-XTEN in subjects who undergo surgery, and to evaluate the safety and tolerability of rFVIII Fc-VWF-XTEN. Further, joint health structural outcomes will be assessed via ultrasound, and the impact of treatment on other quality of life measurements and on healthcare resource utilization will be assessed.

[0374] Study Design

[0375] This is a pivotal, Phase 3, open-label, multicenter study of the safety, efficacy and PK of intravenous rFVIII Fc-VWF-XTEN in patients ≥ 12 years of age with severe hemophilia A (defined as <1 IU/dL [$<1\%$] endogenous FVIII). Approximately twenty-five subjects currently on an on-demand

regimen will receive rFVIII Fc-VWF-XTEN at a dose of 50 IU/kg IV on an on-demand basis for twenty-six weeks, then receive rFVIII Fc-VWF-XTEN at a dose of 50 IU/kg IV once-weekly on a prophylactic treatment regimen for twenty-six weeks. Subjects currently on a prophylactic treatment regimen will receive rFVIII Fc-VWF-XTEN at a dose of 50 IU/kg IV once-weekly on a prophylactic treatment regimen for fifty-two weeks.

[0376] Approximately 140 subjects ≥ 12 years of age will be enrolled; repeat PK assessments will be performed on a subset of approximately sixteen subjects at 12 weeks.

[0377] Subjects will be screened and, after meeting enrollment criteria, proceed to one of two treatment regimens (i.e., on demand or prophylaxis) with rFVIII Fc-VWF-XTEN at a dose of 50 IU/kg IV. All subjects will undergo baseline PK assessments after a washout period (at least 4 to 5 days, depending on current therapy). Subjects will undergo efficacy and safety assessments throughout the study. These safety assessments will include testing for potential inhibitor formation. A follow-up safety visit or telephone call will occur twenty-eight days after the last dose of rFVIII Fc-VWF-XTEN, unless the subject enrolls in the open-label extension study.

[0378] End of study (EOS) may occur when both criteria have been met: (i) at least 104 subjects have reached 50 exposure days (EDs) and have completed a valid inhibitor test after the 50th ED; and (ii) at least twenty-five subjects have completed the on-demand arm of the study, including the 26-week prophylactic treatment period, or withdrawn from the study early. In addition, subjects from any arm who undergo surgery during the study will be included in the surgery subset. A minimum of ten major surgeries in at least five subjects will be targeted to assess control and prevention of bleeding in the surgical setting.

[0379] Subjects will come to the clinic within an approximately 28-day Screening Period for determination of eligibility. In addition to the Screening Visit(s), subjects will return to the clinic for visits at Baseline, Week 4, Week 12, Week 26, Week 36, Week 52, and EOS/ET. The Dosing Period will be over 52 weeks. Subjects who enter on the prophylactic treatment arm will receive 52 once-weekly doses of rFVIII Fc-VWF-XTEN and additional doses as necessary to treat bleeding episodes. Subjects who enter on the on-demand treatment arm will receive rFVIII Fc-VWF-XTEN on-demand during the 26-week on-demand treatment period and 26 once-weekly doses of rFVIII Fc-VWF-XTEN and additional doses as necessary to treat bleeding episodes during the subsequent 26-week prophylactic treatment period. Safety will be assessed throughout the study. A Follow-Up Safety Visit

or Telephone Call will occur 28 days after the last dose of rFVIII-Fc-VWF-XTEN, unless the subject enrolls in the open-label extension study.

[0380] The primary endpoint of the study will be an intra-subject comparison of the Annualized Bleeding Rate (ABR) while subjects are on rFVIII-Fc-VWF-XTEN on-demand treatment (26 weeks) versus once-weekly prophylactic treatment (26 weeks).

[0381] The secondary endpoints of the study will include (i) an intra-subject comparison of ABR on rFVIII-Fc-VWF-XTEN prophylaxis versus the historical ABR (for subjects on prophylaxis who participated in a previous observational study); (ii) the occurrence of bleeding episodes and consumption (overall ABR, ABR by type and location, and total, annualized rFVIII-Fc-VWF-XTEN consumption per subject); (iii) the response to treatment; (iv) efficacy index (percentage of subjects that maintain trough level of L3% at day 7; (v) joint health; and (vi) changes in quality of life measures (haem-A-QoL and PROMIS-SF physical Function for subjects at least 18 years old; and HAEMO-QoL and PROMIS Pediatric-SF Physical Activity for subjects less than 18 years old).

[0382] The response to treatment will include the (i) number of infusions and dose of rFVIII-Fc-VWF-XTEN required to resolve a bleeding episode; (ii) percentage of bleeding episodes that require a single infusion for resolution; (iii) subject's assessment of response to rFVIII-Fc-VWF-XTEN treatment of individual bleeding episodes based on a 4-point response scale; (iv) and investigator's global assessment of subject's response to rFVIII-Fc-VWF-XTEN treatment based on a 4-point response scale.

[0383] Joint health evaluation will include (i) ABR of joint bleeding episodes; (ii) Target joint resolution at 52 weeks, based on the International Society on Thrombosis and Haemostasis (ISTH) criteria; (iii) Functional outcomes based on absolute change from baseline to 52 weeks assessed by the modified Hemophilia Joint Health Score (mHJHS) or HJHS; (iv) Percentage of subjects with no joint deterioration at 52 weeks assessed by the mHJHS or HJHS.

[0384] Additional endpoints include (i) Maximum (peak) plasma drug concentration (C_{max}), elimination half-life ($t_{1/2}$), accumulation index (AI), area under the plasma concentration-time curve (AUC), apparent volume of distribution at steady state (V_{ss}), mean residence time (MRT), incremental recovery (IR), trough plasma concentration (C_{trough}), and time above predefined FVIII activity levels; (ii) Investigators' or Surgeons' assessments of subjects' hemostatic response to rFVIII-Fc-VWF-XTEN treatment on a 4-point response scale, number and dose of infusions required to maintain hemostasis during the surgery, total rFVIII-Fc-VWF-XTEN consumption during the surgical period, estimated

blood loss during surgery, number and type of blood component transfusions required during surgery, and bleeding episodes post-surgery during the surgical period; (iii) the occurrence of adverse events (AEs) and serious adverse events (SAEs), clinically significant abnormalities in physical examination, vital signs, and laboratory tests, and the development of inhibitors (neutralizing antibodies directed against FVIII as determined via the Nijmegen-modified Bethesda assay; and (iv) anatomical structural joint health outcomes via ultrasound imaging in a subpopulation, changes in other QoL measures (EQ-5D-5L, PGIC (week 52 only), PROMIS Pain Intensity, PROMIS-SF Pain Interference (subjects ≥ 18 years old), PROMIS Pediatric-SF Pain Interference (subjects < 18 years old)), and HRU.

[0385] Inclusion/Exclusion Criteria

[0386] Eligible candidates must meet the following eligibility criteria: (1) ≥ 12 years of age at the time of informed consent; (2) severe hemophilia A, defined as < 1 IU/dL ($< 1\%$) endogenous FVIII as documented by a certified clinical laboratory; (3) previous treatment for hemophilia A (prophylactic or on demand) with any recombinant and/or plasma-derived FVIII, or cryoprecipitate for at least 150 EDs; (4) currently on a prophylactic treatment regimen with a marketed FVIII product and had at least four bleeding episodes in the twelve months prior to study enrollment, or currently on an on-demand treatment regimen with a marketed FVIII product and had at least twelve bleeding episodes in the twelve months prior to study enrollment; and (5) platelet count $\geq 100,000$ cells/ μ L at screening (test performed by the central laboratory and reviewed prior to the Day 1 dose). Subjects will be excluded for any of the following reasons: (1) other known coagulation disorder(s) in addition to hemophilia A; (2) history of hypersensitivity or anaphylaxis associated with any FVIII product; (3) history of a positive inhibitor test or clinical signs of decreased response to FVIII administrations (family history of inhibitors will not exclude the subject); (4) positive inhibitor result, taken at screening, defined as ≥ 0.6 BU/mL; (5) abnormal renal function, defined as serum creatinine > 2.0 mg/dL taken at Screening; (6) serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $> 5 \times$ upper limit of normal (ULN) taken at Screening; (7) serum total bilirubin $> 3 \times$ ULN, taken at Screening; (8) fitusiran or emicizumab use within the 12 weeks prior to Screening; (9) treatment within 12 weeks prior to screening with a monoclonal antibody therapeutic, an Fc fusion protein other than rFVIII-Fc, or IV immunoglobulin; (10) Treatment with acetylsalicylic acid (ASA) within 2 weeks prior to screening or treatment with non-steroidal anti-inflammatory drugs (NSAIDs) at or above the maximum dose specified in the regional prescribing information for each product; (11) systemic treatment within 12 weeks prior to screening with chemotherapy and/or other immunosuppressive drugs (except for the treatment of hepatitis C virus [HCV] or HIV; use of corticosteroids is allowed, except for systemic

corticosteroid treatment given daily or on alternate days at 20 mg/day of prednisone or its equivalent for >14 days; local, topical, and/or inhaled steroid use is permitted; and (12) major surgery within 8 weeks prior to screening (major surgery is defined as any surgical procedure (elective or emergent) that usually, but not always, involves general anesthesia and/or respiratory assistance, in which a
5 major body cavity is penetrated and exposed, or a substantial impairment of physical or physiological functions is produced (e.g., laparotomy, thoracotomy, craniotomy, joint replacement, or limb amputation)).

SEQUENCES

VWF031 nucleotide Sequence (SEQ ID NO: 147)

```

1      ATGAT TCCTG CCAGA TTTGC CGGGG TGCTG CTTGC TCTGG CCCTC ATTTT
51     GCCAG GGACC CTTTG TGCAG AAGGA ACTCG CGGCA GGTCA TCCAC GGCCC
5      101     GATGC AGCCT TTTTG GAAGT GACTT CGTCA ACACC TTTGA TGGGA GCATG
151    TACAG CTTTG CGGGA TACTG CAGTT ACCTC CTGGC AGGGG GCTGC CAGAA
201    ACGCT CCTTC TCGAT TATTG GGGAC TTCCA GAATG GCAAG AGAGT GAGCC
251    TCTCC GTGTA TCTTG GGGAA TTTT TGACA TCCAT TTGTT TGTCA ATGGT
301    ACCGT GACAC AGGGG GACCA AAGAG TCTCC ATGCC CTATG CCTCC AAAGG
10     351    GCTGT ATCTA GAAAC TGAGG CTGGG TACTA CAAGC TGTCC GGTGA GGCCT
401    ATGGC TTTGT GGCCA GGATC GATGG CAGCG GCAAC TTTCA AGTCC TGCTG
451    TCAGA CAGAT ACTTC AACAA GACCT GCGGG CTGTG TGGCA ACTTT AACAT
501    CTTTG CTGAA GATGA CTTTA TGACC CAAGA AGGGA CCTTG ACCTC GGACC
551    CTTAT GACTT TGCCA ACTCA TGGGC TCTGA GCAGT GGAGA ACAGT GGTGT
15     601    GAACG GGCAT CTCCT CCCAG CAGCT CATGC AACAT CTCCT CTGGG GAAAT
651    GCAGA AGGGC CTGTG GGAGC AGTGC CAGCT TCTGA AGAGC ACCTC GGTGT
701    TTGCC CGCTG CCACC CTCTG GTGGA CCCC AGCCT TTTGT GGCCC TGTGT
751    GAGAA GACTT TGTGT GAGTG TGCTG GGGGG CTGGA GTGCG CCTGC CCTGC
801    CCTCC TGGAG TACGC CCGGA CCTGT GCCCA GGAGG GAATG GTGCT GTACG
20     851    GCTGG ACCGA CCACA GCGCG TGCAG CCCAG TGTGC CCTGC TGGTA TGGAG
901    TATAG GCAGT GTGTG TCCCC TTGCG CCAGG ACCTG CCAGA GCCTG CACAT
951    CAATG AAATG TGTC AAGAG GATGC GTGGA TGGCT GCAGC TGCCC TGAGG
1001   GACAG CTCCT GGATG AAGGC CTCTG CGTGG AGAGC ACCGA GTGTC CCTGC
1051   GTGCA TTCCG GAAAG CGCTA CCCTC CCGGC ACCTC CCTCT CTCGA GACTG
25     1101   CAACA CCTGC ATTTG CCGAA ACAGC CAGTG GATCT GCAGC AATGA AGAAT
1151   GTCCA GGGGA GTGCC TTGTC ACTGG TCAAT CCCAC TTCAA GAGCT TTGAC
1201   AACAG ATACT TCACC TTCAG TGGGA TCTGC CAGTA CCTGC TGGCC CGGGA
1251   TTGCC AGGAC CACTC CTTCT CCATT GTCAT TGAGA CTGTC CAGTG TGCTG
1301   ATGAC CGCGA CGCTG TGTGC ACCCG CTCCG TCACC GTCCG GCTGC CTGGC
30     1351   CTGCA CAACA GCCTT GTGAA ACTGA AGCAT GGGGC AGGAG TTGCC ATGGA
1401   TGGCC AGGAC ATCCA GCTCC CCCTC CTGAA AGGTG ACCTC CGCAT CCAGC
1451   ATACA GTGAC GGCCT CCGTG CGCCT CAGCT ACGGG GAGGA CCTGC AGATG
1501   GACTG GGATG GCCGC GGGAG GCTGC TGGTG AAGCT GTCCC CCGTC TATGC
1551   CGGGA AGACC TGCAG CCTGT GTGGG AATTA CAATG GCAAC CAGGG CGACG
35     1601   ACTTC CTTAC CCCCT CTGGG CTGGC GGAGC CCCGG GTGGA GGAAT TCGGG
1651   AACGC CTGGA AGCTG CACGG GGAAT GCCAG GACCT GCAGA AGCAG CACAG
1701   CGATC CCTGC GCCCT CAACC CGCGC ATGAC CAGGT TCTCC GAGGA GCGCT
1751   GCGCG GTCCT GACGT CCCC ACATT CGAGG CCTGC CATCG TGCCG TCAGC
1801   CCGCT GCCCT ACCTG CGGAA CTGCC GCTAC GACGT GTGCT CCTGC TCGGA
40     1851   CGGCC GCGAG TGCCT GTGCG GCGCC CTGGC CAGCT ATGCC GCGGC CTGCG
1901   CGGGG AGAGG CGTGC GCGTC GCGTG GCGCG AGCCA GGCCG CTGTG AGCTG
1951   AACTG CCCGA AAGGC CAGGT GTACC TGACG TGCGG GACCC CCTGC AACCT
2001   GACCT GCCGC TCTCT CTCTT ACCCG GATGA GGAAT GCAAT GAGGC CTGCC
2051   TGGAG GGCTG CTTCT GCCCC CCAGG GCTCT ACATG GATGA GAGGG GGGAC
45     2101   TGCGT GCCCA AGGCC CAGTG CCCCT GTTAC TATGA CCGTG AGATC TTCCA
2151   GCCAG AAGAC ATCTT CTCAG ACCAT CACAC CATGT GCTAC TGTGA GGATG
2201   GCTTC ATGCA CTGTA CCATG AGTGG AGTCC CCGGA AGCTT GCTGC CTGAC
2251   GCTGT CCTCA GCAGT CCCCT GTCTC ATCGC AGCAA AAGGA GCCTA TCCTG
2301   TCGGC CCCCC ATGGT CAAGT TGGTG TGTCC CGCTG ACAAC CTGCG GGCTG
50     2351   AAGGG CTCGA GTGTA CAAA ACGTG CCAGA ACTAT GACCT GGAGT GCATG
2401   AGCAT GGGCT GTGTC TCTGG CTGCC TCTGC CCCCC GGGCA TGGTC CGGCA

```

2451 TGAGA ACAGA TGTGT GGCCC TGGAA AGGTG TCCCT GCTTC CATCA GGGCA
 2501 AGGAG TATGC CCCTG GAGAA ACAGT GAAGA TTGGC TGCAA CACTT GTGTC
 2551 TGTCG GGACC GGAAG TGGAA CTGCA CAGAC CATGT GTGTG ATGCC ACGTG
 2601 CTCCA CGATC GGCAT GGCCC ACTAC CTCAC CTTCG ACGGG CTCAA ATACC
 5 2651 TGTTC CCCGG GGAGT GCCAG TACGT TCTGG TGCAG GATTA CTGCG GCAGT
 2701 AACCC TGGGA CCTTT CGGAT CCTAG TGGGG AATAA GGGAT GCAGC CACCC
 2751 CTCAG TGAAA TGCAA GAAAC GGGTC ACCAT CCTGG TGGAG GGAGG AGAGA
 2801 TTGAG CTGTT TGACG GGGAG GTGAA TGTGA AGAGG CCCAT GAAGG ATGAG
 2851 ACTCA CTTTG AGGTG GTGGA GTCTG GCCGG TACAT CATTG TGCTG CTGGG
 10 2901 CAAAG CCCTC TCCGT GGTCT GGGAC CGCCA CCTGA GCATC TCCGT GGTCC
 2951 TGAAG CAGAC ATACC AGGAG AAAGT GTGTG GCCTG TGTGG GAATT TTGAT
 3001 GGCAT CCAGA ACAAT GACCT CACCA GCAGC AACCT CCAAG TGGAG GAAGA
 3051 CCCTG TGGAC TTTGG GAACT CCTGG AAAGT GAGCT CGCAG TGTGC TGACA
 3101 CCAGA AAAGT GCCTC TGGAC TCATC CCCTG CCACC TGCCA TAACA ACATC
 15 3151 ATGAA GCAGA CGATG GTGGA TTCCT CCTGT AGAAT CCTTA CCAGT GACGT
 3201 CTTCC AGGAC TGCAA CAAGC TGGTG GACCC CGAGC CATAT CTGGA TGTCT
 3251 GCATT TACGA CACCT GCTCC TGTGA GTCCA TTGGG GACTG CGCCG CATTG
 3301 TGCGA CACCA TTGCT GCCTA TGCCC ACGTG TGTGC CCAGC ATGGC AAGGT
 3351 GGTGA CCTGG AGGAC GGCCA CATTG TGCCC CCAGA GCTGC GAGGA GAGGA
 20 3401 ATCTC CGGGA GAACG GGTAT GAGGC TGAGT GGCGC TATAA CAGCT GTGCA
 3451 CCTGC CTGTC AAGTC ACGTG TCAGC ACCCT GAGCC ACTGG CCTGC CCTGT
 3501 GCAGT GTGTG GAGGG CTGCC ATGCC CACTG CCCTC CAGGG AAAAT CCTGG
 3551 ATGAG CTTTT GCAGA CCTGC GTTGA CCCTG AAGAC TGTCC AGTGT GTGAG
 3601 GTGGC TGGCC GGCCT TTTGC CTCAG GAAAG AAAGT CACCT TGAAT CCCAG
 25 3651 TGACC CTGAG CACTG CCAGA TTTGC CACTG TGATG TTGTC AACCT CACCT
 3701 GTGAA GCCTG CCAGG AGCCG ATATC TGGCG GTGGA GGTTC CGGTG GCGGG
 3751 GGATC CGGCG GTGGA GGTTC CGGCG GTGGA GGTTC CGGTG GCGGG GGATC
 3801 CGGTG GCGGG GGATC CCTGG TCCCC GGGGG CAGCG GCGGT GGAGG TTCCG
 3851 GTGGC GGGGG ATCCG ACAA ACTCA CACAT GCCCA CCGTG CCCAG CTCCA
 30 3901 GAACT CCTGG GCGGA CCGTC AGTCT TCCTC TTCCC CCAA AACCC AAGGA
 3951 CACCC TCATG ATCTC CCGGA CCCCT GAGGT CACAT GCGTG GTGGT GGACG
 4001 TGAGC CACGA AGACC CTGAG GTCAA GTTCA ACTGG TACGT GGACG GCGTG
 4051 GAGGT GCATA ATGCC AAGC AAAGC CGCGG GAGGA GCAGT ACAAC AGCAC
 4101 GTACC GTGTG GTCAG CTCC TCACC TTCCT GCACC AGGAC TGGT GAATG
 35 4151 GCAAG GAGTA CAAGT GCAAG GTCTC CAACA AAGCC CTCCC AGCCC CCATC
 4201 GAGAA AACCA TCTCC AAAGC CAAAG GGCAG CCCC AGAAC CACAG GTGTA
 4251 CACCC TGCCC CCATC CCGCG ATGAG CTGAC CAAGA ACCAG GTCAG CCTGA
 4301 CCTGC CTGGT CAAAG GCTTC TATCC CAGCG ACATC GCCGT GGAGT GGGAG
 4351 AGCAA TGGGC AGCCG GAGAA CAACT ACAAG ACCAC GCCTC CCGTG TTGGA
 40 4401 CTCCG ACGGC TCCTT CTTCC TCTAC AGCAA GCTCA CCGTG GACAA GAGCA
 4451 GGTGG CAGCA GGGGA ACGTC TTCTC ATGCT CCGTG ATGCA TGAGG CTCTG
 4501 CACAA CCACT ACACG CAGAA GAGCC TCTCC CTGTC TCCGG GTAAA TGA

VWF031 protein Sequence (SEQ ID NO: 86)

45 1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFVNTFDGSM
 51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
 101 TVTQGDQRV MPYASKGLYL ETEAGYYKLS GEAYGFVARI DGSGNFQVLL
 151 SDRYFNKTCG LCGNFNIFAE DDFMTQEGTL TSDPYDFANS WALSSGEQWC
 201 ERASPPSSSC NISSGEMQKG LWEQCQLLKS TSVFARCHPL VDPEPFVALC
 50 251 EKTLCECAGG LECACPALLE YARTCAQEGM VLYGWTDHSA CSPVCPAGME
 301 YRQCVSPCAR TCQSLHINEM CQERCVDGCS CPEGQLLDEG LCVESTTEPC

351 VHSGKRYPPG TSLSRDCNTC ICRNSQWICS NEECPGECLV TGQSHFKSFD
 401 NRYFTFSGIC QYLLARDCQD HSFIVIVETV QCADDRDAVC TRSVTVRLPG
 451 LHNSLVKLKH GAGVAMDGQD IQLPLLKGD LRIQHTVTASV RLSYGEDLQM
 501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
 5 NAWKLHGDCQ DLQKQHS DPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
 601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCCL
 651 NCPKGQVYLQ CGTPCNLTCT SLSYPDEECN EACLEGCFCP PGLYMDERGD
 701 CVPKAQCPCY YDGEIFQPED IFSDHHTMCY CEDGFMHCTM SGVPGSLLPD
 751 AVLSSPLSHR SKRSLSCRPP MVKLVCADN LRAEGLECTK TCQNYDLECM
 10 SMGCVSGCLC PPGMVRHENR CVALERCPCF HQGKEYAPGE TVKIGCNTCV
 851 CRDRKWNCTD HVC DATCSTI GMAHYLTFDG LKYLFPGECQ YVLVQDYCGS
 901 NPGTFRILVG NKGCSPSVK CKKRVTILVE GGEIELFDGE VNVKRPMDKE
 951 THFEVVEGR YIILLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
 1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
 15 1051 MKQTMVDSSC RILTSDVFQD CNKLVDPPEY LDVCIYDTCS CESIGDCAAF
 1101 CDTIAAYAHV CAQHGKVVTW RTATLCPQSC EERNLRENGY EAEWRYNSCA
 1151 PACQVTCQHP EPLACPVQCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE
 1201 VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP ISGGGGSGGG
 1251 GSGGGSGGG GSGGGSGGG GSVLPRGSGG GSGGGGSDK THTCPPCPAP
 20 1301 ELLGGPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV
 1351 EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI
 1401 EKTISKAKGQ PREPQVYTLPSRDELTKNQ VSLTCLVKGF YPSDIAVEWE
 1451 SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRRWQQGNV FSCSVMEAL
 1501 HNHYTQKSLS LSPGK*

VWF034 nucleotide Sequence (SEQ ID NO: 148)

1 ATGAT TCCTG CCAGA TTTGC CGGGG TGCTG CTTGC TCTGG CCCTC ATTTT
 51 GCCAG GGACC CTTTG TGCAG AAGGA ACTCG CGGCA GTTCA TCCAC GGCCC
 101 GATGC AGCCT TTTCG GAAGT GACTT CGTCA ACACC TTTGA TGGGA GCATG
 30 151 TACAG CTTTG CGGGA TACTG CAGTT ACCTC CTGGC AGGGG GCTGC CAGAA
 201 ACGCT CCTTC TCGAT TATTG GGGAC TTCCA GAATG GCAAG AGAGT GAGCC
 251 TCTCC GTGTA TCTTG GGGAA TTTT TGACA TCCAT TTGTT TGTC AATGGT
 301 ACCGT GACAC AGGGG GACCA AAGAG TCTCC ATGCC CTATG CCTCC AAAGG
 351 GCTGT ATCTA GAAAC TGAGG CTGGG TACTA CAAGC TGTCC GGTGA GGCCT
 35 401 ATGGC TTTGT GGCCA GGATC GATGG CAGCG GCAAC TTTCA AGTCC TGCTG
 451 TCAGA CAGAT ACTTC AACAA GACCT GCGGG CTGTG TGGCA ACTTT AACAT
 501 CTTTG CTGAA GATGA CTTTA TGACC CAAGA AGGGA CTTTG ACCTC GGACC
 551 CTTAT GACTT TGCCA ACTCA TGGGC TCTGA GCAGT GGAGA ACAGT GGTGT
 601 GAACG GGCAT CTCCT CCCAG CAGCT CATGC AACAT CTCCT CTGGG GAAAT
 40 651 GCAGA AGGGC CTGTG GGAGC AGTGC CAGCT TCTGA AGAGC ACCTC GGTGT
 701 TTGCC CGCTG CCACC CTCTG GTGGA CCCC AGCCT TTTGT GGCCC TGTGT
 751 GAGAA GACTT TGTGT GAGTG TGCTG GGGGG CTGGA GTGCG CCTGC CCTGC
 801 CCTCC TGGAG TACGC CCGGA CCTGT GCCCA GGAGG GAATG GTGCT GTACG
 851 GCTGG ACCGA CCACA GCGCG TGCAG CCCAG TGTGC CCTGC TGGTA TGGAG
 45 901 TATAG GCAGT GTGTG TCCCC TTGCG CCAGG ACCTG CCAGA GCCTG CACAT
 951 CAATG AAATG TGTC AAGAG GATGC GTGGA TGGCT GCAGC TGCCC TGAGG
 1001 GACAG CTCCT GGATG AAGGC CTCTG CGTGG AGAGC ACCGA GTGTC CCTGC
 1051 GTGCA TTCCG GAAAG CGCTA CCCTC CCGGC ACCTC CCTCT CTCGA GACTG
 1101 CAACA CCTGC ATTTG CCGAA ACAGC CAGTG GATCT GCAGC AATGA AGAAT
 50 1151 GTCCA GGGGA GTGCC TTGTC ACTGG TCAAT CCCAC TTCAA GAGCT TTGAC
 1201 AACAG ATACT TCACC TTCAG TGGGA TCTGC CAGTA CCTGC TGGCC CGGGA

1251 TTGCC AGGAC CACTC CTTCT CCATT GTCAT TGAGA CTGTC CAGTG TGCTG
 1301 ATGAC CGCGA CGCTG TGTGC ACCCG CTCCG TCACC GTCCG GCTGC CTGGC
 1351 CTGCA CAACA GCCTT GTGAA ACTGA AGCAT GGGGC AGGAG TTGCC ATGGA
 1401 TGGCC AGGAC ATCCA GCTCC CCCTC CTGAA AGGTG ACCTC CGCAT CCAGC
 5 1451 ATACA GTGAC GGCCT CCGTG CGCCT CAGCT ACGGG GAGGA CCTGC AGATG
 1501 GACTG GGATG GCCGC GGGAG GCTGC TGGTG AAGCT GTCCC CCGTC TATGC
 1551 CGGGA AGACC TGC GG CCTGT GTGGG AATTA CAATG GCAAC CAGGG CGACG
 1601 ACTTC CTTAC CCCCT CTGGG CTGGC GGAGC CCCGG GTGGA GGA CT TCGGG
 1651 AACGC CTGGA AGCTG CACGG GGA CT GCCAG GACCT GCAGA AGCAG CACAG
 10 1701 CGATC CCTGC GCCCT CAACC CGCG ATGAC CAGGT TCTCC GAGGA GGCCT
 1751 GCGCG GTCCT GACGT CCCCC ACATT CGAGG CCTGC CATCG TGCCG TCAGC
 1801 CCGCT GCCCT ACCTG CGGAA CTGCC GCTAC GACGT GTGCT CCTGC TCAGA
 1851 CGGCC GCGAG TGCCT GTGCG GCGCC CTGGC CAGCT ATGCC GCGGC CTGCG
 1901 CGGGG AGAGG CGTGC GCGTC GCGTG GCGCG AGCCA GGCCG CTGTG AGCTG
 15 1951 AACTG CCCGA AAGGC CAGGT GTACC TGCAG TCGCG GACCC CCTGC AACCT
 2001 GACCT GCCGC TCTCT CTCTT ACCCG GATGA GGAAT GCAAT GAGGC CTGCC
 2051 TGGAG GGCTG CTTCT GCCCC CCAGG GCTCT ACATG GATGA GAGGG GGGAC
 2101 TGCGT GCCCA AGGCC CAGTG CCCCT GTTAC TATGA CCGTG AGATC TTCCA
 2151 GCCAG AAGAC ATCTT CTCAG ACCAT CACAC CATGT GCTAC TGTGA GGATG
 20 2201 GCTTC ATGCA CTGTA CCATG AGTGG AGTCC CCGGA AGCTT GCTGC CTGAC
 2251 GCTGT CCTCA GCAGT CCCCT GTCTC ATCGC AGCAA AAGGA GCCTA TCCTG
 2301 TCGGC CCCCC ATGGT CAAGC TGGTG TGTCC CGCTG ACAAC CTGCG GGCTG
 2351 AAGGG CTCGA GTGTA CAAA ACGTG CCAGA ACTAT GACCT GGAGT GCATG
 2401 AGCAT GGGCT GTGTC TCTGG CTGCC TCTGC CCCCC GGGCA TGGTC CGGCA
 25 2451 TGAGA ACAGA TGTGT GGCCC TGGAA AGGTG TCCCT GCTTC CATCA GGGCA
 2501 AGGAG TATGC CCCTG GAGAA ACAGT GAAGA TTGGC TGCAA CACTT GTGTC
 2551 TGTCG GGACC GGAAG TGGAA CTGCA CAGAC CATGT GTGTG ATGCC ACGTG
 2601 CTCCA CGATC GGCAT GGCCC ACTAC CTCAC CTTCC ACGGG CTC AA ATACC
 2651 TGTTC CCCGG GGAGT GCCAG TACGT TCTGG TGCAG GATTA CTGCG GCAGT
 30 2701 AACCC TGGGA CCTTT CGGAT CCTAG TGGGG AATAA GGGAT GCAGC CACCC
 2751 CTCAG TGAAA TGCAA GAAAC GGGTC ACCAT CCTGG TGGAG GGAGG AGAGA
 2801 TTGAG CTGTT TGACG GGGAG GTGAA TGTGA AGAGG CCCAT GAAGG ATGAG
 2851 ACTCA CTTTG AGGTG GTGGA GTCTG GCCGG TACAT CATTG TGCTG GTGGG
 2901 CAAAG CCCTC TCCGT GGTCT GGGAC CGCCA CCTGA GCATC TCCGT GTGCC
 35 2951 TGAAG CAGAC ATACC AGGAG AAGGT GTGTG GCCTG TGTGG GAATT TTGAT
 3001 GGCAT CCAGA ACAAT GACCT CACCA GCAGC AACCT CCAAG TGGAG GAAGA
 3051 CCCTG TGGAC TTTGG GAACT CCTGG AAAGT GAGCT CGCAG TGTGC TGACA
 3101 CCAGA AAAGT GCCTC TGGAC TCATC CCCTG CCACC TGCCA TAACA ACATC
 3151 ATGAA GCAGA CGATG GTGGA TTCCT CCTGT AGAAT CCTTA CCAGT GACGT
 40 3201 CTTCC AGGAC TGCAA CAAGC TGGTG GACCC CGAGC CATAT CTGGA TGTCT
 3251 GCATT TACGA CACCT GCTCC TGTGA GTCCA TTGGG GACTG CGCCG CATTG
 3301 TGCGA CACCA TTGCT GCCTA TGCCC ACGTG TGTGC CCAGC ATGGC AAGGT
 3351 GGTGA CCTGG AGGAC GGCCA CATTG TGCCC CCAGA GCTGC GAGGA GAGGA
 3401 ATCTC CGGGA GAACG GGTAT GAGGC TGAGT GGCGC TATAA CAGCT GTGCA
 45 3451 CCTGC CTGTC AAGTC ACGTG TCAGC ACCCT GAGCC ACTGG CCTGC CCTGT
 3501 GCAGT GTGTG GAGGG CTGCC ATGCC CACTG CCCTC CAGGG AAAAT CCTGG
 3551 ATGAG CTTTT GCAGA CCTGC GTTGA CCCTG AAGAC TGTCC AGTGT GTGAG
 3601 GTGGC TGGCC GGCCT TTTGC CTCAG GAAAG AAAGT CACCT TGAAT CCCAG
 3651 TGACC CTGAG CACTG CCAGA TTTGC CACTG TGATG TTGTC AACCT CACCT
 50 3701 GTGAA GCCTG CCAGG AGCCG ATATC GGGTA CCTCA GAGTC TGCTA CCCCC
 3751 GAGTC AGGGC CAGGA TCAGA GCCAG CCACC TCCGG GTCTG AGACA CCCGG
 3801 GACTT CCGAG AGTGC CACCC CTGAG TCCGG ACCCG GTCC GAGCC CGCCA
 3851 CTTCC GGCTC CGAAA CTCCC GGCAC AAGCG AGAGC GCTAC CCCAG AGTCA

3901 GGACC AGGAA CATCT ACAGA GCCCT CTGAA GGCTC CGCTC CAGGG TCCCC
 3951 AGCCG GCAGT CCCAC TAGCA CCGAG GAGGG AACCT CTGAA AGCGC CACAC
 4001 CCGAA TCAGG GCCAG GGTCT GAGCC TGCTA CCAGC GGCAG CGAGA CACCA
 4051 GGCAC CTCTG AGTCC GCCAC ACCAG AGTCC GGACC CGGAT CTCCC GCTGG
 5 4101 GAGCC CCACC TCCAC TGAGG AGGGA TCTCC TGCTG GCTCT CCAAC ATCTA
 4151 CTGAG GAAGG TACCT CAACC GAGCC ATCCG AGGGA TCAGC TCCCG GCACC
 4201 TCAGA GTCGG CAACC CCGGA GTCTG GACCC GGAAC TTCCG AAAGT GCCAC
 4251 ACCAG AGTCC GGTCC CGGGA CTTCA GAATC AGCAA CACCC GAGTC CGGCC
 4301 CTGGG TCTGA ACCCG CCACA AGTGG TAGTG AGACA CCAGG ATCAG AACCT
 10 4351 GCTAC CTCAG GGTCA GAGAC ACCCG GATCT CCGGC AGGCT CACCA ACCTC
 4401 CACTG AGGAG GGCAC GAGCA CAGAA CCAAG CGAGG GCTCC GCACC CGGAA
 4451 CAAGC ACTGA ACCCA GTGAG GGTTC AGCAC CCGGC TCTGA GCCGG CCACA
 4501 AGTGG CAGTG AGACA CCCGG CACTT CAGAG AGTGC CACCC CCGAG AGTGG
 4551 CCCAG GCACT AGTAC CGAGC CCTCT GAAGG CAGTG CGCCA GATTC TGGCG
 15 4601 GTGGA GGTTC CGGTG GCGGG GGATC CCGTG GCGGG GGATC CCGTG GCGGG
 4651 GGATC CCGTG GCGGG GGATC CCTGG TCCCC CGGGG CAGCG GAGGC GACAA
 4701 AACTC ACACA TGCCC ACCGT GCCCA GCTCC AGAAC TCCTG GGCGG ACCGT
 4751 CAGTC TTCCT CTTCC CCCC AAACC CAAGG ACACC CTCAT GATCT CCCGG
 4801 ACCCC TGAGG TCACA TGCCT GGTGG TGGAC GTGAG CCACG AAGAC CCTGA
 20 4851 GGTCA AGTTC AACTG GTACG TGGAC GCGGT GGAGG TGCAT AATGC CAAGA
 4901 CAAAG CCGCG GGAGG AGCAG TACAA CAGCA CGTAC CGTGT GGTCA GCGTC
 4951 CTCAC CGTCC TGCAC CAGGA CTGGC TGAAT GGCAA GGAGT ACAAG TGCAA
 5001 GGTCT CCAAC AAAGC CCTCC CAGCC CCCAT CGAGA AAACC ATCTC CAAAG
 5051 CCAAA GGGCA GCCCC GAGAA CCACA GGTGT ACACC CTGCC CCCAT CCCGG
 25 5101 GATGA GCTGA CCAAG AACCA GGTC A CCTG ACCTG CCTGG TCAAA GGCTT
 5151 CTATC CCAGC GACAT CGCCG TGGAG TGGGA GAGCA ATGGG CAGCC GGAGA
 5201 ACAAC TACAA GACCA CGCCT CCCGT GTTGG ACTCC GACGG CTCCT TCTTC
 5251 CTCTA CAGCA AGCTC ACCGT GGACA AGAGC AGGTG GCAGC AGGGG AACGT
 5301 CTTCT CATGC TCCGT GATGC ATGAG GCTCT GCACA ACCAC TACAC GCAGA
 30 5351 AGAGC CTCTC CCTGT CTCCG GTTAA ATGA

VWF034 Protein Sequence (SEQ ID NO: 87)

35 1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFVNTFDGSM
 51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
 101 TVTQGDQ RVS MPYASKGLYL ETEAGYYKLS GEAYGFVARI DGSGNFQVLL
 151 SDRYFNKTCG LCGNFNIFAE DDFMTQEGTL TSDPYDFANS WALSSGEQWC
 201 ERASPPSSSC NISSGEMQKG LWEQCQLLKS TSVFARCHPL VDPEPFVALC
 40 251 ECTLCECAGG LECACPALLE YARTCAQEGM VLYGWTDHSA CSPVCPAGME
 301 YRQCVSPCAR TCQSLHINEM CQERCVDGCS CPEGQLLDEG LCVESTECPC
 351 VHSGKRYPPG TSLSRDCNTC ICRNSQWICS NEECPGECLV TGQSHFKSFD
 401 NRYFTFSGIC QYLLARDCQD HSFSIVIETV QCADDRDAVC TRSVTVRLPG
 451 LHNSLVKLKH GAGVAMDQGD IQLPLLKGD LRIQHTVTASV RLSYGEDLQM
 45 501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
 551 NAWKLHGDCQ DLQKQHS DPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
 601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCCL
 651 NCPKGQVYLQ CGTPCNLT CR SLSYPDEECN EACLEGCFCP PGLYMDERGD
 701 CVPKAQCPCY YDGEIFQPED IFSDHHTMCY CEDGFMHCTM SGVPGSLLPD
 50 751 AVLSSPLSHR SKRSLSCRPP MVKLVCPADN LRAEGLECTK TCQNYDLECM
 801 SMGCVSGCLC PPGMVRHENR CVALERCPCF HQGKEYAPGE TVKIGCNTCV
 851 CRDRKWNCTD HVCDATCSTI GMAHYLTFDG LKYLFPGECQ YVLVQDYCGS

901 NPGTFRILVG NKGCSPSVK CKKRVTLVE GGEIELFDGE VNVKRPMKDE
 951 THFEVVESGR YIILLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
 1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
 1051 MKQTMVDSSC RILTSDVFQD CNKLDPEPY LDVCIYDTCS CESIGDCAAF
 5 1101 CDTIAAYAHV CAQHGKVVTW RTATLCPQSC EERNLRENGY EAEWRYNSCA
 1151 PACQVTCQHP EPLACPVCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE
 1201 VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP ISGTSESATP
 1251 ESGPGSEPAT SGSETPGTSE SATPESGPGS EPATSGSETP GTSESATPES
 1301 GPGTSTEPSE GSAPGSPAGS PTSTEEGTSE SATPESGPGS EPATSGSETP
 10 1351 GTSESATPES GPGSPAGSPT STEEGSPAGS PTSTEEGTST EPSEGSAPGT
 1401 SESATPESGP GTSESATPES GPGTSESATP ESGPGSEPAT SGSETPGSEP
 1451 ATSGSETPGS PAGSPTSTEE GTSTEPSEGS APGTSTEPSE GSAPGSEPAT
 1501 SGSETPGTSE SATPESGPGT STEPSEGSAP DIGGGGGSGG GGS�VPRGS
 1551 GDKTHTCPPC PAPELLGGPS VLFPPPKPD TLMISRTPEV TCVVVDVSHE
 15 1601 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
 1651 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV
 1701 KGFYPSDIAV EWESNGQPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
 1751 GNVFSCSVMH EALHNHYTQK SLSLSPGK*

20

VWF050 nucleotide sequence (IHH triple mutant) (SEQ ID NO: 149)

1 ATGAT TCCTG CCAGA TTTGC CGGGG TGCTG CTTGC TCTGG CCCTC ATTTT
 51 GCCAG GGACC CTTTG TGCAG AAGGA ACTCG CGGCA GTTCA TCCAC GGCCC
 101 GATGC AGCCT TTTTG GAAGT GACTT CGTCA ACACC TTTGA TGGGA GCATG
 25 151 TACAG CTTTG CGGGA TACTG CAGTT ACCTC CTGGC AGGGG GCTGC CAGAA
 201 ACGCT CCTTC TCGAT TATTG GGGAC TTCCA GAATG GCAAG AGAGT GAGCC
 251 TCTCC GTGTA TCTTG GGGAA TTTT TGACA TCCAT TTGTT TGTC AATGGT
 301 ACCGT GACAC AGGGG GACCA AAGAG TCTCC ATGCC CTATG CCTCC AAAGG
 351 GCTGT ATCTA GAAAC TGAGG CTGGG TACTA CAAGC TGTCC GGTGA GGCCT
 30 401 ATGGC TTTGT GGCCA GGATC GATGG CAGCG GCAAC TTTCA AGTCC TGCTG
 451 TCAGA CAGAT ACTTC AACAA GACCT GCGGG CTGTG TGGCA ACTTT AACAT
 501 CTTTG CTGAA GATGA CTTTA TGACC CAAGA AGGGA CCTTG ACCTC GGACC
 551 CTTAT GACTT TGCCA ACTCA TGGG TCTGA GCAGT GGAGA ACAGT GGTGT
 601 GAACG GGCAT CTCCT CCCAG CAGCT CATGC AACAT CTCCT CTGGG GAAAT
 35 651 GCAGA AGGGC CTGTG GGAGC AGTGC CAGCT TCTGA AGAGC ACCTC GGTGT
 701 TTGCC CGCTG CCACC CTCTG GTGGA CCCCC AGCCT TTTGT GGCCC TGTGT
 751 GAGAA GACTT TGTGT GAGTG TGCTG GGGGG CTGGA GTGCG CCTGC CCTGC
 801 CCTCC TGGAG TACGC CCGGA CCTGT GCCCA GGAGG GAATG GTGCT GTACG
 851 GCTGG ACCGA CCACA GCGCG TGCAG CCCAG TGTGC CCTGC TGGTA TGGAG
 40 901 TATAG GCAGT GTGTG TCCCC TTGCG CCAGG ACCTG CCAGA GCCTG CACAT
 951 CAATG AAATG TGTC AAGAG GATGC GTGGA TGGCT GCAGC TGCCC TGAGG
 1001 GACAG CTCCT GGATG AAGGC CTCTG CGTGG AGAGC ACCGA GTGTC CCTGC
 1051 GTGCA TTCCG GAAAG CGCTA CCCTC CCGGC ACCTC CCTCT CTCGA GACTG
 1101 CAACA CCTGC ATTTG CCGAA ACAGC CAGTG GATCT GCAGC AATGA AGAAT
 45 1151 GTCCA GGGGA GTGCC TTGTC ACTGG TCAAT CCCAC TTCAA GAGCT TTGAC
 1201 AACAG ATACT TCACC TTCAG TGGGA TCTGC CAGTA CCTGC TGGCC CGGGA
 1251 TTGCC AGGAC CACTC CTTCT CCATT GTCAT TGAGA CTGTC CAGTG TGCTG
 1301 ATGAC CGCGA CGCTG TGTGC ACCCG CTCCG TCACC GTCCG GCTGC CTGGC
 1351 CTGCA CAACA GCCTT GTGAA ACTGA AGCAT GGGGC AGGAG TTGCC ATGGA
 50 1401 TGGCC AGGAC ATCCA GCTCC CCCTC CTGAA AGGTG ACCTC CGCAT CCAGC
 1451 ATACA GTGAC GGCCT CCGTG CGCCT CAGCT ACGGG GAGGA CCTGC AGATG
 1501 GACTG GGATG GCCGC GGGAG GCTGC TGGTG AAGCT GTCCC CCGTC TATGC

1551 CGGGA AGACC TGCGG CCTGT GTGGG AATTA CAATG GCAAC CAGGG CGACG
 1601 ACTTC CTTAC CCCCT CTGGG CTGGC GGAGC CCCGG GTGGA GGA CT TCGGG
 1651 AACGC CTGGA AGCTG CACGG GGA CT GCCAG GACCT GCAGA AGCAG CACAG
 1701 CGATC CCTGC GCCCT CAACC CGCGC ATGAC CAGGT TCTCC GAGGA GCGCT
 5 1751 GCGCG GTCCT GACGT CCCCC ACATT CGAGG CCTGC CATCG TGCCG TCAGC
 1801 CCGCT GCCCT ACCTG CGGAA CTGCC GCTAC GACGT GTGCT CCTGC TCGGA
 1851 CGGCC GCGAG TGCCT GTGCG GCGCC CTGGC CAGCT ATGCC GCGGC CTGCG
 1901 CGGGG AGAGG CGTGC GCGTC GCGTG GCGCG AGCCA GGCCG CTGTG AGCTG
 1951 AACTG CCCGA AAGGC CAGGT GTACC TGCAG TCGGG GACCC CCTGC AACCT
 10 2001 GACCT GCCGC TCTCT CTCTT ACCCG GATGA GGAAT GCAAT GAGG CTGCC
 2051 TGGAG GGCTG CTTCT GCCCC CCAGG GCTCT ACATG GATGA GAGGG GGGAC
 2101 TGCGT GCCCA AGGCC CAGTG CCCCT GTTAC TATGA CGGTG AGATC TTCCA
 2151 GCCAG AAGAC ATCTT CTCAG ACCAT CACAC CATGT GCTAC TGTGA GGATG
 2201 GCTTC ATGCA CTGTA CCATG AGTGG AGTCC CCGGA AGCTT GCTGC CTGAC
 15 2251 GCTGT CCTCA GCAGT CCCCT GTCTC ATCGC AGCAA AAGGA GCCTA TCCTG
 2301 TCGGC CCCCC ATGGT CAAGC TGGTG TGTCC CGCTG ACAAC CTGCG GGCTG
 2351 AAGGG CTCGA GTGTA CCAA ACGTG CCAGA ACTAT GACCT GGAGT GCATG
 2401 AGCAT GGGCT GTGTC TCTGG CTGCC TCTGC CCCCC GGGCA TGGTC CGGCA
 2451 TGAGA ACAGA TGTGT GGCCC TGGAA AGGTG TCCCT GCTTC CATCA GGGCA
 20 2501 AGGAG TATGC CCCTG GAGAA ACAGT GAAGA TTGGC TGCAA CACTT GTGTC
 2551 TGTCG GGACC GGAAG TGGAA CTGCA CAGAC CATGT GTGTG ATGCC ACGTG
 2601 CTCCA CGATC GGCAT GGCCC ACTAC CTCAC CTTCG ACGGG CTCAA ATACC
 2651 TGTTT CCCGG GGAGT GCCAG TACGT TCTGG TGCAG GATTA CTGCG GCAGT
 2701 AACCC TGGGA CCTTT CGGAT CCTAG TGGGG AATAA GGGAT GCAGC CACCC
 25 2751 CTCAG TGAAA TGCAA GAAAC GGGTC ACCAT CCTGG TGGAG GGAGG AGAGA
 2801 TTGAG CTGTT TGACG GGGAG GTGAA TGTGA AGAGG CCCAT GAAGG ATGAG
 2851 ACTCA CTTTG AGGTG GTGGA GTCTG GCCGG TACAT CATTG TGCTG CTGGG
 2901 CAAAG CCCTC TCCGT GGTCT GGGAC CGCCA CCTGA GCATC TCCGT GGTCC
 2951 TGAAG CAGAC ATACC AGGAG AAAGT GTGTG GCCTG TGTGG GAATT TTGAT
 30 3001 GGCAT CCAGA ACAAT GACCT CACCA GCAGC AACCT CCAAG TGGAG GAAGA
 3051 CCCTG TGGAC TTTGG GAACT CCTGG AAAGT GAGCT CGCAG TGTGC TGACA
 3101 CCAGA AAAGT GCCTC TGGAC TCATC CCCTG CCACC TGCCA TAACA ACATC
 3151 ATGAA GCAGA CGATG GTGGA TTCCT CCTGT AGAAT CCTTA CCAGT GACGT
 3201 CTTCC AGGAC TGCAA CAAGC TGGTG GACCC CGAGC CATAT CTGGA TGTCT
 35 3251 GCATT TACGA CACCT GCTCC TGTGA GTCCA TTGGG GACTG CGCCG CATTG
 3301 TGCGA CACCA TTGCT GCCTA TGCCC ACGTG TGTGC CCAGC ATGGC AAGGT
 3351 GGTGA CCTGG AGGAC GGCCA CATTG TGCCC CCAGA GCTGC GAGGA GAGGA
 3401 ATCTC CGGGA GAACG GGTAT GAGGC TGAGT GGCGC TATAA CAGCT GTGCA
 3451 CCTGC CTGTC AAGTC ACGTG TCAGC ACCCT GAGCC ACTGG CCTGC CCTGT
 40 3501 GCAGT GTGTG GAGGG CTGCC ATGCC CACTG CCCTC CAGGG AAAAT CCTGG
 3551 ATGAG CTTTT GCAGA CCTGC GTTGA CCCTG AAGAC TGTCC AGTGT GTGAG
 3601 GTGGC TGGCC GCGGT TTTGC CTCAG GAAAG AAAGT CACCT TGAAT CCCAG
 3651 TGACC CTGAG CACTG CCAGA TTTGC CACTG TGATG TTGTC AACCT CACCT
 3701 GTGAA GCCTG CCAGG AGCCG ATATC TGGCG GTGGA GTTTC CGGTG GCGGG
 45 3751 GGATC CGGCG GTGGA GTTTC CGGCG GTGGA GTTTC CGGTG GCGGG GGATC
 3801 CGGTG GCGGG GGATC CCTGG TCCCC CGGGG CAGCG GCGGT GGAGG TTCCG
 3851 GTGGC GGGGG ATCCG ACAA ACTCA CACAT GCCCA CCGTG CCCAG CTCCA
 3901 GAACT CCTGG GCGGA CCGTC AGTCT TCCTC TTCCC CCAA AACCC AAGGA
 3951 CACCC TCATG GCCTC CCGGA CCCCT GAGGT CACAT GCGTG GTGGT GGACG
 50 4001 TGAGC CACGA AGACC CTGAG GTCAA GTTCA ACTGG TACGT GGACG GCGTG
 4051 GAGGT GCATA ATGCC AAGAC AAAGC CGCGG GAGGA GCAGT ACAAC AGCAC
 4101 GTACC GTGTG GTCAG CGTCC TCACC GTCCT GGCCC AGGAC TGGCT GAATG
 4151 GCAAG GAGTA CAAGT GCAAG GTCTC CAACA AAGCC CTCCC AGCCC CCATC

4201 GAGAA AACCA TCTCC AAAGC CAAAG GGCAG CCCC AGAAC CACAG GTGTA
 4251 CACCC TGCCC CCATC CCGCG ATGAG CTGAC CAAGA ACCAG GTCAG CCTGA
 4301 CCTGC CTGGT CAAAG GCTTC TATCC CAGCG ACATC GCCGT GGAGT GGGAG
 4351 AGCAA TGGGC AGCCG GAGAA CAACT ACAAG ACCAC GCCTC CCGTG TTGGA
 5 4401 CTCCG ACGGC TCCTT CTTCC TCTAC AGCAA GCTCA CCGTG GACAA GAGCA
 4451 GGTGG CAGCA GGGGA ACGTC TTCTC ATGCT CCGTG ATGCA TGAGG CTCTG
 4501 CACAA CGCCT ACACG CAGAA GAGCC TCTCC CTGTC TCCGG GTAAA TGA

VWF050 protein sequence (IHH triple mutant) (SEQ ID NO: 150)

10 1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFNNTFDGSM
 51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVLSVYLGE FFDIHLFVNG
 101 TVTQGDQRVS MPYASKGLYL ETEAGYYKLS GEAYGFVARI DSGSNFQVLL
 151 SDRYFNKTCG LCGNFNIFAE DDFMTQEGTL TSDPYDFANS WALSSGEQWC
 201 ERASPPSSSC NISSGEMQKG LWEQCQLLKS TSVFARCHPL VDPEPFVALC
 15 251 EKTLCCECAGG LECACPALLE YARTCAQEGM VLYGWTDHSA CSPVCPAGME
 301 YRQCVSPCAR TCQSLHINEM CQERCVDGCS CPEGQLLDEG LCVESTCEPC
 351 VHSGKRYPPG TSLSRDCNTC ICRNSQWICS NEECPGECLV TGQSHFKSFD
 401 NRYFTFSGIC QYLLARDCQD HSFSIVIETV QCADDRDAVC TRSVTVRLPG
 451 LHNSLVKLKH GAGVAMDGQD IQLPLLKGD LRIQHTVTASV RLSYGEDLQM
 20 501 DWDGRGRLLV KLSPPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
 551 NAWKLHGDCQ DLQKQHS DPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
 601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCCL
 651 NCPKGQVYLQ CGTPCNLTCR SLSYPDEECN EACLEGCFCP PGLYMDERGD
 701 CVPKAQCPCY YDGEIFQPED IFSDHHTMCY CEDGFMHCTM SGVPGSLLPD
 25 751 AVLSSPLSHR SKRSLSCRPP MVKLVCPADN LRAEGLECTK TCQNYDLECM
 801 SMGCVSGCLC PPGMVRHENR CVALERCPCF HQGKEYAPGE TVKIGCNTCV
 851 CRDRKWNCTD HVCDATCSTI GMAHYLTFDG LKYLFPGECQ YVLVQDYCGS
 901 NPGTFRILVG NKGCSHPSVK CKKRVTLVE GGEIELFDGE VNVKRPMDKE
 951 THFEVVESGR YIILLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
 30 1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
 1051 MKQTMVDSSC RILTSDVFQD CNKLVDPPEY LDVCIYDTCS CESIGDCAAF
 1101 CDTIAAYAHV CAQHKGKVVW RTATLCPQSC EERNLRENGY EAEWRYNSCA
 1151 PACQVTCQHP EPLACPVCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE
 1201 VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP ISGGGGSGGG
 35 1251 GSGGGSGGG GSGGGSGGG GSVLPRGSGG GSGGGGSDK THTCPPCPAP
 1301 ELLGGPSVFL FPPKPKDTLM ASRTEVTCV VVDVSHEDPE VKFNWYVDGV
 1351 EVHNAKTKPR EEQYNSTYRV VSVLTVLAQD WLNKEYKCK VSNKALPAPI
 1401 EKTISKAKGQ PREPQVYTL PPSRDELTKNQ VSLTCLVKGF YPSDIAVEWE
 1451 SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRLWQQGNV FSCSVMEAL
 40 1501 HNAYTQKSLS LSPGK*

VWF057 nucleotide sequence (SEQ ID NO: 151)

45 1 ATGAT TCCTG CCAGA TTTGC CGGGG TGCTG CTTGC TCTGG CCCTC ATTTT
 51 GCCAG GGACC CTTTG TGCAG AAGGA ACTCG CGGCA GGTCA TCCAC GGCCC
 101 GATGC AGCCT TTTTG GAAGT GACTT CGTCA ACACC TTTGA TGGGA GCATG
 151 TACAG CTTTG CGGGA TACTG CAGTT ACCTC CTGGC AGGGG GCTGC CAGAA
 201 ACGCT CCTTC TCGAT TATTG GGGAC TTCCA GAATG GCAAG AGAGT GAGCC

251 TCTCC GTGTA TCTTG GGGAA TTTTT TGACA TCCAT TTGTT TGTCA ATGGT
 301 ACCGT GACAC AGGGG GACCA AAGAG TCTCC ATGCC CTATG CCTCC AAAGG
 351 GCTGT ATCTA GAAAC TGAGG CTGGG TACTA CAAGC TGTCC GGTGA GGCCT
 401 ATGGC TTTGT GGCCA GGATC GATGG CAGCG GCAAC TTTC AATGCT TGCTG
 5 451 TCAGA CAGAT ACTTC AACAA GACCT GCGGG CTGTG TGGCA ACTTT AACAT
 501 CTTTG CTGAA GATGA CTTTA TGACC CAAGA AGGGA CCTTG ACCTC GGACC
 551 CTTAT GACTT TGCCA ACTCA TGGGC TCTGA GCAGT GGAGA ACAGT GGTGT
 601 GAACG GGCAT CTCCT CCCAG CAGCT CATGC AACAT CTCCT CTGGG GAAAT
 651 GCAGA AGGGC CTGTG GGAGC AGTGC CAGCT TCTGA AGAGC ACCTC GGTGT
 10 701 TTGCC CGCTG CCACC CTCTG GTGGA CCCC AGCCT TTTGT GGCC TGTGT
 751 GAGAA GACTT TGTGT GAGTG TGCTG GGGG CTGGA GTGCG CCTGC CCTGC
 801 CCTCC TGGAG TACGC CCGGA CCTGT GCCCA GGAGG GAATG GTGCT GTACG
 851 GCTGG ACCGA CCACA GCGCG TGCAG CCCAG TGTGC CCTGC TGGTA TGGAG
 901 TATAG GCAGT GTGTG TCCCC TTGCG CCAGG ACCTG CCAGA GCCTG CACAT
 15 951 CAATG AAATG TGTCA GGAGC GATGC GTGGA TGGCT GCAGC TGCCC TGAGG
 1001 GACAG CTCCT GGATG AAGGC CTCTG CGTGG AGAGC ACCGA GTGTC CCTGC
 1051 GTGCA TTCCG GAAAG CGCTA CCCTC CCGGC ACCTC CCTCT CTCGA GACTG
 1101 CAACA CCTGC ATTTG CCGAA ACAGC CAGTG GATCT GCAGC AATGA AGAAT
 1151 GTCCA GGGGA GTGCC TTGTC ACTGG TCAAT CCCAC TTCAA GAGCT TTGAC
 20 1201 AACAG ATACT TCACC TTCAG TGGGA TCTGC CAGTA CCTGC TGGCC CGGGA
 1251 TTGCC AGGAC CACTC CTTCT CCATT GTCAT TGAGA CTGTC CAGTG TGCTG
 1301 ATGAC CGCGA CGCTG TGTGC ACCCG CTCCG TCACC GTCCG GCTGC CTGGC
 1351 CTGCA CAACA GCCTT GTGAA ACTGA AGCAT GGGGC AGGAG TTGCC ATGGA
 1401 TGGCC AGGAC ATCCA GCTCC CCCTC CTGAA AGGTG ACCTC CGCAT CCAGC
 25 1451 ATACA GTGAC GGCCT CCGTG CGCCT CAGCT ACGGG GAGGA CCTGC AGATG
 1501 GACTG GGATG GCCGC GGGAG GCTGC TGGTG AAGCT GTCCC CCGTC TATGC
 1551 CGGGA AGACC TGC GG CCTGT GTGGG AATTA CAATG GCAAC CAGGG CGACG
 1601 ACTTC CTTAC CCCCT CTGGG CTGGC GGAGC CCCGG GTGGA GGAAT TCGGG
 1651 AACGC CTGGA AGCTG CACGG GGAAT GCCAG GACCT GCAGA AGCAG CACAG
 30 1701 CGATC CCTGC GCCCT CAACC CGCGC ATGAC CAGGT TCTCC GAGGA GCGCT
 1751 GCGCG GTCCT GACGT CCCCC ACATT CGAGG CCTGC CATCG TGCCG TCAGC
 1801 CCGCT GCCCT ACCTG CGGAA CTGCC GCTAC GACGT GTGCT CCTGC TCGGA
 1851 CGGGC GCGAG TGCCT GTGCG GCGCC CTGGC CAGCT ATGCC GCGGC CTGGC
 1901 CGGGG AGAGG CGTGC GCGTC GCGTG GCGCG AGCCA GGCCG CTGTG AGCTG
 35 1951 AACTG CCCGA AAGGC CAGGT GTACC TGCAG TCGCG GACCC CCTGC AACCT
 2001 GACCT GCCGC TCTCT CTCTT ACCCG GATGA GGAAT GCAAT GAGGC CTGCC
 2051 TGGAG GGCTG CTTCT GCCCC CCAGG GCTCT ACATG GATGA GAGGG GGGAC
 2101 TGCGT GCCCA AGGCC CAGTG CCCCT GTTAC TATGA CGGTG AGATC TTCCA
 2151 GCCAG AAGAC ATCTT CTCAG ACCAT CACAC CATGT GCTAC TGTGA GGATG
 40 2201 GCTTC ATGCA CTGTA CCATG AGTGG AGTCC CCGGA AGCTT GCTGC CTGAC
 2251 GCTGT CCTCA GCAGT CCCCT GTCTC ATCGC AGCAA AAGGA GCCTA TCCTG
 2301 TCGGC CCCCC ATGGT CAAGC TGGTG TGTCC CGCTG ACAAC CTGCG GGCTG
 2351 AAGGG CTCGA GTGTA CCAAA ACGTG CCAGA ACTAT GACCT GGAGT GCATG
 2401 AGCAT GGGCT GTGTC TCTGG CTGCC TCTGC CCCCC GGGCA TGGTC CGGCA
 45 2451 TGAGA ACAGA TGTGT GGCCC TGGAA AGGTG TCCCT GCTTC CATCA GGGCA
 2501 AGGAG TATGC CCCTG GAGAA ACAGT GAAGA TTGGC TGCAA CACTT GTGTC
 2551 TGTCG GGACC GGAAG TGGAA CTGCA CAGAC CATGT GTGTG ATGCC ACGTG
 2601 CTCCA CGATC GGCAT GGCCC ACTAC CTCAC CTTCT ACGGG CTCAA ATACC
 2651 TGTTT CCCGG GGAGT GCCAG TACGT TCTGG TGCAG GATTA CTGCG GCAGT
 50 2701 AACCC TGGGA CCTTT CGGAT CCTAG TGGGG AATAA GGGAT GCAGC CACCC
 2751 CTCAG TGAAA TGCAA GAAAC GGGTC ACCAT CCTGG TGGAG GGAGG AGAGA
 2801 TTGAG CTGTT TGACG GGGAG GTGAA TGTGA AGAGG CCCAT GAAGG ATGAG
 2851 ACTCA CTTTG AGGTG GTGGA GTCTG GCCGG TACAT CATTCT TGCTG CTGGG

2901 CAAAG CCCTC TCCGT GGTCT GGGAC CGCCA CCTGA GCATC TCCGT GGTCC
 2951 TGAAG CAGAC ATACC AGGAG AAAGT GTGTG GCCTG TGTGG GAATT TTGAT
 3001 GGCAT CCAGA ACAAT GACCT CACCA GCAGC AACCT CCAAG TGGAG GAAGA
 3051 CCCTG TGGAC TTTGG GAACT CCTGG AAAGT GAGCT CGCAG TGTGC TGACA
 5 3101 CCAGA AAAGT GCCTC TGGAC TCATC CCCTG CCACC TGCCA TAACA ACATC
 3151 ATGAA GCAGA CGATG GTGGA TTCCT CCTGT AGAAT CCTTA CCAGT GACGT
 3201 CTTCC AGGAC TGCAA CAAGC TGGTG GACCC CGAGC CATAT CTGGA TGTCT
 3251 GCATT TACGA CACCT GCTCC TGTGA GTCCA TTGGG GACTG CGCCG CATTG
 3301 TGCGA CACCA TTGCT GCCTA TGCCC ACGTG TGTGC CCAGC ATGGC AAGGT
 10 3351 GGTGA CCTGG AGGAC GGCCA CATTG TGCCC CCAGA GCTGC GAGGA GAGGA
 3401 ATCTC CGGGA GAACG GGTAT GAGGC TGAGT GGCGC TATAA CAGCT GTGCA
 3451 CCTGC CTGTC AAGTC ACGTG TCAGC ACCCT GAGCC ACTGG CCTGC CCTGT
 3501 GCAGT GTGTG GAGGG CTGCC ATGCC CACTG CCCTC CAGGG AAAAT CCTGG
 3551 ATGAG CTTTT GCAGA CCTGC GTTGA CCCTG AAGAC TGTCC AGTGT GTGAG
 15 3601 GTGGC TGGCC GGCCT TTTGC CTCAG GAAAG AAAGT CACCT TGAAT CCCAG
 3651 TGACC CTGAG CACTG CCAGA TTTGC CACTG TGATG TTGTC AACCT CACCT
 3701 GTGAA GCCTG CCAGG AGCCG ATATC GGGCG CGCCA ACATC AGAGA GCGCC
 3751 ACCCC TGAAA GTGGT CCCGG GAGCG AGCCA GCCAC ATCTG GGTCG GAAAC
 3801 GCCAG GCACA AGTGA GTCTG CAACT CCCGA GTCCG GACCT GGCTC CGAGC
 20 3851 CTGCC ACTAG CGGCT CCGAG ACTCC GGGAA CTTCC GAGAG CGCTA CACCA
 3901 GAAAG CGGAC CCGGA ACCAG TACCG AACCT AGCGA GGGCT CTGCT CCGGG
 3951 CAGCC CAGCC GGCTC TCCTA CATCC ACGGA GGAGG GCACT TCCGA ATCCG
 4001 CCACC CCGGA GTCAG GGCCA GGATC TGAAC CCGCT ACCTC AGGCA GTGAG
 4051 ACGCC AGGAA CGAGC GAGTC CGCTA CACCG GAGAG TGGGC CAGGG AGCCC
 25 4101 TGCTG GATCT CCTAC GTCCA CTGAG GAAGG GTCAC CAGCG GGCTC GCCCA
 4151 CCAGC ACTGA AGAAG GTGCC TCGAG CGGCG GTGGA GGTTT CCGTG GCGGG
 4201 GGATC CCGTG GCGGG GGATC CCGTG GCGGG GGATC CCGTG GCGGG GGATC
 4251 CCTGG TCCCC CGGGG CAGCG GAGGC GACAA AACTC ACACA TGCCC ACCGT
 4301 GCCCA GCTCC AGAAC TCCTG GCGGG ACCGT CAGTC TTCCT CTTCC CCCCCA
 30 4351 AAACC CAAGG ACACC CTCAT GATCT CCCGG ACCCC TGAGG TCACA TGCCT
 4401 GGTGG TGGAC GTGAG CCACG AAGAC CCTGA GGTCA AGTTC AACTG GTACG
 4451 TGGAC GGCCT GGAGG TGCAT AATGC CAAGA CAAAG CCGCG GGAGG AGCAG
 4501 TACAA CAGCA CGTAC CGTGT GGTCA GCGTC CTCAC CGTCC TGCAC CAGGA
 4551 CTGGC TGAAT GGCAA GGAGT ACAAG TGCAA GGTCT CCAAC AAAGC CCTCC
 35 4601 CAGCC CCCAT CGAGA AAACC ATCTC CAAAG CCAAA GGGCA GCCCC GAGAA
 4651 CCACA GGTGT ACACC CTGCC CCCAT CCCGG GATGA GCTGA CCAAG AACCA
 4701 GGTCA GCCTG ACCTG CCTGG TCAAA GGCTT CTATC CCAGC GACAT CGCCG
 4751 TGGAG TGGGA GAGCA ATGGG CAGCC GGAGA ACAAC TACAA GACCA CGCCT
 4801 CCCGT GTTGG ACTCC GACGG CTCCT TCTTC CTCTA CAGCA AGCTC ACCGT
 40 4851 GGACA AGAGC AGGTG GCAGC AGGGG AACGT CTTCT CATGC TCCGT GATGC
 4901 ATGAG GCTCT GCACA ACCAC TACAC GCAGA AGAGC CTCTC CCTGT CTCCG
 4951 GGTAAT ATGA

VWF057 protein sequence (SEQ ID NO: 152)

45 1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFSGS DFNFTFDGSM
 51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
 101 TVTQGDQRVS MPYASKGLYL ETEAGYYKLS GEAYGFVARI DGSGNFQVLL
 151 SDRYFNKTCG LCGNFNIFAE DDFMTQEGTL TSDPYDFANS WALSSGEQWC
 50 201 ERASPPSSSC NISSGEMQKG LWEQCQLLKS TSVFARCHPL VDPEPFVALC
 251 EKTLCECAGG LECACPALLE YARTCAQEGM VLYGWDHSA CSPVCPAGME
 301 YRQCVSPCAR TCQSLHINEM CQERCVDGCS CPEGQLLDEG LCVESTTEPC
 351 VHSGKRYPPG TSLSRDCNTC ICRNSQWICS NEECPGECLV TGQSHFKSFD

401 NRYFTFSGIC QYLLARDCQD HSFSIVIETV QCADDRDAVC TRSVTVRLPG
 451 LHNSLVKLKH GAGVAMDGQD IQLPLLKGD LRIQHTVTASV RLSYGEDLQM
 501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
 551 NAWKLHGDCQ DLQKQHS DPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
 5 601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCCL
 651 NCPKGQVYLQ CGTPCNLT CR SLSYPDEECN EACLEGCFCP PGLYMDERGD
 701 CVPKAQCPCY YDGEIFQPED IFSDHHTMCY CEDGFMHCTM SGVPGSLLPD
 751 AVLSSPLSHR SKRSLSCRPP MVKLVCPADN LRAEGLECTK TCQNYDLECM
 801 SMGCVSGCLC PPGMVRHENR CVALERCPCF HQGKEYAPGE TVKIGCNTCV
 10 851 CRDRKWNCTD HVC DATCSTI GMAHYLTFDG LKYLFPGEQ YVLVQDYCGS
 901 NPGTFRILVG NKGC SHPSVK CKKRVTILVE GGEIELFDGE VNVKRP MKDE
 951 THFEVVESGR YIILLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
 1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
 1051 MKQTMVDSSC RILTSDVFQD CNKLVDP EY LDVCIYDTCS CESIGDCAAF
 15 1101 CDTIAAYAHV CAQHGKVVTW RTATLCPQSC EERNLRENGY EAEWRYNSCA
 1151 PACQVTCQHP EPLACPVCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE
 1201 VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP ISGAPTESA
 1251 TPESGPGSEP ATSGSETPGT SESATPESGP GSEPATSGSE TPGTSESATP
 1301 ESGPGTSTEP SEGSA PGSPA GSPTSTEEGT SESATPESGP GSEPATSGSE
 20 1351 TPGTSESATP ESGPGSPAGS PTSTEEGSPA GSPTSTEEGA SSGGGGSGGG
 1401 GSGGGGSGGG GSGGGGSLVP RGS GGD KTH T CPPCPAP ELL GGPSVFLFP
 1451 KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ
 1501 YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE
 1551 PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYK TTP
 25 1601 PVLDS DGSFF LYSKLTVDKS RWQQGNV FSC SVMHEALHNH YTQKSLSLSP
 1651 GK*

VWF058 nucleotide sequence (VWF034 with IHH mutation) (SEQ ID NO: 153)

30 1 ATGAT TCCTG CCAGA TTTGC CGGGG TGCTG CTTGC TCTGG CCCTC ATTTT
 51 GCCAG GGACC CTTTG TGCAG AAGGA ACTCG CGGCA GTTCA TCCAC GGCCC
 101 GATGC AGCCT TTTCG GAAGT GACTT CGTCA ACACC TTTGA TGGGA GCATG
 151 TACAG CTTTG CGGA TACTG CAGTT ACCTC CTGGC AGGGG GCTGC CAGAA
 201 ACGCT CCTTC TCGAT TATTG GGGAC TTCCA GAATG GCAAG AGAGT GAGCC
 35 251 TCTCC GTGTA TCTTG GGGAA TTTT TGACA TCCAT TTGTT TGTC A ATGGT
 301 ACCGT GACAC AGGGG GACCA AAGAG TCTCC ATGCC CTATG CCTCC AAAGG
 351 GCTGT ATCTA GAAAC TGAGG CTGGG TACTA CAAGC TGTCC GGTGA GGCCT
 401 ATGGC TTTGT GGCCA GGATC GATGG CAGCG GCAAC TTTCA AGTCC TGCTG
 451 TCAGA CAGAT ACTTC AACAA GACCT GCGGG CTGTG TGGCA ACTTT AACAT
 40 501 CTTTG CTGAA GATGA CTTTA TGACC CAAGA AGGGA CCTTG ACCTC GGACC
 551 CTTAT GACTT TGCCA ACTCA TGGGC TCTGA GCAGT GGAGA ACAGT GGTGT
 601 GAACG GGCAT CTCCT CCCAG CAGCT CATGC AACAT CTCCT CTGGG GAAAT
 651 GCAGA AGGGC CTGTG GGAGC AGTGC CAGCT TCTGA AGAGC ACCTC GGTGT
 701 TTGCC CGCTG CCACC CTCTG GTGGA CCCC AGCCT TTTGT GGCCC TGTGT
 45 751 GAGAA GACTT TGTGT GAGTG TGCTG GGGGG CTGGA GTGCG CCTGC CCTGC
 801 CCTCC TGGAG TACGC CCGGA CCTGT GCCCA GGAGG GAATG GTGCT GTACG
 851 GCTGG ACCGA CCACA GCGCG TGCA G CCCAG TGTGC CCTGC TGGTA TGGAG
 901 TATAG GCAGT GTGTG TCCCC TTGCG CCAGG ACCTG CCAGA GCCTG CACAT
 951 CAATG AAATG TGTC A GGAGC GATGC GTGGA TGGCT GCAGC TGCCC TGAGG
 50 1001 GACAG CTCCT GGATG AAGGC CTCTG CGTGG AGAGC ACCGA GTGTC CCTGC
 1051 GTGCA TTCCG GAAAG CGCTA CCCTC CCGGC ACCTC CCTCT CTCGA GACTG
 1101 CAACA CCTGC ATTTG CCGAA ACAGC CAGTG GATCT GCAGC AATGA AGAAT
 1151 GTCCA GGGGA GTGCC TTGTC ACTGG TCAAT CCCAC TTCAA GAGCT TTGAC

1201 AACAG ATACT TCACC TTCAG TGGGA TCTGC CAGTA CCTGC TGGCC CGGGA
 1251 TTGCC AGGAC CACTC CTTCT CCATT GTCAT TGAGA CTGTC CAGTG TGCTG
 1301 ATGAC CGCGA CGCTG TGTGC ACCCG CTCCG TCACC GTCCG GCTGC CTGGC
 1351 CTGCA CAACA GCCTT GTGAA ACTGA AGCAT GGGGC AGGAG TTGCC ATGGA
 5 1401 TGGCC AGGAC ATCCA GCTCC CCCTC CTGAA AGGTG ACCTC CGCAT CCAGC
 1451 ATACA GTGAC GGCCT CCGTG CGCCT CAGCT ACGGG GAGGA CCTGC AGATG
 1501 GACTG GGATG GCCGC GGGAG GCTGC TGGTG AAGCT GTCCC CCGTC TATGC
 1551 CGGGA AGACC TGC GG CCTGT GTGGG AATTA CAATG GCAAC CAGGG CGACG
 1601 ACTTC CTTAC CCCCT CTGGG CTGGC GGAGC CCCGG GTGGA GGA CT TCGGG
 10 1651 AACGC CTGGA AGCTG CACGG GGACT GCCAG GACCT GCAGA AGCAG CACAG
 1701 CGATC CCTGC GCCCT CAACC CGCGC ATGAC CAGGT TCTCC GAGGA GCGGT
 1751 GCGCG GTCCT GACGT CCCCC ACATT CGAGG CCTGC CATCG TGCCG TCAGC
 1801 CCGCT GCCCT ACCTG CGGAA CTGCC GCTAC GACGT GTGCT CCTGC TCGGA
 1851 CGGCC GCGAG TGCCT GTGCG GCGCC CTGGC CAGCT ATGCC GCGGC CTGCG
 15 1901 CGGGG AGAGG CGTGC GCGTC GCGTG GCGCG AGCCA GGCCG CTGTG AGCTG
 1951 AACTG CCCGA AAGGC CAGGT GTACC TGCAG TCGGG GACCC CCTGC AACCT
 2001 GACCT GCCGC TCTCT CTCTT ACCCG GATGA GGAAT GCAAT GAGGC CTGCC
 2051 TGGAG GGCTG CTTCT GCCCC CCAGG GCTCT ACATG GATGA GAGGG GGGAC
 2101 TGGCT GCCCA AGGCC CAGTG CCCCT GTTAC TATGA CCGTG AGATC TTCCA
 20 2151 GCCAG AAGAC ATCTT CTCAG ACCAT CACAC CATGT GCTAC TGTGA GGATG
 2201 GCTTC ATGCA CTGTA CCATG AGTGG AGTCC CCGGA AGCTT GCTGC CTGAC
 2251 GCTGT CCTCA GCAGT CCCCT GTCTC ATCGC AGCAA AAGGA GCCTA TCCTG
 2301 TCGGC CCCCC ATGGT CAAGC TGGTG TGTCC CGCTG ACAAC CTGCG GGCTG
 2351 AAGGG CTCGA GTGTA CCAAA ACGTG CCAGA ACTAT GACCT GGAGT GCATG
 25 2401 AGCAT GGGCT GTGTC TCTGG CTGCC TCTGC CCCCC GGGCA TGGTC CGGCA
 2451 TGAGA ACAGA TGTGT GGCCC TGGAA AGGTG TCCCT GCTTC CATCA GGGCA
 2501 AGGAG TATGC CCCTG GAGAA ACAGT GAAGA TTGGC TGCAA CACTT GTGTC
 2551 TGTCG GGACC GGAAG TGGAA CTGCA CAGAC CATGT GTGTG ATGCC ACGTG
 2601 CTCCA CGATC GGCAT GGCCC ACTAC CTCAC CTTTC ACGGG CTCAA ATACC
 30 2651 TGTTT CCCGG GGAGT GCCAG TACGT TCTGG TGCAG GATTA CTGCG GCAGT
 2701 AACCC TGGGA CCTTT CGGAT CCTAG TGGGG AATAA GGGAT GCAGC CACCC
 2751 CTCAG TGAAA TGCAA GAAAC GGGTC ACCAT CCTGG TGGAG GGAGG AGAGA
 2801 TTGAG CTGTT TGACG GGGAG GTGAA TGTGA AGAGG CCCAT GAAGG ATGAG
 2851 ACTCA CTTTG AGGTG GTGGA GTCTG GCCGG TACAT CATTG TGCTG CTGGG
 35 2901 CAAAG CCCTC TCCGT GGTCT GGGAC CGCCA CCTGA GCATC TCCGT GGTCC
 2951 TGAAG CAGAC ATACC AGGAG AAAGT GTGTG GCCTG TGTGG GAATT TTGAT
 3001 GGCAT CCAGA ACAAT GACCT CACCA GCAGC AACCT CCAAG TGGAG GAAGA
 3051 CCCTG TGGAC TTTGG GAACT CCTGG AAAGT GAGCT CGCAG TGTGC TGACA
 3101 CCAGA AAAGT GCCTC TGGAC TCATC CCCTG CCACC TGCCA TAACA ACATC
 40 3151 ATGAA GCAGA CGATG GTGGA TTCCT CCTGT AGAAT CCTTA CCAGT GACGT
 3201 CTTCC AGGAC TGCAA CAAGC TGGTG GACCC CGAGC CATAT CTGGA TGTCT
 3251 GCATT TACGA CACCT GCTCC TGTGA GTCCA TTGGG GACTG CGCCG CATTG
 3301 TGCGA CACCA TTGCT GCCTA TGCCC ACGTG TGTGC CCAGC ATGGC AAGGT
 3351 GGTGA CCTGG AGGAC GGCCA CATTG TGCCC CCAGA GCTGC GAGGA GAGGA
 45 3401 ATCTC CGGGA GAACG GGTAT GAGGC TGAGT GGCGC TATAA CAGCT GTGCA
 3451 CCTGC CTGTC AAGTC ACGTG TCAGC ACCCT GAGCC ACTGG CCTGC CCTGT
 3501 GCAGT GTGTG GAGGG CTGCC ATGCC CACTG CCCTC CAGGG AAAAT CCTGG
 3551 ATGAG CTTTT GCAGA CCTGC GTTGA CCCTG AAGAC TGTCC AGTGT GTGAG
 3601 GTGGC TGGCC GCGGT TTTGC CTCAG GAAAG AAAGT CACCT TGAAT CCCAG
 50 3651 TGACC CTGAG CACTG CCAGA TTTGC CACTG TGATG TTGTC AACCT CACCT
 3701 GTGAA GCCTG CCAGG AGCCG ATATC GGGTA CCTCA GAGTC TGCTA CCCCC
 3751 GAGTC AGGGC CAGGA TCAGA GCCAG CCACC TCCGG GTCTG AGACA CCCGG
 3801 GACTT CCGAG AGTGC CACCC CTGAG TCCGG ACCCG GGTCC GAGCC CGCCA

3851 CTTCC GGCTC CGAAA CTCCC GGCAC AAGCG AGAGC GCTAC CCCAG AGTCA
 3901 GGACC AGGAA CATCT ACAGA GCCCT CTGAA GGCTC CGCTC CAGGG TCCCC
 3951 AGCCG GCAGT CCCAC TAGCA CCGAG GAGGG AACCT CTGAA AGCGC CACAC
 4001 CCGAA TCAGG GCCAG GGTCT GAGCC TGCTA CCAGC GGCAG CGAGA CACCA
 5 4051 GGCAC CTCTG AGTCC GCCAC ACCAG AGTCC GGACC CGGAT CTCCC GCTGG
 4101 GAGCC CCACC TCCAC TGAGG AGGGA TCTCC TGCTG GCTCT CCAAC ATCTA
 4151 CTGAG GAAGG TACCT CAACC GAGCC ATCCG AGGGA TCAGC TCCCG GCACC
 4201 TCAGA GTCGG CAACC CCGGA GTCTG GACCC GGAAC TTCCG AAAGT GCCAC
 4251 ACCAG AGTCC GGTCC CGGGA CTTCA GAATC AGCAA CACCC GAGTC CGGCC
 10 4301 CTGGG TCTGA ACCCG CCACA AGTGG TAGTG AGACA CCAGG ATCAG AACCT
 4351 GCTAC CTCAG GGTCA GAGAC ACCCG GATCT CCGGC AGGCT CACCA ACCTC
 4401 CACTG AGGAG GGCAC CAGCA CAGAA CCAAG CGAGG GCTCC GCACC CGGAA
 4451 CAAGC ACTGA ACCCA GTGAG GGTTC AGCAC CCGGC TCTGA GCCGG CCACA
 4501 AGTGG CAGTG AGACA CCCGG CACTT CAGAG AGTGC CACCC CCGAG AGTGG
 15 4551 CCCAG GCACT AGTAC CGAGC CCTCT GAAGG CAGTG CGCCA GATTC TGGCG
 4601 GTGGA GGTTC CGGTG GCGGG GGATC CGGTG GCGGG GGATC CGGTG GCGGG
 4651 GGATC CGGTG GCGGG GGATC CCTGG TCCCC CGGGG CAGCG GAGGC GACAA
 4701 AACTC ACACA TGCCC ACCGT GCCCA GCTCC AGAAC TCCTG GCGCG ACCGT
 4751 CAGTC TTCCT CTTCC CCCC AAACC CAAGG ACACC CTCAT GGCCT CCCGG
 20 4801 ACCCC TGAGG TCACA TCGT GGTGG TGGAC GTGAG CCACG AAGAC CCTGA
 4851 GGTCA AGTTC AACTG GTACG TGGAC GCGGT GGAGG TGCAT AATGC CAAGA
 4901 CAAAG CCGCG GGAGG AGCAG TACAA CAGCA CGTAC CGTGT GGTCA GCGTC
 4951 CTCAC CGTCC TGGCC CAGGA CTGGC TGAAT GGCAA GGAGT ACAAG TGCAA
 5001 GGTCT CCAAC AAAGC CCTCC CAGCC CCCAT CGAGA AAACC ATCTC CAAAG
 25 5051 CCAAA GGGCA GCCCC GAGAA CCACA GGTGT ACACC CTGCC CCCAT CCCGC
 5101 GATGA GCTGA CCAAG AACCA GGTC A CCTG ACCTG CCTGG TCAAA GGCTT
 5151 CTATC CCAGC GACAT CGCCG TGGAG TGGGA GAGCA ATGGG CAGCC GGAGA
 5201 ACAAC TACAA GACCA CGCCT CCCGT GTTGG ACTCC GACGG CTCCT TCTTC
 5251 CTCTA CAGCA AGCTC ACCGT GGACA AGAGC AGGTG GCAGC AGGGG AACGT
 30 5301 CTTCT CATGC TCCGT GATGC ATGAG GCTCT GCACA ACGCC TACAC GCAGA
 5351 AGAGC CTCTC CCTGT CTCCG GTTAA ATGA

VWF058 protein sequence (VWF034 with IHH mutation) (SEQ ID NO: 154)

35 1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFNVTFDGSM
 51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
 101 TVTQGDQRVS MPYASKGLYL ETEAGYYKLS GEAYGFVARI DGSGNFQVLL
 151 SDRYFNKTCG LCGNFNIFAE DDFMTQEGTL TSDPYDFANS WALSSGEQWC
 40 201 ERASPPSSSC NISSGEMQKG LWEQCQLLKS TSVFARCHPL VDPEPFVALC
 251 ECTLCECAGG LECACPALLE YARTCAQEGM VLYGWTDHSA CSPVCPAGME
 301 YRQCVSPCAR TCQSLHINEM CQERCVDGCS CPEGQLLDEG LCVESTECPC
 351 VHSGKRYPPG TSLSRDCNTC ICRNSQWICS NEECPGECLV TGQSHFKSFD
 401 NRYFTFSGIC QYLLARDCQD HSFSIVIETV QCADDRDAVC TRSVTVRLPG
 45 451 LHNSLVKLKH GAGVAMDGQD IQLPLLKGD LRIQHTVTASV RLSYGEDLQM
 501 DWDGRGRLLV KLSVPYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
 551 NAWKLHGDCQ DLQKQHS DPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
 601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCCL
 651 NCPKGQVYLQ CGTPCNLT CR SLSYPDEECN EACLEGCFCP PGLYMDERGD
 50 701 CVPKAQCPCY YDGEIFQPED IFSDHHTMCY CEDGFMHCTM SGVPGSLLPD
 751 AVLSSPLSHR SKRSLSCRPP MVKLVCPADN LRAEGLECTK TCQNYDLECM
 801 SMGCVSGCLC PPGMVRHENR CVALERCPCF HQGKEYAPGE TVKIGCNTCV
 851 CRDRKWNCTD HVCDATCSTI GMAHYLTFDG LKYLFPGEQ YVLVQDYCGS

901 NPGTFRILVG NKGCSPSVK CKKRVTLVE GGEIELFDGE VNVKRPMKDE
 951 THFEVVESGR YIILLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
 1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
 1051 MKQTMVDSSC RILTSDVFQD CNKLDPEPY LDVCIYDTCESIGDCAAF
 5 1101 CDTIAAYAHV CAQHGKVVTW RTATLCPQSC EERNLRENGY EAEWRYNSCA
 1151 PACQVTCQHP EPLACPVCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE
 1201 VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP ISGTSESATP
 1251 ESGPGSEPAT SGSETPGTSE SATPESGPGS EPATSGSETP GTSESATPES
 1301 GPGTSTEPSE GSAPGSPAGS PTSTEEGTSE SATPESGPGS EPATSGSETP
 10 1351 GTSESATPES GPGSPAGSPT STEEGSPAGS PTSTEEGTST EPSEGSAPGT
 1401 SESATPESGP GTSESATPES GPGTSESATP ESGPGSEPAT SGSETPGSEP
 1451 ATSGSETPGS PAGSPTSTEE GTSTEPSEGS APGTSTEPSE GSAPGSEPAT
 1501 SGSETPGTSE SATPESGPGT STEPSEGSAP DSGGGGSGGG GSGGGGSGGG
 1551 GSGGGGSLVP RGSAGDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMASR
 15 1601 TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV
 1651 LTVLAQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR
 1701 DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSGDSFF
 1751 LYSKLTVDKS RWQQGNVFSC SVMHEALHNA YTQKSLSLSP GK*

20

FVIII 169 nucleotide sequence (SEQ ID NO: 155)

1 ATGCA AATAG AGCTC TCCAC CTGCT TCTTT CTGTG CCTTT TGCGA TTCTG
 51 CTTTA GTGCC ACCAG AAGAT ACTAC CTGGG TGCAG TGGAA CTGTC ATGGG
 25 101 ACTAT ATGCA AAGTG ATCTC GGTGA GCTGC CTGTG GACGC AAGAT TTCCT
 151 CCTAG AGTGC CAAAA TCTTT TCCAT TCAAC ACCTC AGTCG TGTAC AAAAA
 201 GACTC TGTTT GTAGA ATTCA CGGAT CACCT TTTCA ACATC GCTAA GCCAA
 251 GGCCA CCCTG GATGG GTCTG CTAGG TCCTA CCATC CAGGC TGAGG TTTAT
 301 GATAC AGTGG TCATT AACT TAAGA ACATG GCTTC CCATC CTGTC AGTCT
 30 351 TCATG CTGTT GGTGT ATCCT ACTGG AAAGC TTCTG AGGGA GCTGA ATATG
 401 ATGAT CAGAC CAGTC AAAGG GAGAA AGAAG ATGAT AAAGT CTTC CTGGT
 451 GGAAG CCATA CATAT GTCTG GCAGG TCCTG AAAGA GAATG GTCCA ATGGC
 501 CTCTG ACCCA CTGTG CCTTA CCTAC TCATA TCTTT CTCAT GTGGA CCTGG
 551 TAAAG GACTT GAATT CAGGC CTCAT TGGAG CCCTA CTAGT ATGTA GAGAA
 35 601 GGGAG TCTGG CCAAG GAAAA GACAC AGACC TTGCA CAAAT TTATA CTACT
 651 TTTTG CTGTA TTTGA TGAAG GAAAA AGTTG GCACT CAGAA AAAAA GAACT
 701 CCTTG ATGCA GGATA GGGAT GCTGC ATCTG CTCGG GCCTG GCCTA AAATG
 751 CACAC AGTCA ATGGT TATGT AAACA GGTCT CTGCC AGGTC TGATT GGATG
 801 CCACA GGAAA TCAGT CTATT GGCAT GTGAT TGGAA TGGGC ACCAC TCCTG
 40 851 AAGTG CACTC AATAT TCCTC GAAGG TCACA CATTT CTTGT GAGGA ACCAT
 901 CGCCA GGCTA GCTTG GAAAT CTCGC CAATA ACTTT CCTTA CTGCT CAAAC
 951 ACTCT TGATG GACCT TGGAC AGTTT CTACT GTTTT GTCAT ATCTC TTCCC
 1001 ACCAA CATGA TGGCA TGGAA GCTTA TGTCA AAGTA GACAG CTGTC CAGAG
 1051 GAACC CCAAC TACGA ATGAA AAATA ATGAA GAAGC GGAAG ACTAT GATGA
 45 1101 TGATC TTAAT GATTG TGAAG TGGAT GTGGT CAGGT TTGAT GATGA CAACT
 1151 CTCCT TCCTT TATCC AAATT CGCTC AGTTG CCAAG AAGCA TCCTA AAAT
 1201 TGGGT ACATT ACATT GCTGC TGAAG AGGAG GACTG GGACT ATGCT CCCTT
 1251 AGTCC TCGCC CCCGA TGACA GAAGT TATAA AAGTC AATAT TTGAA CAATG
 1301 GCCCT CAGCG GATTG GTAGG AAGTA CAAAA AAGTC CGATT TATGG CATAAC
 50 1351 ACAGA TGAAA CCTTT AAGAC TCGTG AAGCT ATTCA GCATG AATCA GGAAT
 1401 CTTGG GACCT TTAAT TTATG GGGAA GTTGG AGACA CACTG TTGAT TATAT
 1451 TTAAG AATCA AGCAA GCAGA CCATA TAACA TCTAC CCTCA CGGAA TCACT
 1501 GATGT CCGTC CTTTG TATTC AAGGA GATTA CCAAA AGGTG TAAAA CATTT

1551 GAAGG ATTTT CCAAT TCTGC CAGGA GAAAT ATTCA AATAT AAATG GACAG
 1601 TGACT GTAGA AGATG GGCCA ACTAA ATCAG ATCCT CGGTG CCTGA CCCGC
 1651 TATTA CTCTA GTTTC GTTAA TATGG AGAGA GATCT AGCTT CAGGA CTCAT
 1701 TGGCC CTCTC CTCAT CTGCT ACAAA GAATC TGTAAG ATCAA AGAGG AAACC
 5 1751 AGATA ATGTC AGACA AGAGG AATGT CATCC TGTTT TCTGT ATTTG ATGAG
 1801 AACCG AAGCT GGTAC CTCAC AGAGA ATATA CAACG CTTTC TCCCC AATCC
 1851 AGCTG GAGTG CAGCT TGAGG ATCCA GAGTT CCAAG CCTCC AACAT CATGC
 1901 ACAGC ATCAA TGGCT ATGTT TTTGA TAGTT TGCAG TTGTC AGTTT GTTTG
 1951 CATGA GGTGG CATACT TGGTA CATTG TAAGC ATTGG AGCAC AGACT GACTT
 10 2001 CCTTT CTGTC TTCTT CTCTG GATAT ACCTT CAAAC ACAA ATGGT CTATG
 2051 AAGAC AACTT CACCC TATTC CCATT CTCAG GAGAA ACTGT CTTCA TGTCC
 2101 ATGGA AAACC CAGGT CTATG GATTC TGGGG TGCCA CAACT CAGAC TTTCG
 2151 GAACA GAGGC ATGAC CGCCT TACTG AAGGT TTCTA GTTGT GACAA GAACA
 2201 CTGGT GATTA TTACG AGGAC AGTTA TGAAG ATATT TCAGC ATACT TGCTG
 15 2251 AGTAA AAACA ATGCC ATTGA ACCAA GAAGC TTCTC TCAAA ACGGC GCGCC
 2301 AGGTA CCTCA GAGTC TGCTA CCCCC GAGTC AGGGC CAGGA TCAGA GCCAG
 2351 CCACC TCCGG GTCTG AGACA CCGGG GACTT CCGAG AGTGC CACCC CTGAG
 2401 TCCGG ACCCG GGTCC GAGCC CGCCA CTTCC GGCTC CGAAA CTCCC GGCAC
 2451 AAGCG AGAGC GCTAC CCCAG AGTCA GGACC AGGAA CATCT ACAGA GCCCT
 20 2501 CTGAA GGCTC CGCTC CAGGG TCCCC AGCCG GCAGT CCCAC TAGCA CCGAG
 2551 GAGGG AACCT CTGAA AGCGC CACAC CCGAA TCAGG GCCAG GGTCT GAGCC
 2601 TGCTA CCAGC GGCAG CGAGA CACCA GGCAC CTCTG AGTCC GCCAC ACCAG
 2651 AGTCC GGACC CGGAT CTCCC GCTGG GAGCC CCACC TCCAC TGAGG AGGGA
 2701 TCTCC TGCTG GCTCT CCAAC ATCTA CTGAG GAAGG TACCT CAACC GAGCC
 25 2751 ATCCG AGGGA TCAGC TCCCC GCACC TCAGA GTCGG CAACC CCGGA GTCTG
 2801 GACCC GGAAC TTCCG AAAGT GCCAC ACCAG AGTCC GGTCC CGGGA CTTC
 2851 GAATC AGCAA CACCC GAGTC CGGCC CTGGG TCTGA ACCCG CCACA AGTGG
 2901 TAGTG AGACA CCAGG ATCAG AACCT GCTAC CTCAG GTTCA GAGAC ACCCG
 2951 GATCT CCGGC AGGCT CACCA ACCTC CACTG AGGAG GGCAC CAGCA CAGAA
 30 3001 CCAAG CGAGG GCTCC GCACC CGGAA CAAGC ACTGA ACCCA GTGAG GGTTC
 3051 AGCAC CCGGC TCTGA GCCGG CCACA AGTGG CAGTG AGACA CCGG CACTT
 3101 CAGAG AGTGC CACCC CCGAG AGTGG CCCAG GCACT AGTAC CGAGC CCTCT
 3151 GAAGG CAGTG CGCCA GCCTC GAGCC CACCA GTCTT GAAAC GCCAT CAAGC
 3201 TGAAA TAACT CGTAC TACTC TTCAG TCAGA TCAAG AGGAA ATCGA TTATG
 35 3251 ATGAT ACCAT ATCAG TTGAA ATGAA GAAGG AAGAT TTTGA CATTG ATGAT
 3301 GAGGA TGAAA ATCAG AGCCC CCGCA GCTTT CAAAA GAAAA CACGA CACTA
 3351 TTTTA TTGCT GCAGT GGAGA GGCTC TGGGA TTATG GGATG AGTAG CTCCC
 3401 CACAT GTTCT AAGAA ACAGG GCTCA GAGTG GCAGT GTCCC TCAGT TCAAG
 3451 AAAGT TGTTT TCCAG GAATT TACTG ATGGC TCCTT TACTC AGCCC TTATA
 40 3501 CCGTG GAGAA CTAAG TGAAC ATTTG GGACT CCTGG GGCCA TATAT AAGAG
 3551 CAGAA GTTGA AGATA ATATC ATGGT AACTT TCAGA AATCA GGCCT CTCGT
 3601 CCCTA TTCCT TCTAT TCTAG CCTTA TTTCT TATGA GGAAG ATCAG AGGCA
 3651 AGGAG CAGAA CCTAG AAAAA ACTTT GTCAA GCCTA ATGAA ACCAA AACTT
 3701 ACTTT TGGAAG AGTGC AACAT CATAT GGCAC CCACT AAAGA TGAGT TTGAC
 45 3751 TGCAA AGCCT GGGCT TATTT CTCTG ATGTT GACCT GGAAA AAGAT GTGCA
 3801 CTCAG GCCTG ATTGG ACCCC TTCTG GTCTG CCACA CTAAC AACTT GAACC
 3851 CTGCT CATGG GAGAC AAGTG ACAGT ACAGG AATTT GCTCT GTTTT TCACC
 3901 ATCTT TGATG AGACC AAAAG CTGGT ACTTC ACTGA AAATA TGGAA AGAAA
 3951 CTGCA GGGCT CCCTG CAATA TCCAG ATGGA AGATC CCACT TTAA AGAGA
 50 4001 ATTAT CGCTT CCATG CAATC AATGG CTACA TAATG GATAC ACTAC CTGGC
 4051 TTAGT AATGG CTCAG GATCA AAGGA TTCGA TGGTA TCTGC TCAGC ATGGG
 4101 CAGCA ATGAA AACAT CCATT CTATT CATTT CAGTG GACAT GTGTT CACTG
 4151 TACGA AAAAA AGAGG AGTAT AAAAT GGCAC TGTAC AATCT CTATC CAGGT

4201 GTTTT TGAGA CAGTG GAAAT GTTAC CATCC AAAGC TGGAA TTTGG CGGGT
 4251 GGAAT GCCTT ATTGG CGAGC ATCTA CATGC TGGGA TGAGC AACTT TTTTC
 4301 TGGTG TACAG CAATA AGTGT CAGAC TCCCC TGGGA ATGGC TTCTG GACAC
 4351 ATTAG AGATT TTCAG ATTAC AGCTT CAGGA CAATA TGGAC AGTGG GCCCC
 5 4401 AAAGC TGGCC AGACT TCATT ATTCC GGATC AATCA ATGCC TGGAG CACCA
 4451 AGGAG CCCTT TTCTT GGATC AAGGT GGATC TGTG GCACC AATGA TTATT
 4501 CACGG CATCA AGACC CAGGG TGCCC GTCAG AAGTT CTCCA GCCTC TACAT
 4551 CTCTC AGTTT ATCAT CATGT ATAGT CTTGA TGGGA AGAAG TGGCA GACTT
 4601 ATCGA GGAAA TTCCA CTGGA ACCTT AATGG TCTTC TTTGG CAATG TGGAT
 10 4651 TCATC TGGGA TAAAA CACAA TATTT TTAAC CCTCC AATTA TTGT CGATA
 4701 CATCC GTTTG CACCC AACTC ATTAT AGCAT TCGCA GCACT CTTCG CATGG
 4751 AGTTG ATGGG CTGTG ATTTA AATAG TTGCA GCATG CCATT GGGAA TGGAG
 4801 AGTAA AGCAA TATCA GATGC ACAGA TTAAT GCTTC ATCCT ACTTT ACCAA
 4851 TATGT TTGCC ACCTG GTCTC CTTCA AAAGC TCGAC TTCAC CTCCA AGGGA
 15 4901 GGAGT AATGC CTGGA GACCT CAGGT GAATA ATCCA AAAGA GTGGC TGCAA
 4951 GTGGA CTTCC AGAAG ACAAT GAAAG TCACA GGAGT AACTA CTCAG GGAGT
 5001 AAAAT CTCTG CTTAC CAGCA TGTAT GTGAA GGAGT TCCTC ATCTC CAGCA
 5051 GTCAA GATGG CCATC AGTGG ACTCT CTTTT TTCAG AATGG CAAAG TAAAG
 5101 GTTTT TCAGG GAAAT CAAGA CTCCT TCACA CCTGT GGTGA ACTCT CTAGA
 20 5151 CCCAC CGTTA CTGAC TCGCT ACCTT CGAAT TCACC CCCAG AGTTG GGTGC
 5201 ACCAG ATTGC CCTGA GGATG GAGGT TCTGG GCTGC GAGGC ACAGG ACCTC
 5251 TACGA CAAAA CTCAC ACATG CCCAC CGTGC CCAGC TCCAG AACTC CTGGG
 5301 CGGAC CGTCA GTCTT CCTCT TCCCC CCAAA ACCCA AGGAC ACCCT CATGA
 5351 TCTCC CGGAC CCCTG AGGTC ACATG CGTGG TGGTG GACGT GAGCC ACGAA
 25 5401 GACCC TGAGG TCAAG TTCAA CTGGT ACGTG GACGG CGTGG AGGTG CATAA
 5451 TGCCA AGACA AAGCC GCGGG AGGAG CAGTA CAACA GCACG TACCG TGTGG
 5501 TCAGC GTCCT CACCG TCCTG CACCA GGAAT GGCTG AATGG CAAGG AGTAC
 5551 AAGTG CAAGG TCTCC AACA AGCCC TCCA GCCCC CATCG AGAAA ACCAT
 5601 CTCCA AAGCC AAAGG GCAGC CCCGA GAACC ACAGG TGTAC ACCCT GCCCC
 30 5651 CATCC CGGGA TGAGC TGACC AAGAA CCAGG TCAGC CTGAC CTGCC TGGTC
 5701 AAAGG CTTCT ATCCC AGCGA CATCG CCGTG GAGTG GGAGA GCAAT GGGCA
 5751 GCCGG AGAAC AACTA CAAGA CCACG CCTCC CGTGT TGGAC TCCGA CGGCT
 5801 CCTTC TTCCT CTACA GCAAG CTCAC CGTGG ACAAG AGCAG GTGGC AGCAG
 5851 GGGAA CGTCT TCTCA TGCTC GTGCA TGCAT GAGGC TCTGC ACAAC CACTA
 35 5901 CACGC AGAAG AGCCT CTCCC TGTCT CCGGG TAAAT GA

FVIII 169 protein sequence(SEQ ID NO: 70)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAWE LSWDYMQSDL GELPVDARFP
 40 51 PRVPKSFNPN TSVVYKKTFL VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 101 DTVVITLKNM ASHPVSLHAV GVSYWKAEG AEYDDQTSQR EKEDDKVFPQ
 151 GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 201 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 251 HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
 45 301 RQASLEISPI TFLTAQTLLM DLGQFLFCH ISSHQHDGME AYVKVDSCPE
 351 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 401 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 451 TDETFKTREA IQHESGILGP LLYGEVGDIT LIIFKNQASR PYNIPHGIT
 501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 50 551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 601 NRSWYL TENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVEYEDTLTLF PFSGETVFMS
 701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYED SYEDISAYLL

751 SKNNAIEPRS FSQNGAPGTS ESATPESGPG SEPATSGSET PGTSESATPE
 801 SGPGSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG SPAGSPTSTE
 851 EGTSESATPE SGPGSEPATS GSETPGTSES ATPESGPGSP AGSPTSTEEG
 901 SPAGSPTSTE EGTSTEPSEG SAPGTSESAT PESGPGTSES ATPESGPGTS
 5 951 ESATPESGPG SEPATSGSET PGSEPATSGS ETPGSPAGSP TSTEEGTSTE
 1001 PSEGSAPGTS TEPSEGSAPG SEPATSGSET PGTSESATPE SGPGTSTEPS
 1051 EGSAPASSPP VLKRHQAEIT RTTLQSDQEE IDYDDTISVE MKKEDFDIYD
 1101 EDENQSPRSF QKKTRHYFIA AVERLWDYGM SSSPHVLRNR AQSGSVPQFK
 1151 KVVVFQFTDG SFTQPLYRGE LNEHLGLLGP YIRAEVEDNI MVTFRNQASR
 10 1201 PYSFYSSLIS YEEDQRQGA PRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
 1251 CKAWAYFSDV DLEKDVHSG LIGPLL VCHTN TLNPAHGRQV TVQEFALFFT
 1301 IFDETKSWYF TENMERN CRA PCNIQMEDPT FKENYRFHAI NGYIMDTLPG
 1351 LVMAQDQIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
 1401 VFETVEMLP KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPLGMASGH
 15 1451 IRDFQITASG QYGQWAPKLA RLHYSGSINA WSTKEPFSWI KVDLLAPMII
 1501 HGIKTQGARQ KFSSLYISQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
 1551 SSGIKHNIFN PPIARYIRL HPTHYSIRST LRMELMGCDL NSCSMPLGME
 1601 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ
 1651 VDFQKTMKVT GVTQGVKSL LTSMYVKEFL ISSQDGHQW TLFFQNGKVK
 20 1701 VFQGNQDSFT PVVNSLDPL LTRYLRIHPQ SWVHQIALRM EVLGCEAQLD
 1751 YDKTHTCPPC PAPELLGPGS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
 1801 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
 1851 KCKVSNKALP APIEKTISKA KGQPREPVY TLPPSRDELT KNQVSLTCLV
 1901 KGFYPSDIAV EWESNGQPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
 25 1951 GNVFSCSVMH EALHNHYTQK SLSLSPGK*

FVIII 263 nucleotide sequence (IHH triple mutant) (SEQ ID NO: 156)

1 ATGCA AATAG AGCTC TCCAC CTGCT TCTTT CTGTG CCTTT TGCGA TTCTG
 30 51 CTTTA GTGCC ACCAG AAGAT ACTAC CTGGG TGCAG TGGAA CTGTC ATGGG
 101 ACTAT ATGCA AGGCG CGCCA ACATC AGAGA GCGCC ACCCC TGAAA GTGGT
 151 CCCGG GAGCG AGCCA GCCAC ATCTG GGTCG GAAAC GCCAG GCACA AGTGA
 201 GTCTG CAACT CCCGA GTCCG GACCT GGCTC CGAGC CTGCC ACTAG CGGT
 251 CCGAG ACTCC GGGAA CTTCG GAGAG CGCTA CACCA GAAAG CGGAC CCGGA
 35 301 ACCAG TACCG AACCT AGCGA GGGCT CTGCT CCGGG CAGCC CAGCC GGCTC
 351 TCCTA CATCC ACGGA GGAGG GCACT TCCGA ATCCG CCACC CCGGA GTCAG
 401 GGCCA GGATC TGAAC CCGCT ACCTC AGGCA GTGAG ACGCC AGGAA CGAGC
 451 GAGTC CGCTA CACCG GAGAG TGGGC CAGGG AGCCC TGCTG GATCT CCTAC
 501 GTCCA CTGAG GAAGG GTCAC CAGCG GGCTC GCCCA CCAGC ACTGA AGAAG
 40 551 GTGCC TCGAG CAGTG ATCTC GGTGA GCTGC CTGTG GACGC AAGAT TTCCT
 601 CCTAG AGTGC CAAAA TCTTT TCCAT TCAAC ACCTC AGTCG TGTAC AAAAA
 651 GACTC TGTTT GTAGA ATTCA CGGAT CACCT TTTCA ACATC GCTAA GCCAA
 701 GGCCA CCCTG GATGG GTCTG CTAGG TCCTA CCATC CAGGC TGAGG TTTAT
 751 GATAC AGTGG TCATT AACT TAAGA ACATG GCTTC CCATC CTGTC AGTCT
 45 801 TCATG CTGTT GGTGT ATCCT ACTGG AAAGC TTCTG AGGGA GCTGA ATATG
 851 ATGAT CAGAC CAGTC AAAGG GAGAA AGAAG ATGAT AAAGT CTTC CTGGT
 901 GGAAG CCATA CATAT GTCTG GCAGG TCCTG AAAGA GAATG GTCCA ATGGC
 951 CTCTG ACCCA CTGTG CCTTA CCTAC TCATA TCTTT CTCAT GTGGA CCTGG
 1001 TAAAA GACTT GAATT CAGGC CTCAT TGGAG CCCTA CTAGT ATGTA GAGAA
 50 1051 GGGAG TCTGG CCAAG GAAAA GACAC AGACC TTGCA CAAAT TTATA CTACT
 1101 TTTTG CTGTA TTTGA TGAAG GGAAG AGTTG GCACT CAGAA ACAA GAACT
 1151 CCTTG ATGCA GGATA GGGAT GCTGC ATCTG CTCGG GCCTG GCCTA AAATG
 1201 CACAC AGTCA ATGGT TATGT AAACA GGTCT CTGCC AGGTC TGATT GGATG

1251 CCACA GGAAA TCAGT CTATT GGCAT GTGAT TGGAA TGGGC ACCAC TCCTG
 1301 AAGTG CACTC AATAT TCCTC GAAGG TCACA CATTT CTTGT GAGGA ACCAT
 1351 CGCCA GGCTA GCTTG GAAAT CTCGC CAATA ACTTT CCTTA CTGCT CAAAC
 1401 ACTCT TGATG GACCT TGGAC AGTTT CTACT GTTTT GTCAT ATCTC TTCCC
 5 1451 ACCAA CATGA TGGCA TGGAA GCTTA TGTCA AAGTA GACAG CTGTC CAGAG
 1501 GAACC CCAAC TACGA ATGAA AAATA ATGAA GAAGC GGAAG ACTAT GATGA
 1551 TGATC TTACT GATTG TGAAG TGGAT GTGGT CAGGT TTGAT GATGA CAACT
 1601 CTCCT TCCTT TATCC AAATT CGCTC AGTTG CCAAG AAGCA TCCTA AAAT
 1651 TGGGT ACATT ACATT GCTGC TGAAG AGGAG GACTG GACT ATGCT CCCTT
 10 1701 AGTCC TCGCC CCCGA TGACA GAAGT TATAA AAGTC AATAT TTGAA CAATG
 1751 GCCCT CAGCG GATTG GTAGG AAGTA CAAAA AAGTC CGATT TATGG CATAAC
 1801 ACAGA TGAAG CCTTT AAGAC TCGTG AAGCT ATTCA GCATG AATCA GGAAT
 1851 CTTGG GACCT TTACT TTATG GGGAA GTTGG AGACA CACTG TTGAT TATAT
 1901 TTAAG AATCA AGCAA GCAGA CCATA TAACA TCTAC CCTCA CGGAA TCACT
 15 1951 GATGT CCGTC CTTTG TATTC AAGGA GATTA CCAAA AGGTG TAAAA CATTT
 2001 GAAGG ATTTT CCAAT TCTGC CAGGA GAAAT ATTCA AATAT AAATG GACAG
 2051 TGACT GTAGA AGATG GGCCA ACTAA ATCAG ATCCT CGGTG CCTGA CCCGC
 2101 TATTA CTCTA GTTTC GTTAA TATGG AGAGA GATCT AGCTT CAGGA CTCAT
 2151 TGGCC CTCTC CTCAT CTGCT ACAA GAATC TGTAG ATCAA AGAGG AAACC
 20 2201 AGATA ATGTC AGACA AGAGG AATGT CATCC TGTTT TCTGT ATTTG ATGAG
 2251 AACCG AAGCT GGTAC CTCAC AGAGA ATATA CAACG CTTTC TCCCC AATCC
 2301 AGCTG GAGTG CAGCT TGAGG ATCCA GAGTT CCAAG CCTCC AACAT CATGC
 2351 ACAGC ATCAA TGGCT ATGTT TTTGA TAGTT TGCAG TTGTC AGTTT GTTTG
 2401 CATGA GGTGG CATAAC TGGTA CATTG TAAGC ATTGG AGCAC AGACT GACTT
 25 2451 CCTTT CTGTC TTCTT CTCTG GATAT ACCTT CAAAC ACAA ATGGT CTATG
 2501 AAGAC AACT CACCC TATTC CCATT CTCAG GAGAA ACTGT CTTCA TGTCG
 2551 ATGGA AAACC CAGGT CTATG GATTG TGGGG TGCCA CAACT CAGAC TTTCG
 2601 GAACA GAGGC ATGAC CGCCT TACTG AAGGT TTCTA GTTGT GACAA GAACA
 2651 CTGGT GATTA TTACG AGGAC AGTTA TGAAG ATATT TCAGC ATACT TGCTG
 30 2701 AGTAA AAACA ATGCC ATTGA ACCAA GAAGC TTCTC TCAA ACGGC GCGCC
 2751 AGGTA CCTCA GAGTC TGCTA CCCCC GAGTC AGGGC CAGGA TCAGA GCCAG
 2801 CCACC TCCGG GTCTG AGACA CCGG GACTT CCGAG AGTGC CACCC CTGAG
 2851 TCCGG ACCCG GGTCC GAGCC CGCCA CTTCC GGCTC CGAAA CTCCC GGCAC
 2901 AAGCG AGAGC GGTAC CCCAG AGTCA GGACC AGGAA CATCT ACAGA GCCCT
 35 2951 CTGAA GGCTC CGCTC CAGGG TCCCC AGCCG GCAGT CCCAC TAGCA CCGAG
 3001 GAGGG AACCT CTGAA AGCGC CACAC CCGAA TCAGG GCCAG GGTCT GAGCC
 3051 TGCTA CCAGC GGCAG CGAGA CACCA GGCAC CTCTG AGTCC GCCAC ACCAG
 3101 AGTCC GGACC CGGAT TCCCC GCTGG GAGCC CCACC TCCAC TGAGG AGGGA
 3151 TCTCC TGCTG GCTCT CCAAC ATCTA CTGAG GAAGG TACCT CAACC GAGCC
 40 3201 ATCCG AGGGA TCAGC TCCCG GCACC TCAGA GTCGG CAACC CCGGA GTCTG
 3251 GACCC GGAAC TTCCG AAAGT GCCAC ACCAG AGTCC GGTCC CGGGA CTTCA
 3301 GAATC AGCAA CACCC GAGTC CGGCC CTGGG TCTGA ACCCG CCACA AGTGG
 3351 TAGTG AGACA CCAGG ATCAG AACCT GCTAC CTCAG GGTCA GAGAC ACCCG
 3401 GATCT CCGGC AGGCT CACCA ACCTC CACTG AGGAG GGCAC CAGCA CAGAA
 45 3451 CCAAG CGAGG GCTCC GCACC CGGAA CAAGC ACTGA ACCCA GTGAG GGTTC
 3501 AGCAC CCGGC TCTGA GCCGG CCACA AGTGG CAGTG AGACA CCGG CACTT
 3551 CAGAG AGTGC CACCC CCGAG AGTGG CCCAG GCACT AGTAC CGAGC CCTCT
 3601 GAAGG CAGTG CGCCA GCCTC GAGCC CACCA GTCTT GAAAC GCCAT CAAGC
 3651 TGAAG TAACT CGTAC TACTC TTCAG TCAGA TCAAG AGGAA ATCGA TTATG
 50 3701 ATGAT ACCAT ATCAG TTGAA ATGAA GAAGG AAGAT TTTGA CATTT ATGAT
 3751 GAGGA TGAAG ATCAG AGCCC CCGCA GCTTT CAAAA GAAAA CACGA CACTA
 3801 TTTTA TTGCT GCAGT GGAGA GGCTC TGGGA TTATG GGATG AGTAG CTCCC
 3851 CACAT GTTCT AAGAA ACAGG GCTCA GAGTG GCAGT GTCCC TCAGT TCAAG

3901 AAAGT TGTTT TCCAG GAATT TACTG ATGGC TCCTT TACTC AGCCC TTATA
 3951 CCGTG GAGAA CTAAG TGAAC ATTTG GGAAT CCTGG GGCCA TATAT AAGAG
 4001 CAGAA GTTGA AGATA ATATC ATGGT AACTT TCAGA AATCA GGCCT CTCGT
 4051 CCCTA TTCCT TCTAT TCTAG CCTTA TTTCT TATGA GGAAG ATCAG AGGCA
 5 4101 AGGAG CAGAA CCTAG AAAAA ACTTT GTCAA GCCTA ATGAA ACCAA AACTT
 4151 ACTTT TGGAA AGTGC AACAT CATAT GGCAC CCACT AAAGA TGAGT TTGAC
 4201 TGCAA AGCCT GGGCT TATTT CTCTG ATGTT GACCT GGAAG AAGAT GTGCA
 4251 CTCAG GCCTG ATTGG ACCCC TTCTG GTCTG CCACA CTAAC AACTT GAACC
 4301 CTGCT CATGG GAGAC AAGTG ACAGT ACAGG AATTT GCTCT GTTTT TCACC
 10 4351 ATCTT TGATG AGACC AAAAG CTGGT ACTTC ACTGA AAATA TGGAA AGAAA
 4401 CTGCA GGGCT CCCTG CAATA TCCAG ATGGA AGATC CCACT TTAA AGAGA
 4451 ATTAT CGCTT CCATG CAATC AATGG CTACA TAATG GATAC ACTAC CTGGC
 4501 TTAGT AATGG CTCAG GATCA AAGGA TTCGA TGGTA TCTGC TCAGC ATGGG
 4551 CAGCA ATGAA AACAT CCATT CTATT CATT T CAGTG GACAT GTGTT CACTG
 15 4601 TACGA AAAAA AGAGG AGTAT AAAAT GGCAC TGTAC AATCT CTATC CAGGT
 4651 GTTTT TGAGA CAGTG GAAAT GTTAC CATCC AAAGC TGGAA TTTGG CGGGT
 4701 GGAAT GCCTT ATTGG CGAGC ATCTA CATGC TGGGA TGAGC AACTT TTTTC
 4751 TGGTG TACAG CAATA AGTGT CAGAC TCCCC TGGGA ATGGC TTCTG GACAC
 4801 ATTAG AGATT TTCAG ATTAC AGCTT CAGGA CAATA TGGAC AGTGG GCCCC
 20 4851 AAAGC TGGCC AGACT TCATT ATTCC GGATC AATCA ATGCC TGGAG CACCA
 4901 AGGAG CCCTT TTCTT GGATC AAGGT GGATC TGTG GCACC AATGA TTATT
 4951 CACGG CATCA AGACC CAGGG TGCCC GTCAG AAGTT CTCCA GCCTC TACAT
 5001 CTCTC AGTTT ATCAT CATGT ATAGT CTTGA TGGGA AGAAG TGGCA GACTT
 5051 ATCGA GGAAG TTCCA CTGGA ACCTT AATGG TCTTC TTTGG CAATG TGGAT
 25 5101 TCATC TGGGA TAAAA CACAA TATTT TTAAC CCTCC AATTA TTGCT CGATA
 5151 CATCC GTTTG CACCC AACTC ATTAT AGCAT TCGCA GCACT CTTCC CATGG
 5201 AGTTG ATGGG CTGTG ATTTA AATAG TTGCA GCATG CCATT GGGAA TGGAG
 5251 AGTAA AGCAA TATCA GATGC ACAGA TTAAT GCTTC ATCCT ACTTT ACCAA
 5301 TATGT TTGCC ACCTG GTCTC CTTCA AAAGC TCGAC TTCAC CTCCA AGGGA
 30 5351 GGAGT AATGC CTGGA GACCT CAGGT GAATA ATCCA AAAGA GTGGC TGCAA
 5401 GTGGA CTTCC AGAAG ACAAT GAAAG TCACA GGAGT AACTA CTCAG GGAGT
 5451 AAAAT CTCTG CTTAC CAGCA TGTAT GTGAA GGAGT TCCTC ATCTC CAGCA
 5501 GTCAA GATGG CCATC AGTGG ACTCT CTTTT TTCAG AATGG CAAAG TAAAG
 5551 GTTTT TCAGG GAAAT CAAGA CTCCT TCACA CCTGT GGTGA ACTCT CTAGA
 35 5601 CCCAC CGTTA CTGAC TCGCT ACCTT CGAAT TCACC CCCAG AGTTG GGTGC
 5651 ACCAG ATTGC CCTGA GGATG GAGGT TCTGG GCTGC GAGGC ACAGG ACCTC
 5701 TACGA CAAAA CTCAC ACATG CCCAC CGTGC CCAGC TCCAG AACTC CTGGG
 5751 CGGAC CGTCA GTCTT CCTCT TCCCC CAAA ACCCA AGGAC ACCCT CATGG
 5801 CCTCC CGGAC CCCTG AGGTC ACATG CGTGG TGGTG GACGT GAGCC ACGAA
 40 5851 GACCC TGAGG TCAAG TTCAA CTGGT ACGTG GACGG CGTGG AGGTG CATAA
 5901 TGCCA AGACA AAGCC GCGGG AGGAG CAGTA CAACA GCACG TACCG TGTGG
 5951 TCAGC GTCCT CACCG TCCTG GCCCA GGAAT GGCTG AATGG CAAGG AGTAC
 6001 AAGTG CAAGG TCTCC AACA AGCCC TCCA GCCCC CATCG AGAAA ACCAT
 6051 CTCCA AAGCC AAAGG GCAGC CCCGA GAACC ACAGG TGTAC ACCCT GCCCC
 45 6101 CATCC CGCGA TGAGC TGACC AAGAA CCAGG TCAGC CTGAC CTGCC TGGTC
 6151 AAAGG CTTCT ATCCC AGCGA CATCG CCGTG GAGTG GGAGA GCAAT GGGCA
 6201 GCCGG AGAAC AACTA CAAGA CCACG CCTCC CGTGT TGGAC TCCGA CGGCT
 6251 CCTTC TTCCT CTACA GCAAG CTCAC CGTGG ACAAG AGCAG GTGGC AGCAG
 6301 GGGAA CGTCT TCTCA TGCTC CGTGA TGCAT GAGGC TCTGC ACAAC GCCTA
 50 6351 CACGC AGAAG AGCCT CTCCC TGTCT CCGGG TAAAT GA

FVIII 263 protein sequence(IHH triple mutant) (SEQ ID NO: 157)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAWE LSWDYMQGAP TSESATPESG
 51 PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
 101 TSTEPSEGS SPAGSPTSTE EGSPAGSPTS TEEGASSSDL GELPVDARFP
 151 ESATPESGPG SPAGSPTSTE EGSPAGSPTS TEEGASSSDL GELPVDARFP
 5 201 PRVPKSFPFN TSVVYKKTFL VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 251 DTVVITLKNM ASHPVSLHAV GVSYWKASEG AEYDDQTSQR EKEDDKVFPG
 301 GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 351 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 401 HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
 10 451 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
 501 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 551 WWHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 601 TDETFKTREA IQHESGILGP LLYGEVGDIT LIIFKNQASR PYNIPHGIT
 651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 15 701 YYSSFNVMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 751 NRSWYL TENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 801 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVEYEDTLTLF PFSGETVFMS
 851 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYED SYEDISAYLL
 901 SKNNAIEPRS FSQNGAPGTS ESATPESGPG SEPATSGSET PGTSESATPE
 20 951 SGPGSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG SPAGSPTSTE
 1001 EGTSESATPE SGPGSEPATS GSETPGTSES ATPESGPGSP AGSPTSTEEG
 1051 SPAGSPTSTE EGTSTEPSEG SAPGTSESAT PESGPGTSES ATPESGPGTS
 1101 ESATPESGPG SEPATSGSET PGSEPATSGS ETPGSPAGSP TSTEEGTSTE
 1151 PSEGSAPGTS TEPSEGSAPG SEPATSGSET PGTSESATPE SGPGTSTEPS
 25 1201 EGSAPASSPP VLKRHQAEIT RTTLQSDQEE IDYDDTISVE MKKEDFDIYD
 1251 EDENQSPRSF QKKTTRHYFIA AVERLWDYGM SSSPHVLRNR AQSGSVPOFK
 1301 KVVVFQFTDG SFTQPLYRGE LNEHLGLLGP YIRAEVEDNI MVTFRNQASR
 1351 PYSFYSSLIS YEEDQRQGA PRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
 1401 CKAWAYFSDV DLEKDVHSGI IGPLLCHTN TLNPAHGRQV TVQEFALFFT
 30 1451 IFDETKSWYF TENMERNCR PCNIQMEDPT FKENYRFHAI NGYIMDTLPG
 1501 LVMAQDQIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
 1551 VFETVEMLP KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPGLMASGH
 1601 IRDFQITASG QYGQWAPKLA RLHYSGSINA WSTKEPFSWI KVDLLAPMII
 1651 HGIKTQGARQ QYGSYLYSQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
 35 1701 SSGIKHNIFN PPIIARYIL HPHTYSIRST LRMELMGCDL NSCSMPLGME
 1751 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ
 1801 VDFQKTMKVT GVTTOGVKSL LSTMYVKEFL ISSSQDGHQW TLFFQNGKVK
 1851 VFQGNQDSFT PVVNSLDPPL LTRYLRIHPQ SWVHQIALRM EVLGCEAQDL
 1901 YDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMSRTPEV TCVVVDVSHE
 40 1951 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL AQDWLNGKEY
 2001 KCKVSNKALP APIEKTISKA KGQPREPVY TLPPSRDELT KNQVSLTCLV
 2051 KGFYPSDIAV EWESNGQPN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
 2101 GNVFSCSVMH EALHNAYTQK SLSLSPGK*

45 **FVIII 282 nucleotide sequence(SEQ ID NO: 158)**

1 ATGCA AATAG AGCTC TCCAC CTGCT TCTTT CTGTG CCTTT TGCGA TTCTG
 51 CTTTA GTGCC ACCAG AAGAT ACTAC CTGGG TGCAG TGGAA CTGTC ATGGG
 101 ACTAT ATGCA AAGTG ATCTC GGTGA GCTGC CTGTG GACGC AAGAT TTCCT
 50 151 CCTAG AGTGC CAAAA TCTTT TCCAT TCAAC ACCTC AGTCG TGTAC AAAAA
 201 GACTC TGTTT GTAGA ATTCA CGGAT CACCT TTTCA ACATC GCTAA GCCAA
 251 GGCCA CCCTG GATGG GTCTG CTAGG TCCTA CCATC CAGGC TGAGG TTTAT
 301 GATAC AGTGG TCATT AACT TAAGA ACATG GCTTC CCATC CTGTC AGTCT

351 TCATG CTGTT GGTGT ATCCT ACTGG AAAGC TTCTG AGGGA GCTGA ATATG
 401 ATGAT CAGAC CAGTC AAAGG GAGAA AGAAG ATGAT AAAGT CTTCC CTGGT
 451 GGAAG CCATA CATAT GTCTG GCAGG TCCTG AAAGA GAATG GTCCA ATGGC
 501 CTCTG ACCCA CTGTG CCTTA CCTAC TCATA TCTTT CTCAT GTGGA CCTGG
 5 551 TAAAA GACTT GAATT CAGGC CTCAT TGGAG CCCTA CTAGT ATGTA GAGAA
 601 GGGAG TCTGG CCAAG GAAAA GACAC AGACC TTGCA CAAAT TTATA CTACT
 651 TTTTG CTGTA TTTGA TGAAG GGAAA AGTTG GCACT CAGAA ACAA GAACT
 701 CCTTG ATGCA GGATA GGGAT GCTGC ATCTG CTCGG GCCTG GCCTA AAATG
 751 CACAC AGTCA ATGGT TATGT AAACA GGTCT CTGCC AGGTC TGATT GGATG
 10 801 CCACA GGAAA TCAGT CTATT GGCAT GTGAT TGGAA TGGGC ACCAC TCCTG
 851 AAGTG CACTC AATAT TCCTC GAAGG TCACA CATTT CTTGT GAGGA ACCAT
 901 CGCCA GGCTA GCTTG GAAAT CTCGC CAATA ACTTT CCTTA CTGCT CAAAC
 951 ACTCT TGATG GACCT TGGAC AGTTT CTA CTACT GTTTT GTCAT ATCTC TTCCC
 1001 ACCAA CATGA TGGCA TGGAA GCTTA TGTCA AAGTA GACAG CTGTC CAGAG
 15 1051 GAACC CCAAC TACGA ATGAA AAATA ATGAA GAAGC GGAAG ACTAT GATGA
 1101 TGATC TTA CTGATT TGA AAA TGGAT GTGGT CAGGT TTGAT GATGA CAACT
 1151 CTCCT TCCTT TATCC AAATT CGCTC AGTTG CCAAG AAGCA TCCTA AAAT
 1201 TGGGT ACATT ACATT GCTGC TGAAG AGGAG GACTG GGACT ATGCT CCCTT
 1251 AGTCC TCGCC CCCGA TGACA GAAGT TATAA AAGTC AATAT TTGAA CAATG
 20 1301 GCCCT CAGCG GATTG GTAGG AAGTA CAAAA AAGTC CGATT TATGG CATACT
 1351 ACAGA TGAAA CCTTT AAGAC TCGTG AAGCT ATTCA GCATG AATCA GGAAT
 1401 CTTGG GACCT TTA CTGATT TATG GGGAA GTTGG AGACA CACTG TTGAT TATAT
 1451 TTAAG AATCA AGCAA GCAGA CCATA TAACA TCTAC CCTCA CGGAA TCACT
 1501 GATGT CCGTC CTTTG TATTC AAGGA GATTA CCAAA AGGTG TAAAA CATTT
 25 1551 GAAGG ATTTT CCAAT TCTGC CAGGA GAAAT ATTCA AATAT AAATG GACAG
 1601 TGACT GTAGA AGATG GGCCA ACTAA ATCAG ATCCT CGGTG CCTGA CCCGC
 1651 TATTA CTCTA GTTTC GTTAA TATGG AGAGA GATCT AGCTT CAGGA CTCAT
 1701 TGGCC CTCTC CTCAT CTGCT ACAA GAATC TGTA ATCAA AGAGG AAACC
 1751 AGATA ATGTC AGACA AGAGG AATGT CATCC TGTTT TCTGT ATTTG ATGAG
 30 1801 AACCG AAGCT GGTAC CTCAC AGAGA ATATA CAACG CTTTC TCCCC AATCC
 1851 AGCTG GAGTG CAGCT TGAGG ATCCA GAGTT CCAAG CCTCC AACAT CATGC
 1901 ACAGC ATCAA TGGCT ATGTT TTTGA TAGTT TGCAG TTGTC AGTTT GTTTG
 1951 CATGA GGTGG CATACT TGGTA CATT TAAGC ATTGG AGCAC AGACT GACTT
 2001 CCTTT CTGTC TTCTT CTCTG GATAT ACCTT CAAAC ACAA ATGGT CTATG
 35 2051 AAGAC AACT CACCC TATTC CCATT CTCAG GAGAA ACTGT CTTCA TGTCG
 2101 ATGGA AAACC CAGGT CTATG GATTC TGGGG TGCCA CAACT CAGAC TTTCG
 2151 GAACA GAGGC ATGAC CGCCT TACTG AAGGT TTCTA GTTGT GACAA GAACA
 2201 CTGGT GATTA TTACG AGGAC AGTTA TGAAG ATATT TCAGC ATACT TGCTG
 2251 AGTAA AAACA ATGCC ATTGA ACCAA GAAGC TTCTC TCAAA ACGGC GCGCC
 40 2301 AACAT CAGAG AGCGC CACCC CTGAA AGTGG TCCCG GGAGC GAGCC AGCCA
 2351 CATCT GGGTC GGAAA CGCCA GGCAC AAGTG AGTCT GCAAC TCCCG AGTCC
 2401 GGACC TGGCT CCGAG CCTGC CACTA GCGGC TCCGA GACTC CGGGA ACTTC
 2451 CGAGA GCGCT ACACC AGAAA GCGGA CCCGG AACCA GTACC GAACC TAGCG
 2501 AGGGC TCTGC TCCGG GCAGC CCAGC CGGCT CTCCT ACATC CACGG AGGAG
 45 2551 GGCAC TTCCG AATCC GCCAC CCCGG AGTCA GGGCC AGGAT CTGAA CCCGC
 2601 TACCT CAGGC AGTGA GACGC CAGGA ACGAG CGAGT CCGCT ACACC GGAGA
 2651 GTGGG CCAGG GAGCC CTGCT GGATC TCCTA CGTCC ACTGA GGAAG GGTC
 2701 CCAGC GGGCT CGCCC ACCAG CACTG AAGAA GGTGC CTCGA GCCCA CCAGT
 2751 CTTGA AACGC CATCA AGCTG AAATA ACTCG TACTA CTCTT CAGTC AGATC
 50 2801 AAGAG GAAAT CGATT ATGAT GATAC CATAT CAGTT GAAAT GAAGA AGGAA
 2851 GATTT TGACA TTTAT GATGA GGATG AAAAT CAGAG CCCCC GCAGC TTTC
 2901 AAAGA AAACA CGACA CTATT TTATT GCTGC AGTGG AGAGG CTCTG GGATT
 2951 ATGGG ATGAG TAGCT CCCCC CATGT TCTAA GAAAC AGGGC TCAGA GTGGC

3001 AGTGT CCCTC AGTTC AAGAA AGTTG TTTTC CAGGA ATTTA CTGAT GGCTC
 3051 CTTTA CTCAG CCCTT ATACC GTGGA GAACT AAATG AACAT TTGGG ACTCC
 3101 TGGGG CCATA TATAA GAGCA GAAGT TGAAG ATAAT ATCAT GGTA CTTTC
 3151 AGAAA TCAGG CCTCT CGTCC CTATT CCTTC TATTC TAGCC TTATT TCTTA
 5 3201 TGAGG AAGAT CAGAG GCAAG GAGCA GAACC TAGAA AAAAC TTTGT CAAGC
 3251 CTAAT GAAAC CAAAA CTTAC TTTTG GAAAG TGCAA CATCA TATGG CACCC
 3301 ACTAA AGATG AGTTT GACTG CAAAG CCTGG GCTTA TTTCT CTGAT GTTGA
 3351 CCTGG AAAAA GATGT GCACT CAGGC CTGAT TGGAC CCCTT CTGGT CTGCC
 3401 ACACT AACAC ACTGA ACCCT GCTCA TGGGA GACAA GTGAC AGTAC AGGAA
 10 3451 TTTGC TCTGT TTTTC ACCAT CTTTG ATGAG ACCAA AAGCT GGTAC TTCAC
 3501 TGAAA ATATG GAAAG AAAC TGCAGG GCTCC CTGCA ATATC CAGAT GGAAG
 3551 ATCCC ACTTT TAAAG AGAAT TATCG CTTCC ATGCA ATCAA TGGCT ACATA
 3601 ATGGA TACAC TACCT GGCTT AGTAA TGGCT CAGGA TCAAA GGATT CGATG
 3651 GTATC TGCTC AGCAT GGGCA GCAAT GAAAA CATCC ATTCT ATTCA TTTCA
 15 3701 GTGGA CATGT GTTCA CTGTA CGAAA AAAAG AGGAG TATAA AATGG CACTG
 3751 TACAA TCTCT ATCCA GGTGT TTTTG AGACA GTGGA AATGT TACCA TCCAA
 3801 AGCTG GAATT TGGCG GGTGG AATGC CTTAT TGGCG AGCAT CTACA TGCTG
 3851 GGATG AGCAC ACTTT TTCTG GTGTA CAGCA ATAAG TGTCA GACTC CCCTG
 3901 GGAAT GGCTT CTGGA CACAT TAGAG ATTTT CAGAT TACAG CTTCA GGACA
 20 3951 ATATG GACAG TGGGC CCCAA AGCTG GCCAG ACTTC ATTAT TCCGG ATCAA
 4001 TCAAT GCCTG GAGCA CCAAG GAGCC CTTTT CTTGG ATCAA GGTGG ATCTG
 4051 TTGGC ACCAA TGATT ATTCA CGGCA TCAAG ACCCA GGGTG CCCGT CAGAA
 4101 GTTCT CCAGC CTCTA CATCT CTCAG TTTAT CATCA TGTAT AGTCT TGATG
 4151 GGAAG AAGTG GCAGA CTTAT CGAGG AAATT CCACT GGAAC CTAA TGGTC
 25 4201 TTCTT TGGCA ATGTG GATTC ATCTG GGATA AAACA CAATA TTTTT AACCC
 4251 TCCAA TTATT GCTCG ATACA TCCGT TTGCA CCCAA CTCAT TATAG CATTG
 4301 GCAGC ACTCT TCGCA TGGAG TTGAT GGGCT GTGAT TTAAG TAGTT GCAGC
 4351 ATGCC ATTGG GAATG GAGAG TAAAG CAATA TCAGA TGCAC AGATT ACTGC
 4401 TTCAT CCTAC TTTAC CAATA TGTTT GCCAC CTGGT CTCCT TCAAA AGCTC
 30 4451 GACTT CACCT CCAAG GGAGG AGTAA TGCCT GGAGA CCTCA GGTGA ATAAT
 4501 CCAAA AGAGT GGCTG CAAGT GCACT TCCAG AAGAC AATGA AAGTC ACAGG
 4551 AGTAA CTACT CAGGG AGTAA AATCT CTGCT TACCA GCATG TATGT GAAGG
 4601 AGTTC CTCAT CTCCA GCAGT CAAGA TGGCC ATCAG TGGAC TCTCT TTTTT
 4651 CAGAA TGGCA AAGTA AAGGT TTTTC AGGGA AATCA AGACT CTTTC ACACC
 35 4701 TGTGG TGAAC TCTCT AGACC CACCG TTAAT GACTC GCTAC CTTTC AATTC
 4751 ACCCC CAGAG TTGGG TGCAC CAGAT TGCCC TGAGG ATGGA GGTTC TGGGC
 4801 TGGCA GGCAC AGGAC CTCTA CGACA AAAC TACAC ATGCC CACCG TGCCC
 4851 AGCTC CAGAA CTCCT GGGCG GACCG TCAGT CTTCC TCTTC CCCCC AAAAC
 4901 CCAAG GACAC CCTCA TGATC TCCCG GACCC CTGAG GTCAC ATGCG TGGTG
 40 4951 GTGGA CGTGA GCCAC GAAGA CCCTG AGGTC AAGTT CAACT GGTAC GTGGA
 5001 CGGCG TGGAG GTGCA TAATG CCAAG ACAA GCCGC GGGAG GAGCA GTACA
 5051 ACAGC ACGTA CCGTG TGGTC AGCGT CCTCA CCGTC CTGCA CCAGG ACTGG
 5101 CTGAA TGGCA AGGAG TACAA GTGCA AGGTC TCCAA CAAAG CCCTC CCAGC
 5151 CCCC TCGAG AAAAC CATCT CCAAA GCAA AGGGC AGCCC CGAGA ACCAC
 45 5201 AGGTG TACAC CCTGC CCCC TCCCG GGATG AGCTG ACCAA GAACC AGGTC
 5251 AGCCT GACCT GCCTG GTCAA AGGCT TCTAT CCCAG CGACA TCGCC GTGGA
 5301 GTGGG AGAGC AATGG GCAGC CGGAG ACAA CTACA AGACC ACGCC TCCCG
 5351 TGTTG GACTC CGACG GCTCC TTCTT CCTCT ACAGC AAGCT CACCG TGGAC
 5401 AAGAG CAGGT GGCAG CAGGG GAACG TCTTC TCATG CTCCG TGATG CATGA
 50 5451 GGCTC TGCAC AACCA CTACA CGCAG AAGAG CCTCT CCCTG TCTCC GGGTA
 5501 AATGA

FVIII 282 protein sequence(SEQ ID NO: 159)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAWE LSWDYMQSDI GELPVDARFP
 51 PRVPKSF PFN TSVVYKKTIF VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 101 DTVVITLKNM ASHPVSLHAV GVSYWKA SEG AEYDDQTSQR EKEDDKVFPG
 5 151 GSHTYVWQVL KENGP MASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 201 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 251 HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
 301 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
 351 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 10 401 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 451 TDETFKTREA IQHESGILGP LLYGEVGDIT LIIFKNQASR PYNIYPHGIT
 501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 601 NRSWYL TENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 15 651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MUYEDTLTLF PFSGETVFMS
 701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL
 751 SKNNAIEPRS FSQNGAPTSE SATPESGPGS EPATSGSETP GTSESATPES
 801 GPGSEPATSG SETPGTSESA TPESGPGTST EPSEGSAPGS PAGSPTSTEE
 851 GTSESATPES GPGSEPATSG SETPGTSESA TPESGPGSPA GSPTSTEEGS
 20 901 PAGSPTSTEE GASSPPVLKR HQAEITRTTL QSDQEEIDYD DTISVEMKKE
 951 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP HVLNRNAQSG
 1001 SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
 1051 RNQASRPYSF YSSLISYEED QRQGAEPKRN FVKPNETKTY FWKVQH HMAP
 1101 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE
 25 1151 FALFFTIFDE TKSUYFTENM ERNCRAPCNI QMEDPTFKEN YRFHAINGYI
 1201 MDTLPGLVMA QDQRIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
 1251 YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
 1301 GMASGHIRDF QITASGQYQG WAPKLARLHY SGSINAWSTK EPFSWIKVDL
 1351 LAPMIIHGK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
 30 1401 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS
 1451 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
 1501 PKEWLQVDFQ KTMKVTGVTT QGVKSLTSM YVKEFLISS QDGHQWTLFF
 1551 QNGKVKVFQ NQDSFTPVVN SLDPLLTRY LRIHPQSWVH QIALRMEVLG
 1601 CEAQDLYDKT HTPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
 35 1651 VDVSHEDPEV KFNWYVDGVE VHNATKPRE EQYNSTYRVV SVLTVLHQDW
 1701 LNGKEYKCKV SNKALPAPIE KTISKAKGP REPQVYTLPP SRDELTKNQV
 1751 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD
 1801 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

40

FVIII 283 nucleotide sequence (FVIII 169 with IHH triple mutation) (SEQ ID NO: 160)

1 ATGCA AATAG AGCTC TCCAC CTGCT TCTTT CTGTG CCTTT TGCGA TTCTG
 51 CTTTA GTGCC ACCAG AAGAT ACTAC CTGGG TGCAG TGGAA CTGTC ATGGG
 45 101 ACTAT ATGCA AAGTG ATCTC GGTGA GCTGC CTGTG GACGC AAGAT TTCCT
 151 CCTAG AGTGC CAAAA TCTTT TCCAT TCAAC ACCTC AGTCG TGTAC AAAAA
 201 GACTC TGTTT GTAGA ATTCA CGGAT CACCT TTTCA ACATC GCTAA GCCAA
 251 GGCCA CCCTG GATGG GTCTG CTAGG TCCTA CCATC CAGGC TGAGG TTTAT
 301 GATAC AGTGG TCATT AACT TAAGA ACATG GCTTC CCATC CTGTC AGTCT
 50 351 TCATG CTGTT GGTGT ATCCT ACTGG AAAGC TTCTG AGGGA GCTGA ATATG
 401 ATGAT CAGAC CAGTC AAAGG GAGAA AGAAG ATGAT AAAGT CTTCC CTGGT
 451 GGAAG CCATA CATAT GTCTG GCAGG TCCTG AAAGA GAATG GTCCA ATGGC
 501 CTCTG ACCCA CTGTG CCTTA CCTAC TCATA TCTTT CTCAT GTGGA CCTGG

551 TAAAA GACTT GAATT CAGGC CTCAT TGGAG CCCTA CTAGT ATGTA GAGAA
 601 GGGAG TCTGG CCAAG GAAAA GACAC AGACC TTGCA CAAAT TTATA CTACT
 651 TTTTG CTGTA TTTGA TGAAG GGAAA AGTTG GCACT CAGAA ACAA GAACT
 701 CTTTG ATGCA GGATA GGGAT GCTGC ATCTG CTCGG GCCTG GCCTA AAATG
 5 751 CACAC AGTCA ATGGT TATGT AAACA GGTCT CTGCC AGGTC TGATT GGATG
 801 CCACA GGAAA TCAGT CTATT GGCAT GTGAT TGGAA TGGGC ACCAC TCCTG
 851 AAGTG CACTC AATAT TCCTC GAAGG TCACA CATTT CTTGT GAGGA ACCAT
 901 CGCCA GGCTA GCTTG GAAAT CTCGC CAATA ACTTT CCTTA CTGCT CAAAC
 951 ACTCT TGATG GACCT TGGAC AGTTT CTACT GTTTT GTCAT ATCTC TTCCC
 10 1001 ACCAA CATGA TGGCA TGGAA GCTTA TGTCA AAGTA GACAG CTGTC CAGAG
 1051 GAACC CCAAC TACGA ATGAA AAATA ATGAA GAAGC GGAAG ACTAT GATGA
 1101 TGATC TTAAT GATTC TGAAA TGGAT GTGGT CAGGT TTGAT GATGA CAACT
 1151 CTCCT TCCTT TATCC AAATT CGCTC AGTTG CCAAG AAGCA TCCTA AAATC
 1201 TGGGT ACATT ACATT GCTGC TGAAG AGGAG GACTG GGACT ATGCT CCCTT
 15 1251 AGTCC TCGCC CCCGA TGACA GAAGT TATAA AAGTC AATAT TTGAA CAATG
 1301 GCCCT CAGCG GATTG GTAGG AAGTA CAAAA AAGTC CGATT TATGG CATACT
 1351 ACAGA TGAAA CCTTT AAGAC TCGTG AAGCT ATTCA GCATG AATCA GGAAT
 1401 CTTGG GACCT TTAAT TTATG GGGAA GTTGG AGACA CACTG TTGAT TATAT
 1451 TTAAG AATCA AGCAA GCAGA CCATA TAACA TCTAC CCTCA CGGAA TCACT
 20 1501 GATGT CCGTC CTTTG TATTC AAGGA GATTA CCAAA AGGTG TAAAA CATTT
 1551 GAAGG ATTTT CCAAT TCTGC CAGGA GAAAT ATTCA AATAT AAATG GACAG
 1601 TGACT GTAGA AGATG GGCCA ACTAA ATCAG ATCCT CGGTG CCTGA CCCGC
 1651 TATTA CTCTA GTTTC GTTAA TATGG AGAGA GATCT AGCTT CAGGA CTCAT
 1701 TGGCC CTCTC CTCAT CTGCT ACAA GAATC TGTAG ATCAA AGAGG AAACC
 25 1751 AGATA ATGTC AGACA AGAGG AATGT CATCC TGTTT TCTGT ATTTG ATGAG
 1801 AACCG AAGCT GGTAC CTCAC AGAGA ATATA CAACG CTTTC TCCCC AATCC
 1851 AGCTG GAGTG CAGCT TGAGG ATCCA GAGTT CCAAG CCTCC AACAT CATGC
 1901 ACAGC ATCAA TGGCT ATGTT TTTGA TAGTT TGCAG TTGTC AGTTT GTTTG
 1951 CATGA GGTGG CATACT TGGTA CATTG TAAGC ATTGG AGCAC AGACT GACTT
 30 2001 CCTTT CTGTC TTCTT CTCTG GATAT ACCTT CAAAC ACAA ATGGT CTATG
 2051 AAGAC AACT CACCC TATTC CCATT CTCAG GAGAA ACTGT CTTCA TGTCG
 2101 ATGGA AAACC CAGGT CTATG GATTC TGGGG TGCCA CAACT CAGAC TTTCG
 2151 GAACA GAGGC ATGAC CGCCT TACTG AAGGT TTCTA GTTGT GACAA GAACA
 2201 CTGGT GATTA TTACG AGGAC AGTTA TGAAG ATATT TCAGC ATACT TGCTG
 35 2251 AGTAA AAACA ATGCC ATTGA ACCAA GAAGC TTCTC TCAAA ACGGC GCGCC
 2301 AGGTA CCTCA GAGTC TGCTA CCCCC GAGTC AGGGC CAGGA TCAGA GCCAG
 2351 CCACC TCCGG GTCTG AGACA CCGG GACTT CCGAG AGTGC CACCC CTGAG
 2401 TCCGG ACCCG GGTCC GAGCC CGCCA CTTCC GGCTC CGAAA CTCCC GGCAC
 2451 AAGCG AGAGC GCTAC CCCAG AGTCA GGACC AGGAA CATCT ACAGA GCCCT
 40 2501 CTGAA GGCTC CGCTC CAGGG TCCCC AGCCG GCAGT CCCAC TAGCA CCGAG
 2551 GAGGG AACCT CTGAA AGCGC CACAC CCGAA TCAGG GCCAG GGTCT GAGCC
 2601 TGCTA CCAGC GGCAG CGAGA CACCA GGCAC CTCTG AGTCC GCCAC ACCAG
 2651 AGTCC GGACC CGGAT TCCCC GCTGG GAGCC CCACC TCCAC TGAGG AGGGA
 2701 TCTCC TGCTG GCTCT CCAAC ATCTA CTGAG GAAGG TACCT CAACC GAGCC
 45 2751 ATCCG AGGGA TCAGC TCCCC GCACC TCAGA GTCGG CAACC CCGGA GTCTG
 2801 GACCC GGAAC TTCCG AAAGT GCCAC ACCAG AGTCC GGTCC CGGGA CTTCA
 2851 GAATC AGCAA CACCC GAGTC CGGCC CTGGG TCTGA ACCCG CCACA AGTGG
 2901 TAGTG AGACA CCAGG ATCAG AACCT GCTAC CTCAG GGTCA GAGAC ACCCG
 2951 GATCT CCGGC AGGCT CACCA ACCTC CACTG AGGAG GGCAC CAGCA CAGAA
 50 3001 CCAAG CGAGG GCTCC GCACC CGGAA CAAGC ACTGA ACCCA GTGAG GGTTC
 3051 AGCAC CCGGC TCTGA GCCGG CCACA AGTGG CAGTG AGACA CCCGG CACTT
 3101 CAGAG AGTGC CACCC CCGAG AGTGG CCCAG GCACT AGTAC CGAGC CCTCT
 3151 GAAGG CAGTG CGCCA GCCTC GAGCC CACCA GTCTT GAAAC GCCAT CAAGC

3201 TGAAA TAACT CGTAC TACTC TTCAG TCAGA TCAAG AGGAA ATCGA TTATG
 3251 ATGAT ACCAT ATCAG TTGAA ATGAA GAAGG AAGAT TTTGA CATTG ATGAT
 3301 GAGGA TGAAA ATCAG AGCCC CCGCA GCTTT CAAAA GAAAA CACGA CACTA
 3351 TTTTA TTGCT GCAGT GGAGA GGCTC TGGGA TTATG GGATG AGTAG CTCCC
 5 3401 CACAT GTTCT AAGAA ACAGG GCTCA GAGTG GCAGT GTCCC TCAGT TCAAG
 3451 AAAGT TGTTT TCCAG GAATT TACTG ATGGC TCCTT TACTC AGCCC TTATA
 3501 CCGTG GAGAA CTAAG TGAAC ATTTG GGACT CCTGG GGCCA TATAT AAGAG
 3551 CAGAA GTTGA AGATA ATATC ATGGT AACTT TCAGA AATCA GGCCT CTCGT
 3601 CCCTA TTCCT TCTAT TCTAG CCTTA TTTCT TATGA GGAAG ATCAG AGGCA
 10 3651 AGGAG CAGAA CCTAG AAAAA ACTTT GTCAA GCCTA ATGAA ACCAA AACTT
 3701 ACTTT TGGAA AGTGC AACAT CATAT GGCAC CCACT AAAGA TGAGT TTGAC
 3751 TGCAA AGCCT GGGCT TATTT CTCTG ATGTT GACCT GGAAG AAGAT GTGCA
 3801 CTCAG GCCTG ATTGG ACCCC TTCTG GTCTG CCACA CTAAC AACTT GAACC
 3851 CTGCT CATGG GAGAC AAGTG ACAGT ACAGG AATTT GCTCT GTTTT TCACC
 15 3901 ATCTT TGATG AGACC AAAAG CTGGT ACTTC ACTGA AAATA TGGAA AGAAA
 3951 CTGCA GGGCT CCCTG CAATA TCCAG ATGGA AGATC CCACT TTAA AGAGA
 4001 ATTAT CGCTT CCATG CAATC AATGG CTACA TAATG GATAC ACTAC CTGGC
 4051 TTAGT AATGG CTCAG GATCA AAGGA TTCGA TGGTA TCTGC TCAGC ATGGG
 4101 CAGCA ATGAA AACAT CCATT CTATT CATTG CAGTG GACAT GTGTT CACTG
 20 4151 TACGA AAAAA AGAGG AGTAT AAAAT GGCAC TGTAC AATCT CTATC CAGGT
 4201 GTTTT TGAGA CAGTG GAAAT GTTAC CATCC AAAGC TGGAA TTTGG CGGGT
 4251 GGAAT GCCTT ATTGG CGAGC ATCTA CATGC TGGGA TGAGC AACTT TTTTC
 4301 TGGTG TACAG CAATA AGTGT CAGAC TCCCC TGGGA ATGGC TTCTG GACAC
 4351 ATTAG AGATT TTCAG ATTAC AGCTT CAGGA CAATA TGGAC AGTGG GCCCC
 25 4401 AAAGC TGGCC AGACT TCATT ATTCC GGATC AATCA ATGCC TGGAG CACCA
 4451 AGGAG CCCTT TTCTT GGATC AAGGT GGATC TGTG GCACC AATGA TTATT
 4501 CACGG CATCA AGACC CAGGG TGCCC GTCAG AAGTT CTCCA GCCTC TACAT
 4551 CTCTC AGTTT ATCAT CATGT ATAGT CTTGA TGGGA AGAAG TGGCA GACTT
 4601 ATCGA GGAAG TTCCA CTGGA ACCTT AATGG TCTTC TTTGG CAATG TGGAT
 30 4651 TCATC TGGGA TAAAA CACAA TATTT TTAAC CCTCC AATTA TTGCT CGATA
 4701 CATCC GTTTG CACCC AACTC ATTAT AGCAT TCGCA GCACT CTTCC CATGG
 4751 AGTTG ATGGG CTGTG ATTTA AATAG TTGCA GCATG CCATT GGGAA TGGAG
 4801 AGTAA AGCAA TATCA GATGC ACAGA TTAAT GCTTC ATCTT ACTTT ACCAA
 4851 TATGT TTGCC ACCTG GTCTC CTTCA AAAGC TCGAC TTCAC CTCCA AGGGA
 35 4901 GGAGT AATGC CTGGA GACCT CAGGT GAATA ATCCA AAAGA GTGGC TGCAA
 4951 GTGGA CTTCC AGAAG ACAAT GAAAG TCACA GGAGT AACTA CTCAG GGAGT
 5001 AAAAT CTCTG CTTAC CAGCA TGTAT GTGAA GGAGT TCCTC ATCTC CAGCA
 5051 GTCAA GATGG CCATC AGTGG ACTCT CTTTT TTCAG AATGG CAAAG TAAAG
 5101 GTTTT TCAGG GAAAT CAAGA CTCCT TCACA CCTGT GGTGA ACTCT CTAGA
 40 5151 CCCAC CGTTA CTGAC TCGCT ACCTT CGAAT TCACC CCCAG AGTTG GGTGC
 5201 ACCAG ATTGC CCTGA GGATG GAGGT TCTGG GCTGC GAGGC ACAGG ACCTC
 5251 TACGA CAAAA CTCAC ACATG CCCAC CGTGC CCAGC TCCAG AACTC CTGGG
 5301 CGGAC CGTCA GTCTT CCTCT TCCCC CCAAA ACCCA AGGAC ACCCT CATGG
 5351 CCTCC CGGAC CCCTG AGGTC ACATG CGTGG TGGTG GACGT GAGCC ACGAA
 45 5401 GACCC TGAGG TCAAG TTCAA CTGGT ACGTG GACGG CGTGG AGGTG CATAA
 5451 TGCCA AGACA AAGCC GCGGG AGGAG CAGTA CAACA GCACG TACCG TGTGG
 5501 TCAGC GTCCT CACCG TCCTG GCCCA GGAAG GGCTG AATGG CAAGG AGTAC
 5551 AAGTG CAAGG TCTCC ACAA AGCCC TCCA GCCCC CATCG AGAAA ACCAT
 5601 CTCCA AAGCC AAAGG GCAGC CCCGA GAACC ACAGG TGTAC ACCCT GCCCC
 50 5651 CATCC CGGGA TGAGC TGACC AAGAA CCAGG TCAGC CTGAC CTGCC TGGTC
 5701 AAAGG CTTCT ATCCC AGCGA CATCG CCGTG GAGTG GGAGA GCAAT GGGCA
 5751 GCCGG AGAAC AACTA CAAGA CCACG CCTCC CGTGT TGGAC TCCGA CGGCT
 5801 CCTTC TTCCT CTACA GCAAG CTCAC CGTGG ACAAG AGCAG GTGGC AGCAG

5851 GGGAA CGTCT TCTCA TGCTC CGTGA TGCAT GAGGC TCTGC ACAAC GCCTA
 5901 CACGC AGAAG AGCCT CTCCC TGTCT CCGGG TAAAT GA

5

FVIII 283 protein sequence (FVIII 169 with IHH triple mutation) (SEQ ID NO: 161)

1 MQIELSTCFF LCLLRFCFSA TRYYLGAWE LSWDYMQSDL GELPVDARFP
 10 51 PRVPKSFPFN TSVVYKKTLL VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 101 DTVVITLKNM ASHPVSLHAV GVSYWKASEG AEYDDQTSQR EKEDDKVFPG
 151 GSHTYVWQVL KENGPMA SDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 201 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 251 HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
 15 301 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
 351 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 401 WVHYIAAEEE DWDYAPLVA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 451 TDETFKTREA IQHESGILGP LLYGEVGD TL LIIFKNQASR PYNIYPHGIT
 501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 20 551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 601 NRSWYL TENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS
 701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL
 751 SKNNAIEPRS FSQNGAPGTS ESATPESGPG SEPATSGSET PGTSESATPE
 25 801 SGPGSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG SPAGSPTSTE
 851 EGTSESATPE SGPGSEPATS GSETPGTSES ATPESGPGSP AGSPTSTEEG
 901 SPAGSPTSTE EGTSTEPSEG SAPGTSESAT PESGPGTSES ATPESGPGTS
 951 ESATPESGPG SEPATSGSET PGSEPATSGS ETPGSPAGSP TSTEEGTSTE
 1001 PSEGSAPGTS TEPSEGSAPG SEPATSGSET PGTSESATPE SGPSTSTEPS
 30 1051 EGSAPASSPP VLKRHQAEIT RTTLQSDQEE IDYDDTISVE MKKEDFDIYD
 1101 EDENQSPRSF QKKTRHYFIA AVERLWDYGM SSSPHVLRNR AQSGSVPOFK
 1151 KVVVFQFTDG SFTQPL YRGE LNEHLG LLLGP YIRAEVEDNI MVTFRNQASR
 1201 PYSFYSSLIS YEEDQRQGA EPRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
 1251 CKAWAYFSDV DLEKDVHSLG LFP LLVCHTN TLNPAHGRQV TVQEFALFFT
 35 1301 IFDETKSWYF TENMERN CRA PCNIQMEDPT FKENYRFHAI NGYIMDTLPG
 1351 LVMAQDQIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
 1401 VFETVEMLP S KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPLGMASGH
 1451 IRDFQITASG QYGQWAPKLA RLHYS GSINA WSTKEPFSWI KVDLLAPMII
 1501 HGIKTQGARQ KFSSLYISQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
 40 1551 SSGIKHNIFN PPIIARYIRL HPTHYSIRST LRMELMGCDL NSCSMPLGME
 1601 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ
 1651 VDFQKTMKVT GVTTQGVKSL LTS MYVKEFL ISSSQDGHQW TLFFQNGKVK
 1701 VFQGNQDSFT PVVNSLDPPL LTRYLRIHPQ SWVHQIALRM EVLGCEAQDL
 1751 YDKTHTCPPC PAPELLG GPS VFLFPPKPKD TLMASRTPEV TCVVVDVSHE
 45 1801 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL AQDWLNGKEY
 1851 KCKVSNKALP APIEKTISKA KGQPREPVY TLPPSRDELT KNQVSLTCLV
 1901 KGFYPSDIAV EWESNGQPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
 1951 GNVFSCSVMH EALHNAYTQK SLSLSPGK*

pSYNFVIII 010 nucleotide sequence-(Dual chain FVIII Fc) (SEQ ID NO: 162)

1 ATGCAAATAG AGCTCTCCAC CTGCTTCTTT CTGTGCCTTT TGCGATTCTG
 51 CTTTAGTGCC ACCAGAAGAT ACTACCTGGG TGCAGTGGA CTGTCATGGG

101 ACTATATGCA AAGTGATCTC GGTGAGCTGC CTGTGGACGC AAGATTTCCCT
 151 CCTAGAGTGC CAAAATCTTT TCCATTCAAC ACCTCAGTCG TGTACAAAAA
 201 GACTCTGTTT GTAGAATTCA CGGATCACCT TTTCAACATC GCTAAGCCAA
 251 GGCCACCCTG GATGGGTCTG CTAGGTCCTA CCATCCAGGC TGAGGTTTAT
 5 301 GATACAGTGG TCATTACACT TAAGAACATG GCTTCCCATC CTGTCAGTCT
 351 TCATGCTGTT GGTGTATCCT ACTGGAAAGC TTCTGAGGGA GCTGAATATG
 401 ATGATCAGAC CAGTCAAAGG GAGAAAGAAG ATGATAAAGT CTTCCCTGGT
 451 GGAAGCCATA CATATGTCTG GCAGGTCCTG AAAGAGAATG GTCCAATGGC
 501 CTCTGACCCA CTGTGCCTTA CCTACTCATA TCTTTCTCAT GTGGACCTGG
 10 551 TAAAAGACTT GAATTCAGGC CTCATTGGAG CCCTACTAGT ATGTAGAGAA
 601 GGGAGTCTGG CCAAGGAAAA GACACAGACC TTGCACAAAT TTATACTACT
 651 TTTTGCTGTA TTTGATGAAG GGAAAAGTTG GCACTCAGAA ACAAAGAACT
 701 CCTTGATGCA GGATAGGGAT GCTGCATCTG CTCGGGCCTG GCCTAAAATG
 751 CACACAGTCA ATGGTTATGT AAACAGGTCT CTGCCAGGTC TGATTGGATG
 15 801 CCACAGGAAA TCAGTCTATT GGCATGTGAT TGGAAATGGGC ACCACTCCTG
 851 AAGTGCACTC AATATTCCTC GAAGGTCACA CATTTCTTGT GAGGAACCAT
 901 CGCCAGGCGT CTTTGGAAT CTCGCCAATA ACTTTCCTTA CTGCTCAAAC
 951 ACTCTTGATG GACCTTGGAC AGTTTCTACT GTTTTGTCTAT ATCTCTTCCC
 1001 ACCAACATGA TGGCATGGAA GCTTATGTCA AAGTAGACAG CTGTCCAGAG
 20 1051 GAACCCCAAC TACGAATGAA AAATAATGAA GAAGCGGAAG ACTATGATGA
 1101 TGATCTTACT GATTCTGAAA TGGATGTGGT CAGGTTTGAT GATGACAACT
 1151 CTCCTTCCTT TATCCAAATT CGCTCAGTTG CCAAGAAGCA TCCTAAAACT
 1201 TGGGTACATT ACATTGCTGC TGAAGAGGAG GACTGGGACT ATGCTCCCTT
 1251 AGTCCTCGCC CCCGATGACA GAAGTTATAA AAGTCAATAT TTGAACAATG
 25 1301 GCCCTCAGCG GATTGGTAGG AAGTACAAAA AAGTCCGATT TATGGCATAAC
 1351 ACAGATGAAA CCTTTAAGAC TCGTGAAGCT ATTCAGCATG AATCAGGAAT
 1401 CTTGGGACCT TTACTTTATG GGGAAAGTTG AGACACACTG TTGATTATAT
 1451 TTAAGAATCA AGCAAGCAGA CCATATAACA TCTACCCTCA CGGAATCACT
 1501 GATGTCCGTC CTTTGTATTC AAGGAGATTA CCAAAAGGTG TAAAACATTT
 30 1551 GAAGGATTTT CCAATTCTGC CAGGAGAAAT ATTCAAATAT AAATGGACAG
 1601 TGACTGTAGA AGATGGGCCA ACTAAATCAG ATCCTCGGTG CCGTACCCGC
 1651 TATTACTCTA GTTTCGTTAA TATGGAGAGA GATCTAGCTT CAGGACTCAT
 1701 TGGCCCTCTC CTCATCTGCT ACAAAGAATC TGTAGATCAA AGAGGAAACC
 1751 AGATAATGTC AGACAAGAGG AATGTCATCC TGTTTCTGT ATTTGATGAG
 35 1801 AACCGAAGCT GGTACCTCAC AGAGAATATA CAACGCTTTC TCCCCAATCC
 1851 AGCTGGAGTG CAGCTTGAGG ATCCAGAGTT CCAAGCCTCC AACATCATGC
 1901 ACAGCATCAA TGGCTATGTT TTTGATAGTT TGCAGTTGTC AGTTTGTGTTG
 1951 CATGAGGTGG CATACTGGTA CATTCTAAGC ATTGGAGCAC AGACTGACTT
 2001 CCTTTCTGTC TTCTTCTCTG GATATACCTT CAAACACAAA ATGGTCTATG
 40 2051 AAGACACACT CACCCTATTC CCATTCTCAG GAGAAACTGT CTTTATGTCTG
 2101 ATGGAAAACC CAGGTCTATG GATTCTGGGG TGCCACAACCT CAGACTTTCG
 2151 GAACAGAGGC ATGACCGCCT TACTGAAGGT TTCTAGTTGT GACAAGAACA
 2201 CTGGTGATTA TTACGAGGAC AGTTATGAAG ATATTTTCAGC ATACTTGCTG
 2251 AGTAAAAACA ATGCCATTGA ACCAAGAAGC TTCTCTCAA ACCCACCAGT
 45 2301 CTTGAAACGC CATCAACGGG AAATAACTCG TACTACTCTT CAGTCAGATC
 2351 AAGAGGAAAT TGACTATGAT GATACCATAT CAGTTGAAAT GAAGAAGGAA
 2401 GATTTTGACA TTTATGATGA GGATGAAAAT CAGAGCCCCC GCAGCTTTCA
 2451 AAAGAAAACA CGACACTATT TTATTGCTGC AGTGGAGAGG CTCTGGGATT
 2501 ATGGGATGAG TAGCTCCCCA CATGTTCTAA GAAACAGGGC TCAGAGTGGC
 50 2551 AGTGTCCCTC AGTTCAAGAA AGTTGTTTTC CAGGAATTTA CTGATGGCTC
 2601 CTTTACTCAG CCCTTATACC GTGGAGAACT AAATGAACAT TTGGGACTCC
 2651 TGGGGCCATA TATAAGAGCA GAAGTTGAAG ATAATATCAT GGTAACCTTC
 2701 AGAAATCAGG CCTCTCGTCC CTATTCCTTC TATTCTAGCC TTATTTCTTA

2751 TGAGGAAGAT CAGAGGCAAG GAGCAGAACC TAGAAAAAAC TTTGTCAAGC
 2801 CTAATGAAAC CAAAACCTTAC TTTTGGAAG TGCAACATCA TATGGCACCC
 2851 ACTAAAGATG AGTTTGACTG CAAAGCCTGG GCTTATTTCT CTGATGTTGA
 2901 CCTGGAAAAA GATGTGCACT CAGGCCTGAT TGGACCCCTT CTGGTCTGCC
 5 2951 AACTAACAC ACTGAACCCT GCTCATGGGA GACAAGTGAC AGTACAGGAA
 3001 TTTGCTCTGT TTTTCACCAT CTTTGATGAG ACCAAAAGCT GGTACTTCAC
 3051 TGAAAATATG GAAAGAACT GCAGGGCTCC CTGCAATATC CAGATGGAAG
 3101 ATCCCACCTT TAAAGAGAAT TATCGCTTCC ATGCAATCAA TGGCTACATA
 3151 ATGGATACAC TACCTGGCTT AGTAATGGCT CAGGATCAAA GGATTCTGATG
 10 3201 GTATCTGCTC AGCATGGGCA CGAATGAAAA CATCCATTCT ATTCATTTC
 3251 GTGGACATGT GTTCACTGTA CGAAAAAAG AGGAGTATAA AATGGCACTG
 3301 TACAATCTCT ATCCAGGTGT TTTTGAGACA GTGGAAATGT TACCATCCAA
 3351 AGCTGGAATT TGGCGGGTGG AATGCCTTAT TGGCGAGCAT CTACATGCTG
 3401 GGATGAGCAC ACTTTTTCTG GTGTACAGCA ATAAGTGTCA GACTCCCCTG
 15 3451 GGAATGGCTT CTGGACACAT TAGAGATTTT CAGATTACAG CTTCAGGACA
 3501 ATATGGACAG TGGGCCCCAA AGCTGGCCAG ACTTCATTAT TCCGGATCAA
 3551 TCAATGCCTG GAGACCAAG GAGCCCTTTT CTTGGATCAA GGTGGATCTG
 3601 TTGGCACCAA TGATTATTCA CGGCATCAAG ACCCAGGGTG CCCGTCAGAA
 3651 GTTCTCCAGC CTCTACATCT CTCAGTTTAT CATCATGTAT AGTCTTGATG
 20 3701 GGAAGAAGTG GCAGACTTAT CGAGGAAATT CCACTGGAAC CTTAATGGTC
 3751 TTCTTTGGCA ATGTGGATTG ATCTGGGATA AAACACAATA TTTTAAACCC
 3801 TCCAATTATT GCTCGATACA TCCGTTTGCA CCCAACTCAT TATAGCATTC
 3851 GCAGCACTCT TCGCATGGAG TTGATGGGCT GTGATTTAAA TAGTTGCAGC
 3901 ATGCCATTGG GAATGGAGAG TAAAGCAATA TCAGATGCAC AGATTACTGC
 25 3951 TTCATCTAC TTTACCAATA TGTTTGCCAC CTGGTCTCCT TCAAAAGCTC
 4001 GACTTCACCT CCAAGGGAGG AGTAATGCCT GGAGACCTCA GGTGAATAAT
 4051 CCAAAAGAGT GGCTGCAAGT GGAATCCAG AAGACAATGA AAGTCACAGG
 4101 AGTAACTACT CAGGGAGTAA AATCTCTGCT TACCAGCATG TATGTGAAGG
 4151 AGTTCCTCAT CTCCAGCAGT CAAGATGGCC ATCAGTGGAC TCTCTTTTTT
 30 4201 CAGAATGGCA AAGTAAAGGT TTTTCAGGGA AATCAAGACT CTTTCACACC
 4251 TGTGGTGAAC TCTCTAGACC CACCGTTACT GACTCGCTAC CTTTGAATTC
 4301 ACCCCAGAG TTGGGTGCAC CAGATTGCCC TGAGGATGGA GGTCTGGGC
 4351 TGCGAGGAGC AGGACCTCTA CGACAAAAC CACACATGCC CACCGTGGCC
 4401 AGCTCCAGAA CTCCTGGGCG GACCTCAGT CTTCTCTTC CCCCCAAAC
 35 4451 CCAAGGACAC CCTCATGATC TCCCGGACCC CTGAGGTCAC ATGCGTGGTG
 4501 GTGGACGTGA GCCACGAAGA CCCTGAGGTC AAGTTCAACT GGTACGTGGA
 4551 CGGCGTGGAG GTGCATAATG CCAAGACAAA GCCGCGGGAG GAGCAGTACA
 4601 ACAGCACGTA CCGTGTGGTC AGCGTCCTCA CCGTCCTGCA CCAGGACTGG
 4651 CTGAATGGCA AGGAGTACAA GTGCAAGGTC TCCAACAAAG CCCTCCCAGC
 40 4701 CCCATCGAG AAAACCATCT CCAAAGCCAA AGGGCAGCCC CGAGAACCAC
 4751 AGGTGTACAC CCTGCCCCCA TCCCGGGATG AGCTGACCAA GAACCAGGTC
 4801 AGCCTGACCT GCCTGGTCAA AGGCTTCTAT CCCAGCGACA TCGCCGTGGA
 4851 GTGGGAGAGC AATGGGCAGC CGGAGAACAA CTACAAGACC ACGCCTCCCC
 4901 TGTTGGACTC CGACGGCTCC TTCTTCTCT ACAGCAAGCT CACCGTGGAC
 45 4951 AAGAGCAGGT GGCAGCAGGG GAACGTCTC TCATGCTCCG TGATGCATGA
 5001 GGCTCTGCAC AACCCTACA CGCAGAAGAG CCTCTCCCTG TCTCCGGTA
 5051 AATGA

pSYNFVIII 010 protein sequence-(Dual chain FVIII_{FC}) (SEQ ID NO: 163)

50 1 MQIELSTCFF LCLLRFCFSA TRYYLGAVE LSWDYMQSDL GELPVDARFP
 51 PRVPKSPFN TSVVYKKTLE VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 101 DTVVITLKNM ASHPVSLHAV GVSYWKA SEG AEYDDQTSQR EKEDDKVFP

151 GSHTYVWQVL KENGPMA SDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 201 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 251 HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
 301 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
 5 351 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 401 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 451 TDETFKTREA IQHESGILGP LLYGEVGD TL LIIFKNQASR PYNIPHGIT
 501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 10 601 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MUYEDTLTLF PFSGETVFMS
 701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL
 751 SKNNAIEPRS FSQNPPVLKR HQREITRTTL QSDQEEIDYD DTISVEMKKE
 801 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP HVLNRNAQSG
 15 851 SVPQFKKVV FQEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
 901 RNQASRPYSF YSSLISYEED QRQGAEPKRN FVKPNETKTY FWKVQH HMAP
 951 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE
 1001 FALFFTIFDE TKS WYFTENM ERNCRAPCNI QMEDPTFKEN YRFHAINGYI
 1051 MDTLPLGVMA QDQIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYK MAL
 20 1101 YNLYPGVFET VEMPLSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
 1151 GMASGHIRDF QITASGQYGG WAPKLARLHY SGSINAWSTK EPFSWIKVDL
 1201 LAPMIIHGK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
 1251 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGC DLNSCS
 1301 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
 25 1351 PKEWLQVDFQ KTMKVTGVTT QGVKSLTSM YVKEFLISS QDGHQWTLFF
 1401 QNGKVKVFQ NQDSFTPVVN SLDPPLTRY LRIHPQSWVH QIALRMEVLG
 1451 CEAQDLYDKT HTPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
 1501 VDVSHEDPEV KFNWYVDGVE VHNATKPRE EQYNSTYRVV SVLTVLHQDW
 1551 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV
 30 1601 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDS DGS FFLYSKLTVD
 1651 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

FVIII 195 protein sequence (dual chain FVIII Fc with two 144 AE XTENs at amino acid 1656 and 1900) (SEQ ID NO: 73)

35 1 MQIELSTCFF LCLLRFCFSA TRRYYLGA VE LSWDYMQSDL GELPVDARFP
 51 PRVPKSF PFN TSVVYKKT LF VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 101 DTVVITLKNM ASHPVSLHAV GVS YWKASEG AEYDDQTSQR EKEDDKVFPG
 151 GSHTYVWQVL KENGPMA SDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 201 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 40 251 HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
 301 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
 351 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 401 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 451 TDETFKTREA IQHESGILGP LLYGEVGD TL LIIFKNQASR PYNIPHGIT
 45 501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 601 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MUYEDTLTLF PFSGETVFMS
 701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL
 50 751 SKNNAIEPRS FSQNPPVLKR HQREITRTTL QGAPGTPGSG TASSSPGASP
 801 GTSSTGSPGA SPGTSSTGSP GASPGTSSTG SPGSSPSAST GTGPGTPGSG
 851 TASSSPGASP GTSSTGSPGA SPGTSSTGSP GASPGTSSTG SPGSSTPSGA

901 TGSPGSSTPS GATGSPGASP GTSSTGSPAS SSDQEEIDYD DTISVEMKKE
 951 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP HVLRNRAQSG
 1001 SVPQFKKVV FQEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
 1051 RNQASRPYSF YSSLISYEED QRQGAEPKRN FVKPNETKTY FWKVQHHPMAP
 5 1101 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNLTNP AHGRQVTVQE
 1151 FALFFTIFDE TKSIFYFTENM ERNCRGAPTS ESATPESGPG SEPATSGSET
 1201 PGTSESATPE SGPGSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG
 1251 TSESATPESG PGSPAGSPTS TEEGSPAGSP TSTEESGSPAG SPTSTEEGTS
 1301 ESATPESGPG TSTEPSEGS PGASSAPCNI QMEDPTFKEN YRFHAINGYI
 10 1351 MDTLPLGLVMA QDQRIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
 1401 YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
 1451 GMASGHIRDF QITASGQYQG WAPKLARLHY SGSINAWSTK EPFSWIKVDL
 1501 LAPMIIHGK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
 1551 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS
 15 1601 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
 1651 PKEWLQVDFQ KTMKVTGVTT QGVKSLTSM YVKEFLISS QDGHQWTLFF
 1701 QNGKVKVFQ NQDSFTPVVN SLDPPLTRY LRIHPQSWVH QIALRMEVLG
 1751 CEAQDLYDKT HTCPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
 1801 VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW
 20 1851 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV
 1901 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSGGS FFLYSKLTVD
 1951 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

25 **pSYN-FVIII-173 mature Protein sequencing (SEQ ID NO: 72):**

1 ATRRYYLGA VELS WDYMQSD LGELPVDARF PPRVPKSFPF NTSVVYKKT
 51 FVEFTDHLFN IAKPRPPWMG LLGPTIAEV YDTVVITLKN MASHPVS LHA
 101 VGVSYWKASE GA EYDDQTSQ REKEDDKVFP GGSHTYVWQV LKENGPMASD
 151 PLCLTYSYLS HVDLVKDLNS GLIGALLVCR EGSLAKEKTQ TLHKFILLFA
 30 201 VFDEGKSWHS ETKNSLMQDR DAASARAWPK MHTVNGYVNR SLPGLIGCHR
 251 KSVYWHVIGM GTTPEVHSIF LEGHTFLVRN HRQASLEISP ITFLTAQTLL
 301 MDLGQFLLC HISSHQHDGM EAYVKVDSCP EEPQLRMKNN EEAEDYDDDL
 351 TDSEMDVVR FDDD NPSFIQ IRVAKKHPK TWVHYIAAEE EDWDYAPLV L
 401 APDDRSYKSQ YLNNGPQRIG RKYKKVRFMA YTDFTFKTRE AIQHESGILG
 35 451 PLYGEVGD TLLIFKNQAS RPYNIYPHGI TDVRPLYSR LPKGVKHLKD
 501 FPILPGEIFK YKWTVTVEDG PTKSDPRCLT RYYSFVNME RDLASGLIGP
 551 LLICYKESVD QRGNQIMSDK RNVLFSVFD ENRSWYL TENIQRFLPNPAG
 601 VQLEDPEFQA SNIMHSINGY VFDSLQLSVC LHEVAYWYIL SIGAQTDFLS
 651 VFFSGYTFKH KVMYEDTLTL PFPSGETVFM SMENPGLWIL GCHNSDFRNR
 40 701 GMTALLKVSS CDKNTGDYEE DSYEDISAYL LSKNNAIEPR SFSQNGAPGT
 751 SESATPESGP GSEPATSGSE TPGTSESATP ESGPGSEPAT SGSETPGTSE
 801 SATPESGPGT STEPSEGSAP GSPAGSPTST EEGTSESATP ESGPGSEPAT
 851 SGSETPGTSE SATPESGPGS PAGSPTSTEE GSPAGSPTST EEGTSTEPSE
 901 GSAPGTSESA TPESGPGTSE SATPESGPGT SESATPESGP GSEPATSGSE
 45 951 TPGSEPATSG SETPGSPAGS PTSTEEGTST EPSEGSAPGT STEPSEGSAP
 1001 GSEPATSGSE TPGTSESATP ESGPGTSTEP SEGSAPASSP PVLKRHQREI
 1051 TRTTLQSDQE EIDYDDTISV EMKKEDFDIY DEDENQSPRS FQKKTRHYFI
 1101 AAVRLWDYQ MSSSPHVLNR RAQSGSVQF KKVV FQEFTD GSFTQPLYRG
 1151 ELNEHLGLLG PYIRAEVEDN IMVTFRNQAS RPYSFYSSLI SYEEDQRQGA
 50 1201 EPRKNFVKPN ETKTYFWKVQ HHMAPTKDEF DCKAWAYFSD VDLEKDVHSG
 1251 LIGPLLVCHT NTLNPAHGRQ VTQEFALFF TIFDETKSWY FTENMERNCR
 1301 APCNIQMEDP TFKENYRFHA INGYIMDTLP GLVMAQDQRI RWYLLSMGSN
 1351 ENIHSIHFSG HVFTVRKKEE YKMALYNLYP GVFETVEMLP SKAGIWRVEC

1401 LIGEHLHAGM STLFLVYSNK CQTPLGMASG HIRDFQITAS GQYQGWAPKL
 1451 ARLHYSGSIN AWSTKEPFSW IKVDLLAPMI IHGIKTQGAR QKFSSLYISQ
 1501 FIIMYSLDGK KWQTYRGNST GTLMVFFGNV DSSGIKHNIF NPPIARYIR
 1551 LHPHTYSIRS TLRMELMGCD LNSCSMPLGM ESKAISDAQI TASSYFTNMF
 5 1601 ATWSPSKARL HLQGRSNAWR PQVNNPKEWL QVDFQKTMKV TGVTTQGVKS
 1651 LLTSMYVKEF LISSSQDGHQ WTLFFQNGKV KVFQGNQDSF TPVVNSLDPP
 1701 LLTRYLRIHP QSWVHQIALR MEVLGCEAQD LYDKTHTCPP CPAPELLGGP
 1751 SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK
 1801 TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK
 10 1851 AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE
 1901 NNYKTPPVVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVML HEALHNHYTQ
 1951 KSLSLSPGK

FVIII 196 protein sequence (dual chain FVIII Fc with three 144 AE XTENs at amino acid 26, 1656 and 1900) (SEQ ID NO: 74)

15 1 MQIELSTCFF LCLLRFCFSA TRRYYLGAWE LSWDYMQSDL GELPVGAPGS
 51 SPSASTGTGP GSSPSASTGT GPGASPGTSS TGSPGASPGT SSTGSPGSST
 101 PSGATGSPGS SPSASTGTGP GASPGTSSTG SPGSSPSAST GTGPGTPGSG
 151 TASSSPGSST PSGATGSPGS STPSGATGSP GASPGTSSTG SPASSDARFP
 20 201 PRVPKSFPPN TSVVYKKTLE VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 251 DTVVITLKNM ASHPVSLHAV GVSYWKASEG AEYDDQTSQR EKEDDKVFPG
 301 GSHTYVWQVL KENGPMSADP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 351 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 401 HTVNGYVNRS LPLIGCHRK SVYWHVIGMG TPEVHSIFL EGHTFLVRNH
 25 451 RQASLEISPI TFLTAQTLLM DLGQFLFCH ISSHQHDGME AYVKVDSCPE
 501 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 551 WWHYIAAEEE DWDYAPLVA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 601 TDETFKTREA IQHESGILGP LLYGEVGDLE LIIFKNQASR PYNIPHGIT
 651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 30 701 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 751 NRSWYL TENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 801 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVEYEDTLTLF PFSGETVFMS
 851 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL
 901 SKNNAIEPRS FSQNPPVLKR HQREITRRTL QGAPGTPGSG TASSSPGASP
 35 951 GTSSTGSPGA SPGTSSTGSP GASPGTSSTG SPGSSPSAST GTGPGTPGSG
 1001 TASSSPGASP GTSSTGSPGA SPGTSSTGSP GASPGTSSTG SPGSSTPSGA
 1051 TGSPGSSTPS GATGSPGASP GTSSTGSPAS SSDQEEDIDYD DTISVEMKKE
 1101 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP HVLNRNAQSG
 1151 SVPQFKKVVV QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
 40 1201 RNQASRPYSF YSSLISYEED QRQGAEPKRN FVKPNETKTY FWKVQHHPMAP
 1251 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNLTNP AHGRQVTVQE
 1301 FALFFTIFDE TKSIFYTENM ERNCRGAPTS ESATPESGPG SEPATSGSET
 1351 PGTSESATPE SGPGSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG
 1401 TSESATPESG PGSPAGSPTS TEEGSPAGSP TSTEEGSPAG SPTSTEEGTS
 45 1451 ESATPESGPG TSTEPSEGA PGASSAPCNI QMEDPTFKEN YRFHAINGYI
 1501 MDTLPLGLVMA QDQIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
 1551 YNLYPGVFET VEMLPKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPLE
 1601 GMASGHIRDF QITASGYGQ WAPKLARLHY SGSINAWSTK EPFSWIKVDL
 1651 LAPMIIHGK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
 50 1701 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS
 1751 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
 1801 PKEWLQVDFQ KTMKVTVGVT QGVKSLTSM YVKEFLISS QDGHQWTLFF
 1851 QNGKVKVFQG NQDSFTPVVN SLDPPLTRY LRIHPQSWVH QIALRMEVLG

1901 CEAQDLYDKT HTCPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
 1951 VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW
 2001 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV
 2051 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSGDS FFLYSKLTVD
 5 2101 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

**FVIII 199 protein sequence (single chain FVIII Fc with three 144 AE XTENS
 at amino acid 1656 and 1900) (SEQ ID NO: 75)**

10 1 MQIELSTCFF LCLLRFCFSA TRRYYLGAWE LSWDYMQSDL GELPVDARFP
 51 PRVPKSF PFN TSVVYKKTLF VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 101 DTVVITLKNM ASHPVSLHAV GVSYWKA SEG AEYDDQTSQR EKEDDKVFPG
 151 GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 201 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 15 251 HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
 301 RQASLEISPI TFLTAQTLLM DLGQFLFCH ISSHQHDGME AYVKVDSCPE
 351 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 401 WVHYIAAEEE DWDYAPLVA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 451 TDETFKTREA IQHESGILGP LLYGEVGD TL LIIFKNQASR PYNIPHGIT
 20 501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 601 NRSWYL TENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVEYEDTLTLF PFSGETVFMS
 701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYD YEDISAYLL
 25 751 SKNNAIEPRS FSQNPVLKR HQAEITRTTL QGAPGTPGSG TASSSPGASP
 801 GTSSTGSPGA SPGTSSTGSP GASPGTSSTG SPGSSPSAST GTGPGTPGSG
 851 TASSSPGASP GTSSTGSPGA SPGTSSTGSP GASPGTSSTG SPGSSPSGA
 901 TGSPGSSTPS GATGSPGASP GTSSTGSPAS SSDQEEIDYD DTISVEMKKE
 951 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP HVLRNRAQSG
 30 1001 SVPQFKKVV F QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
 1051 RNQASRPYSF YSSLISYEED QRQGAEP RKN FVKPNETKTY FWKVQH HMAP
 1101 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE
 1151 FALFFTIFDE TKS WYFTENM ERNCRGAPTS ESATPESGPG SEPATSGSET
 1201 PGTSESATPE SGPGSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG
 35 1251 TSESATPESG PGSPAGSPTS TEEGSPAGSP TSTEEGSPAG SPTSTEEGTS
 1301 ESATPESGPG TSTEPSEGS A PGASSAPCNI QMEDPTFKEN YRFHAINGYI
 1351 MDTLPGLVMA QDQRIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
 1401 YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
 1451 GMASGHIRDF QITASGQY GQ WAPKLARLHY SGSINAWSTK EPFSWIKVDL
 40 1501 LAPMIIHG IK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
 1551 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS
 1601 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
 1651 PKEWLQVDFQ KTMKVTGVTT QGVKSLLTSM YVKEFLISS QDGHQWTLFF
 1701 QNGKVKVFQG NQDSFTPVVN SLDPPLTRY LRIHPQSWVH QIALRMEVLG
 45 1751 CEAQDLYDKT HTCPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
 1801 VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW
 1851 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV
 1901 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSGDS FFLYSKLTVD
 1951 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

FVIII 201 protein sequence (single chain FVIII Fc with three 144 AE XTENS

at amino acid 26, 1656 & 1900) (SEQ ID NO: 76)

1 MQIELSTCFF LCLLRFCFSA TRYYLGAVE LSWDYMQSDL GELPVGAPGS
 51 SPSASTGTGP GSSPSASTGT GPGASPGTSS TGSPGASPGT SSTGSPGSST
 5 101 PSGATGSPGS SPSASTGTGP GASPGTSSTG SPGSSPSAST GTGPGTPGSG
 151 TASSSPGSST PSGATGSPGS STPSGATGSP GASPGTSSTG SPASSDARFP
 201 PRVPKSFPFN TSVVYKKTFL VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 251 DTVVITLKNM ASHPVSLHAV GVSYWKASEG AEYDDQTSQR EKEDDKVFPG
 301 GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 10 351 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 401 HTVNGYVNRS LPLIGCHRK SVYWHVIGMG TPEVHSIFL EGHTFLVRNH
 451 RQASLEISPI TFLTAQTLLM DLGQFLFCH ISSHQHDGME AYVKVDSCE
 501 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 551 WVHYIAAEEE DWDYAPLVA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 15 601 TDETFKTREA IQHESGILGP LLYGEVGDIT LIIFKNQASR PYNIYPHGIT
 651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 701 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 751 NRSWYL TENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 801 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVEYEDTLTLF PFSGETVFMS
 20 851 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL
 901 SKNNAIEPRS FSQNPPVLKR HQAEITRTTL QGAPGTPGSG TASSSPGASP
 951 GTSSTGSPGA SPGTSSTGSP GASPGTSSTG SPGSSPSAST GTGPGTPGSG
 1001 TASSSPGASP GTSSTGSPGA SPGTSSTGSP GASPGTSSTG SPGSSTPSGA
 1051 TGSPGSSTPS GATGSPGASP GTSSTGSPAS SSDQEEIDYD DTISVEMKKE
 25 1101 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP HVLNRNAQSG
 1151 SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
 1201 RNQASRPYSF YSSLISYEED QRQGAEPKRN FVKPNETKTY FWKVQHMAP
 1251 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE
 1301 FALFFTIFDE TKSIFYTENM ERNCRGAPTS ESATPESGPG SEPATSGSET
 30 1351 PGTSESATPE SGPSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG
 1401 TSESATPESG PGSPAGSPTS TEEGSPAGSP TSTEEGSPAG SPTSTEEGTS
 1451 ESATPESGPG TSTEPSEGA PGASSAPCNI QMEDPTFKEN YRFHAINGYI
 1501 MDLTPGLVMA QDQIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
 1551 YNLYPGVFET VEMLPKAGI WRVECLIGEH LHAGMSTLFL VYSNKQCTPL
 35 1601 GMASGHIRDF QITASGQYQG WAPKLARLHY SGSINAWSTK EPFSWIKVDL
 1651 LAPMIIHGK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
 1701 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSC
 1751 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
 1801 PKEWLQVDFQ KTMKVTGVTT QGVKSLTSM YVKEFLISS QDGHQWTLFF
 40 1851 QNGKVKVFQ NQDSFTPVVN SLDPLLTRY LRIHPQSWVH QIALRMEVLG
 1901 CEAQDLYDKT HTCPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
 1951 VDVSHEDPEV KFNWYVDGVE VNAKTKPRE EQYNSTYRVV SVLTVLHQDW
 2001 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV
 2051 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSGGS FFLYSKLTVD
 45 2101 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

FVIII 203 protein sequence (single chain FVIIIc with two AE XTENS; one 288AE XTEN in B-domain and one 144 AE XTEN at amino acid 1900) (SEQ ID NO: 77)

50 1 MQIELSTCFF LCLLRFCFSA TRYYLGAVE LSWDYMQSDL GELPVDARFP
 51 PRVPKSFPFN TSVVYKKTFL VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 101 DTVVITLKNM ASHPVSLHAV GVSYWKASEG AEYDDQTSQR EKEDDKVFPG
 151 GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE

201 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 251 HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
 301 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
 351 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 5 401 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 451 TDETFKTREA IQHESGILGP LLYGEVGD TL LIIFKNQASR PYNIPHGIT
 501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 601 NRSWYL TENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 10 651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVEDTLTLF PFSGETVFMS
 701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYED SYEDISAYLL
 751 SKNNAIEPRS FSQNGAPGTS ESATPESGPG SEPATSGSET PGTSESATPE
 801 SGPGSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG SPAGSPTSTE
 851 EGTSESATPE SGPGSEPATS GSETPGTSES ATPESGPGSP AGSPTSTEEG
 15 901 SPAGSPTSTE EGTSTEPSEG SAPGTSESAT PESGPGTSES ATPESGPGTS
 951 ESATPESGPG SEPATSGSET PGSEPATSGS ETPGSPAGSP TSTEEGTSTE
 1001 PSEGSAPGTS TEPSEGSAPG SEPATSGSET PGTSESATPE SGPSTSTEPS
 1051 EGSAPASSPP VLKRHQAEIT RTTLQSDQEE IDYDDTISVE MKKEDFDIYD
 1101 EDENQSPRSF QKKTRHYFIA AVERLWDYGM SSSPHVLRNR AQSGSVQPK
 20 1151 KVVVFQFTDG SFTQPLRGE LNEHLGGLGP YIRAEVEDNI MVTFRNQASR
 1201 PYSFYSSLIS YEEDQRQGA PRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
 1251 CKAWAYFSDV DLEKDVHSGI IGPLL VCHTN TLNPAHGRQV TVQEFALFFT
 1301 IFDETKSWYF TENMERNCRG APTSESATPE SGPGSEPATS GSETPGTSES
 1351 ATPESGPGSE PATSGSETPG TSESATPESG PGTSTEPSEG SAPGTSESAT
 25 1401 PESGPGSPAG SPTSTEEGSP AGSPTSTEEG SPAGSPTSTE EGTSESATPE
 1451 SGPSTSTEPS EGSAPGASSA PCNIQMEDPT FKENYRFHAI NGYIMDTLPG
 1501 LVMAQDQIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
 1551 VFETVEMLP KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPLGMASGH
 1601 IRDFQITASG QYGQWAPKLA RLHYSGSINA WSTKEPFSWI KVDLLAPMII
 30 1651 HGIKTQGARQ KFSSLYISQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
 1701 SSGIKHNIFN PPIARYIRL HPTHYSIRST LRMELMGCDL NSCSMPLGME
 1751 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ
 1801 VDFQKTMKVT GVTQGVKSL L TSMYVKEFL ISSQDGHQW TLFFQNGKVK
 1851 VFQGNQDSFT PVVNSLDPL LTRYLRHPQ SWVHQIALRM EVLGCEAQDL
 35 1901 YDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
 1951 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
 2001 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDEL TKNQVSLTCLV
 2051 KGFYPSDIAV EWESNGQPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
 2101 GNVFSCSVMH EALHNHYTQK SLSLSPGK*

FVIII 204 protein sequence (single chain FVIII Fc with two AE XTENs; one 288AE XTEN in B-domain and one 144 AE XTEN at amino acid 403) (SEQ ID NO: 78)

45 1 MQIELSTCFF LCLLRFCFSA TRRYYLGA VE LSWDYMQSDL GELPVDARFP
 51 PRVPKSFPFN TSVVYKKT LF VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 101 DTVVITLKNM ASHPVSLHAV GVSYWKA SEG AEYDDQTSQR EKEDDKVFPG
 151 GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 201 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 50 251 HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
 301 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
 351 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 401 WVHYIAAEEE DWDYAPLVLA PDGAPTSTEP SEGSA PGSPA GSPTSTEEGT

451 STEPSEGSAP GTSTEPSEGS APGTSESATP ESGPGTSTEP SEGSAPGTSE
 501 SATPESGPGS EPATSGSETP GTSTEPSEGS APGTSTEPSE GSAPGTSESA
 551 TPESGPGTSE SATPESGPGA SSDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 601 TDETFKTREA IQHESGILGP LLYGEVGD TL LIIFKNQASR PYNIYPHGIT
 5 651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 701 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 751 NRSWYL TENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 801 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MUYEDTLTLF PFSGETVFMS
 851 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYED SYEDISAYLL
 10 901 SKNNAIEPRS FSQNGAPGTS ESATPESGPG SEPATSGSET PGTSESATPE
 951 SGPGSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG SPAGSPTSTE
 1001 EGTSESATPE SGPGSEPATS GSETPGTSES ATPESGPGSP AGSPTSTEEG
 1051 SPAGSPTSTE EGTSTEPSEG SAPGTSESAT PESGPGTSES ATPESGPGTS
 1101 ESATPESGPG SEPATSGSET PGSEPATSGS ETPGSPAGSP TSTEEGTSTE
 15 1151 PSEGSAPGTS TEPSEGSAPG SEPATSGSET PGTSESATPE SGPGTSTEPS
 1201 EGSAPASSPP VLKRHQAEIT RTTLQSDQEE IDYDDTISVE MKKEDFDIYD
 1251 EDENQSPRSF QKKTRHYFIA AVERLWDYGM SSSPHVLRNR AQSGSVQPK
 1301 KVVVFQFTDG SFTQPL YRGE LNEHLG LLGP YIRAEVEDNI MVTFRNQASR
 1351 PYSFYSSLIS YEEDQRQGA PRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
 20 1401 CKAWAYFSDV DLEKDVHSGI IGPLLCHTN TLNPAHGRQV TVQEFALFFT
 1451 IFDETKSWYF TENMERN CRA PCNIQMEDPT FKENYRFHAI NGYIMDTLPG
 1501 LVMAQDQIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
 1551 VFETVEMLP S KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPLGMASGH
 1601 IRDFQITASG QYGQWAPKLA RLHYSGSINA WSTKEPFSWI KVDLLAPMII
 25 1651 HGIKTQGARQ KFSSLYISQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
 1701 SSGIKHNIFN PPIIARYIRL HPTHYSIRST LRMELMGCDL NSCSMPLGME
 1751 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ
 1801 VDFQKTMKVT GVTTQGVKSL L TSMYVKEFL ISSSQDGHQW TLFFQNGKVK
 1851 VFQGNQDSFT PVVNSLDPL LTRYLRIHPQ SWVHQIALRM EVLGCEAQDL
 30 1901 YDKTHTCPC PAPERLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
 1951 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
 2001 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV
 2051 KGFYPSDIAV EWESNGOPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
 2101 GNVFSCSVMH EALHNHYTQK SLSLSPGK*
 35

FVIII 205 protein sequence (single chain FVIIIc with two AE XTENs; one 288AE XTEN in B-domain and one 144 AE XTEN at amino acid 18) (SEQ ID NO: 79)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGA VE LSWDYMQGAP TSESATPESG
 40 51 PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
 101 TSTEPSEGA PGSPAGSPTS TEEGTSESAT PESGPGSEPA TSGSETPGTS
 151 ESATPESGPG SPAGSPTSTE EGSPAGSPTS TEEGASSDL GELPVDARF
 201 PRVPKSPFN TSVVYKKT LF VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 251 DTVVITLKNM ASHPVSLHAV GVS YWKASEG AEYDDQTSQR EKEDDKVFP
 45 301 GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 351 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 401 HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
 451 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
 501 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 50 551 WVHYIAAEEE DWDYAPLVA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 601 TDETFKTREA IQHESGILGP LLYGEVGD TL LIIFKNQASR PYNIYPHGIT
 651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 701 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE

751 NRSWYL TENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 801 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MUYEDTLTLF PFSGETVFMS
 851 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYED SYEDISAYLL
 901 SKNNAIEPRS FSQNGAPGTS ESATPESGPG SEPATSGSET PGTSESATPE
 5 951 SGPGSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG SPAGSPTSTE
 1001 EGTSESATPE SGPGSEPATS GSETPGTSES ATPESGPGSP AGSPTSTEEG
 1051 SPAGSPTSTE EGTSTEPSEG SAPGTSESAT PESGPGTSES ATPESGPGTS
 1101 ESATPESGPG SEPATSGSET PGSEPATSGS ETPGSPAGSP TSTEEGTSTE
 1151 PSEGSAPGTS TEPSEGSAPG SEPATSGSET PGTSESATPE SGPSTSTEPS
 10 1201 EGSAPASSPP VLKRHQAEIT RTTLQSDQEE IDYDDTISVE MKKEDFDIYD
 1251 EDENQSPRSF QKKTRHYFIA AVERLWDYGM SSSPHVLRNR AQSGSVQFK
 1301 KVVVFQFTDG SFTQPLYRGE LNEHLGLLGP YIRAEVEDNI MVTFRNQASR
 1351 PYSFYSSLIS YEEDQRQGA EPRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
 1401 CKAWAYFSDV DLEKDVHSG LIGPLLCHTN TLNPAHGRQV TVQEFALFFT
 15 1451 IFDETKSWYF TENMERN CRA PCNIQMEDPT FKENYRFHAI NGYIMDTLPG
 1501 LVMAQDQIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
 1551 VFETVEMLP S KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPLGMASGH
 1601 IRDFQITASG QYGQWAPKLA RLHYSGSINA WSTKEPFSWI KVDLLAPMII
 1651 HGIKTQGARQ KFSSLYISQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
 20 1701 SSGIKHNIFN PPIIARYIRL HPTHYSIRST LRMELMGCDL NSCSMPLGME
 1751 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ
 1801 VDFQKTMKVT GVTQGVKSL L TSMYVKEFL ISSSQDGHQW TLFFQNGKVK
 1851 VFQGNQDSFT PVVNSLD PPL LTRYLRIHPQ SWVHQIALRM EVLGCEAQDL
 1901 YDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
 25 1951 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
 2001 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDEL TKNQVSLTCLV
 2051 KGFYPSDIAV EWESNGQPEN NYKTTTPVLD SDGSFFLYSK LTVDKSRWQQ
 2101 GNVFSCSVMH EALHNHYTQK SLSLSPGK*

30

pSYN FVIII 266 protein sequence (FVIII Fc with 42 AE-XTEN at amino acid 18 and 288 AE XTEN in B-domain) SEQ ID NO: 80)

35 1 MQIELSTCFF LCLLRFCFSA TRRYYLGA VE LSWDYMQGAP GSPAGSPTST
 51 EGTSESATP ESGPGSEPA T SGSETPASSS DLGELPVDAR FPPRVPKSF
 101 FNTSVVYKKT LFVEFTDHLF NIAKPRPPWM GLLGPTIQAE VYDTVVITLK
 151 NMASHPVSLH AVGVSYWKAS EGA EYDDQTS QREKEDDKVF PGGSHTYVWQ
 201 VLKENGPMAS DPLCLTYSYL SHVDLVKDLN SGLIGALLVC REGSLAKEKT
 40 251 QTLHKFILLF AVFDEGKSWH SETKNSLMQD RDAASARAWP KMHTVNGYVN
 301 RSLPGLIGCH RKS VYWHVIG MGTTPPEVHSI FLEGHTFLVR NHRQASLEIS
 351 PITFLTAQTL LMDLGQFLLF CHISSHQHDG MEAYVKVDSC PEEPQLRMKN
 401 NEEAEDYDDD LTDSEMDVVR FDDDNPSFI QIRSVAKKHP KTWVHYIAAE
 451 EEDWDYAPLV LAPDDRSYKS QYLNNGPQRI GRKYKKVRFM AYTDETFKTR
 45 501 EAIQHESGIL GPLLYGEVGD TLLIIFKNQA SRPYNIPHG ITDVRPLYSR
 551 RLPKGVKHLK DFPILPGEIF KYKWTVTVED GPTKSDPRCL TRYYSFVNM
 601 ERDLASGLIG PLLICYKESV DQRGNQIMSD KRNVLFSVF DENRSWYLTE
 651 NIQRFLPNPA GVQLEDPEFQ ASNIMHSING YVFDSLQLSV CLHEVAYWYI
 701 LSIGAQTDFL SVFFSGYTFK HKMUYEDTLT LFPFSGETVF MSMENPGLWI
 50 751 LGCHNSDFRN RGMTALLKVS SCDKNTGDY EDSYEDISAY LLSKNNAIEP
 801 RSFSQNGAPG TSESATPESG PGSEPATSGS ETPGTSESAT PESGPGSEPA
 851 TSGSETPGTS ESATPESGPG TSTEPSEGS A PGSPAGSPTS TEEGTSESAT
 901 PESGPGSEPA TSGSETPGTS ESATPESGPG SPAGSPTSTE EGSPAGSPTS

951 TEEGTSTEPS EGSAPGTSES ATPESGPGTS ESATPESGPG TSESATPESG
 1001 PGSEPATSGS ETPGSEPATS GSETPGSPAG SPTSTEEGTS TEPSEGSAPG
 1051 TSTEPSEGS A PGSEPATSGS ETPGTSESAT PESGPGTSTE PSEGSAPASS
 1101 PPVLKRHQAE ITRTTLQSDQ EEIDYDDTIS VEMKKEDFDI YDEDENQSPR
 5 1151 SFQKKTRHYF IAAVERLWDY GMSSSPHVLN NRAQSGSVPQ FKKVVFQEFT
 1201 DGSFTQPLYR GELNEHLGGL GPYIRAEVED NIMVTFRNQA SRPYSFYSSL
 1251 ISYEEDQRQG AEPRKNFVKP NETKTYFWKV QHHMAPTKDE FDCKAWAYFS
 1301 DVDLEKDVHS GLIGPLL VCH TNTLNPAHGR QVTVQEFALF FTIFDETKSW
 1351 YFTENMERN RAPCNIQMED PTFKENYRFH AINGYIMDTL PGLVMAQDQR
 10 1401 IRWYLLSMGS RAPHNIHFS GHVFTVRKKE EYKMALYNLY PGVFETVEML
 1451 PSKAGIWRVE CLIGELHAG MSTLFLVYSN KCQTPLGMAS GHIRDFQITA
 1501 SGQYGQWAPK LARLHYSGLI NAWSTKEPFS WIKVDLLAPM IIHGIKTQGA
 1551 RQKFSSLYIS QFIIMYSLDG KKWQTYRGNS TGTLMVFFGN VDSSGIKHNI
 1601 FNPPIIARYI RLHPHTHSIR STLRMELMGC DLNSCSMPLG MESKAISDAQ
 15 1651 ITASSYFTNM FATWSPSKAR LHLQGRSNAW RPQVNNPKKEW LQVDFQKTMK
 1701 VTGVTQGVK SLLTSMYVKE FLISSQDGH QWTLFFQNGK VKVFQGNQDS
 1751 FTPVVNSLDP PLLTRYLRIH PQSWVHQIAL RMEVLGCEAQ DLYDKTHTCP
 1801 PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW
 1851 YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLNQDQWLNGK EYKCKVSNKA
 20 1901 LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE LTKNQVSLTLC LVKGFYPSDI
 1951 AVEWESNGQP ENNYKTPPV LQSDGSFFLY SKLTVDKSRW QQGNVVFSCSV
 2001 MHEALHNHYT QKSLSLSPGK *

25 **pSYN FVIII 267 protein sequence (FVIII Fc with 72 AE-XTEN at amino acid 18 and 288
 AE XTEN in B-domain) SEQ ID NO: 81)**

1 MQIELSTCFF LCLLRFCFSA TRYYLGAVE LSWDYMQGAP TSESATPESG
 51 PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
 30 101 TSTEPSEGS A PGASSDLGE LPVDARFPPR VPKSFPFNTS VVYKKTFLVE
 151 FTDHLFNIAK PRPPWMGLLG PTIQAEVYDT VVITLKNMAS HPVSLHAVGV
 201 SYWKASEGAE YDDQTSQREK EDDKVFPFGS HTYVWQVLKE NGPMASDPLC
 251 LTYSYLSHVD LVKDLNSGLI GALLVCREGS LAKEKTQTLH KFIILLFAVFD
 301 EGKSWHSETK NSLMQDRDAA SARAWPKMHT VNGYVNRSLP GLIGCHRKSV
 35 351 YWHVIGMGTT PEVHSIFLEG HTFLVRNHRQ ASLEISPITF LTAQTLLMDL
 401 GQFLLFCHIS SHQHDGMEAY VKVDSCPEEP QLRMKNNEEA EDYDDDLTDS
 451 EMDVVRFDLDD NSPSFIQIRS VAKKHPKTWV HYIAAEEEDW DYAPLV LAPD
 501 DRSYKSQYLN NGPQRIGRKY KKVRFMAYTD ETFKTREAIQ HESGILGPLL
 551 YGEVGDITLL IFKNQASRPY NIYPHGITDV RPLYSRRLPK GVKHLKDFPI
 40 601 LPGEIFKYKW TVTVEDGPTK SDPRCLTRY Y SSFVNMERDL ASGLIGPLLI
 651 CYKESVDQRG NQIMSDKRN ILFSVFDENR SWYLTENIQR FLPNPAGVQL
 701 EDPEFQASNI MHSINGYVFD SLQLSVCLHE VAYWYILSIG AQTDFLSVFF
 751 SGYTFKHKMMV YEDTLTLFPF SGETVFMSME NPGLWILGCH NSDFRNRGMT
 801 ALLKVSSCDK NTGDYYEDSY EDISAYLLSK NNAIEPRSF S QNGAPGTSES
 45 851 ATPESGPGSE PATSGSETPG TSESATPESG PGSEPATSGS ETPGTSESAT
 901 PESGPGTSTE PSEGSAPGSP AGSPTSTEEG TSESATPESG PGSEPATSGS
 951 ETPGTSESAT PESGPGSPAG SPTSTEEGSP AGSPTSTEEG TSTEPSEGS A
 1001 PGTSESATPE SGPSTSESAT PESGPGTSES ATPESGPGSE PATSGSETPG
 1051 SEPATSGSET PGSPAGSPTS TEEGTSTEPS EGSAPGTSTE PSEGSAPGSE
 50 1101 PATSGSETPG TSESATPESG PGTSTEPSEG SAPASSPPVL KRHQAEITRT
 1151 TLQSDQEEID YDDTISVEMK KEDFDIYDED ENQSPRSFQK KTRHYFIAAV
 1201 ERLWDYGMSS SPHVLNRNAQ SGSVPQFQKV VFQEFTDGSF TQPLYRGELN
 1251 EHLGLLGPYI RAEVEDNIMV TFRNQASRPY SFYSSLISYE EDQRQGAEP

1301 KNFVKPNETK TYFWKVQHMH APTKDEFDCK AWAYFSDVDL EKDVHSGSLIG
 1351 PLLVCHTNLT NPAHGRQVTV QEFALFFTIF DETKSWYFTE NMERNCRAPC
 1401 NIQMEDPTFK ENYRFHAING YIMDTLPGLV MAQDQIRWY LLSMGSNENI
 1451 HSIHFSGHVF TVRKKEEYKM ALYNLYPGVF ETVEMLPSKA GIWRVECLIG
 5 1501 EHLHAGMSTL FLVYSNKCQT PLGMASGHIR DFQITASGQY GQWAPKLARL
 1551 HYSGSINAWS TKEPFSWIKV DLLAPMIIHG IKTQGARQKF SSLYISQFII
 1601 MYSLDGKKWQ TYRGNSTGTL MVFFGNVDSS GIKHNIFNPP IIARYIRLHP
 1651 THYSIRSTLR MELMGCDLNS CSMPLGMESK AISDAQITAS SYFTNMFATW
 1701 SPSKARLHLQ GRSNAWRPQV NNPKEWLQVD FQKTMKVTGV TTQGVKSLLT
 10 1751 SMYVKEFLIS SSQDGHQWTL FFQNGKVKVF QGNQDSFTPV VNSLDPPLLT
 1801 RYLRIHPQSW VHQLALRMEV LGCEAQDLYD KTHTCPPCPA PELLGPGSVF
 1851 LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP
 1901 REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNAKALPAP IEKTISKAKG
 1951 QPREPQVYTL PPSRDELTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY
 15 2001 KTTTPVLDSG GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL
 2051 SLSPGK*

pSYN FVIII 268 protein sequence (FVIII Fc with 144 AE-XTEN at amino acid 18) SEQ ID NO: 82)

20 1 MQIELSTCFF LCLLRFCFSA TRYYLGAWE LSWDYMQGAP TSESATPESG
 51 PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
 101 TSTEPSEGS PGSPAGSPTS TEEGTSESAT PESGPGSEPA TSGSETPGTS
 151 ESATPESGPG SPAGSPTS EGSAGSPTS TEEGASSSDL GELPVDARFP
 25 201 PRVPKSFPFN TSVVYKKTFL VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 251 DTVVITLKNM ASHPVSLHAV GVSYWKASEG AEYDDQTSQR EKEDDKVFPG
 301 GSHTYVWQVL KENGPASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 351 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 401 HTVNGYVNRSLPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
 30 451 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
 501 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 551 WWHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 601 TDETFKTREA IQHESGILGP LLYGEVGDIT LIIFKNQASR PYNITYPHGIT
 651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 35 701 YYSSFNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 751 NRSWYL TENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 801 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVEYEDTLTLF PFSGETVFMS
 851 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYED SYEDISAYLL
 901 SKNNAIEPRS FSQNPVLKR HQAEITRTTL QSDQEEIDYD DTISVEMKKE
 40 951 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LDWYGMSSSP HVLNRNAQSG
 1001 SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
 1051 RNQASRPYSF YSSLISYED QRQGAEPKRN FVKPNETKTY FWKVQHMHMAP
 1101 TKDEFDCKAW AYFSDVDLEK DVHSGSLIGPL LVCHTNLTNP AHGRQVTVQE
 1151 FALFFTIFDE TKSIFYTENM ERNCRAPCNI QMEDPTFKEN YRFHAINGYI
 45 1201 MDTLPGLVMA QDQIRRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
 1251 YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
 1301 GMASGHIRDF QITASGQYQG WAPKLARLHY SGSINAWSTK EPFSWIKVDL
 1351 LAPMIIHGK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
 1401 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS
 50 1451 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
 1501 PKEWLQVDFQ KTMKVTGVTT QGVKSLTSM YVKEFLISS QDGHQWTLFF
 1551 QNGKVKVFQ NQDSFTPVVN SLDPPLTRY LRIHPQSWVH QIALRMEVLG
 1601 CEAQDLYDKT HTCPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV

1651 VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW
 1701 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV
 1751 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSGDS FFLYSKLTVD
 1801 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

5

pSYN FVIII 269 protein sequence (FVIII Fc with 72 AE-XTEN at amino acid 18) SEQ ID NO: 83)

10 1 MQIELSTCFF LCLLRFCFSA TRRYYLGAWE LSWDYMQGAP TSESATPESG
 51 PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
 101 TSTEPSEGS PGASSSDLGE LPVDARFPPR VPKSFPFNTS VVYKKTFLFE
 151 FTDHLFNI AK PRPPWMGLLG PTIQAEVYDT VVITLKNMAS HPVSLHAVGV
 201 SYWKASEGAE YDDQTSQREK EDDKVFPFGS HTYVWQVLKE NGPMASDPLC
 15 251 LTYSYLSHVD LVKDLNSGLI GALLVCREGS LAKEKTQTLH KFILLFAVFD
 301 EGKSWHSETK NSLMQDRDAA SARAWPKMHT VNGYVNRSLP GLIGCHRKSV
 351 YWHVIGMGTT PEVHSIFLEG HTFLVRNHRQ ASLEISPITF LTAQTLLMDL
 401 GQFLLFCHIS SHQHDGMEAY VKVDSCPEEP QLRMKNNEEA EDYDDDLTDS
 451 EMDVVRFD DD NSPSFIQIRS VAKKHPKTWV HYIAAEEEDW DYAPLV LAPD
 20 501 DRSYKSQYLN NGPQRIGRKY KKVRFMAYTD ETFKTREAIQ HESGILGPLL
 551 YGEVGD TLLI IFKNQASRPY NIYPHGITDV RPLYSRRLPK GVKHLKDFPI
 601 LPGEIFKYKW TVTVEDGPTK SDPRCLTRY Y SSFVNMERDL ASGLIGPLLI
 651 CYKESVDQRG NQIMSDKRN V ILFSVFDENR SWYLTENIQR FLPNPAGVQL
 701 EDPEFQASNI MHSINGYVFD SLQLSVCLHE VAYWYILSIG AQTDFLSVFF
 25 751 SGYTFKH KMV YEDTLTLFPF SGETVFMSME NPGLWILGCH NSDFRNRGMT
 801 ALLKVSSCDK NTGDYEDSY EDISAYLLSK NNAIEPRSFS QNPPVLKRHQ
 851 AEITRTTLQS DQEEIDYDDT ISVEMKKEDF DIYDEDENQS PRSFQKKTRH
 901 YFIAAVERLW DYGMSSSPHV LRNRAQSGSV PQFKKVVFQE FTDGSFTQPL
 951 YRGELNEHLG LLGPYIRAEV EDNIMVTFRN QASRPYSFYS SLISYEEDQR
 30 1001 QGAEPKRN FV KPNETKTYFW KVQH HMAPTK DEFDC KAWAY FSDVDLEKDV
 1051 HSLIGLPLLV CHTNTLNPAH GRQVTVQEFA LFFTIFDETK SWYFTENMER
 1101 NCRAPCNIQM EDPTFKENYR FHAINGYIMD TLPGLVMAQD QRIRWYLLSM
 1151 GSNENIHSIH FSGHVFTVRK KEEYKMALYN LYPGVFETVE MLPSKAGIWR
 1201 VECLIGEHLH AGMSTLFLVY SNKCQTPLGM ASGHIRDFQI TASGQYGQWA
 35 1251 PKLARLHYS G SINAWSTKEP FSWIKVDLLA PMIIHG IKTQ GARQKFSSLY
 1301 ISQFIIMYSL DGKKWQTYRG NSTGTLMVFF GNVDSSGIKH NIFNPPIAR
 1351 YIRLHPHYS IRSTLRMELM GCDLNSCSMP LGMESKAISD AQITASSYFT
 1401 NMFATWSPSK ARLHLQGRSN AWRPQVNNPK EWLQVDFQKT MKVTGVTTQG
 1451 VKSLLTSMYV KEFLISSSQD GHQWTLFFQN GKVKVFQGNQ DSFTPVVNSL
 40 1501 DPPLLTRYLR IHPQSWVHQI ALRMEVLGCE AQDLYDKTHT CPPCPAPELL
 1551 GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH
 1601 NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT
 1651 ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG
 1701 QPENNYKTTP PVLDSGDSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH
 45 1751 YTQKSLSLSP GK*

pSYNFVIII 271 protein sequence (FVIII Fc with 42 AE-XTEN at amino acid 18) SEQ ID NO: 84)

50

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAWE LSWDYMQGAP GSPAGSPTST
 51 EEGTSESATP ESGPGSEPAT SGSETPASSS DLGELPVDAR FPPRVPKSFP
 101 FNTSVVYKKT LFVEFTDHLF NIAKPRPPWM GLLGPTIQAE VYD TVVITLK

151 NMASHPVSLH AVGVSYWKAS EGAEYDDQTS QREKEDDKVF PGGSHTYVWQ
 201 VLKENGPMAS DPLCLTYSYL SHVDLVKDLN SGLIGALLVC REGSLAKEKT
 251 QTLHKFILLF AVFDEGKSWH SETKNSLMQD RDAASARAWP KMHTVNGYVN
 301 RSLPGLIGCH RKSVMYWHVIG MGTTPVHSHI FLEGHTFLVR NHRQASLEIS
 5 351 PITFLTAQTL LMDLGQFLLF CHISSHQHDG MEAYVKVDSC PEEPQLRMKN
 401 NEEAEDYDDD LTDSEMDVVR FDDDNPSFI QIRSVAKKHP KTWVHYIAAE
 451 EEDWDYAPLV LAPDDRSYKS QYLNNGPQRI GRKYKKVRFM AYTDETFKTR
 501 EAIQHESGIL GPLLYGEVGD TLLIIFKNQA SRPYNIYPHG ITDVRPLYSR
 551 RLPKGVKHLK DFPILPGEIF KYKWTVTVED GPTKSDPRCL TRYSSSFVNM
 10 601 ERDLASGLIG PLLICYKESV DQRGNQIMSD KRNVLFSVF DENRSWYLTE
 651 NIQRFLPNPA GVQLEDPEFQ ASNIMHSING YVFDLSQLSV CLHEVAYWYI
 701 LSGAQTDFL SVFFSGYTFK HKMVYEDTLT LFPFSGETVF MSMENPGLWI
 751 LGCHNSDFRN RGMTALLKVS SCDKNTGDYY EDSYEDISAY LLSKNNIAIEP
 801 RSFSQNPPVL KRHQAEITRT TLQSDQEEID YDDTISVEMK KEDFDIYDED
 15 851 ENQSPRSFQK KTRHYFIAAV ERLWDYGMSS SPHVLNRNAQ SGSVPQFKKV
 901 VFQEFTDGSF TQPLYRGELN EHLGLLGPYI RAEVEDNIMV TFRNQASRPY
 951 SFYSSLISYE EDQRQGAEPK KNFVKPNETK TYFWKVQHMM APTKDEFDCK
 1001 AWAYFSDVDL EKD VHSGLIG PLLVCHTNTL NPAHGRQVTV QEFALFFTIF
 1051 DETKSWYFTE NMERNCRAPC NIQMEDPTFK ENYRFHAING YIMDTLPGLV
 20 1101 MAQDQRIRWY LLSMGSNENI HSIHFSGHVF TVRKKEEYKM ALYNLYPGVF
 1151 ETVEMLPSKA GIWRVECLIG EHLHAGMSTL FLVYSNKCQT PLGMASGHIR
 1201 DFQITASGQY GQWAPKLARL HYSGSINAW S TKEPFSWIKV DLLAPMIHIG
 1251 IKTQGARQKF SSLYISQFII MYSLDGKKWQ TYRGNSTGTL MVFFGNVDSS
 1301 GIKHNIFNPP IIRYIRLHP THYSIRSTLR MELMGCDLNS CSMPPLGMESK
 25 1351 AISDAQITAS SYFTNMFATW SPSKARLHLQ GRSNAWRPQV NNPKEWLQVD
 1401 FQKTMKVTGV TTQGVKSLT SMYVKEFLIS SSQDGHQWTL FFQNGKVKVF
 1451 QGNQDSFTPV VNSLDPPLT RYLRIHPQSW VHQIALRMEV LGCEAQDLYD
 1501 KTHTCPPCPA PELLGGPSVF LFPKPKDTL MISRTPEVTC VVVDVSHEDP
 1551 EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC
 30 1601 KVSNAKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN QVSLTCLVKG
 1651 FYPSDIAVEW ESNGQPENNY KTTTPVLDSG GSFFLYSKLT VDKSRWQQGN
 1701 VFSCSVMHEA LHNHYTQKSL SLSPGK*

35 **pSYN FVIII protein sequence 272 (FVIII with 144 AE XTEN at amino acid 18 and 244 AE XTEN in B-domain- no Fc) SEQ ID NO: 85)**

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAWE LSWDYMQGAP TSESATPESG
 51 PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
 40 101 TSTEPSEGS PGSPAGSPTS TEEGTSESAT PESGPGSEPA TSGSETPGTS
 151 ESATPESGPG SPAGSPTS EGPAGSPTS TEEGASSDL GELPVDARFP
 201 PRVPKSFPFN TSVVYKKTFL VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 251 DTVVITLKNM ASHPVSLHAV GVSYWKAEG AEYDDQTSQR EKEDDKVFPG
 301 GSHTYVWQVL KENGPMASDP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 45 351 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 401 HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TPPEVHSIFL EGHTFLVRNH
 451 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
 501 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNPSFIIQI RSVAKKHPKT
 551 WVHYIAAEED DWYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 50 601 TDETFKTREA IQHESGILGP LLYGEVGDIT LIIFKNQASR PYNIYPHGIT
 651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 701 YYSSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 751 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL

801 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS
 851 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL
 901 SKNNAIEPRS FSQNGAPGTS ESATPESGPG SEPATSGSET PGTSESATPE
 951 SGPSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG SPAGSPTSTE
 5 1001 EGTSESATPE SGPSEPATS GSETPGTSES ATPESGPGSP AGSPTSTEEG
 1051 SPAGSPTSTE EGTSTEPSEG SAPGTSESAT PESGPGTSES ATPESGPGTS
 1101 ESATPESGPG SEPATSGSET PGSEPATSGS ETPGSPAGSP TSTEEGTSTE
 1151 PSEGSAPGTS TEPSEGSAPG SEPATSGSET PGTSESATPE SGPSTSTEPS
 1201 EGSAPASSPP VLKRHQAEIT RTTLQSDQEE IDYDDTISVE MKKEDFDIYD
 10 1251 EDENQSPRSF QKKTRHYFIA AVERLWDYGM SSSPHVLRNR AQSGSVQFK
 1301 KVVVFQFTDG SFTQPLYRGE LNEHLGLLGP YIRAEVEDNI MVTFRNQASR
 1351 PYSFYSSLIS YEEDQRQGA PRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
 1401 CKAWAYFSDV DLEKDVHSLG IGPLLVCHTN TLNPAHGRQV TVQEFALFFT
 1451 IFDETKSWYF TENMERNCR PCNIQMEDPT FKENYRFHAI NGYIMDTLPG
 15 1501 LVMAQDQIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
 1551 VFETVEMLP KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPMGASGH
 1601 IRDFQITASG QYGQWAPKLA RLHYSGSINA WSTKEPFSWI KVDLLAPMII
 1651 HGIKTQGARQ KFSSLYISQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
 1701 SSGIKHNIFN PPIARYIRL HPTHYSIRST LRMELMGCDL NSCSMPLGME
 20 1751 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ
 1801 VDFQKTMKVT GVTQGVKSL LTSYVKEFL ISSSQDGHQW TLFFQNGKVK
 1851 VFQGNQDSFT PVVNSLDPPL LTRYLRIHPQ SWVHQIALRM EVLGCEAQDL
 1901 Y*

25

pSYN-FVIII-161 protein sequence (SEQ ID NO: 69) (FVIII sequence amino acid position 1-1457;
underlined region represents Fc region; curvy underline represents cleavable linker in between first Fc
and VWF fragment; double underlined region represents VWF fragment; bold region represents
cleavable linker in between VWF fragment and Fc).

30 1 MQIELSTCFF LCLLRFCFSA TRYYLGAVE LSWDYMQSDL GELPVDARFP
 51 PRVPKSFPFN TSVVYKKTFL VEFTDHLFNI AKPRPPWMGL LGPTIQAEVY
 101 DTVVITLKNM ASHPVSLHAV GVSYWKA SEG AEYDDQTSQR EKEDDKVFPG
 35 151 GSHTYVWQVL KENGPMSADP LCLTYSYLSH VDLVKDLNSG LIGALLVCRE
 201 GSLAKEKTQT LHKFILLFAV FDEGKSWHSE TKNSLMQDRD AASARAWPKM
 251 HTVNGYVNRS LPGLIGCHRK SVYWHVIGMG TTPEVHSIFL EGHTFLVRNH
 301 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
 351 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
 40 401 WVHYIAEEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
 451 TDETFKTREA IQHESGILGP LLYGEVGD TL LIIFKNQASR PYNIPHGIT
 501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
 551 YYSSFNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
 601 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
 45 651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS
 701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL
 751 SKNNAIEPRS FSQNPVLKR HQREITRTTL QSDQEEIDYD DTISVEMKKE
 801 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP HVLRNRAQSG
 851 SVPQFKKVVV QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
 50 901 RNQASRPYSF YSSLISYED QRQGAEPKRN FVKPNETKTY FWKVQHMAP
 951 TKDEFDCAW AYFSDVLEK DVHSLGILPL LVCHTNLNP AHGRQVTVQE
 1001 FALFFTIFDE TKSIFYTENM ERNCRAPCNI QMEDPTFKEN YRFHAINGYI
 1051 MDTLPGLVMA QDQIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL

1101 YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
 1151 GMASGHIRD F QITASGQYQG WAPKLARLHY SGSINAWSTK EPFSWIKVDL
 1201 LAPMIIHGIK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
 1251 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS
 5 1301 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
 1351 PKEWLQVDFQ KTMKVTGVTT QGVKSLTSM YVKEFLISS QDGHQWTLFF
 1401 QNGKVKVFQ NQDSFTPVVN SLDPPLTRY LRIHPQSWVH QIALRMEVLG
 1451 CEAQDLYDKT HTCPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
 1501 VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHODW
 10 1551 LNGKEYKCKV SNKALPAIE KTISKAKGP REPQVYTLPP SRDELTKNOV
 1601 SLTCLVKGFY PSDIAVEWES NGOPENNYKT TPPVLDSGGS FFLYSKLTVD
 1651 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGKRRRRSG GGGSGGGGSG
 1701 GGGSGGGGSG GGGSGGGGSR KRRKRSLSR PPMVKLVCPA DNLRAEGLEC
 1751 TKTCQNYDLE CMSMGCVSGC LCPPGMVRHE NRCVALERCP CFHQGKEYAP
 15 1801 GETVKIGCNT CVCRRDKWNC TDHVC DATCS TIGMAHYLTF DGLKYLFPGE
 1851 COYVLVDY C GSNPGTFRIL VGNGKCSHPS VKCKKRVTL VEGGEIELFD
 1901 GEVNVKRP MK DETHFEVVES GRYIILLGK ALSVWDRHL SISVVLKQTY
 1951 QEKVCGLCGN FDGIONNDLT SSNLQVEEDP VDFGNSWKVS SOCADTRKVP
 2001 LDSSPATCHN NIMKQTMVDS SCRILTSDF QDCNKLVDP PYLDVCIYDT
 20 2051 CSCESIGDCA AFCDTIAAYA HVCAOHGKVV TWRTATLCPQ SCEERNLREN
 2101 G YEA EWRYNS CAPACQVTCQ HPEPLACPVO CVEGCHAHCP PGKILDELLO
 2151 TCVDPEDCPV CEVAGRRFAS GKKVTLNPSD PEHCQICHCD VVNL TCEACO
 2201 EPISG TSESA TPESGPGSEP ATSGSETPGT SESATPESGP GSEPATSGSE
 2251 TPGTSESATP ESGPGTSTEP SEGSAPGSPA GSPTSTEEGT SESATPESGP
 25 2301 GSEPATSGSE TPGTSESATP ESGPGSPAGS PTSTEEGSPA GSPTSTEEGT
 2351 STEPSEGSAP GTSESATPES GPGTSESATP ESGPGTSESA TPESGPGSEP
 2401 ATSGSETPGS EPATSGSETP GSPAGSPTST EGTSTEPSE GSAPGTSTEP
 2451 SEGSAPGSEP ATSGSETPGT SESATPESGP GTSTEPSEGS APDSGGGGSG
 2501 GGGSGGGGSG GGGSGGGGSL VPRGSGGDKT HTCPCPAPE LLGGPSVFLF
 30 2551 PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE
 2601 EQYNSTYRVV SVLTVLHODW LNGKEYKCKV SNKALPAIE KTISKAKGP
 2651 REPQVYTLPP SRDELTKNOV SLTCLVKGFY PSDIAVEWES NGOPENNYKT
 2701 TPPVLDSGGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL
 2751 SPGK

pSYN-FVIII-170 protein sequence (SEQ ID NO: 71)

1 SLSCRPPMVK LVCPADNLRA EGGLECKTCQ NYDLECMMSG CVSGCLCPPG
 51 MVRHENRCVA LERCPFHQG KEYAPGETVK IGCNTCVC RD RKWNCTDHVC
 40 101 DATCSTIGMA HYLTFDGLKY LFPGEQYVL VQDYCGSNPG TFRILVGNGK
 151 CSHPSVKCKK RVTILVEGGE IELFDGEVNV KRPMKDETHF EVVESGRYII
 201 LLLGKALS VV WDRHLSISV V LKQTYQEKVC GLCGNFDGIQ NNDLTSSNLQ
 251 VEEDPVDFGN SWKVSSQCAD TRKVPLDSSP ATCHNNIMKQ TMVDSSCRIL
 301 TSDVFQDCNK LVDPEPYLDV CIYDTCSCES IGDCAAFCDT IAAYAHVCAQ
 45 351 HGKVVTWRTA TLCPQSCEER NRENGYEA E WRYNSCAPAC QVTCQHPEPL
 401 ACPVQCVEGC HAHCPPGKIL DELLQTCVDP EDCPVCEVAG RRFASGKKVT
 451 LNPSDPEHCQ ICHCDVVNL T CEACQEPISG TSESATPESG PGSEPATSGS
 501 ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG TSTEPSEGSA
 551 PGSPAGSPTS TEEGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
 50 601 SPAGSPTSTE EGSPAGSPTS TEEGTSTEPS EGSAPGTSES ATPESGPGTS
 651 ESATPESGPG TSESATPESG PGSEPATSGS ETPGSEPATS GSETPGSPAG
 701 SPTSTEEGTS TEPSEGSAPG TSTEPSEGSA PGSEPATSGS ETPGTSESAT
 751 PESGPGTSTE PSEGSAPDSG GGGSGGGGSG GGGSGGGGSG GGGSLVPRGS

801 GGASATRRYY LGAVELSWDY MQSDLGELPV DARFPPRVPK SFPFNTSVVY
 851 KKTLEFVEFTD HLFNIAKPRP PWMGLLGPTI QAEVYDTPVI TLKNMASHPV
 901 SLHAVGVSYW KASEGAEYDD QTSQREKEDD KVFPGGSHY VWQVLKENG
 951 MASDPLCLTY SYLSHVDLVK DLNSGLIGAL LVCREGSLAK EKTQTLHKFI
 5 1001 LLFAVFDEGK SWHSETKNSL MQDRDAASAR AWPKMHTVNG YVNRSLPGLI
 1051 GCHRKSVYWH VIGMGTTPV HSIFLEGHTF LVRNHRQASL EISPITFLTA
 1101 QTLLMDLGQF LLFCHISSHQ HDGMEAYVKV DSCPEEPQLR MKNNEEAEDY
 1151 DDDLTDSEMD VVRFDDDNSP SFIQIRSVAK KHPKTWVHYI AAEEDWDYA
 1201 PLVLAPDDRS YKSQYLNNGP QRIGRKYKKV RFMAYTDETF KTREAIQHS
 10 1251 GILGPLLYGE VGDTLIIFK NQASRPYNIY PHGITDVRPL YSRRLPKGVK
 1301 HLKDFPILPG EIFKYKWTVT VEDGPTKSDP RCLTRYYSF VNMERDLASG
 1351 LIGPLLCYK ESVDQGRNQI MSDKRNVLV SVFDENRSWY LTENIQRFLP
 1401 NPAGVQLED PEFQASNIMHS INGYVFDSLQ LSVCLHEVAY WYILSIGAQT
 1451 DFLSVFFSGY TFKHKMVEYD TLTLFPFSGE TVFMSMENPG LWILGCHNSD
 15 1501 FRNRGMTALL KVSSCDKNTG DYYEDSYEDI SAYLLSKNNA IEPRSFSQNP
 1551 PVLKRHQREI TRTTLQSDQE EIDYDDTISV EMKKEDFDIY DEDENQSPRS
 1601 FQKTRHYFI AAVERLWDYG MSSSPHVLN RAQSGSVQF KKVVFQEFTD
 1651 GSFTQPLYRG ELNEHLGLLG PYIRAEVEDN IMVTFRNQAS RPYSFYSLI
 1701 SYEEDQRQGA EPRKNFVKPN ETCTYFWKVQ HHMAPTKDEF DCKAWAYFSD
 20 1751 VDLEKDVHSG LIGPLLVCHT NTLNPAHGRQ VTVQEFALFF TIFDETKSWY
 1801 FTENMERNCR APCNIQMEDP TFKENYRFHA INGYIMDTLP GLVMAQDQRI
 1851 RWYLLSMGSN ENIHSIHFSG HVFTVRKKEE YKMALYNLYP GVFETVEMLP
 1901 SKAGIWRVEC LIGEHLHAGM STLFLVYSNK CQTPLGMASG HIRDFQITAS
 1951 GQYGQWAPKL ARLHYSGSIN AWSTKEPFSW IKVDLLAPMI IHGIKTQGAR
 25 2001 QKFSSLYISQ FIIMYSLDGK KWQTYRGNST GTLMVFFGNV DSSGIKHNI
 2051 NPPIIARYIR LHPHTYSIRS TLRMELMGCD LNSCSMPLGM ESKAISDAQI
 2101 TASSYFTNMF ATWSPSKARL HLQGRSNAWR PQVNNPKEWL QVDFQKTMKV
 2151 TGVTTQGVKS LLTSMYVKEF LISSSQDGHQ WTLFFQNGKV KVFQGNQDSF
 2201 TPVNSLDPP LLTRYLRIHP QSWVHQIALR MEVLGCEAQD LY
 30

pSYN FVIII 310 nucleotide sequence (encoding FVIII with complete B-domain deletion except 2 amino acid residues and 288 AE-XTEN inserted after aa 742) (SEQ ID NO:170)

35 1 ATGCAAATAG AGCTCTCCAC CTGCTTCTTT CTGTGCCTTT TGCGATTCTG
 51 CTTTAGTGCC ACCAGAAGAT ACTACCTGGG TGCACTGGAA CTGTCATGGG
 101 ACTATATGCA AAGTGATCTC GGTGAGCTGC CTGTGGACGC AAGATTTCTT
 151 CCTAGAGTGC CAAAATCTTT TCCATTCAAC ACCTCAGTCG TGTACAAAAA
 201 GACTCTGTTT GTAGAATTCA CGGATCACCT TTTCAACATC GCTAAGCCAA
 40 251 GGCCACCCTG GATGGGTCTG CTAGGTCCTA CCATCCAGGC TGAGGTTTAT
 301 GATACAGTGG TCATTACACT TAAGAACATG GCTTCCCATC CTGTCACTCT
 351 TCATGCTGTT GGTGTATCCT ACTGGAAGC TTCTGAGGGA GCTGAATATG
 401 ATGATCAGAC CAGTCAAAGG GAGAAAGAAG ATGATAAAGT CTTCCTGGT
 451 GGAAGCCATA CATATGTCTG GCAGGTCCTG AAAGAGAATG GTCCAATGGC
 45 501 CTCTGACCCA CTGTGCCTTA CCTACTCATA TCTTTCTCAT GTGGACCTGG
 551 TAAAAGACTT GAATTCAGGC CTCATTGGAG CCCTACTAGT ATGTAGAGAA
 601 GGGAGTCTGG CCAAGGAAAA GACACAGACC TTGCACAAAT TTATACTACT
 651 TTTTGCTGTA TTTGATGAAG GGAAAAGTTG GCACTCAGAA ACAAAGAACT
 701 CCTTGATGCA GGATAGGGAT GCTGCATCTG CTCGGGCCTG GCCTAAAATG
 50 751 CACACAGTCA ATGGTTATGT AAACAGGTCT CTGCCAGGTC TGATTGGATG
 801 CCACAGGAAA TCAGTCTATT GGCATGTGAT TGGAATGGGC ACCACTCCTG
 851 AAGTGCACTC AATATTCCTC GAAGGTCACA CATTTCTTGT GAGGAACCAT
 901 CGCCAGGCGT CTTTGAAAT CTCGCCAATA ACTTTCCTTA CTGCTCAAAC

951 ACTCTTGATG GACCTTGGAC AGTTTCTACT GTTTTGTCAT ATCTCTTCCC
 1001 ACCAACATGA TGGCATGGAA GCTTATGTCA AAGTAGACAG CTGTCCAGAG
 1051 GAACCCCAAC TACGAATGAA AAATAATGAA GAAGCGGAAG ACTATGATGA
 1101 TGATCTTACT GATTCTGAAA TGGATGTGGT CAGGTTTGAT GATGACAACT
 5 1151 CTCCTTCCTT TATCCAAATT CGCTCAGTTG CCAAGAAGCA TCCTAAACT
 1201 TGGGTACATT ACATTGCTGC TGAAGAGGAG GACTGGGACT ATGCTCCCTT
 1251 AGTCCTCGCC CCCGATGACA GAAGTTATAA AAGTCAATAT TTGAACAATG
 1301 GCCCTCAGCG GATTGGTAGG AAGTACAAAA AAGTCCGATT TATGGCATACT
 1351 ACAGATGAAA CCTTTAAGAC TCGTGAAGCT ATTCAGCATG AATCAGGAAT
 10 1401 CTTGGGACCT TTACTTTATG GGAAGTTGG AGACACACTG TTGATTATAT
 1451 TTAAGAATCA AGCAAGCAGA CCATATAACA TCTACCCTCA CGGAATCACT
 1501 GATGTCCGTC CTTTGTATTC AAGGAGATTA CCAAAAGGTG TAAAACATTT
 1551 GAAGGATTTT CCAATTCTGC CAGGAGAAAT ATTCAAATAT AAATGGACAG
 1601 TGACTGTAGA AGATGGGCCA ACTAAATCAG ATCCTCGGTG CCTGACCCGC
 15 1651 TATTACTCTA GTTTCGTAA TATGGAGAGA GATCTAGCTT CAGGACTCAT
 1701 TGGCCCTCTC CTCATCTGCT ACAAAGAATC TGTAGATCAA AGAGGAAACC
 1751 AGATAATGTC AGACAAGAGG AATGTCATCC TGTTTTCTGT ATTTGATGAG
 1801 AACCGAAGCT GGTACCTCAC AGAGAATATA CAACGCTTTC TCCCCAATCC
 1851 AGCTGGAGTG CAGCTTGAGG ATCCAGAGTT CCAAGCCTCC AACATCATGC
 20 1901 ACAGCATCAA TGGCTATGTT TTTGATAGTT TGCAGTTGTC AGTTTGTTTG
 1951 CATGAGGTGG CATACTGGTA CATTCTAAGC ATTGGAGCAC AGACTGACTT
 2001 CCTTTCTGTC TTCTTCTCTG GATATACCTT CAAACACAAA ATGGTCTATG
 2051 AAGACACACT CACCCTATTC CCATTCTCAG GAGAAACTGT CTTCATGTCC
 2101 ATGGAAAACC CAGGTCTATG GATTCTGGGG TGCCACAACCT CAGACTTTCCG
 25 2151 GAACAGAGGC ATGACCGCCT TACTGAAGGT TTCTAGTTGT GACAAGAACA
 2201 CTGGTGATTA TTACGAGGAC AGTTATGAAG ATATTTTCAGC ATACTTGCTG
 2251 AGTAAAAACA ATGCCATTGA ACCAAGAAGC TTCGGTACCT CAGAGTCTGC
 2301 TACCCCCGAG TCAGGGCCAG GATCAGAGCC AGCCACCTCC GGGTCTGAGA
 2351 CACCCGGGAC TTCCGAGAGT GCCACCCCTG AGTCCGGACC CGGGTCCGAG
 30 2401 CCCGCCACTT CCGGCTCCGA AACTCCCGGC ACAAGCGAGA GCGCTACCCC
 2451 AGAGTCAGGA CCAGGAACAT CTACAGAGCC CTCTGAAGGC TCCGCTCCAG
 2501 GGTCCCCAGC CGGCAGTCCC ACTAGCACCG AGGAGGGAAC CTCTGAAAGC
 2551 GCCACACCCG AATCAGGGCC AGGGTCTGAG CCTGCTACCA GCGGCAGCGA
 2601 GACACCAAGC ACCTCTGAGT CCGCCACACC AGAGTCCGGA CCCGATCTC
 35 2651 CCGCTGGGAG CCCCACCTCC ACTGAGGAGG GATCTCCTGC TGGCTCTCCA
 2701 ACATCTACTG AGGAAGGTAC CTCAACCGAG CCATCCGAGG GATCAGCTCC
 2751 CGGCACCTCA GAGTCGGCAA CCCCAGGAGT TGGACCCGGA ACTTCCGAAA
 2801 GTGCCACACC AGAGTCCGGT CCCGGGACTT CAGAATCAGC AACACCCGAG
 2851 TCCGGCCCTG GGTCTGAACC CGCCACAAGT GGTAGTGAGA CACCAGGATC
 40 2901 AGAACCTGCT ACCTCAGGGT CAGAGACACC CGGATCTCCG GCAGGCTCAC
 2951 CAACCTCCAC TGAGGAGGGC ACCAGCACAG AACCAAGCGA GGGCTCCGCA
 3001 CCCGGAACAA GCACTGAACC CAGTGAGGGT TCAGCACCCG GCTCTGAGCC
 3051 GGCCACAAGT GGCAGTGAGA CACCCGGCAC TTCAGAGAGT GCCACCCCCG
 3101 AGAGTGGCCC AGGCACTAGT ACCGAGCCCT CTGAAGGCAG TGCGCCAGCC
 45 3151 TCGAGCGAAA TAACTCGTAC TACTCTTCAG TCAGATCAAG AGGAAATCGA
 3201 TTATGATGAT ACCATATCAG TTGAAATGAA GAAGGAAGAT TTTGACATTT
 3251 ATGATGAGGA TGAAAATCAG AGCCCCGCA GCTTTCAAAA GAAAACACGA
 3301 CACTATTTTA TTGCTGCAGT GGAGAGGCTC TGGGATTATG GGATGAGTAG
 3351 CTCCCCACAT GTTCTAAGAA ACAGGGCTCA GAGTGGCAGT GTCCCTCAGT
 50 3401 TCAAGAAAGT TGTTTTCCAG GAATTTACTG ATGGCTCCTT TACTCAGCCC
 3451 TTATACCGTG GAGAACTAAA TGAACATTTG GGAATCCTGG GGCCATATAT
 3501 AAGAGCAGAA GTTGAAGATA ATATCATGGT AACTTTCAGA AATCAGGCCT
 3551 CTCGTCCCTA TTCCTTCTAT TCTAGCCTTA TTTCTTATGA GGAAGATCAG

3601 AGGCAAGGAG CAGAACCTAG AAAAACTTT GTCAAGCCTA ATGAAACCAA
 3651 AACTTACTTT TGGAAAGTGC AACATCATAT GGCACCCACT AAAGATGAGT
 3701 TTGACTGCAA AGCCTGGGCT TATTTCTCTG ATGTTGACCT GGAAAAAGAT
 3751 GTGCACTCAG GCCTGATTGG ACCCCTTCTG GTCTGCCACA CTAACACACT
 5 3801 GAACCCTGCT CATGGGAGAC AAGTGACAGT ACAGGAATTT GCTCTGTTTT
 3851 TCACCATCTT TGATGAGACC AAAAGCTGGT ACTTCACTGA AAATATGGAA
 3901 AGAAACTGCA GGGCTCCCTG CAATATCCAG ATGGAAGATC CCACTTTTAA
 3951 AGAGAATTAT CGCTTCCATG CAATCAATGG CTACATAATG GATACACTAC
 4001 CTGGCTTAGT AATGGCTCAG GATCAAAGGA TTCGATGGTA TCTGCTCAGC
 10 4051 ATGGGCAGCA ATGAAAACAT CCATTCTATT CATTTCACTG GACATGTGTT
 4101 CACTGTACGA AAAAAAGAGG AGTATAAAAT GGCCTGTAC AATCTCTATC
 4151 CAGGTGTTTT TGAGACAGTG GAAATGTTAC CATCCAAAGC TGGAATTTGG
 4201 CGGGTGGAAT GCCTTATTGG CGAGCATCTA CATGCTGGGA TGAGCACACT
 4251 TTTTCTGGTG TACAGCAATA AGTGTCAGAC TCCCCTGGGA ATGGCTTCTG
 15 4301 GACACATTAG AGATTTTCAG ATTACAGCTT CAGGACAATA TGGACAGTGG
 4351 GCCCCAAAGC TGGCCAGACT TCATTATTCC GGATCAATCA ATGCCTGGAG
 4401 CACCAAGGAG CCCTTTTCTT GGATCAAGGT GGATCTGTTG GCACCAATGA
 4451 TTATTCACGG CATCAAGACC CAGGGTGCCC GTCAGAAGTT CTCCAGCCTC
 4501 TACATCTCTC AGTTTATCAT CATGTATAGT CTTGATGGGA AGAAGTGGCA
 20 4551 GACTTATCGA GGAAATTCCA CTGGAACCTT AATGGTCTT TTTGGCAATG
 4601 TGGATTCATC TGGGATAAAA CACAATATTT TTAACCCTCC AATTATTGCT
 4651 CGATACATCC GTTTGCACCC AACTCATTAT AGCATTTCGA GCACTCTTCG
 4701 CATGGAGTTG ATGGGCTGTG ATTTAAATAG TTGCAGCATG CCATTGGGAA
 4751 TGGAGAGTAA AGCAATATCA GATGCACAGA TTA CTGCTT C ATCCTACTTT
 25 4801 ACCAATATGT TTGCCACCTG GTCTCCTTCA AAAGCTCGAC TTCACCTCCA
 4851 AGGGAGGAGT AATGCCTGGA GACCTCAGGT GAATAATCCA AAAGAGTGGC
 4901 TGCAAGTGGA CTTCCAGAAG ACAATGAAAG TCACAGGAGT AACTACTCAG
 4951 GGAGTAAAAT CTCTGCTTAC CAGCATGTAT GTGAAGGAGT TCCTCATCTC
 5001 CAGCAGTCAA GATGGCCATC AGTGGACTCT CTTTTTTCAG AATGGCAAAG
 30 5051 TAAAGGTTTT TCAGGGAAAT CAAGACTCCT TCACACCTGT GGTGAACCTC
 5101 CTAGACCCAC CGTTACTGAC TCGCTACCTT CGAATTCACC CCCAGAGTTG
 5151 GGTGCACCAG ATTGCCCTGA GGATGGAGGT TCTGGGCTGC GAGGCACAGG
 5201 ACCTCTACGA CAAAACCTAC ACATGCCAC CGTGCCCAGC TCCAGAATCT
 5251 CTGGGCGGAC CGTCAGTCTT CCTCTTCCCC CAAAACCCA AGGACACCT
 35 5301 CATGATCTCC CGGACCCCTG AGGTCACATG CGTGGTGGTG GACGTGAGCC
 5351 ACGAAGACCC TGAGGTCAAG TTCAACTGGT ACGTGGACGG CGTGGAGGTG
 5401 CATAATGCCA AGACAAAGCC GCGGGAGGAG CAGTACAACA GCACGTACCG
 5451 TGTGGTCAGC GTCCTACCG TCCTGCACCA GGACTGGCTG AATGGCAAGG
 5501 AGTACAAGTG CAAGGTCTCC AACAAAGCCC TCCAGCCCC CATCGAGAAA
 40 5551 ACCATCTCCA AAGCCAAAGG GCAGCCCCGA GAACCACAGG TGTACACCCT
 5601 GCCCCATCC CGGGATGAGC TGACCAAGAA CCAGGTCAGC CTGACCTGCC
 5651 TGGTCAAAGG CTTCTATCCC AGCGACATCG CCGTGGAGTG GGAGAGCAAT
 5701 GGGCAGCCGG AGAACAACCTA CAAGACCACG CCTCCCGTGT TGGACTCCGA
 5751 CGGCTCCTTC TTCCTCTACA GCAAGCTCAC CGTGGACAAG AGCAGGTGGC
 45 5801 AGCAGGGGAA CGTCTTCTCA TGCTCCGTGA TGCATGAGGC TCTGCACAAC
 5851 CACTACACGC AGAAGAGCCT CTCCCTGTCT CCGGGTAAAT GA

pSYN FVIII 310 protein sequence (FVIII with complete B-domain deletion except 2 amino acid residues and 288 AE-XTEN inserted after aa 742) (SEQ ID NO:171)

50

1 ATRRYYLGA V ELSWDYMQSD LGELPVDARF PPRVPKSFPF NTSVVYKCTL
 51 FVEFTDHLFN IAKPRPPWMG LLGPTIQAEV YDTVVITLKN MASHPVSLHA

101 VGVSYWKASE GA EYDDQTSQ REKEDDKVFP GGSHTYVWQV LKENGPMASD
 151 PLCLTYSYLS HVDLVKDLNS GLIGALLVCR EGSLAKEKTQ TLHKFILLFA
 201 VFDEGKSWHS ETKNSLMQDR DAASARAWPK MHTVNGYVNR SLPGLIGCHR
 251 KSVYWHVIGM GTTPEVHSIF LEGHTFLVRN HRQASLEISP ITFLTAQTLL
 5 301 MDLGQFLLFC HISSHQHDGM EAYVKVDSCP EEPQLRMKNN EEAEDYDDDL
 351 TDSEMDVVRF DDDNSPSFIQ IRSVAKKHPK TWVHYIAAEE EDWDYAPLVL
 401 APDDRSYKSQ YLNNGPQRIG RKYKKVRFMA YDDETFKTRE AIQHESGILG
 451 PLYGEVGD TLLIFKNQAS RPYNIYPHGI TDVRPLYSRP LPKGVKHLKD
 501 FPILPGEIFK YKWTVTVEDG PTKSDPRCLT RYYSSFVNME RDLASGLIGP
 10 551 LLICYKESVD QRGNQIMSDK RNVILFSVFD ENRSWYLTEN IQRFLPNPAG
 601 VQLEDPEFQA SNIMHSINGY VFDSLQLSVC LHEVAYWYIL SIGAQTDFLS
 651 VFFSGYTFKH KMYVEDTLTL PFPSGETVFM SMENPGLWIL GCHNSDFRNR
 701 GMTALLKVSS CDKNTGDYEE DSYEDISAYL LSKNNAIEPR SFGTSESATP
 751 ESGPGSEPAT SGSETPGTSE SATPESGPGS EPATSGSETP GTSESATPES
 15 801 GPGTSTEPSE GSAPGSPAGS PTSTEEGTSE SATPESGPGS EPATSGSETP
 851 GTSESATPES GPGSPAGSPT STEEGSPAGS PTSTEEGTST EPSEGSAPGT
 901 SESATPESGP GTSESATPES GPGTSESATP ESGPGSEPAT SGSETPGSEP
 951 ATSGSETPGS PAGSPTSTEE GTSTEPSEGS APGTSTEPSE GSAPGSEPAT
 1001 SGSETPGTSE SATPESGPGT STEPSEGSAP ASSEITRTTL QSDQEEIDYD
 20 1051 DTISVEMKKE DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP
 1101 HVLNRNAQSG SVPQFKKVV FQEFTDGSFTQ PLYRGELNEH LGLLGPYIRA
 1151 EVEDNIMVTF RNQASRPYSF YSSLISYEED QRQGAEPKRN FVKPNETKTY
 1201 FWKVQHMAP TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP
 1251 AHGRQVTVQE FALFFTIFDE TKSIFYTENM ERNCRAPCNI QMEDPTFKEN
 25 1301 YRFHAINGYI MDTLPLGLVMA QDQIRRWYLL SMGSNENIHS IHFSGHVFTV
 1351 RKKEEYKMAL YNLYPGVFET VEMPLPSKAGI WRVECLIGEH LHAGMSTLFL
 1401 VYSNKCQTPL GMASGHIRDF QITASGQYQG WAPKLARLHY SGSINAWSTK
 1451 EPFSWIKVDL LAPMIIHGIK TQGARQKFSS LYISQFIIMY SLDGKKWQTY
 1501 RGNSTGTLMV FFGNVDSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME
 30 1551 LMGCDLNSCS MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR
 1601 SNAWRPQVNN PKEWLQVDFQ KTMKVTGVT QGVKSLTSM YVKEFLISS
 1651 QDGHQWTLFF QNGKVKVFQ NQDSFTPVVN SLDPPLTRY LRIHPQSWVH
 1701 QIALRMEVLG CEAQDLYDKT HTCPCPAPE LLGGPSVFLF PPKPKDTLMI
 1751 SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV
 35 1801 SVLTVLHQDW LNGKEYCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP
 1851 SRDELTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSGDS
 1901 FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

40 **pSYN FVIII 312 nucleotide sequence (encoding FVIII with complete B-domain deletion except
 5 amino acid residues and 288 AE-XTEN inserted after aa 745- B5 version) (SEQ ID NO:172)**

1 ATGCAAATAG AGCTCTCCAC CTGCTTCTTT CTGTGCCTTT TGCATTCTG
 51 CTTTAGTGCC ACCAGAAGAT ACTACCTGGG TGCAGTGGAA CTGTCATGGG
 45 101 ACTATATGCA AAGTGATCTC GGTGAGCTGC CTGTGGACGC AAGATTTCTT
 151 CCTAGAGTGC CAAAATCTTT TCCATTCAAC ACCTCAGTCG TGTACAAAAA
 201 GACTCTGTTT GTAGAATTCA CGGATCACCT TTTCAACATC GCTAAGCCAA
 251 GGCCACCCTG GATGGGTCTG CTAGGTCCTA CCATCCAGGC TGAGGTTTAT
 301 GATACAGTGG TCATTACACT TAAGAACATG GCTTCCCATC CTGTCAGTCT
 50 351 TCATGCTGTT GGTGTATCCT ACTGGAAAGC TTCTGAGGGA GCTGAATATG
 401 ATGATCAGAC CAGTCAAAGG GAGAAAGAAG ATGATAAAGT CTTCCTGGT
 451 GGAAGCCATA CATATGTCTG GCAGGTCCTG AAAGAGAATG GTCCAATGGC
 501 CTCTGACCCA CTGTGCCTTA CCTACTCATA TCTTTCTCAT GTGGACCTGG

551 TAAAAGACTT GAATTCAGGC CTCATTGGAG CCCTACTAGT ATGTAGAGAA
 601 GGGAGTCTGG CCAAGGAAAA GACACAGACC TTGCACAAAT TTATACTACT
 651 TTTTGCTGTA TTTGATGAAG GGAAAAGTTG GCACTCAGAA ACAAAGAACT
 701 CCTTGATGCA GGATAGGGAT GCTGCATCTG CTCGGGCCTG GCCTAAAATG
 5 751 CACACAGTCA ATGGTTATGT AAACAGGTCT CTGCCAGGTC TGATTGGATG
 801 CCACAGGAAA TCAGTCTATT GGCATGTGAT TGGAATGGGC ACCACTCCTG
 851 AAGTGCCTC AATATTCCTC GAAGGTCACA CATTTCCTTG GAGGAACCAT
 901 CGCCAGGCGT CCTTGAAAT CTCGCCAATA ACTTTCCTTA CTGCTCAAAC
 951 ACTCTTGATG GACCTTGGAC AGTTTCTACT GTTTTGTCT ATCTCTTCCC
 10 1001 ACCAACATGA TGGCATGGAA GCTTATGTCA AAGTAGACAG CTGTCCAGAG
 1051 GAACCCCAAC TACGAATGAA AAATAATGAA GAAGCGGAAG ACTATGATGA
 1101 TGATCTTACT GATTCTGAAA TGGATGTGGT CAGGTTTGAT GATGACAACT
 1151 CTCCTTCCTT TATCCAAATT CGCTCAGTTG CCAAGAAGCA TCCTAAAAC
 1201 TGGGTACATT ACATTGCTGC TGAAGAGGAG GACTGGGACT ATGCTCCCTT
 15 1251 AGTCTCGCC CCCGATGACA GAAGTTATAA AAGTCAATAT TTGAACAATG
 1301 GCCCTCAGCG GATTGGTAGG AAGTACAAAA AAGTCCGATT TATGGCATACT
 1351 ACAGATGAAA CCTTTAAGAC TCGTGAAGCT ATTCAGCATG AATCAGGAAT
 1401 CTTGGGACCT TTACTTTATG GGGAAGTTGG AGACACACTG TTGATTATAT
 1451 TTAAGAATCA AGCAAGCAGA CCATATAACA TCTACCCTCA CGGAATCACT
 20 1501 GATGTCCGTC CTTTGTATTC AAGGAGATTA CAAAAGGTG TAAAACATTT
 1551 GAAGGATTTT CCAATTCTGC CAGGAGAAAT ATTCAAATAT AAATGGACAG
 1601 TGACTGTAGA AGATGGGCCA ACTAAATCAG ATCCTCGGTG CCTGACCCGC
 1651 TATTACTCTA GTTTCGTAA TATGGAGAGA GATCTAGCTT CAGGACTCAT
 1701 TGGCCCTCTC CTCATCTGCT ACAAAGAATC TGTAGATCAA AGAGGAAACC
 25 1751 AGATAATGTC AGACAAGAGG AATGTCATCC TGTTTTCTGT ATTTGATGAG
 1801 AACCGAAGCT GGTACCTCAC AGAGAATATA CAACGCTTTC TCCCAATCC
 1851 AGCTGGAGTG CAGCTTGAGG ATCCAGAGTT CCAAGCCTCC AACATCATGC
 1901 ACAGCATCAA TGGCTATGTT TTTGATAGTT TGCAGTTGTC AGTTTGTGTTG
 1951 CATGAGGTGG CATACTGGTA CATTCTAAGC ATTGGAGCAC AGACTGACTT
 30 2001 CCTTTCTGTC TTCTTCTCTG GATATACCTT CAAACACAAA ATGGTCTATG
 2051 AAGACACACT CACCCTATTC CCATTCTCAG GAGAACTGT CTTTCTGTCG
 2101 ATGGAACACC CAGGTCTATG GATTCTGGGG TGCCACAAC CAGACTTTCG
 2151 GAACAGAGGC ATGACCGCCT TACTGAAGGT TTCTAGTTGT GACAAGAAC
 2201 CTGGTGATTA TTACGAGGAC AGTTATGAAG ATATTTTCAGC ATACTTGCTG
 35 2251 AGTAAAAACA ATGCCATTGA ACCAAGAAGC TTCTCTCAA ACGGTACCTC
 2301 AGAGTCTGCT ACCCCGAGT CAGGGCCAGG ATCAGAGCCA GCCACCTCCG
 2351 GGTCTGAGAC ACCCGGGACT TCCGAGAGTG CCACCCCTGA GTCCGGACCC
 2401 GGGTCCGAGC CCGCCACTTC CGGCTCCGAA ACTCCCGGCA CAAGCGAGAG
 2451 CGCTACCCA GAGTCAGGAC CAGGAACATC TACAGAGCCC TCTGAAGGCT
 40 2501 CCGCTCCAGG GTCCCCAGCC GGCAGTCCA CTAGCACCGA GGAGGGAACC
 2551 TCTGAAAGCG CCACACCCGA ATCAGGGCCA GGGTCTGAGC CTGCTACCAG
 2601 CGGCAGCGAG ACACCAGGCA CCTCTGAGTC CGCCACACCA GAGTCCGGAC
 2651 CCGGATCTCC CGCTGGGAGC CCCACCTCCA CTGAGGAGGG ATCTCCTGCT
 2701 GGCTCTCAA CATCTACTGA GGAAGGTACC TCAACCGAGC CATCCGAGGG
 45 2751 ATCAGTCCC GGCACCTCAG AGTCGGCAAC CCCGGAGTCT GGACCCGGAA
 2801 CTTCCGAAAG TGCCACACCA GAGTCCGGTC CCGGGACTTC AGAATCAGCA
 2851 ACACCCGAGT CCGGCCCTGG GTCTGAACCC GCCACAAGTG GTAGTGAGAC
 2901 ACCAGGATCA GAACCTGCTA CCTCAGGGTC AGAGACACCC GGATCTCCGG
 2951 CAGGCTCACC AACCTCCACT GAGGAGGGCA CCAGCACAGA ACCAAGCGAG
 50 3001 GGCTCCGCAC CCGGAACAAG CACTGAACCC AGTGAGGGTT CAGCACCCGG
 3051 CTCTGAGCCG GCCACAAGTG GCAGTGAGAC ACCCGGCACT TCAGAGAGTG
 3101 CCACCCCGCA GAGTGGCCCA GGCAGTAGTA CCGAGCCCTC TGAAGGCAGT
 3151 GCGCCAGCCT CGAGCGAAAT AACTCGTACT ACTCTTCAGT CAGATCAAGA

3201 GGAAATCGAT TATGATGATA CCATATCAGT TGAAATGAAG AAGGAAGATT
 3251 TTGACATTTA TGATGAGGAT GAAAATCAGA GCCCCGCAG CTTTCAAAAG
 3301 AAAACACGAC ACTATTTTAT TGCTGCAGTG GAGAGGCTCT GGGATTATGG
 3351 GATGAGTAGC TCCCCACATG TTCTAAGAAA CAGGGCTCAG AGTGGCAGTG
 5 3401 TCCCTCAGTT CAAGAAAGTT GTTTTCCAGG AATTTACTGA TGGCTCCTTT
 3451 ACTCAGCCCT TATACCGTGG AGAACTAAAT GAACATTTGG GACTCCTGGG
 3501 GCCATATATA AGAGCAGAAG TTGAAGATAA TATCATGGTA ACTTTCAGAA
 3551 ATCAGGCCTC TCGTCCCTAT TCCTTCTATT CTAGCCTTAT TTCTTATGAG
 3601 GAAGATCAGA GGCAAGGAGC AGAACCTAGA AAAAAGCTTTG TCAAGCCTAA
 10 3651 TGAAACCAAA ACTTACTTTT GGAAAGTGCA ACATCATATG GCACCCCTAA
 3701 AAGATGAGTT TGACTGCAAA GCCTGGGCTT ATTTCTCTGA TGTGACCTG
 3751 GAAAAAGATG TGCACCTCAGG CCTGATTGGA CCCCTTCTGG TCTGCCACAC
 3801 TAACACACTG AACCCTGCTC ATGGGAGACA AGTGACAGTA CAGGAATTTG
 3851 CTCTGTTTTT CACCATCTTT GATGAGACCA AAAGCTGGTA CTTCAGTAA
 15 3901 AATATGGAAG GAAACTGCAG GGCTCCCTGC AATATCCAGA TGGAAGATCC
 3951 CACTTTTAAA GAGAATTATC GCTTCCATGC AATCAATGGC TACATAATGG
 4001 ATACACTACC TGGCTTAGTA ATGGCTCAGG ATCAAAGGAT TCGATGGTAT
 4051 CTGCTCAGCA TGGGCAGCAA TGAAAACATC CATTCTATTC ATTTCACTGG
 4101 ACATGTGTTT ACTGTACGAA AAAAAGAGGA GTATAAAATG GCACTGTACA
 20 4151 ATCTCTATCC AGGTGTTTTT GAGACAGTGG AAATGTTACC ATCCAAAGCT
 4201 GGAATTTGGC GGGTGGAATG CTTATTGGC GAGCATCTAC ATGCTGGGAT
 4251 GAGCACACTT TTTCTGGTGT ACAGCAATAA GTGTCAGACT CCCCTGGGAA
 4301 TGGCTTCTGG ACACATTAGA GATTTTCAGA TTACAGCTTC AGGACAATAT
 4351 GGACAGTGGG CCCCAGAGCT GGCCAGACTT CATTATTCCG GATCAATCAA
 25 4401 TGCCTGGAGC ACCAAGGAGC CTTTTTCTTG GATCAAGGTG GATCTGTTGG
 4451 CACCAATGAT TATTCACGGC ATCAAGACCC AGGGTGCCCC TCAGAAAGTTC
 4501 TCCAGCCTCT ACATCTCTCA GTTTATCATC ATGTATAGTC TTGATGGGAA
 4551 GAAGTGGCAG ACTTATCGAG GAAATTCCAC TGGAACCTTA ATGGTCTTCT
 4601 TTGGCAATGT GGATTCATCT GGGATAAAAC ACAATATTTT TAACCCTCCA
 30 4651 ATTATTGCTC GATACATCCG TTTGCACCCA ACTCATTATA GCATTGCGAG
 4701 CACTCTTCGC ATGGAGTTGA TGGGCTGTGA TTTAAATAGT TGCAGCATGC
 4751 CATTGGGAAT GGAGAGTAAA GCAATATCAG ATGCACAGAT TACTGCTTCA
 4801 TCCTACTTTA CCAATATGTT TGCCACCTGG TCTCCTTCAA AAGCTCGACT
 4851 TCACCTCAA GGGAGGAGTA ATGCCTGGAG ACCTCAGGTG AATAATCCAA
 35 4901 AAGAGTGGCT GCAAGTGGAC TTCCAGAAGA CAATGAAAGT CACAGGAGTA
 4951 ACTACTCAGG GAGTAAAATC TCTGCTTACC AGCATGTATG TGAAGGAGTT
 5001 CCTCATCTCC AGCAGTCAAG ATGGCCATCA GTGGACTCTC TTTTTTCAGA
 5051 ATGGCAAAGT AAAGGTTTTT CAGGGAAATC AAGACTCCTT CACACCTGTG
 5101 GTGAACTCTC TAGACCCACC GTTACTGACT CGCTACCTTC GAATTCACCC
 40 5151 CCAGAGTTGG GTGCACCAGA TTGCCCTGAG GATGGAGGTT CTGGGCTGCG
 5201 AGGCACAGGA CCTCTACGAC AAAACTCACA CATGCCCACC GTGCCAGCT
 5251 CCAGAACTCC TGGGCGGACC GTCAGTCTTC CTCTTCCCCC CAAAACCCAA
 5301 GGACACCCTC ATGATCTCCC GGACCCCTGA GGTACATGC GTGGTGGTGG
 5351 ACGTGAGCCA CGAAGACCCT GAGGTCAAGT TCAACTGGTA CGTGGACGGC
 45 5401 GTGGAGGTGC ATAATGCCAA GACAAAGCCG CGGGAGGAGC AGTACAACAG
 5451 CACGTACCGT GTGGTCAGCG TCCTCACCGT CCTGCACCAG GACTGGCTGA
 5501 ATGGCAAGGA GTACAAGTGC AAGGTCTCCA ACAAAGCCCT CCCAGCCCCC
 5551 ATCGAGAAAA CCATCTCCAA AGCCAAAGGG CAGCCCCGAG AACCACAGGT
 5601 GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC CAGGTCAGCC
 50 5651 TGACCTGCCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG
 5701 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGTT
 5751 GGACTCCGAC GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA
 5801 GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT

5851 CTGCACAACC ACTACACGCA GAAGAGCCTC TCCCTGTCTC CGGGTAAATG

pSYN FVIII 312 protein sequence (FVIII with complete B-domain deletion except 5 amino acid residues and 288 AE-XTEN inserted after aa 745- B5 version) (SEQ ID NO:173)

5
1 ATRRYYLGA V ELSWDYMQSD LGELPVDARF PPRVPKSFPF NTSVVYKCTL
51 FVEFTDHLFN IAKPRPPWMG LLGPTIQAEV YDTVVITLKN MASHPVSLHA
101 VGVSYWKASE GA EYDDQTSQ REKEDDKVFP GGSHTYVWQV LKENGPMASD
10 PLCLTYSYLS HVDLVKDLNS GLIGALLVCR EGSLAKEKTQ TLHKFILLFA
201 VFDEGKSWHS ETKNSLMQDR DAASARAWPK MHTVNGYVNR SLPGLIGCHR
251 KSVYWHVIGM GTTPEVHSIF LEGHTFLVRN HRQASLEISP ITFLTAQTLL
301 MDLGQFLLFC HISSHQHDGM EAYVKVDSCP EEPQLRMKNN EEAEDYDDDL
351 TDSEMDVVRF DDDNSPSFIQ IRSVAKKHPK TWVHYIAAEE EDWDYAPLVL
15 401 APDDRYSYQ YLNNGPQRIG RKYKKVRFMA YDDETFKTRE AIQHEGILG
451 PLLYGEVGDT LLIFKNQAS RPYNIYPHGI TDVRPLYSRP LPKG VKHLKD
501 FPILPGEIFK YKWTVTVEDG PTKSDPRCLT RYYSFVNME RDLASGLIGP
551 LLICYKESVD QRGNQIMSDK RNVILFSVFD ENRSWYLTEN IQRFLPNPAG
601 VQLEDPEFQA SNIMHSINGY VFDSLQLSVC LHEVAYWYIL SIGAQTDFLS
20 651 VFFSGYTFKH KMYVEDTLTL PPFSGETVFM SMENPGLWIL GCHNSDFRNR
701 GMTALLKVSS CDKNTGDYEE DSYEDISAYL LSKNNAIEPR SFSQNGTSES
751 ATPESGPGSE PATSGSETPG TSESATPESG PGSEPATSGS ETPGTSESAT
801 PESGPGTSTE PSEGSAPGSP AGSPTSTEEG TSESATPESG PGSEPATSGS
851 ETPGTSESAT PESGPGSPAG SPTSTEEGSP AGSPTSTEEG TSTEPSEGS
25 901 PGTSESATPE SGPSTSESAT PESGPGTSES ATPESGPGSE PATSGSETPG
951 SEPATSGSET PGSPAGSPTS TEEGTSTEPS EGSAPGTSTE PSEGSAPGSE
1001 PATSGSETPG TSESATPESG PGTSTEPSEG SAPASSEITR TTLQSDQEEI
1051 DYDDTISVEM KKEDFDIYDE DENQSPRSFQ KKTRHYFIAA VERLWDYGMS
1101 SSPHLVRNRA QSGSVPPQFKK VVFQEFTDGS FTQPLYRGEL NEHLGLLGPY
30 1151 IRAEVEDNIM VTFRNQASRP YSFYSSLISY EEDQRQGAEP RKNFVKPNET
1201 KTYFWKVQHH MAPTKDEFDC KAWAYFSDVD LEKDVHSGLI GPLL VCHTNT
1251 LNPAHGRQVT VQEFALFFTI FDETKSWYFT ENMERNCRAP CNIQMEDPTF
1301 KENYRFHAIN GYIMDTLPGL VMAQDQRIW YLLSMGSNEN IHSIHFSGHV
1351 FTVRKKEEYK MALYNLYPGV FETVEMLPSK AGIWRVECLI GEHLHAGMST
35 1401 LFLVYSNKCQ TPLGMASGHI RDFQITASGQ YGQWAPKLAR LHYSGSINAW
1451 STKEPFSWIK VDLLAPMIH GIKTQGARQK FSSLYISQFI IMYSLDGKKW
1501 QTYRGNSTGT LMVFFGNVDS SGIKHNIFNP PIARYIRLH PTHYSIRSTL
1551 RMELMGCDLN SCSMPLGMES KAISDAQITA SSYFTNMFAT WSPSKARLHL
1601 QGRSNAWRPQ VNNPKEWLQV DFQKTMKVTG VTTQGVKSLL TSMYVKEFLI
40 1651 SSSQDGHQWT LFFQNGKVKV FQGNQDSFTP VVNSLDPPLL TRYLRHPQS
1701 WVHQIALRME VLGCEAQDLY DKTHTCPPCP APELLGGPSV FLFPPKPKDT
1751 LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY
1801 RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT
1851 LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTTPVLDL
45 1901 DGSFFLYSKL TVDKSRWQQG NVFSCSVME ALHNHYTQKS LSLSPGK*

pSYN VWF059 nucleotide sequence (encoding VWF D'D3-Fc with acidic region 2 (a2) thrombin site in the linker) (SEQ ID NO: 196)

50
1 ATGATTCCTG CCAGATTTGC CGGGGTGCTG CTTGCTCTGG CCCTCATTTT
51 GCCAGGGACC CTTTGTGCAG AAGGAACCTG CGGCAGGTCA TCCACGGCCC
101 GATGCAGCCT TTTCGGAAGT GACTTCGTCA ACACCTTTGA TGGGAGCATG

151 TACAGCTTTG CGGGATACTG CAGTTACCTC CTGGCAGGGG GCTGCCAGAA
 201 ACGCTCCTTC TCGATTATTG GGGACTTCCA GAATGGCAAG AGAGTGAGCC
 251 TCTCCGTGTA TCTTGGGGAA TTTTGTGACA TCCATTTGTT TGTCAATGGT
 301 ACCGTGACAC AGGGGGACCA AAGAGTCTCC ATGCCCTATG CCTCCAAAGG
 5 351 GCTGTATCTA GAAACTGAGG CTGGGTACTA CAAGCTGTCC GGTGAGGCCT
 401 ATGGCTTTGT GGCCAGGATC GATGGCAGCG GCAACTTTCA AGTCCTGCTG
 451 TCAGACAGAT ACTTCAACAA GACCTGCGGG CTGTGTGGCA ACTTTAACAT
 501 CTTTGCTGAA GATGACTTTA TGACCCAAGA AGGGACCTTG ACCTCGGACC
 551 CTTATGACTT TGCCAACCTCA TGGGCTCTGA GCAGTGGAGA ACAGTGGTGT
 10 601 GAACGGGCAT CTCCTCCAG CAGCTCATGC AACATCTCCT CTGGGGAAAT
 651 GCAGAAGGGC CTGTGGGAGC AGTGCCAGCT TCTGAAGAGC ACCTCGGTGT
 701 TTGCCCGCTG CCACCCTCTG GTGGACCCCG AGCCTTTTGT GGCCCTGTGT
 751 GAGAAGACTT TGTGTGAGTG TGCTGGGGGG CTGGAGTGCG CCTGCCCTGC
 801 CCTCTGGAG TACGCCCCGA CCTGTGCCCA GGAGGGAATG GTGCTGTACG
 15 851 GCTGGACCGA CCACAGCGCG TGCAGCCCAG TGTGCCCTGC TGGTATGGAG
 901 TATAGGCAGT GTGTGTCCCC TTGCGCCAGG ACCTGCCAGA GCCTGCACAT
 951 CAATGAAATG TGTCAGGAGC GATGCGTGGA TGGCTGCAGC TGCCCTGAGG
 1001 GACAGCTCCT GGATGAAGGC CTCTGCGTGG AGAGCACCGA GTGTCCCTGC
 1051 GTGCATTCCG GAAAGCGCTA CCCTCCCGG ACCTCCCTCT CTCGAGACTG
 20 1101 CAACACCTGC ATTTGCCGAA ACAGCCAGTG GATCTGCAGC AATGAAGAAT
 1151 GTCCAGGGGA GTGCCTTGTC ACTGGTCAAT CCCACTTCAA GAGCTTTGAC
 1201 AACAGATACT TCACCTTCAG TGGGATCTGC CAGTACCTGC TGGCCCGGGA
 1251 TTGCCAGGAC CACTCCTTCT CCATTGTCAT TGAGACTGTC CAGTGTGCTG
 1301 ATGACCGCGA CGCTGTGTGC ACCCGCTCCG TCACCGTCCG GCTGCCTGGC
 25 1351 CTGCACAACA GCCTTGTAAG ACTGAAGCAT GGGGCAGGAG TTGCCATGGA
 1401 TGGCCAGGAC ATCCAGCTCC CCCTCCTGAA AGGTGACCTC CGCATCCAGC
 1451 ATACAGTGAC GGCTCCGTG CGCCTCAGCT ACGGGGAGGA CCTGCAGATG
 1501 GACTGGGATG GCCGCGGGAG GCTGCTGGTG AAGCTGTCCC CCGTCTATGC
 1551 CGGGAAGACC TGCGGCCTGT GTGGGAATTA CAATGGCAAC CAGGGCGACG
 30 1601 ACTTCCTTAC CCCCTCTGGG CTGGCGGAGC CCCGGGTGGA GGAATTCGGG
 1651 AACGCCTGGA AGCTGCACGG GGAAGTCCAG GACCTGCAGA AGCAGCACAG
 1701 CGATCCCTGC GCCCTCAACC CGCGCATGAC CAGGTTCTCC GAGGAGGCGT
 1751 GCGCGTCTCT GACGTCCCCC ACATTCGAGG CCTGCCATCG TGCCGTGACG
 1801 CCGTCCCCCT ACCTGCGGAA CTGCCGCTAC GACGTGTGCT CTGCTCGGA
 35 1851 CGGCCGCGAG TGCTGTGCG GCGCCCTGGC CAGCTATGCC GCGGCCTGCG
 1901 CGGGGAGAGG CGTGCGCGTC GCGTGGCGCG AGCCAGGCCG CTGTGAGCTG
 1951 AACTGCCCCA AAGGCCAGGT GTACCTGCAG TGCGGGACCC CCTGCAACCT
 2001 GACCTGCCGC TCTCTCTCTT ACCCGGATGA GGAATGCAAT GAGGCCTGCC
 2051 TGGAGGGCTG CTTCTGCCCC CCAGGGCTCT ACATGGATGA GAGGGGGGAC
 40 2101 TGCGTGCCCA AGGCCAGTG CCCCTGTTAC TATGACGGTG AGATCTTCCA
 2151 GCCAGAAGAC ATCTTCTCAG ACCATCACAC CATGTGCTAC TGTGAGGATG
 2201 GCTTCATGCA CTGTACCATG AGTGGAGTCC CCGGAAGCTT GCTGCCTGAC
 2251 GCTGTCTCA GCAGTCCCCT GTCTCATCGC AGCAAAAGGA GCCTATCCTG
 2301 TCGGCCCCC ATGGTCAAGC TGGTGTGTCC CGCTGACAAC CTGCGGGCTG
 45 2351 AAGGGCTCGA GTGTACAAA ACGTGCCAGA ACTATGACCT GGAGTGCATG
 2401 AGCATGGGCT GTGTCTCTGG CTGCCTCTGC CCCCCGGGCA TGGTCCGGCA
 2451 TGAGAACAGA TGTGTGGCCC TGGAAAGGTG TCCCTGCTTC CATCAGGGCA
 2501 AGGAGTATGC CCCTGGAGAA ACAGTGAAGA TTGGCTGCAA CACTTGTGTC
 2551 TGTCGGGACC GGAAGTGGAA CTGCACAGAC CATGTGTGTG ATGCCACGTG
 50 2601 CTCCACGATC GGCATGGCCC ACTACCTCAC CTTGACGGG CTCAAATACC
 2651 TGTTCCCCCG GGAGTGCCAG TACGTTCTGG TGCAGGATTA CTGCGGCAGT
 2701 AACCCTGGGA CTTTCGGAT CTAAGTGGGG AATAAGGGAT GCAGCCACCC
 2751 CTCAGTGAAA TGCAAGAAAC GGGTCACCAT CCTGGTGGAG GGAGGAGAGA

2801 TTGAGCTGTT TGACGGGGAG GTGAATGTGA AGAGGCCCAT GAAGGATGAG
 2851 ACTCACTTTG AGGTGGTGGG GTCTGGCCGG TACATCATTC TGCTGCTGGG
 2901 CAAAGCCCTC TCCGTGGTCT GGGACCGCCA CCTGAGCATC TCCGTGGTCC
 2951 TGAAGCAGAC ATACCAGGAG AAAGTGTGTG GCCTGTGTGG GAATTTTGAT
 5 3001 GGCATCCAGA ACAATGACCT CACCAGCAGC AACCTCCAAG TGGAGGAAGA
 3051 CCCTGTGGAC TTTGGGAACT CCTGGAAAGT GAGCTCGCAG TGTGCTGACA
 3101 CCAGAAAAGT GCCTCTGGAC TCATCCCCTG CCACCTGCCA TAACAACATC
 3151 ATGAAGCAGA CGATGGTGGG TTCCTCCTGT AGAATCCTTA CCAGTGACGT
 3201 CTTCCAGGAC TGCAACAAGC TGGTGGACCC CGAGCCATAT CTGGATGTCT
 10 3251 GCATTTACGA CACCTGCTCC TGTGAGTCCA TTGGGGACTG CGCCGCATTC
 3301 TGGCAGACCA TTGCTGCCTA TGCCACGTG TGTGCCAGC ATGGCAAGGT
 3351 GGTGACCTGG AGGACGGCCA CATTGTGCCC CCAGAGCTGC GAGGAGAGGA
 3401 ATCTCCGGGA GAACGGGTAT GAGGCTGAGT GGCCTATAA CAGCTGTGCA
 3451 CCTGCCTGTC AAGTCACGTG TCAGCACCTT GAGCCACTGG CCTGCCCTGT
 15 3501 GCAGTGTGTG GAGGGCTGCC ATGCCACTG CCCTCCAGGG AAAATCCTGG
 3551 ATGAGCTTTT GCAGACCTGC GTTGACCCTG AAGACTGTCC AGTGTGTGAG
 3601 GTGGCTGGCC GGCCTTTTGC CTCAGGAAAG AAAGTCACCT TGAATCCAG
 3651 TGACCCTGAG CACTGCCAGA TTTGCCACTG TGATGTTGTC AACCTCACCT
 3701 GTGAAGCCTG CCAGGAGCCG ATATCGGGCG CGCCAACATC AGAGAGCGCC
 20 3751 ACCCTGAAA GTGGTCCCGG GAGCGAGCCA GCCACATCTG GGTCGGAAAC
 3801 GCCAGGCACA AGTGAGTCTG CAACTCCCGA GTCCGGACCT GGCTCCGAGC
 3851 CTGCCACTAG CGGCTCCGAG ACTCCGGGAA CTTCCGAGAG CGCTACACCA
 3901 GAAAGCGGAC CCGGAACCAG TACCGAACCT AGCGAGGGCT CTGCTCCGGG
 3951 CAGCCCAGCC GGCTCTCCTA CATCCACGGA GGAGGGCACT TCCGAATCCG
 25 4001 CCACCCCGGA GTCAGGGCCA GGATCTGAAC CCGCTACCTC AGGCAGTGAG
 4051 ACGCCAGGAA CGAGCGAGTC CGCTACACCG GAGAGTGGGC CAGGGAGCCC
 4101 TGCTGGATCT CTAAGTCCA CTGAGGAAGG GTCACCAGCG GGCTCGCCCA
 4151 CCAGCACTGA AGAAGGTGCC TCGATATCTG ACAAGAACAC TGGTGATTAT
 4201 TACGAGGACA GTTATGAAGA TATTTACGCA TACTTGCTGA GTAAAAACAA
 30 4251 TGCCATTGAA CCAAGAAGCT TCTCTGACAA AACTCACACA TGCCCACCGT
 4301 GCCCAGCTCC AGAACTCCTG GGCGGACCGT CAGTCTTCCT CTTCCCCCA
 4351 AAACCCAAGG ACACCCTCAT GATCTCCCGG ACCCCTGAGG TCACATGCGT
 4401 GGTGGTGGAG GTGAGCCACG AAGACCCTGA GGTCAAGTTC AACTGGTACG
 4451 TGGACGGCGT GGAGGTGCAT AATGCCAAGA CAAAGCCGCG GGAGGAGCAG
 35 4501 TACAACAGCA CGTACCGTGT GGTCAGCGTC CTCACCGTCC TGCACCAGGA
 4551 CTGGCTGAAT GGCAAGGAGT ACAAGTGCAA GGTCTCCAAC AAAGCCCTCC
 4601 CAGCCCCCAT CGAGAAAACC ATCTCCAAAG CCAAAGGGCA GCCCCGAGAA
 4651 CCACAGGTGT ACACCCTGCC CCCATCCCGG GATGAGCTGA CCAAGAACCA
 4701 GGTCAGCCTG ACCTGCCTGG TCAAAGGCTT CTATCCCAGC GACATCGCCG
 40 4751 TGGAGTGGGA GAGCAATGGG CAGCCGGAGA ACAACTACAA GACCACGCT
 4801 CCCGTGTTGG ACTCCGACGG CTCCTTCTTC CTCTACAGCA AGCTCACCGT
 4851 GGACAAGAGC AGGTGGCAGC AGGGGAACGT CTTCTCATGC TCCGTGATGC
 4901 ATGAGGCTCT GCACAACCAC TACACGCAGA AGAGCCTCTC CCTGTCTCCG
 4951 GGTAATGA

pSYN VWF059 protein sequence (VWF D'D3-Fc with a2 region of FVIII thrombin site in the linker) - bold underlined area shows a2 region (SEQ ID NO: 197)

1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFNFTFDGSM
 50 51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
 101 TVTQGDQKRS MPYASKGLYL ETEAGYYKLS GEAYGFVARI DGSGNFQVLL
 151 SDRYFNKTCG LCGNFNIFAE DDFMTQEGTL TSDPYDFANS WALSSGEQWC
 201 ERASPPSSSC NISSGEMQKG LWEQCQLLKS TSVFARCHPL VDPEPFVALC

251 EKTLCCECAGG LECACPALLE YARTCAQEGM VLYGWTDHSA CSPVCPAGME
 301 YRQCVSPCAR TCQSLHINEM CQERCVDGCS CPEGQLLDEG LCVESTTEPC
 351 VHSBKRYPPG TSLSRDCNTC ICRNSQWICS NEECPGECLV TGQSHFKSFD
 401 NRYFTFSGIC QYLLARDCQD HSFISVIETV QCADDRDAVC TRSVTVRLPG
 5 451 LHNSLVKLKH GAGVAMDGQD IQLPLLKGD LRIQHTVTASV RLSYGEDLQM
 501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
 551 NAWKLHGDCQ DLQKQHS DPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
 601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCCL
 651 NCPKGQVYLQ CGTPCNLTCT SLSYPDEECN EACLEGCFCP PGLYMDERGD
 10 701 CVPKAQCPCY YDGEIFQPED IFSDHHTMCY CEDGFMHCTM SGVPGSLLPD
 751 AVLSSPLSHR SKRSLSCRPP MVKLVC PADN LRAEGLECTK TCQNYDLECM
 801 SMGCVSGCLC PPGMVRHENR CVALERCPCF HQGKEYAPGE TVKIGCNTCV
 851 CRDRKWNCTD HVCDATCSTI GMAHYLTFDG LKYLFPGECC YVLVQDYCGS
 901 NPGTFRILVG NKGCSHPSVK CKKRVTILVE GGEIELFDGE VNVKRPMDKE
 15 951 THFEVVEGR YIILLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
 1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
 1051 MKQTMVDSSC RILTSDVFQD CNKLVDPPEY LDVCIYDTCS CESIGDCAAF
 1101 CDTIAAYAHV CAQHKGKVVW RTATLCPQSC EERNLRENGY EAEWRYNSCA
 1151 PACQVTCQHP EPLACPVCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE
 20 1201 VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP ISGAPTESA
 1251 TPESGPGSEP ATSGSETPGT SESATPESGP GSEPATSGSE TPGTSESATP
 1301 ESGPGTSTEP SEGSA PGSPA GSPTSTEEGT SESATPESGP GSEPATSGSE
 1351 TPGTSESATP ESGPGSPAGS PTSTEEGSPA GSPTSTEEGA **SISDKNTGDY**
 1401 **YEDSYEDISA YLLSKNNAIE PRFS**DKTHT CPPCPAPELL GGPSVFLFPP
 25 1451 KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ
 1501 YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE
 1551 PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTP
 1601 PVLDS DGSFF LYSKLTVDKS RWQQGNVFC SVMHEALHNH YTQKSLSLSP
 1651 GK*

pSYN VWF062 nucleotide sequence (encoding VWF D'D3-Fc with no thrombin site in the linker) (SEQ ID NO: 198)

1 ATGATTCCTG CCAGATTTGC CGGGGTGCTG CTTGCTCTGG CCCTCATTTT
 35 51 GCCAGGGACC CTTTGTGCAG AAGGAACTCG CGGCAGGTCA TCCACGGCCC
 101 GATGCAGCCT TTTCGGAAGT GACTTCGTCA ACACCTTTGA TGGGAGCATG
 151 TACAGCTTTG CGGGATACTG CAGTTACCTC CTGGCAGGGG GCTGCCAGAA
 201 ACGCTCCTTC TCGATTATTG GGGACTTCCA GAATGGCAAG AGAGTGAGCC
 251 TCTCCGTGTA TCTGGGGGAA TTTTGTGACA TCCATTTGTT TGTCAATGGT
 40 301 ACCGTGACAC AGGGGGACCA AAGAGTCTCC ATGCCCTATG CCTCCAAAGG
 351 GCTGTATCTA GAAACTGAGG CTGGGTACTA CAAGCTGTCC GGTGAGGCCT
 401 ATGGCTTTGT GGCCAGGATC GATGGCAGCG GCAACTTTCA AGTCCTGCTG
 451 TCAGACAGAT ACTTCAACAA GACCTGCGGG CTGTGTGGCA ACTTTAACAT
 501 CTTTGCTGAA GATGACTTTA TGACCCAAGA AGGGACCTTG ACCTCGGACC
 45 551 CTTATGACTT TGCCAACTCA TGGGCTCTGA GCAGTGGAGA ACAGTGGTGT
 601 GAACGGGCAT CTCCTCCCAG CAGCTCATGC AACATCTCCT CTGGGGAAAT
 651 GCAGAAGGGC CTGTGGGAGC AGTGCCAGCT TCTGAAGAGC ACCTCGGTGT
 701 TTGCCCGCTG CCACCCTCTG GTGGACCCCG AGCCTTTTGT GGCCCTGTGT
 751 GAGAAGACTT TGTGTGAGTG TGCTGGGGGG CTGGAGTGCG CCTGCCCTGC
 50 801 CCTCCTGGAG TACGCCCGGA CCTGTGCCCA GGAGGGAATG GTGCTGTACG
 851 GCTGGACCGA CCACAGCGCG TGCAGCCCAG TGTGCCCTGC TGGTATGGAG
 901 TATAGGCAGT GTGTGTCCCC TTGCGCCAGG ACCTGCCAGA GCCTGCACAT
 951 CAATGAAATG TGTCAGGAGC GATGCGTGGA TGGCTGCAGC TGCCCTGAGG

1001 GACAGCTCCT GGATGAAGGC CTCTGCGTGG AGAGCACCGA GTGTCCCTGC
 1051 GTGCATTCCG GAAAGCGCTA CCCTCCCGGC ACCTCCCTCT CTCGAGACTG
 1101 CAACACCTGC ATTTGCCGAA ACAGCCAGTG GATCTGCAGC AATGAAGAAT
 1151 GTCCAGGGGA GTGCCTTGTC ACTGGTCAAT CCCACTTCAA GAGCTTTGAC
 5 1201 AACAGATACT TCACCTTCAG TGGGATCTGC CAGTACCTGC TGGCCCCGGA
 1251 TTGCCAGGAC CACTCCTTCT CCATTGTCAT TGAGACTGTC CAGTGTGCTG
 1301 ATGACCGCGA CGCTGTGTGC ACCCGCTCCG TCACCGTCCG GCTGCCTGGC
 1351 CTGCACAACA GCCTTGTGAA ACTGAAGCAT GGGGCAGGAG TTGCCATGGA
 1401 TGGCCAGGAC ATCCAGCTCC CCCTCCTGAA AGGTGACCTC CGCATCCAGC
 10 1451 ATACAGTGAC GGCCTCCGTG CGCCTCAGCT ACGGGGAGGA CCTGCAGATG
 1501 GACTGGGATG GCCGCGGGAG GCTGCTGGTG AAGCTGTCCC CCGTCTATGC
 1551 CGGGAAGACC TGCGGCCTGT GTGGGAATTA CAATGGCAAC CAGGGCGACG
 1601 ACTTCCTTAC CCCCTCTGGG CTGGCGGAGC CCCGGGTGGA GGACTTCGGG
 1651 AACGCCTGGA AGCTGCACGG GGACTGCCAG GACCTGCAGA AGCAGCACAG
 15 1701 CGATCCCTGC GCCCTCAACC CGCGCATGAC CAGGTTCTCC GAGGAGGCGT
 1751 GCGCGGTCTT GACGTCCCCC ACATTCGAGG CCTGCCATCG TGCCGTCAGC
 1801 CCGCTGCCCT ACCTGCGGAA CTGCCGCTAC GACGTGTGCT CCTGCTCGGA
 1851 CGGCCGCGAG TGCCTGTGCG GCGCCCTGGC CAGCTATGCC GCGGCCTGCG
 1901 CGGGGAGAGG CGTGCGCGTC GCGTGGCGCG AGCCAGGCCG CTGTGAGCTG
 20 1951 AACTGCCCCA AAGGCCAGGT GTACCTGCAG TCGGGGACCC CCTGCAACCT
 2001 GACCTGCCGC TCTCTCTCTT ACCCGGATGA GGAATGCAAT GAGGCCTGCC
 2051 TGGAGGGCTG CTTCTGCCCC CCAGGGCTCT ACATGGATGA GAGGGGGGAC
 2101 TCGTGCCCA AGGCCAGTG CCCCTGTTAC TATGACGGTG AGATCTTCCA
 2151 GCCAGAAGAC ATCTTCTCAG ACCATCACAC CATGTGCTAC TGTGAGGATG
 25 2201 GCTTCATGCA CTGTACCATG AGTGGAGTCC CCGGAAGCTT GCTGCCTGAC
 2251 GCTGTCTCA GCAGTCCCCT GTCTCATCGC AGCAAAAGGA GCCTATCCTG
 2301 TCGGCCCCC ATGGTCAAGC TGGTGTGTCC CGCTGACAACTGCGGGCTG
 2351 AAGGGCTCGA GTGTACAAA ACGTGCCAGA ACTATGACCT GGAGTGCATG
 2401 AGCATGGGCT GTGTCTCTGG CTGCCTCTGC CCCCCGGGCA TGGTCCGGCA
 30 2451 TGAGAACAGA TGTGTGGCCC TGGAAAGGTG TCCCTGCTTC CATCAGGGCA
 2501 AGGAGTATGC CCCTGGAGAA ACAGTGAAGA TTGGCTGCAA CACTTGTGTC
 2551 TGTCGGGACC GGAAGTGGAA CTGCACAGAC CATGTGTGTG ATGCCACGTG
 2601 CTCCACGATC GGCATGGCCC ACTACCTCAC CTTGACGGG CTCAAATACC
 2651 TGTCCCCCG GGAGTGCCAG TACGTTCTGG TGCAGGATTA CTGCGGCAGT
 35 2701 AACCCTGGGA CCTTTCGGAT CTAGTGGGG AATAAGGGAT GCAGCCACCC
 2751 CTCAGTGAAA TGCAAGAAAC GGGTCAACAT CCTGGTGGAG GGAGGAGAGA
 2801 TTGAGCTGTT TGACGGGGAG GTGAATGTGA AGAGGCCCAT GAAGGATGAG
 2851 ACTCACTTTG AGGTGGTGGG GTCTGGCCGG TACATCATTC TGCTGCTGGG
 2901 CAAAGCCCTC TCCGTGGTCT GGGACCGCCA CCTGAGCATC TCCGTGGTCC
 40 2951 TGAAGCAGAC ATACCAGGAG AAAGTGTGTG GCCTGTGTGG GAATTTTGAT
 3001 GGCATCCAGA ACAATGACCT CACCAGCAGC AACCTCCAAG TGGAGGAAGA
 3051 CCCTGTGGAC TTTGGGAACT CCTGGAAAGT GAGCTCGCAG TGTGCTGACA
 3101 CCAGAAAAGT GCCTCTGGAC TCATCCCCTG CCACCTGCCA TAACAACATC
 3151 ATGAAGCAGA CGATGGTGGG TTCCTCCTGT AGAATCCTTA CCAGTGACGT
 45 3201 CTTCCAGGAC TGCAACAAGC TGGTGGACCC CGAGCCATAT CTGGATGTCT
 3251 GCATTTACGA CACCTGCTCC TGTGAGTCCA TTGGGGACTG CGCCGCATTC
 3301 TGCGACACCA TTGCTGCCTA TGCCACCGTG TGTGCCCAGC ATGGCAAGGT
 3351 GGTGACCTGG AGGACGGCCA CATTGTGCCC CCAGAGCTGC GAGGAGAGGA
 3401 ATCTCCGGGA GAACGGGTAT GAGGCTGAGT GGCGCTATAA CAGCTGTGCA
 50 3451 CCTGCCTGTC AAGTCACGTG TCAGCACCTT GAGCCACTGG CCTGCCCTGT
 3501 GCAGTGTGTG GAGGGCTGCC ATGCCCACTG CCCTCCAGGG AAAATCCTGG
 3551 ATGAGCTTTT GCAGACCTGC GTTGACCCTG AAGACTGTCC AGTGTGTGAG
 3601 GTGGCTGGCC GGCGTTTTGC CTCAGGAAAG AAAGTCACCT TGAATCCAG

3651 TGACCCTGAG CACTGCCAGA TTTGCCACTG TGATGTTGTC AACCTCACCT
 3701 GTGAAGCCTG CCAGGAGCCG ATATCGGGCG CGCCAACATC AGAGAGCGCC
 3751 ACCCCTGAAA GTGGTCCCGG GAGCGAGCCA GCCACATCTG GGTCGGAAAC
 3801 GCCAGGCACA AGTGAGTCTG CAACTCCCGA GTCCGGACCT GGCTCCGAGC
 5 3851 CTGCCACTAG CGGCTCCGAG ACTCCGGGAA CTTCCGAGAG CGCTACACCA
 3901 GAAAGCGGAC CCGGAACCAG TACCGAACCT AGCGAGGGCT CTGCTCCGGG
 3951 CAGCCCAGCC GGCTCTCCTA CATCCACGGA GGAGGGCACT TCCGAATCCG
 4001 CCACCCCGGA GTCAGGGCCA GGATCTGAAC CCGCTACCTC AGGCAGTGAG
 4051 ACGCCAGGAA CGAGCGAGTC CGCTACACCG GAGAGTGGGC CAGGGAGCCC
 10 4101 TGCTGGATCT CTTACGTCCA CTGAGGAAGG GTCACCAGCG GGCTCGCCCA
 4151 CCAGCACTGA AGAAGGTGCC TCGAGCGACA AAACCTACAC ATGCCACCG
 4201 TGCCCAGCTC CAGAACTCCT GGGCGGACCG TCAGTCTTCC TCTTCCCCC
 4251 AAAACCCAAG GACACCCTCA TGATCTCCCG GACCCCTGAG GTCACATGCG
 4301 TGGTGGTGGA CGTGAGCCAC GAAGACCCTG AGGTCAAGTT CAACTGGTAC
 15 4351 GTGGACGGCG TGGAGGTGCA TAATGCCAAG ACAAAGCCGC GGGAGGAGCA
 4401 GTACAACAGC ACGTACCGTG TGGTCAGCGT CCTCACCGTC CTGCACCAGG
 4451 ACTGGCTGAA TGGCAAGGAG TACAAGTGCA AGGTCTCAA CAAAGCCCTC
 4501 CCAGCCCCCA TCGAGAAAAC CATCTCCAAA GCCAAAGGGC AGCCCCGAGA
 4551 ACCACAGGTG TACACCCTGC CCCCATCCCG GGATGAGCTG ACCAAGAACC
 20 4601 AGGTCAGCCT GACCTGCCTG GTCAAAGGCT TCTATCCAG CGACATCGCC
 4651 GTGGAGTGGG AGAGCAATGG GCAGCCGAG AACAACTACA AGACCACGCC
 4701 TCCCGTGTTG GACTCCGACG GTCCTTCTT CCTCTACAGC AAGCTCACCG
 4751 TGGACAAGAG CAGGTGGCAG CAGGGGAACG TCTTCTCATG CTCCGTGATG
 4801 CATGAGGCTC TGCACAACCA CTACACGCAG AAGAGCCTCT CCCTGTCTCC
 25 4851 GGGTAAATGA

pSYN VWF062 protein sequence (VWF D'D3-Fc with no thrombin site in the linker) (SEQ ID NO: 199)

30 1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFNFTFDGSM
 51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
 101 TVTQGDQ RVS MPYASKGLYL ETEAGYYKLS GEAYGFVARI DSGSNFQVLL
 151 SDRYFNKTCG LCGNFNIFAE DDFMTQEGTL TSDPYDFANS WALSSGEQWC
 35 201 ERASPPSSSC NISSGEMQKG LWEQCQLLKS TSVFARCHPL VDPEPFVALC
 251 EKTLC ECAGG LECACPALLE YARTCAQEGM VLYGWDHSA CSPVCPAGME
 301 YRQCVSPCAR TCQSLHINEM CQERCVDGCS CPEGQLLDEG LCVESTCPC
 351 VHSGKRYPPG TSLSRDCNTC ICRNSQWICS NEECPGECLV TGQSHFKSFD
 401 NRYFTFSGIC QYLLARDCQD HSFSIVIETV QCADDRDAVC TRSVTVRLPG
 40 451 LHNSLVKLKH GAGVAMDQD IQLPLLKGD LRIQHTVTASV RLSYGEDLQM
 501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
 551 NAWKLHGDCQ DLQKQHS DPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
 601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCEL
 651 NCPKGQVYLQ CGTPCNLTCR SLSYPDEECN EACLEGCFCP PGLYMDERGD
 45 701 CVPKAQCPCY YDGEIFQPED IFSDHHTMCY CEDGFMHCTM SGVPGSLLPD
 751 AVLSSPLSHR SKRSLSCRPP MVKLVCPADN LRAEGLECTK TCQNYDLECM
 801 SMGCVSGCLC PPGMVRHENR CVALERCPCF HQGKEYAPGE TVKIGCNTCV
 851 CRDRKWNCTD HVCDATCSTI GMAHYLTFDG LKYLFPGEQ YVLVQDYCGS
 901 NPGTFRILVG NKGCSHPSVK CKKRVTILVE GGEIELFDGE VNVKRPMKDE
 50 951 THFEVVESGR YIILLGLKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
 1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
 1051 MKQTMVDSSC RILTSDVFQD CNKLVDPEPY LDVCIYDTCS CESIGDCAAF
 1101 CDTIAAYAHV CAQHKG VVTW RTATLCPQSC EERNLRENGY EAEWRYNSCA

1151 PACQVTCQHP EPLACPVQCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE
 1201 VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP ISGAPTSESA
 1251 TPESGPGSEP ATSGSETPGT SESATPESGP GSEPATSGSE TPGTSESATP
 1301 ESGPGTSTEP SEGSAPGSPA GSPTSTEEGT SESATPESGP GSEPATSGSE
 5 1351 TPGTSESATP ESGPGSPAGS PTSTEEGSPA GSPTSTEEGA SSDKTHTCPP
 1401 CPAPELLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY
 1451 VDGVEVHNAK TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL
 1501 PAPIEKTISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA
 1551 VEWESNGQPE NNYKTTPPV L DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM
 10 1601 HEALHNHYTQ KSLSLSPGK*

pSYN VWF073 nucleotide sequence- (encoding VWFD1D2D'D3- 144 AE XTEN- FVIII truncated a2 thrombin site-Fc) (SEQ ID NO:174)

15 1 ATGATTCCTG CCAGATTTGC CGGGGTGCTG CTTGCTCTGG CCCTCATTTT
 51 GCCAGGGACC CTTTGTGCAG AAGGAACTCG CGGCAGGTCA TCCACGGCCC
 101 GATGCAGCCT TTTCGGAAGT GACTTCGTCA ACACCTTTGA TGGGAGCATG
 151 TACAGCTTTG CGGGATACTG CAGTTACCTC CTGGCAGGGG GCTGCCAGAA
 20 201 ACGCTCCTTC TCGATTATTG GGGACTTCCA GAATGGCAAG AGAGTGAGCC
 251 TCTCCGTGTA TCTTGGGGAA TTTTGTGACA TCCATTTGTT TGTCAATGGT
 301 ACCGTGACAC AGGGGGACCA AAGAGTCTCC ATGCCCTATG CCTCCAAAGG
 351 GCTGTATCTA GAAACTGAGG CTGGGTACTA CAAGCTGTCC GGTGAGGCCT
 401 ATGGCTTTGT GGCCAGGATC GATGGCAGCG GCAACTTTCA AGTCCTGCTG
 25 451 TCAGACAGAT ACTTCAACAA GACCTGCGGG CTGTGTGGCA ACTTTAACAT
 501 CTTTGCTGAA GATGACTTTA TGACCCAAGA AGGGACCTTG ACCTCGGACC
 551 CTTATGACTT TGCCAACTCA TGGGCTCTGA GCAGTGGAGA ACAGTGGTGT
 601 GAACGGGCAT CTCCTCCCAG CAGCTCATGC AACATCTCCT CTGGGGAAAT
 651 GCAGAAGGGC CTGTGGGAGC AGTGCCAGCT TCTGAAGAGC ACCTCGGTGT
 30 701 TTGCCCGCTG CCACCCTCTG GTGGACCCCG AGCCTTTTGT GGCCCTGTGT
 751 GAGAAGACTT TGTGTGAGTG TGCTGGGGGG CTGGAGTGCG CCTGCCCTGC
 801 CCTCTGGAG TACGCCCGGA CCTGTGCCCA GGAGGGAATG GTGCTGTACG
 851 GCTGGACCGA CCACAGCGCG TGCAGCCCAG TGTGCCCTGC TGGTATGGAG
 901 TATAGGCAGT GTGTGTCCCC TTGCGCCAGG ACCTGCCAGA GCCTGCACAT
 35 951 CAATGAAATG TGTCAGGAGC GATGCGTGGA TGGCTGCAGC TGCCCTGAGG
 1001 GACAGCTCCT GGATGAAGGC CTCTGCGTGG AGAGCACCGA GTGTCCCTGC
 1051 GTGCATTCCG GAAAGCGCTA CCCTCCCGGC ACCTCCCTCT CTCGAGACTG
 1101 CAACACCTGC ATTTGCCGAA ACAGCCAGTG GATCTGCAGC AATGAAGAAT
 1151 GTCCAGGGGA GTGCCTTGTC ACTGGTCAAT CCCACTTCAA GAGCTTTGAC
 40 1201 AACAGATACT TCACCTTCAG TGGGATCTGC CAGTACCTGC TGGCCCGGGA
 1251 TTGCCAGGAC CACTCCTTCT CCATTGTCAT TGAGACTGTC CAGTGTGCTG
 1301 ATGACCGCGA CGCTGTGTGC ACCCGCTCCG TCACCGTCCG GCTGCCTGGC
 1351 CTGCACAACA GCCTTGTA GAA ACTGAAGCAT GGGGCAGGAG TTGCCATGGA
 1401 TGGCCAGGAC ATCCAGCTCC CCCTCCTGAA AGGTGACCTC CGCATCCAGC
 45 1451 ATACAGTGAC GGCCTCCGTG CGCCTCAGCT ACGGGGAGGA CCTGCAGATG
 1501 GACTGGGATG GCCGCGGGAG GCTGCTGGTG AAGCTGTCCC CCGTCTATGC
 1551 CGGGAAGACC TGCGGCCTGT GTGGGAATTA CAATGGCAAC CAGGGCGACG
 1601 ACTTCCTTAC CCCCTCTGGG CTGGCGGAGC CCCGGGTGGA GGACTTCGGG
 1651 AACGCCTGGA AGCTGCACGG GGACTGCCAG GACCTGCAGA AGCAGCACAG
 50 1701 CGATCCCTGC GCCCTCAACC CGCGCATGAC CAGGTTCTCC GAGGAGGCGT
 1751 GCGCGGTCTC GACGTCCCCC ACATTCGAGG CCTGCCATCG TGCCGTCAGC
 1801 CCGCTGCCCT ACCTGCGGAA CTGCCGCTAC GACGTGTGCT CCTGCTCGGA

1851 CGGCCGCGAG TGCCTGTGCG GCGCCCTGGC CAGCTATGCC GCGGCCTGCG
 1901 CGGGGAGAGG CGTGCGCGTC GCGTGGCGCG AGCCAGGCCG CTGTGAGCTG
 1951 AACTGCCCCA AAGGCCAGGT GTACCTGCAG TGCGGGACCC CCTGCAACCT
 2001 GACCTGCCGC TCTCTCTCTT ACCCGGATGA GGAATGCAAT GAGGCCTGCC
 5 2051 TGGAGGGCTG CTTCTGCCCC CCAGGGCTCT ACATGGATGA GAGGGGGGAC
 2101 TGCGTGCCCA AGGCCAGTG CCCCTGTTAC TATGACGGTG AGATCTTCCA
 2151 GCCAGAAGAC ATCTTCTCAG ACCATCACAC CATGTGCTAC TGTGAGGATG
 2201 GCTTCATGCA CTGTACCATG AGTGGAGTCC CCGGAAGCTT GCTGCCTGAC
 2251 GCTGTCCTCA GCAGTCCCCT GTCTCATCGC AGCAAAAGGA GCCTATCCTG
 10 2301 TCGGCCCCC ATGGTCAAGC TGGTGTGTCC CGCTGACAAC CTGCGGGCTG
 2351 AAGGGCTCGA GTGTACAAA ACGTGCCAGA ACTATGACCT GGAGTGCATG
 2401 AGCATGGGCT GTGTCTCTGG CTGCCTCTGC CCCCCGGGCA TGGTCCGGCA
 2451 TGAGAACAGA TGTGTGGCCC TGGAAAGGTG TCCCTGCTTC CATCAGGGCA
 2501 AGGAGTATGC CCCTGGAGAA ACAGTGAAGA TTGGCTGCAA CACTTGTGTC
 15 2551 TGTCGGGACC GGAAGTGGAA CTGCACAGAC CATGTGTGTG ATGCCACGTG
 2601 CTCCACGATC GGCATGGCCC ACTACCTCAC CTTGACGGG CTCAAATACC
 2651 TGTTCCCCCG GGAGTGCCAG TACGTTCTGG TGCAGGATTA CTGCGGCAGT
 2701 AACCCTGGGA CCTTTCGGAT CTAGTGGGG AATAAGGGAT GCAGCCACCC
 2751 CTCAGTGAAA TGCAAGAAAC GGGTCACCAT CCTGGTGGAG GGAGGAGAGA
 20 2801 TTGAGCTGTT TGACGGGGAG GTGAATGTGA AGAGGCCCAT GAAGGATGAG
 2851 ACTCACTTTG AGGTGGTGGG GTCTGGCCGG TACATCATTC TGCTGCTGGG
 2901 CAAAGCCCTC TCCGTGGTCT GGGACCGCCA CCTGAGCATC TCCGTGGTCC
 2951 TGAAGCAGAC ATACCAGGAG AAAGTGTGTG GCCTGTGTGG GAATTTTGAT
 3001 GGCATCCAGA ACAATGACCT CACCAGCAGC AACCTCCAAG TGGAGGAAGA
 25 3051 CCCTGTGGAC TTTGGGAACT CCTGGAAGT GAGCTCGCAG TGTGCTGACA
 3101 CCAGAAAAGT GCCTCTGGAC TCATCCCCTG CCACCTGCCA TAACAACATC
 3151 ATGAAGCAGA CGATGGTGGA TTCCTCCTGT AGAATCCTTA CCAGTGACGT
 3201 CTTCCAGGAC TGCAACAAGC TGGTGGACCC CGAGCCATAT CTGGATGTCT
 3251 GCATTTACGA CACCTGCTCC TGTGAGTCCA TTGGGGACTG CGCCGCATTC
 30 3301 TGCGACACCA TTGCTGCCTA TGCCACGTG TGTGCCCAGC ATGGCAAGGT
 3351 GGTGACCTGG AGGACGGCCA CATTGTGCC CCAGAGCTGC GAGGAGAGGA
 3401 ATCTCCGGGA GAACGGGTAT GAGGCTGAGT GGCGCTATAA CAGCTGTGCA
 3451 CCTGCCTGTC AAGTCACGTG TCAGCACCTT GAGCCACTGG CCTGCCCTGT
 3501 GCAGGTGTG GAGGGCTGCC ATGCCACTG CCCTCCAGGG AAAATCTTGG
 35 3551 ATGAGCTTTT GCAGACCTGC GTTGACCCTG AAGACTGTCC AGTGTGTGAG
 3601 GTGGCTGGCC GGCGTTTTGC CTCAGGAAAG AAAGTCACCT TGAATCCCAG
 3651 TGACCCTGAG CACTGCCAGA TTTGCCACTG TGATGTTGTC AACCTCACCT
 3701 GTGAAGCCTG CCAGGAGCCG GGCGCGCCAA CATCAGAGAG CGCCACCCCT
 3751 GAAAGTGGTC CCGGGAGCGA GCCAGCCACA TCTGGGTCCG AAACGCCAGG
 40 3801 CACAAGTGAG TCTGCAACTC CCGAGTCCCG ACCTGGCTCC GAGCCTGCCA
 3851 CTAGCGGCTC CGAGACTCCG GGAACCTCCG AGAGCGCTAC ACCAGAAAGC
 3901 GGACCCGGAA CCAGTACCGA ACCTAGCGAG GGCTCTGCTC CGGGCAGCCC
 3951 AGCCGGCTCT CCTACATCCA CGGAGGAGGG CACTTCCGAA TCCGCCACCC
 4001 CGGAGTCAGG GCCAGGATCT GAACCCGCTA CCTCAGGCAG TGAGACGCCA
 45 4051 GGAACGAGCG AGTCCGCTAC ACCGAGAGT GGGCCAGGGA GCCCTGCTGG
 4101 ATCTCCTACG TCCACTGAGG AAGGGTCACC AGCGGGCTCG CCCACCAGCA
 4151 CTGAAGAAGG TGCCTCGAGC GGCGGTGGAG GATCCGGTGG CGGGGGATCC
 4201 GGTGGCGGGG GATCCGGTGG CGGGGGATCC GGTGGCGGGG GATCCGGTGG
 4251 CGGGGGATCC ATTGAACCAA GAAGCTTCTC TGGCAGCGGA GGCGACAAAA
 50 4301 CTCACACATG CCCACCGTGC CCAGCTCCAG AACTCCTGGG CGGACCGTCA
 4351 GTCTTCTCT TCCCCCAA ACCCAAGGAC ACCCTCATGA TCTCCCGGAC
 4401 CCCTGAGGTC ACATGCGTGG TGGTGGACGT GAGCCACGAA GACCTGAGG
 4451 TCAAGTTCAA CTGGTACGTG GACGGCGTGG AGGTGCATAA TGCCAAGACA

4501 AAGCCGCGGG AGGAGCAGTA CAACAGCACG TACCGTGTGG TCAGCGTCCT
 4551 CACCGTCCTG CACCAGGACT GGCTGAATGG CAAGGAGTAC AAGTGCAAGG
 4601 TCTCCAACAA AGCCCTCCCA GCCCCATCG AGAAAACCAT CTCCAAAGCC
 4651 AAAGGGCAGC CCCGAGAACC ACAGGTGTAC ACCCTGCCCC CATCCCGGGA
 5 4701 TGAGCTGACC AAGAACCAGG TCAGCCTGAC CTGCCTGGTC AAAGGCTTCT
 4751 ATCCCAGCGA CATCGCCGTG GAGTGGGAGA GCAATGGGCA GCCGGAGAAC
 4801 AACTACAAGA CCACGCCTCC CGTGTTGGAC TCCGACGGCT CCTTCTTCCT
 4851 CTACAGCAAG CTCACCGTGG ACAAGAGCAG GTGGCAGCAG GGGAACGTCT
 4901 TCTCATGCTC CGTGATGCAT GAGGCTCTGC ACAACCACTA CACGCAGAAG
 10 4951 AGCCTCTCCC TGTCTCCGG TAAATGA

pSYN VWF073 protein sequence- (VWFD1D2D'D3- 144 AE XTEN- truncated a2 thrombin site-Fc) (SEQ ID NO:175)

15 1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFVNTFDGSM
 51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVLSVYLGE FFDIHLFVNG
 101 TVTQGDQ RVS MPYASKGLYL ETEAGYYKLS GEAYGFVARI DGSGNFQVLL
 151 SDRYFNKTCG LCGNFNIFAE DDFMTQEGTL TSDPYDFANS WALSSGEQWC
 20 201 ERASPPSSSC NISSGEMQKG LWEQCQLLKS TSVFARCHPL VDPEPFVALC
 251 EKTLC ECAGG LECACPALLE YARTCAQEGM VLYGWTDHSA CSPVCPAGME
 301 YRQCVSPCAR TCQSLHINEM CQERCVDGCS CPEGQLLDEG LCVESTPCPC
 351 VHS GKRYPPG TSLSRDCNTC ICRNSQWICS NEECPGECLV TGQSHFKSFD
 401 NRYFTFSGIC QYLLARDCQD HSF SIVIETV QCADDRDAVC TRSVTVRLPG
 25 451 LHNSLVKLKH GAGVAMDGQD IQLPLLKGD L RIQHTVTASV RLSYGEDLQM
 501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTSPG LAEPRVEDFG
 551 NAWKLHGDCQ DLQKQHSDPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
 601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCCL
 651 NCPKGQVYLQ CGTPCNLT CR SLSYPDEECN EACLEGCFCP PGLYMDERGD
 30 701 CVPKAQCPCY YDGEIFQPED IFSDHHTMCY CEDGFMHCTM SGVPGSLLPD
 751 AVLSSPLSHR SKRSLSCRPP MVKLVC PADN LRAEGLECTK TCQNYDLECM
 801 SMGCVSGCLC PPGMVRHENR CVALERCPCF HQGKEYAPGE TVKIGCNTCV
 851 CRDRKWNCTD HVCDATCSTI GMAHYLTFDG LKYLFPGECQ YVLVQDYCGS
 901 NPGTFRILVG NKGCSHPSVK CKKRVTLVE GGEIELFDGE VNVKRPMKDE
 35 951 THFEVVESGR YIILLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
 1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
 1051 MKQTMVDSSC RILTSDVFQD CNKLVDPEPY LDVCIYDTCS CESIGDCAAF
 1101 CDTIAAYAHV CAQH GKVVTVW RTATLCPQSC EERNLRENGY EAEWRYNSCA
 1151 PACQVTCQHP EPLACPVCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE
 40 1201 VAGR RFASGK KVT LNPSDPE HCQICHCDVV NLTCEACQEP GAPTSESATP
 1251 ESGPGSEPAT SGSETPGTSE SATPESGPGS EPATSGSETP GTSESATPES
 1301 GPGTSTEPSE GSAPGSPAGS PTSTEEGTSE SATPESGPGS EPATSGSETP
 1351 GTSESATPES GPGSPAGSPT STEEGSPAGS PTSTEEGASS GGGGSGGGGS
 1401 GGGGSGGGGS GGGGSGGGGS IEPRSFSGSG GDKTHTCPPC PAPELLGGPS
 45 1451 VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT
 1501 KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA
 1551 KGQPREPQVY TLPPSRDEL T KNQVSLTCLV KGFYPSDIAV EWESNGQPEN
 1601 NYKTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK
 1651 SLSLSPGK*

Table 18: Exemplary Chimeric Polypeptide Sequences

FVIII-XTEN-Fc: SEQ ID NO: 201
TRYYLGAVELSWDYMQSDLGELPVDARFPPRVPKSFPFNTSVVYKKTFLVEFTDHLFNIAKP RPPWMGLLGPTIQAEVYDTVVITLKNMASHPVSLHAVGVSYWKASEGAEYDDQTSQREKED DKVFPGGSHTYVWQVLKENGPMASDPLCLTYSYLSHVDLVKDLNSGLIGALLVCREGSLAKE KTQTLHKFILLFAVFDEGKSWHSETKNSLMQDRDAASARAWPKMHTVNGYVNRSLPGLIGC HRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQASLEISPITFLTAQTLLMDLGQFLLFCHIS SHQHDGMEAYVKVDSCEEPQLRMKNNEEAEDYDDDLTDSEMDVVRFDDDNPSFIQIRSV KKHPTWVHYIAAEEEDWDYAPLVLPDDRYSKSYLNNGPQRIGRKYKKVRFMAYTDETF KTREAIQHESGILGPLYGEVGDLLIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDF PILPGEIFKYKWTVTVEDGPTKSDPRCLTRYSSVFNMERDLASGLIGPLLCYKESVDQGRNQ IMSDKRNVILFSVFDENRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSV CLHEVAYWYILSIGAQTDFLSVFFSGYTFKHKMYEDTLTLFPFSGETVFMMSMENPGLWILGC HNSDFRNRGMTALLKVSSCDKNTGDYYEDSYEDISAYLLSKNNAIEPRSFQNGTSESATPES GPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTE EGTSTEPSEGSAPGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPAT SGSETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPG TSTEPSEGSAPASSEITRITLQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSPRSFQKKTRHYFI AAVERLWDYGMSSSPHVLNRNAQSGSVQFKKVVFEFTDGSFTQPLYRGELNEHLGLLGPY IRAEVEDNIMVTFRNQASRPYSFYSSLISYEEDQRQGAEPKRFVKNPNETKTYFWKVQHMAP TKDEFDCKAWAYFSDVDLEKDVHSGLIGPLLCHTNLNPAGHGRQVTVQEFALFFTIFDETKS WYFTENMERNCRAPCNQMEDPTFKENYRFHAINGYIMDTLPLGLVMAQDQIRWYLLSMGS NENIHSIHFSGHVFTVRKKKEEYKMALYNLYPGVFETVEMLPKAGIWRVECLIGEHLHAGMST LFLVYSNKCQTPLGMASGHIRDFQITASGQYQGWAPKLARLHYSGSINAWSTKEPFSWIKVDL LAPMIIHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGNVDSSGIKHNF NPPIARYIRLHPHTYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSYFTNMFATWSP SKARLHLQGRSNAWRPQVNNPKEWLQVDFQKTMKVTGVTTQGVKSLTSMYVKEFLISSSQ DGHQWTLFFQNGKVKVFQGNQDSFTPVVNSLDPPLLTRYLRHPQSWVHQIALRMEVLGCEA QDLYDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
VWF(D'D3)-XTEN-a2 Linker-Fc: SEQ ID NO: 202
SLSCRPPMVKLVCADNLRAEGLECTKTCQNYDLECMMSGCVSGCLCPPGMVRHENRCVAL ERPCFHHQKEYAPGETVKIGCNTCVCRDRKWNCTDHVCDATCSTIGMAHYLTFDGLKYLPF GECQYVLVQDYCGSNPGTFRILVGNGCSPSVCKKRVTLVEGGEIELFDGEVNVKRP DETHFEVVESGRYIILLGKALSVDWRHLSISVVLKQTYQEKVCGLCGNFDGIQNNDLTSSN LQVEEDPVDFGNSWKVSSQCADTRKVPDSSPATCHNNIMKQTMVDSSCRILTSDVFQDCNK LVDPEPYLDVCIYDTCSCESIGDCAAFCDTIAAYAHVCAQHGVVTVWRTATLCPQSCEERNLR ENGYEAEWRYNSCAPACQVTCQHPEPLACPVQCVGCHAHCPPGKILDELLQTCVDPEDCPV CEVAGRRFASGKKVTLNPSDPEHCQICHCDVNNLTCEACQEPGTSESATPESGPGSEPATSGSE TPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSES ATPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGASSDKNTGDY YEDSYEDISAYLLSKNNAIEPRSFSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

Amino acid sequence of FVIII protein (312A): SEQ ID NO: 203

1	MQIELSTCFF	LCLLRFCFSA	TRRYYLGAVE	LSWDYMQSDL	GELPVDARFP
51	PRVPKSFPPN	TSVVYKKTFL	VEFTDHLFNI	AKPRPPWMGL	LGPTIQAEVY
101	DTVVITLKNM	ASHPVSLHAV	GVSYWKASEG	AEYDDQTSQR	EKEDDKVFPG
151	GSHTYVWQVL	KENGPMASDP	LCLTYSYLSH	VDLVKDLNSG	LIGALLVCRE
201	GSLAKEKTQT	LHKFILLFAV	FDEGKSWHSE	TKNSLMQDRD	AASARAWPKM
251	HTVNGYVNRS	LPGLIGCHRK	SVYWHVIGMG	TTPEVHSIFL	EGHTFLVRNH
301	RQASLEISPI	TFLTAQTLLM	DLGQFLLFCH	ISSHQHDGME	AYVKVDSCPE
351	EPQLRMKNN	EAEDYDDDLT	DSEMDVVRFD	DDNSPSFIQI	RSVAKKHPKT
401	WVHYIAAEEE	DWDYAPLVLA	PDDRSYKSQY	LNNGPQRIGR	KYKKVRFMAY
451	TDETFTKTR	IQHESGILGP	LLYGEVGDTL	LIIFKNQASR	PYNIYPHGIT
501	DVRPLYSRRL	PKGKHLKDF	PILPGEIFKY	KWTVTVEDGP	TKSDPRCLTR
551	YYSSFVNMER	DLASGLIGPL	LICYKESVDQ	RGNQIMSDKR	NVILFSVFDE
601	NRSWYL TENI	QRFLPNPAGV	QLEDPEFQAS	NIMHSINGYV	FDSLQLSVCL
651	HEVAYWYILS	IGAQTDFLSV	FFSGYTFKHK	MVYEDTLTLF	PFSGETVFMS
701	MENPGLWLIG	CHNSDFRNRG	MTALLKVSSC	DKNTGDYED	SYEDISAYLL
751	SKNNAIEPRS	FSQNGTSESA	TPESGPGSEP	ATSGSETPGT	SESATPESGP
801	GSEPATSGSE	TPGTSESATP	ESGPGTSTEP	SEGSAPGSPA	GSPTSTEEGT
851	SESATPESGP	GSEPATSGSE	TPGTSESATP	ESGPGSPAGS	PTSTEEGSPA
901	GSPTSTEEGT	STEPSEGSAP	GTSESATPES	GPGTSESATP	ESGPGTSESA
951	TPESGPGSEP	ATSGSETPGS	EPATSGSETP	GSPAGSPTST	EEGTSTEPSE
1001	GSAPGTSTEP	SEGSAPGSEP	ATSGSETPGT	SESATPESGP	GTSTEPSEGS
1051	APASSEITRT	TLQSDQEEID	YDDTISVEMK	KEDFDIYDED	ENQSPRSFQK
1101	KTRHYFIAAV	ERLWDYGMSS	SPHVLNRNAQ	SGSVPQFKKV	VFQEFDTGSF
1151	TQPLYRGELN	EHLGLLGPYI	RAEVEDNIMV	TFRNQASRPY	SFYSSLISYE
1201	EDQRQGAEP	KNFVKPNETK	TYFWKVQHMM	APTKDEFDCK	AWAYFSDVDL
1251	EKDVHSGLIG	PLLVCHTNTL	NPAHGRQVTV	QEFALFFTIF	DETKSWYFTE
1301	NMERNCRAPC	NIQMEDPTFK	ENYRFHAING	YIMDTLPGLV	MAQDQIRRWY
1351	LLSMGSNENI	HSIHFSGHVF	TVRKKEEYKM	ALYNLYPGVF	ETVEMLP SKA
1401	GIWRVECLIG	EHLHAGMSTL	FLVYSNKCQT	PLGMASGHIR	DFQITASGQY
1451	GQWAPKLARL	HYSGSINAWS	TKEPFSWIKV	DLLAPMIIHG	IKTQGARQKF
1501	SSLYISQFII	MYSLDGKKWQ	TYRGNSTGTL	MVFFGNVDSS	GIKHNI FNPP
1551	IIARYIRLHP	THYSIRSTLR	MELMGCDLNS	CSMPLGMESK	AISDAQITAS
1601	SYFTNMFATW	SPSKARLHLQ	GRSNAWRPQV	NNPKEWLQVD	FQKTMKVTVG
1651	TTQGVKSLLT	SMYVKEFLIS	SSQDGHQWTL	FFQNGKV KVF	QGNQDSFTPV
1701	VNSLDPPLLT	RYLRIHPQSW	VHQIALRMEV	LGCEAQDLYD	KTHTCPPCPA
1751	PELLGGPSVF	LFPPKPKDTL	MISRTPEVTC	VVVDVSHEDP	EVKFNWYVDG
1801	VEVHNAKTKP	REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKC	KVSNKALPAP
1851	IEKTISKAKG	QPREPQVYTL	PPSRDELTKN	QVSLTCLVKG	FYP S DIAVEW
1901	ESNGQPENNY	KTPPVLDSD	GSFFLYSKLT	VDKSRWQQGN	VFSCSVMHEA
1951	LHNHYTQKSL	SLSPG*			

Nucleotide sequence encoding FVIII 312A: SEQ ID NO: 204

1	ATGCAAATAG	AGCTCTCCAC	CTGCTTCTTT	CTGTGCCTTT	TGCGATTCTG
51	CTTTAGTGCC	ACCAGAAGAT	ACTACCTGGG	TGCAGTGGAA	CTGTCATGGG
101	ACTATATGCA	AAGTGATCTC	GGTGAGCTGC	CTGTGGACGC	AAGATTTCTT
151	CCTAGAGTGC	CAAAATCTTT	TCCATTCAAC	ACCTCAGTCG	TGTACAAAAA

201	GACTCTGTTT	GTAGAATTCA	CGGATCACCT	TTTCAACATC	GCTAAGCCAA
251	GGCCACCCTG	GATGGGTCTG	CTAGGTCTTA	CCATCCAGGC	TGAGGTTTAT
301	GATACAGTGG	TCATTACACT	TAAGAACATG	GCTTCCCATC	CTGTCACTCT
351	TCATGCTGTT	GGTGTATCCT	ACTGGAAAGC	TTCTGAGGGA	GCTGAATATG
401	ATGATCAGAC	CAGTCAAAGG	GAGAAAGAAG	ATGATAAAGT	CTTCCCTGGT
451	GGAAGCCATA	CATATGTCTG	GCAGGTCCTG	AAAGAGAATG	GTCCAATGGC
501	CTCTGACCCA	CTGTGCCTTA	CCTACTCATA	TCTTTCTCAT	GTGGACCTGG
551	TAAAAGACTT	GAATTCAGGC	CTCATTGGAG	CCCTACTAGT	ATGTAGAGAA
601	GGGAGTCTGG	CCAAGGAAAA	GACACAGACC	TTGCACAAAT	TTATACTACT
651	TTTTGCTGTA	TTTGATGAAG	GGAAAAGTTG	GCACTCAGAA	ACAAAGAACT
701	CCTTGATGCA	GGATAGGGAT	GCTGCATCTG	CTCGGGCCTG	GCCTAAAATG
751	CACACAGTCA	ATGGTTATGT	AAACAGGTCT	CTGCCAGGTG	TGATTGGATG
801	CCACAGGAAA	TCAGTCTATT	GGCATGTGAT	TGGAATGGGC	ACCACTCCTG
851	AAGTGCACTC	AATATTCCTC	GAAGGTCACA	CATTTCTTGT	GAGGAACCAT
901	CGCCAGGCGT	CCTTGGAAT	CTCGCCAATA	ACTTTCTTGA	CTGCTCAAAC
951	ACTCTTGATG	GACCTTGGAC	AGTTTCTACT	GTTTTGTCTA	ATCTCTTCCC
1001	ACCAACATGA	TGGCATGGAA	GCTTATGTCA	AAGTAGACAG	CTGTCCAGAG
1051	GAACCCCAAC	TACGAATGAA	AAATAATGAA	GAAGCGGAAG	ACTATGATGA
1101	TGATCTTACT	GATTCTGAAA	TGGATGTGGT	CAGGTTTGAT	GATGACAACT
1151	CTCCTTCCTT	TATCCAAATT	CGCTCAGTTG	CCAAGAAGCA	TCCTAAAAC
1201	TGGGTACATT	ACATTGCTGC	TGAAGAGGAG	GACTGGGACT	ATGCTCCCTT
1251	AGTCCTCGCC	CCCATGACA	GAAGTTATAA	AAGTCAATAT	TTGAACAATG
1301	GCCCTCAGCG	GATTGGTAGG	AAGTACAAAA	AAGTCCGATT	TATGGCATA
1351	ACAGATGAAA	CCTTTAAGAC	TCGTGAAGCT	ATTCAGCATG	AATCAGGAAT
1401	CTTGGGACCT	TTACTTTATG	GGGAAGTTGG	AGACACACTG	TTGATTATAT
1451	TTAAGAATCA	AGCAAGCAGA	CCATATAACA	TCTACCCTCA	CGGAATCACT
1501	GATGTCCGTC	CTTTGTATTG	AAGGAGATTA	CCAAAAGGTG	TAAAACATTT
1551	GAAGGATTTT	CCAATTCTGC	CAGGAGAAAT	ATTCAAATAT	AAATGGACAG
1601	TGACTGTAGA	AGATGGGCCA	ACTAAATCAG	ATCCTCGGTG	CCTGACCCGC
1651	TATTACTCTA	GTTTCGTTAA	TATGGAGAGA	GATCTAGCTT	CAGGACTCAT
1701	TGGCCCTCTC	CTCATCTGCT	ACAAAGAATC	TGTAGATCAA	AGAGGAACCC
1751	AGATAATGTC	AGACAAGAGG	AATGTCATCC	TGTTTTCTGT	ATTTGATGAG
1801	AACCGAAGCT	GGTACCTCAC	AGAGAATATA	CAACGCTTTC	TCCCCAATCC
1851	AGCTGGAGTG	CAGCTTGAGG	ATCCAGAGTT	CCAAGCCTCC	AACATCATGC
1901	ACAGCATCAA	TGGCTATGTT	TTTGATAGTT	TGCAGTTGTC	AGTTTGTTTG
1951	CATGAGGTGG	CATACTGGTA	CATTCTAAGC	ATTGGAGCAC	AGACTGACTT
2001	CCTTTCTGTC	TTCTTCTCTG	GATATACCTT	CAAACACAAA	ATGGTCTATG
2051	AAGACACACT	CACCCTATTG	CCATTCTCAG	GAGAACTGT	CTTCATGTCG
2101	ATGGAAAACC	CAGGTCTATG	GATTCTGGGG	TGCCACAAC	CAGACTTTTCG
2151	GAACAGAGGC	ATGACCGCCT	TACTGAAGGT	TTCTAGTTGT	GACAAGAACA
2201	CTGGTGATTA	TTACGAGGAC	AGTTATGAAG	ATATTTTCAGC	ATACTTGCTG
2251	AGTAAAAACA	ATGCCATTGA	ACCAAGAAGC	TTCTCTCAAA	ACGGTACCTC
2301	AGAGTCTGCT	ACCCCGGAGT	CAGGGCCAGG	ATCAGAGCCA	GCCACCTCCG
2351	GGTCTGAGAC	ACCCGGGACT	TCCGAGAGTG	CCACCCCTGA	GTCCGGACCC
2401	GGGTCCGAGC	CCGCCACTTC	CGGCTCCGAA	ACTCCCGGCA	CAAGCGAGAG
2451	CGTACCCCA	GAGTCAGGAC	CAGGAACATC	TACAGAGCCC	TCTGAAGGCT
2501	CCGCTCCAGG	GTCCCCAGCC	GGCAGTCCCA	CTAGCACCGA	GGAGGGAACC
2551	TCTGAAAGCG	CCACACCCGA	ATCAGGGCCA	GGGTCTGAGC	CTGCTACCAG
2601	CGGCAGCGAG	ACACCAGGCA	CCTCTGAGTC	CGCCACACCA	GAGTCCGGAC
2651	CCGGATCTCC	CGCTGGGAGC	CCACCTCCA	CTGAGGAGGG	ATCTCCTGCT
2701	GGCTCTCCAA	CATCTACTGA	GGAAGGAACC	TCAACCGAGC	CATCCGAGGG
2751	ATCAGCTCCC	GGCACCTCAG	AGTCGGCAAC	CCCGGAGTCT	GGACCCGGAA
2801	CTTCCGAAAG	TGCCACACCA	GAGTCCGGTC	CCGGGACTTC	AGAATCAGCA
2851	ACACCCGAGT	CCGGCCCTGG	GTCTGAACCC	GCCACAAGTG	GTAGTGAGAC

2901	ACCAGGATCA	GAACCTGCTA	CCTCAGGGTC	AGAGACACCC	GGATCTCCGG
2951	CAGGCTCACC	AACCTCCACT	GAGGAGGGCA	CCAGCACAGA	ACCAAGCGAG
3001	GGCTCCGCAC	CCGGAACAAG	CACTGAACCC	AGTGAGGGTT	CAGCACCCGG
3051	CTCTGAGCCG	GCCACAAGTG	GCAGTGAGAC	ACCCGGCACT	TCAGAGAGTG
3101	CCACCCCGA	GAGTGGCCCA	GGCACTAGTA	CCGAGCCCTC	TGAAGGCAGT
3151	GCGCCAGCCT	CGAGCGAAAT	AACCTCGTACT	ACTCTTCAGT	CAGATCAAGA
3201	GGAAATTGAC	TATGATGATA	CCATATCAGT	TGAAATGAAG	AAGGAAGATT
3251	TTGACATTTA	TGATGAGGAT	GAAAATCAGA	GCCCCCGCAG	CTTTCAAAAG
3301	AAAACACGAC	ACTATTTTAT	TGCTGCAGTG	GAGAGGCTCT	GGGATTATGG
3351	GATGAGTAGC	TCCCCACATG	TTCTAAGAAA	CAGGGCTCAG	AGTGGCAGTG
3401	TCCCTCAGTT	CAAGAAAGTT	GTTTTCCAGG	AATTTACTGA	TGGCTCCTTT
3451	ACTCAGCCCT	TATACCGTGG	AGAACTAAAT	GAACATTTGG	ACTTCCTGGG
3501	GCCATATATA	AGAGCAGAAG	TTGAAGATAA	TATCATGGTA	ACTTTTCAGAA
3551	ATCAGGCCTC	TCGTCCCTAT	TCCTTCTATT	CTAGCCTTAT	TTCTTATGAG
3601	GAAGATCAGA	GGCAAGGAGC	AGAACCTAGA	AAAAACTTTG	TCAAGCCTAA
3651	TGAAACCAAA	ACTTACTTTT	GGAAAGTGCA	ACATCATATG	GCACCCACTA
3701	AAGATGAGTT	TGACTGCAAA	GCCTGGGCTT	ATTTCTCTGA	TGTTGACCTG
3751	GAAAAAGATG	TGCACTCAGG	CCTGATTGGA	CCCCTTCTGG	TCTGCCACAC
3801	TAACACACTG	AACCCTGCTC	ATGGGAGACA	AGTGACAGTA	CAGGAATTTG
3851	CTCTGTTTTT	CACCATCTTT	GATGAGACCA	AAAGCTGGTA	CTTCACTGAA
3901	AATATGGAAA	GAAACTGCAG	GGCTCCCTGC	AATATCCAGA	TGGAAGATCC
3951	CACTTTTAAA	GAGAATTATC	GCTTCCATGC	AATCAATGGC	TACATAATGG
4001	ATACACTACC	TGGCTTAGTA	ATGGCTCAGG	ATCAAAGGAT	TCGATGGTAT
4051	CTGCTCAGCA	TGGGCAGCAA	TGAAAACATC	CATTCTATTG	ATTTTCAGTGG
4101	ACATGTGTTT	ACTGTACGAA	AAAAAGAGGA	GTATAAAATG	GCACTGTACA
4151	ATCTCTATCC	AGGTGTTTTT	GAGACAGTGG	AAATGTTACC	ATCCAAAGCT
4201	GGAATTTGGC	GGGTGGAATG	CCTTATTGGC	GAGCATCTAC	ATGCTGGGAT
4251	GAGCACACTT	TTTCTGGTGT	ACAGCAATAA	GTGTCAGACT	CCCCTGGGAA
4301	TGGCTTCTGG	ACACATTAGA	GATTTTCAGA	TTACAGCTTC	AGGACAATAT
4351	GGACAGTGGG	CCCCAAAGCT	GGCCAGACTT	CATTATTCCG	GATCAATCAA
4401	TGCCTGGAGC	ACCAAGGAGC	CCTTTTCTTG	GATCAAGGTG	GATCTGTTGG
4451	CACCAATGAT	TATTCACGGC	ATCAAGACCC	AGGGTGCCCG	TCAGAAGTTC
4501	TCCAGCCTCT	ACATCTCTCA	GTTTATCATC	ATGTATAGTC	TTGATGGGAA
4551	GAAGTGGCAG	ACTTATCGAG	GAAATTCCAC	TGGAACCTTA	ATGGTCTTCT
4601	TTGGCAATGT	GGATTTCATCT	GGGATAAAAC	ACAATATTTT	TAACCCCTCA
4651	ATTATTGCTC	GATACATCCG	TTTGACCCCA	ACTCATTATA	GCATTTCGAG
4701	CACTCTTCGC	ATGGAGTTGA	TGGGCTGTGA	TTTAAATAGT	TGCAGCATGC
4751	CATTGGGAAT	GGAGAGTAAA	GCAATATCAG	ATGCACAGAT	TACTGCTTCA
4801	TCCTACTTTA	CCAATATGTT	TGCCACCTGG	TCTCCTTCAA	AAGCTCGACT
4851	TCACCTCCAA	GGGAGGAGTA	ATGCCTGGAG	ACCTCAGGTG	AATAATCCAA
4901	AAGAGTGGCT	GCAAGTGGAC	TTCCAGAAGA	CAATGAAAGT	CACAGGAGTA
4951	ACTACTCAGG	GAGTAAAATC	TCTGCTTACC	AGCATGTATG	TGAAGGAGTT
5001	CCTCATCTCC	AGCAGTCAAG	ATGGCCATCA	GTGGACTCTC	TTTTTTTCAGA
5051	ATGGCAAAGT	AAAGGTTTTT	CAGGGAAATC	AAGACTCCTT	CACACCTGTG
5101	GTGAACTCTC	TAGACCCACC	GTTACTGACT	CGCTACCTTC	GAATTACCCC
5151	CCAGAGTTGG	GTGCACCAGA	TTGCCCTGAG	GATGGAGGTT	CTGGGCTGCG
5201	AGGCACAGGA	CCTCTACGAC	AAAACCTACA	CATGCCACCC	GTGCCACACT
5251	CCAGAATCTC	TGGGCGGACC	GTCAGTCTTC	CTCTTCCCCC	CAAAACCCAA
5301	GGACACCCTC	ATGATCTCCC	GGACCCCTGA	GGTCACATGC	GTGGTGGTGG
5351	ACGTGAGCCA	CGAAGACCCT	GAGGTCAAGT	TCAACTGGTA	TGTGGACGGC
5401	GTGGAAGTGC	ATAATGCCAA	GACAAAGCCG	CGGGAGGAGC	AGTACAACAG
5451	CACGTACCGT	GTGGTCAGCG	TCCTCACCGT	CCTGCACCAA	GACTGGCTGA
5501	ATGGCAAGGA	GTACAAGTGC	AAGGTCTCCA	ACAAAGCCCT	CCCAGCCCCC
5551	ATCGAGAAAA	CCATCTCCAA	AGCCAAAGGG	CAGCCCCGAG	AACCACAGGT

5601	GTACACCCTG	CCCCATCCC	GGGATGAGCT	GACCAAGAAC	CAAGTTAGCC
5651	TGACCTGCCT	GGTCAAAGGC	TTCTATCCCA	GCGACATCGC	CGTGGAGTGG
5701	GAGAGCAATG	GGCAGCCGGA	GAACAACACTAC	AAGACCACGC	CTCCCGTGTT
5751	GGACTCCGAC	GGCTCCTTCT	TCCTCTACTC	CAAGCTCACC	GTGGACAAGA
5801	GCAGGTGGCA	GCAGGGGAAC	GTCTTCTCAT	GCTCCGTGAT	GCATGAGGCT
5851	CTGCACAACC	ACTACACGCA	GAAGAGCCTC	TCCCTGTCTC	CGGGTTGA

Amino acid sequence of VWF059A protein: SEQ ID NO: 205

1	MIPARFAGVL	LALALILPGT	LCAEGTRGRS	STARCSLFGS	DFVNTFDGSM
51	YSFAGYCSYL	LAGGCQKRSF	SIIGDFQNGK	RVSLSVYLGE	FFDIHLFVNG
101	TVTQGDQRV	MPYASKGLYL	ETEAGYYKLS	GEAYGFVARI	DGSGNFQVLL
151	SDRYFNKTCG	LCGNFNIFAE	DDFMTQEGTL	TSDPYDFANS	WALSSGEQWC
201	ERASPPSSSC	NISSGEMQKG	LWEQCQLLKS	TSVFARCHPL	VDPEPFVALC
251	EKTLCECAGG	LECACPALLE	YARTCAQEGM	VLYGWTDHSA	CSPVCPAGME
301	YRQCVSPCAR	TCQSLHINEM	CQERCVDGCS	CPEGQLLDEG	LCVESTECPC
351	VHSGKRYPPG	TSLSRDCNTC	ICRNSQWICS	NEECPGECLV	TGQSHFKSFD
401	NRYFTFSGIC	QYLLARDCQD	HSFSIVIETV	QCADDRDAVC	TRSVTVRLPG
451	LHNSLVKLKH	GAGVAMDGQD	IQLPLLKGD	RIQHTVTASV	RLSYGEDLQM
501	DWDGRGRLLV	KLSPVYAGKT	CGLCGNYNGN	QGDDFLTPSG	LAEPRVEDFG
551	NAWKHLHGDCQ	DLQKQHSDFC	ALNPRMTRFS	EEACAVLTSP	TFEACHRAVS
601	PLPYLRNCRY	DVCSCSDGRE	CLCGALASYA	AACAGRGVRV	AWREPGRCEL
651	NCPKGQVYLQ	CGTPCNLTCT	SLSYPDEECN	EACLEGCFCP	PGLYMDERGD
701	CVPKAQCPCY	YDGEIFQPED	IFSDHHTMCY	CEDGFMHCTM	SGVPGSLLPD
751	AVLSSPLSHR	SKRSLSCRPP	MVKLVCPADN	LRAEGLECTK	TCQNYDLECM
801	SMGCVSGCLC	PPGMVRHENR	CVALERCPCF	HQGKEYAPGE	TVKIGCNTCV
851	CRDRKWNCTD	HVCDATCSTI	GMAHYLTFDG	LKYLFPGECQ	YVLVQDYCGS
901	NPGTFRILVG	NKGCSHPSVK	CKKRVITLVE	GGEIELFDGE	VNVKRPMDKE
951	THFEVVESEGR	YIILLGKAL	SVVWDRHLSI	SVVLKQTYQE	KVCGLCGNFD
1001	GIQNNDLTSS	NLQVEEDPVD	FGNSWKVSSQ	CADTRKVPLD	SSPATCHNNI
1051	MKQTMVDSSC	RILTSDFVQD	CNKLVDPPEY	LDVCIYDTCS	CESIGDCAAF
1101	CDTIAAYAHV	CAQHGVVVTW	RTATLCPQSC	EERNLRENGY	EAEWRYNSCA
1151	PACQVTCQHP	EPLACPVQCV	EGCHAHCPPG	KILDELLQTC	VDPEDCPVCE
1201	VAGRRFASGK	KVTLNPSDPE	HCQICHCDVV	NLTCEACQEP	GTSESATPES
1251	GPGSEPATSG	SETPGTSESA	TPESGPGSEP	ATSGSETPGT	SESATPESGP
1301	GTSTEPSEGS	APGSPAGSPT	STEEGTSESA	TPESGPGSEP	ATSGSETPGT
1351	SESATPESGP	GSPAGSPTST	EEGSPAGSPT	STEEGASSDK	NTGDYEDSY
1401	EDISAYLLSK	NNAIEPRSFS	DKTHTCPPCP	APELLGGPSV	FLFPPKPKDT
1451	LMISRTPEVT	CVVVDVSHED	PEVKFNWYVD	GVEVHNAKTK	PREEQYNSTY
1501	RVSVLTVLH	QDWLNGKEYK	CKVSNKALPA	PIEKTISKAK	GQPREPQVYT
1551	LPPSRDELTK	NQVSLTCLVK	GFYPSDIAVE	WESNGQPENN	YKTTTPVLDL
1601	DGSFFLYSKL	TVDKSRWQGG	NVFSCSVMHE	ALHNHYTQKS	LSLSPG*

Nucleotide sequence encoding VWF059A protein: SEQ ID NO: 206

1	ATGATTCCTG	CCAGATTTGC	CGGGGTGCTG	CTTGCTCTGG	CCCTCATTTT
51	GCCAGGGACC	CTTTGTGCAG	AAGGAACTCG	CGGCAGGTCA	TCCACGGCCC
101	GATCAGCCT	TTTCGGAAGT	GACTTCGTCA	ACACCTTTGA	TGGGAGCATG
151	TACAGCTTTG	CGGGATACTG	CAGTTACCTC	CTGGCAGGGG	GCTGCCAGAA
201	ACGCTCCTTC	TCGATTATTG	GGGACTTCCA	GAATGGCAAG	AGAGTGAGCC
251	TCTCCGTGTA	TCTTGGGGAA	TTTTTTGACA	TCCATTTGTT	TGTCAATGGT

301	ACCGTGACAC	AGGGGGACCA	AAGAGTCTCC	ATGCCCTATG	CCTCCAAAGG
351	GCTGTATCTA	GAAACTGAGG	CTGGGTACTA	CAAGCTGTCC	GGTGAGGCCT
401	ATGGCTTTGT	GGCCAGGATC	GATGGCAGCG	GCAACTTTCA	AGTCCTGCTG
451	TCAGACAGAT	ACTTCAACAA	GACCTGCGGG	CTGTGTGGCA	ACTTTAACAT
501	CTTTGCTGAA	GATGACTTTA	TGACCCAAGA	AGGGACCTTG	ACCTCGGACC
551	CTTATGACTT	TGCCAACTCA	TGGGCTCTGA	GCAGTGGAGA	ACAGTGGTGT
601	GAACGGGCAT	CTCCTCCCAG	CAGCTCATGC	AACATCTCCT	CTGGGGAAAT
651	GCAGAAGGGC	CTGTGGGAGC	AGTGCCAGCT	TCTGAAGAGC	ACCTCGGTGT
701	TTGCCCCGCTG	CCACCCTCTG	GTGGACCCCG	AGCCTTTTGT	GGCCCTGTGT
751	GAGAAGACTT	TGTGTGAGTG	TGCTGGGGGG	CTGGAGTGCG	CCTGCCCTGC
801	CCTCCTGGAG	TACGCCCCGA	CCTGTGCCCA	GGAGGGAATG	GTGCTGTACG
851	GCTGGACCGA	CCACAGCGCG	TGCAGCCCAG	TGTGCCCTGC	TGGTATGGAG
901	TATAGGCAGT	GTGTGTCCCC	TTGCGCCAGG	ACCTGCCAGA	GCCTGCACAT
951	CAATGAAATG	TGTCAGGAGC	GATGCGTGGA	TGGCTGCAGC	TGCCCTGAGG
1001	GACAGCTCCT	GGATGAAGGC	CTCTGCGTGG	AGAGCACCGA	GTGTCCCTGC
1051	GTGCATTCCG	GAAAGCGCTA	CCCTCCCAGC	ACCTCCCTCT	CTCGAGACTG
1101	CAACACCTGC	ATTTGCCGAA	ACAGCCAGTG	GATCTGCAGC	AATGAAGAAT
1151	GTCCAGGGGA	GTGCCTTGTC	ACTGGTCAAT	CCCACTTCAA	GAGCTTTGAC
1201	AACAGATACT	TCACCTTCAG	TGGGATCTGC	CAGTACCTGC	TGGCCCCGGA
1251	TTGCCAGGAC	CACTCCTTCT	CCATTGTCAT	TGAGACTGTC	CAGTGTGCTG
1301	ATGACCGCGA	CGCTGTGTGC	ACCCGCTCCG	TCACCGTCCG	GCTGCCTGGC
1351	CTGCACAACA	GCCTTGTAAG	ACTGAAGCAT	GGGGCAGGAG	TTGCCATGGA
1401	TGGCCAGGAC	ATCCAGCTCC	CCCTCCTGAA	AGGTGACCTC	CGCATCCAGC
1451	ATACAGTGAC	GGCCTCCGTG	CGCCTCAGCT	ACGGGGAGGA	CCTGCAGATG
1501	GACTGGGATG	GCCGCGGGAG	GTGCTGGTGG	AAGCTGTCCC	CCGTCTATGC
1551	CGGGAAGACC	TGCGGCCTGT	GTGGGAATTA	CAATGGCAAC	CAGGGCGACG
1601	ACTTCCTTAC	CCCCTCTGGG	CTGGCGGAGC	CCCGGGTGGA	GGACTTCGGG
1651	AACGCCTGGA	AGCTGCACGG	GGACTGCCAG	GACCTGCAGA	AGCAGCACAG
1701	CGATCCCTGC	GCCCTCAACC	CGCGCATGAC	CAGGTTCTCC	GAGGAGGCGT
1751	GCGCGGTCC	GACGTCCCCC	ACATTGAGAG	CCTGCCATCG	TGCCGTGAGC
1801	CCGCTGCCCT	ACCTGCGGAA	CTGCCGCTAC	GACGTGTGCT	CCTGCTCGGA
1851	CGGCCGCGAG	TGCCTGTGCG	GCGCCCTGGC	CAGCTATGCC	GCGGCCTGCG
1901	CGGGGAGAGG	CGTGCGCGTC	GCGTGGCGCG	AGCCAGGCCG	CTGTGAGCTG
1951	AAC TGCCCGA	AAGGCCAGGT	GTACCTGCAG	TGCGGGACCC	CCTGCAACCT
2001	GACCTGCCCG	TCTCTCTCTT	ACCCGGATGA	GGAATGCAAT	GAGGCCTGCC
2051	TGGAGGGCTG	CTTCTGCCCC	CCAGGGCTCT	ACATGGATGA	GAGGGGGGAC
2101	TGCGTGCCCA	AGGCCCAAGT	CCCCTGTTAC	TATGACGGTG	AGATCTTCCA
2151	GCCAGAAGAC	ATCTTCTCAG	ACCATCACAC	CATGTGCTAC	TGTGAGGATG
2201	GCTTCATGCA	CTGTACCATG	AGTGGAGTCC	CCGGAAGCTT	GCTGCCTGAC
2251	GCTGTCCCTCA	GCAGTCCCCT	GTCTCATCGC	AGCAAAAGGA	GCCTATCCTG
2301	TCGGCCCCCC	ATGGTCAAGC	TGGTGTGTCC	CGCTGACAAC	CTGCGGGCTG
2351	AAGGGCTCGA	GTGTACCAAA	ACGTGCCAGA	ACTATGACCT	GGAGTGCATG
2401	AGCATGGGCT	GTGTCTCTGG	CTGCCTCTGC	CCCCCGGGCA	TGGTCCGGCA
2451	TGAGAACAGA	TGTGTGGCCC	TGGAAAGGTG	TCCCTGCTTC	CATCAGGGCA
2501	AGGAGTATGC	CCCTGGAGAA	ACAGTGAAGA	TTGGCTGCAA	CACCTGTGTC
2551	TGTCGGGACC	GGAAGTGGA	CTGCACAGAC	CATGTGTGTG	ATGCCACGTG
2601	CTCCACGATC	GGCATGGCCC	ACTACCTCAC	CTTCGACGGG	CTCAAATACC
2651	TGTTCCCCCG	GGAGTGCCAG	TACGTTCTGG	TGCAGGATTA	CTGCGGCAGT
2701	AACCCTGGGA	CCTTTCGGAT	CCTAGTGGGG	AATAAGGGAT	GCAGCCACCC
2751	CTCAGTGAAA	TGCAAGAAAC	GGGTCACCAT	CCTGGTGGAG	GGAGGAGAGA
2801	TTGAGCTGTT	TGACGGGGAG	GTGAATGTGA	AGAGGCCCCT	GAAGGATGAG
2851	ACTCACTTTG	AGGTGGTGGG	GTCTGGCCCG	TACATCATTC	TGCTGCTGGG
2901	CAAAGCCCTC	TCCGTGGTCT	GGGACCGCCA	CCTGAGCATC	TCCGTGGTCC
2951	TGAAGCAGAC	ATACCAGGAG	AAAGTGTGTG	GCCTGTGTGG	GAATTTTGAT

3001	GGCATCCAGA	ACAATGACCT	CACCAGCAGC	AACCTCCAAG	TGGAGGAAGA
3051	CCCTGTGGAC	TTTGGGAACT	CCTGGAAAGT	GAGCTCGCAG	TGTGCTGACA
3101	CCAGAAAAGT	GCCTCTGGAC	TCATCCCCTG	CCACCTGCCA	TAACAACATC
3151	ATGAAGCAGA	CGATGGTGGG	TTCCTCCTGT	AGAATCCTTA	CCAGTGACGT
3201	CTTCCAGGAC	TGCAACAAGC	TGGTGGACCC	CGAGCCATAT	CTGGATGTCT
3251	GCATTTACGA	CACCTGCTCC	TGTGAGTCCA	TTGGGGACTG	CGCCGCATTC
3301	TGCGACACCA	TTGCTGCCTA	TGCCCACGTG	TGTGCCCAGC	ATGGCAAGGT
3351	GGTGACCTGG	AGGACGGCCA	CATTGTGCCC	CCAGAGCTGC	GAGGAGAGGA
3401	ATCTCCGGGA	GAACGGGTAT	GAGGCTGAGT	GGCGCTATAA	CAGCTGTGCA
3451	CCTGCCTGTC	AAGTCACGTG	TCAGCACCTT	GAGCCACTGG	CCTGCCCTGT
3501	GCAGTGTGTG	GAGGGCTGCC	ATGCCCACTG	CCCTCCAGGG	AAAATCCTGG
3551	ATGAGCTTTT	GCAGACCTGC	GTTGACCCTG	AAGACTGTCC	AGTGTGTGAG
3601	GTGGCTGGCC	GGCGTTTTGC	CTCAGGAAAG	AAAGTCACCT	TGAATCCCAG
3651	TGACCCTGAG	CACTGCCAGA	TTTGCCACTG	TGATGTTGTC	AACCTCACCT
3701	GTGAAGCCTG	CCAGGAGCCG	GGTACATCAG	AGAGCGCCAC	CCCTGAAAGT
3751	GGTCCCAGGA	GCGAGCCAGC	CACATCTGGG	TCGAAACGC	CAGGCACATC
3801	CGAGTCTGCA	ACTCCCGAGT	CCGGACCTGG	CTCCGAGCCT	GCCACTAGCG
3851	GCTCCGAGAC	TCCGGGAACT	TCCGAGAGCG	CTACACCAGA	AAGCGGACCC
3901	GGAACCAGTA	CCGAACCTAG	CGAGGGCTCT	GCTCCGGGCA	GCCCAGCCGG
3951	CTCTCCTACA	TCCACGGAGG	AGGGCACTTC	CGAATCCGCC	ACCCCGGAGT
4001	CAGGGCCAGG	ATCTGAACCC	GCTACCTCAG	GCAGTGAGAC	GCCAGGAACG
4051	AGCGAGTCCG	CTACACCGGA	GAGTGGGCCA	GGGAGCCCTG	CTGGATCTCC
4101	TACGTCCACT	GAGGAAGGGT	CACCAGCGGG	CTCGCCCACC	AGCACTGAAG
4151	AAGGTGCCTC	GTCTGACAAG	AACACTGGTG	ATTATTACGA	GGACAGTTAT
4201	GAAGATATTT	CAGCATACTT	GCTGAGTAAA	AACAATGCCA	TTGAACCAAG
4251	AAGCTTCTCT	GACAAAACTC	ACACATGCCC	ACCGTGCCCA	GCTCCAGAAC
4301	TCCTGGGCGG	ACCGTCAGTC	TTCCTCTTCC	CCCCAAAACC	CAAGGACACC
4351	CTCATGATCT	CCCGGACCCC	TGAGGTCACA	TGCGTGGTGG	TGGACGTGAG
4401	CCACGAAGAC	CCTGAGGTCA	AGTTCAACTG	GTATGTGGAC	GGCGTGGAAG
4451	TGCATAATGC	CAAGACAAAG	CCGCGGGAGG	AGCAGTACAA	CAGCACGTAC
4501	CGTGTGGTCA	GCGTCCTCAC	CGTCCTGCAC	CAAGACTGGC	TGAATGGCAA
4551	GGAGTACAAG	TGCAAGGTCT	CCAACAAAGC	CCTCCCAGCC	CCCATCGAGA
4601	AAACCATCTC	CAAAGCCAAA	GGGCAGCCCC	GAGAACCACA	GGTGTACACC
4651	CTGCCCCCAT	CCCGGGATGA	GCTGACCAAG	AACCAAGTTA	GCCTGACCTG
4701	CCTGGTCAAA	GGCTTCTATC	CCAGCGACAT	CGCCGTGGAG	TGGGAGAGCA
4751	ATGGGCAGCC	GGAGAACAAC	TACAAGACCA	CGCCTCCCGT	GTTGGACTCC
4801	GACGGCTCCT	TCTTCCTCTA	CTCCAAGCTC	ACCGTGGACA	AGAGCAGGTG
4851	GCAGCAGGGG	AACGTCTTCT	CATGCTCCGT	GATGCATGAG	GCTCTGCACA
4901	ACCACTACAC	GCAGAAGAGC	CTCTCCCTGT	CTCCGGGTTG	A

A-FVIII(XTEN)-Fc: SEQ ID NO: 207

ATRRRYYLGAVELSWDYMQSDLGELPVDARFPFPRVPSKSPFNSTSVVYKKTLFVEFTDHLFNIK
 PRPPWMGLLGPTIQAEVYDTVVITLKNMASHPVSLHAVGVSYWKASEGAEYDDQTSQREKE
 DDKVFPGGSHTYVWQVLKENGPMASDPLCLTYSYLSHVDLVKDLNSGLIGALLVCREGLAK
 EKTQTLHKFILLFAVFDEGKSWHSETKNSLMQDRDAASARAWPKMHTVNGYVNRSLPGLIGC
 HRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQASLEISPITFLTAQTLLMDLGQFLLFCHIS
 SHQHDGMEAYVKVDSCPEEPQLRMKNNEEAEDYDDDLTDSEMDVVRFDDDNPSFIQIRSA
 KKHPKTWVHYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQIRGRKYKKVRFMAYTDETF
 KTREAIQHESGILGPLLYGEVGDLLIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDF
 PILPGEIFKYKWTVTVEDGPTKSDPRCLTRYSSFNMERDLASGLIGPLLYCYKESVDQGRNQ
 IMSDKRNVILFSVF DENRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSV
 CLHEVAYWYILSIGAQTDFLSVFFSGYTFKHKMYEDTLTLFPFSGETVFMSMENPGLWILGC
 HNSDFRNRGMTALLKVSSCDKNTGDYYEDSYEDISAYLLSKNNAIEPRSFSSQNGTSESATPESG

PGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGSPAGS
PTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEG
TSTEPSEGSAPGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSG
SETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTS
TEPSEGSAPASSEITRTTLQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSPRSFQKKTRHYFIA
AVERLWDYGMSSSPHVLNRNAQSGSVPPQFKKVVFEFTDGSFTQPLRYGELNEHLGLLGPYIR
AEVEDNIMVTFRNQASRPYSFYSSLISYEEDQRQGAEPKRFVVKPNETKTYFWKVQHMAPT
KDEFDCKAWAYFSDVDLEKDVHSLIGLPLLVCHTNLNPAGHRQVTVQEFALFFTIFDETKS
WYFTENMERNCRAPCNQMEDPTFKENYRFHAINGYIMDTLPLGLVMAQDQRRIRWYLLSMGS
NENIHSIHFSGHVFTVRKKKEEYKMALYNLYPGVFETVEMLPKAGIWRVECLIGEHLHAGMST
LFLVYSNKCQTPLGMASGHIRDFQITASGQYQGWAPKLARLHYSGSINAWSTKEPFSWIKVDL
LAPMIIHGKIQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGNVDSSGIKHNF
NPPIIARYIRLHPHTYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSYFTNMFATWSP
SKARLHLQGRSNAWRPQVNNPKEWLQVDFQKTMKVTVGVTQGVKSLTSMYVKEFLISSSQ
DGHQWTLFFQNGKVKVFQGNQDSFTPVVNSLDPPLLTRYLRHPQSWVHQIALRMEVLGCEA
QDLYDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREEQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

Table 19. Additional chimeric polypeptide sequences

Description / SEQ ID NO.	Sequence
AE288	GTSESATPES GPGSEPATSG SETPGTSESA TPESGPGSEP ATSGSETPGT SESATPESGP 60 GTSTEPSEGS APGSPAGSPT STEEGTSESA TPESGPGSEP ATSGSETPGT SESATPESGP 120 SEQ ID NO: 8 GSPAGSPTST EEGSPAGSPT STEEGTSTEP SEGSAAGTSE SATPESGPGT SESATPESGP 180 GTSESATPES GPGSEPATSG SETPGSEPAT SGSETPGSPA GSPTSTEEGT STEPSEGSAP 240 GTSTEPSEGS APGSEPATSG SETPGTSESA TPESGPGTST EPSEGSAP 288
pSYN VWF059	TSTEEGASIS DKNTGDYYED SYEDISAYLL SKNNAIEPRS FSDKTH
SEQ ID NO: 13	
pSYN VWF059A	TSTEEGASSD KNTGDYYEDS YEDISAYLLS KNNAIEPRSF SDKTH
SEQ ID NO: 22	
pSYN FVIII 312	ATRRYYLGAV ELSWDYMQSD LGELPVDARF PPRVPKSEFP NTSVVYKCTL FVEFTDHLFN 60 IAKPRPPWMG LLGPTIQAEV YDTVVITLKN MASHPVSLHA VGVSYWKASE GAEDDQTSQ 120 SEQ ID NO: 173 REKEDDKVFP GGSHTYVWQV LKENGPMASD PLCLTYSYLS HVDLVKDLNS GLIGALLVCR 180 EGSLAKEKTQ TLHKFILLFA VFDEGKSWHS ETKNSLMQDR DAASARAWPK MHTVNGYVNR 240 SLPGLIGCHR KSVYWHVIGM GTTPEVHSIF LEGHTFLVRN HRQASLEISP ITFLTAQTLL 300 MDLGQFLLFC HISSHQHDGM EAYVKVDSCP EEPQLRMKN EEAEDYDDDL TDSEMDVVRV 360 DDDNSPSFIQ IRSVAKKHPK TWVHYIAAEE EDWDYAPLVL APDDRSYKSQ YLNNGPQRIG 420 RKYKQVRFMA YTDETFKTRE AIQHESGILG PLYGVEGDT LLIIFKNQAS RPYNIYPHGI 480 TDVRPLYSRP LPKGVKHLKD FPILPGEIFK YKWTVTVEDG PTKSDPRCLT RYSSSFVNME 540 RDLASGLIGP LLIYKESVD QRGNQIMSDK RNVILFSVFD ENRSWYLTEN IQRFLPNPAG 600 VQLEDPEFQA SNIMHSINGY VFDSLQLSVC LHEVAYWYIL SIGAQTDFLS VFFSGYTFKH 660 KMYEDTTLTLP FPFSGETVFM SMENPGLWIL GCHNSDFRNR GMTALLKVSS CDKNTGDYYE 720 DSYEDISAYL LSKNNAIEPR SFSQNGTSES ATPESGPGSE PATSGSETPG TSESATPESG 780

	PGSEPATSGS ETPGTSESAT PESGPGTSTE PSEGSAPGSP AGSPTSTEEG TSESATPESG 840 PGSEPATSGS ETPGTSESAT PESGPGSPAG SPTSTEEGSP AGSPTSTEEG TSTEPSEGSAP 900 PGTSESATPE SGPGTSESAT PESGPGTSES ATPESGPGSE PATSGSETPG SEPATSGSET 960 PGSPAGSPTS TEEGTSTEPS EGSAPGTSTE PSEGSAPGSE PATSGSETPG TSESATPESG 1020 PGTSTEPSEG SAPASSEITR TTLQSDQEEI DYDDTISVEM KKEDFDIYDE DENQSPRSFQ 1080 KKTRHYFIAA VERLWDYGMS SSPHVLNRRA QSGSVPPQFKK VVFQEFTHDGS FTQPLYRGEL 1140 NEHLGLLGPY IRAEVEDNIM VTFRNQASRP YSFYSSLSY EEDQRQGAEP RKNFVKPNET 1200 KTYFWKVQHH MAPTKDEFDC KAWAYFSDVD LEKDVHSGLI GPLLVCHTNT LNPAGHRQVT 1260 VQEFALFFTI FDETKSWYFT ENMERNCRAP CNIQMEDPTF KENYRFHAIN GYIMDTLPGL 1320 VMAQDQRIW YLLSMGSNEN IHSIHFSGHV FTVRKKEEYK MALYNLYPGV FETVEMLP SK 1380 AGIWRVECLI GEHLHAGMST LFLVYSNKCQ TPLGMASGHI RDFQITASGQ YGQWAPKLAR 1440 LHYSGSINAW STKEPFSWIK VDLLAPMIH GIKTQGARQK FSSLYISQFI IMYSLDGKKW 1500 QTYRGNSTGT LMVFFGNVDS SGIKHNI FNP PIARYIRLH PTHYSIRSTL RMELMGCDLN 1560 SCSMPLGMES KAISDAQITA SSYFTNMFAT WSPSKARLHL QGRSNAWRPQ VNNPKEWLQV 1620 DFQTKMKVTG VTTQGVKSLL TSMYVKEFLI SSSQDGHQWT LFFQNGKVKV FQGNQDSFTP 1680 VVNSLDPPLL TRYLRIPHQS WWHQIALRME VLGCEAQDLY DKTHTCPPCP APELLGGPSV 1740 FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY 1800 RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSRDELTK 1860 NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTPPPVLD SDFSFFLYSKL TVDKSRWQQG 1920 NVFSCSVME ALHNHYTQKS LSLSPGK
XTEN_AE288_2 SEQ ID NO: 54	GSPAGSPTST EEGTSESATP ESGPGSEPAT SGSETPGTSE SATPESGPGT STEPSEGSAP 60 GTSTEPSEGS APTGTSTEPSE GSAPGTSTEP SEGSAPGTST EPSEGSAPGT STEPSEGSAP 120 GSPAGSPTST EEGTSTEPSE GSAPGTSESA TPESGPGSEP ATSGSETPGT SESATPESGP 180 GSEPATSGSE TPGTSESATP ESGPGTSTEP SEGSAPGTSE SATPESGPGS PAGSPTSTEE 240 GSPAGSPTST EEGSPAGSPT STEEGTSESA TPESGPGTST EPSEGSAP 288
XTEN AE144_5A SEQ ID NO: 58	TSESATPESG PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG 60 TSTEPSEGSAP PGSPAGSPTS TEEGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG 120 SPAGSPTSTE EGSPAGSPTS TEEG
a2 Linker of chimeric polypeptide SEQ ID NO: 88	DKNTGDYYED SYEDISAYLL SKNNAIEPRS FS 32
Signal Peptide of FVIII SEQ ID NO: 64	MQIELSTCFFLCLLRFCFS
FVIII fragment 1 of chimeric polypeptide SEQ ID NO: 215	ATTRYYLGAV ELSWDYMQSD LGELPVDARF PPRVPKSPFP NTSVVYKCTL FVEFTDHLFN 60 IAKPRPPWMG LLGPTIQA EV YDTVVITLKN MASHPVSLHA VGVSYWKASE GA EYDDQTSQ 120 REKEDDKVFP GGSHTYVWQV LKENGPMASD PLCLTYSYLS HVDLVKDLNS GLIGALLVCR 180 EGSLAKEKTQ TLHKFILLFA VFDEGKSWHS ETKNLSLMQDR DAASARAWPK MHTVNGYVNR 240 SLPGLIGCHR KSVYWHVIGM GTTPEVHSIF LEGHTFLVRN HRQASLEISP ITFLTAQTLL 300 MDLGQFLLFC HISSHQHDGM EAYVKVDSCP EEPQLRMKN EEAEDYDDDL TDSEMDVVR 360 DDDNPSFIFQ IRSVAKKHPK TWVHYIAAEE EDWDYAPLVL APDDRSYKSQ YLNNGPQRIG 420 RKYKKVRFMA YTDETFKTR EAIQHEGILG PLYGEVGD LLIIFKNQAS RPYNIYPHGI 480 TDVRPLYSR LKPGVKHLKD FPILPGEIFK YKWTVTVEDG PTKSDPRCLT RYSSFVNME 540 RDLASGLIGP LLICYKESVD QRGNQIMSDK RNVILFSVFD ENRSWYL TEN IQRFLPNPAG 600 VQLEDPEFQA SNIMHSINGY VFDLSQLSVC LHEVAYWYIL SIGAQTDFLS VFFSGYTFKH 660 KMYEDTTLTLP FFSGETVFM SMENPGLWIL GCHNSDFRNR GMTALLKVSS CDKNTGDYYE 720 DSYEDISAYL LSKNNAIEPR SFSQN
FVIII fragment 2 of chimeric polypeptide	EITRTTLQSD QEEIDYDDTI SVMKKEDFD IYDEDENQSP RSFQKKTRHY FIAAVERLWD 60 YGMSSSPHVL RNRAQSGSVF QFKKVVFQEF TDGSFTQPLY RGELNEHLGL LGPYIRAEVE 120 DNIMVTFRNQ ASRPYSFYSS LISYEEDQRQ GAEPKKNFVK PNETKTYFWK VQHHMAPTKD 180 EFDCKAWAYF SDVDLEKDVH SGLIGPLLCV HTNTLNPAHG RQVTVQEFAL FFTIFDET KS 240

SEQ ID NO. 216	WYFTENMERN	CRAPCNIQME	DPTFKENYRF	HAINGYIMDT	LPGLVMAQDQ	RIRWYLLSMG	300
	SNENIHSIHF	SGHVFTVRKK	EEYKMALYNL	YPGVFETVEM	LPSKAGIWRV	ECLIGEHLHA	360
	GMSTLFLVYS	NKCQTPGLMA	SGHIRDFQIT	ASGQYQWAP	KLARLHYSGS	INAWSTKEPF	420
	SWIKVDLLAP	MIIHGIKTQG	ARQKFSSLYI	SQFIIMYSLD	GKKWQTYRGN	STGTLMVFFG	480
	NVDSSGIKHN	IFNPPIIARY	IRLHPHYSI	RSTLRMELMG	CDLNSCSMPL	GMESKAISDA	540
	QITASSYFTN	MFATWSPSKA	RLHLQGRSNA	WRPQVNNPKE	WLQVDFQKTM	KVTGVTQGV	600
	KSLTSMYVK	EFLISSSQDG	HQWTLFFQNG	KVKVFQGNQD	SFTPVVNSLD	PPLLTRYLRI	660
	HPQSWVHQIA	LRMEVLGCEA	QDLY				
VWF Signal Peptide	MIPARFAGVL LALALILPGT LC						
SEQ ID NO: 208							
VWF D1D2 domain of chimeric polypeptide	AEGTRGRSST	ARCSLFGSDF	VNTFDGSMYS	FAGYCSYLLA	GGCQKRSFSI	IGDFQNGKRV	60
	SLSVYLGEFF	DIHLFVNGTV	TQGDQRVSMF	YASKGLYLET	EAGYYKLSGE	AYGFVARIDG	120
	SGNFQVLLSD	RYFNKTCGLC	GNFNIFAEDD	FMTQEGTLTS	DPYDFANSWA	LSSGEQWCER	180
	ASPPSSSCNI	SSGEMQKGLW	EQCQLLKSTS	VFARCHPLVD	PEPFVALCEK	TLCECAGGLE	240
	CACPALLEYA	RTCAQEGMVL	YGWTDHSACS	PVCPAGMEYR	QCVSPCARTC	QSLHINEMCQ	300
	ERCVDGSCSP	EGQLLDEGLC	VESTTECPVH	SGKRYPPGTS	LSRDCNTCIC	RNSQWICSNE	360
	ECPGECVLTG	QSHFKSFDNR	YFTFSGICQY	LLARDCQDHS	FSIVIETVQC	ADDRDAVCTR	420
	SVTVRLPGLH	NSLVKLKHGA	GVAMDGGQDIQ	LPLLKGDLRI	QHTVTASVRL	SYGEDLQMDW	480
SEQ ID NO: 209	DGRGRLLVKL	SPVYAGKTCG	LCGNYNNGQG	DDFLTTPSGLA	EPRVEDFGNA	WKLHGDCQDL	540
	QKQHSDDPCAL	NPRMTRFSEE	ACAVLTSPTF	EACHRAVSPL	PYLRNCRYDV	CSCSDGRECL	600
	CGALASYAAA	CAGRGVVRVAW	REPGRCELNC	PKGQVYLQCG	TPCNLTCSRSL	SYPDDEECNEA	660
	CLEGCFPCPPG	LYMDERGDV	PKAQCPCCYYD	GEIFQPEDIF	SDHHTMCYCE	DGFMHCTMSG	720
	VPGSLLPDAV	LSSPLSHRSK	R				
VWF D' domain of chimeric polypeptide	SLSCRPPMVK	LVCPADNLRA	EGLECTKTCQ	NYDLECMSMG	CVSGCLCPPG	MVRHENRCVA	60
	LERPCPCFHQ	KEYAPGETVK	IGCNTCVCRD	RKWNCTDHVC	DAT		103
SEQ ID NO: 210							
VWF D3 domain of chimeric polypeptide	CSTIGMAHYL	TFDGLKYLFP	GECQYVLVQD	YCGSNPGTFR	ILVGNKGCSH	PSVKCKKRV	60
	ILVEGGEIEL	FDGEVNVKRP	MKDETHFEVV	ESGRYIILLL	GKALSVVWDR	HLISVVLKQ	120
	TYQEKVCGLC	GNFDGIQNN	LTSSNLQVEE	DPVDFGNSWK	VSSQCADTRK	VPLDSSPATC	180
	HNNIMKQTMV	DSSCRILTSD	VFQDCNKLVD	PEPYLDVCIY	DTCSCESIGD	CAAFCDTIAA	240
	YAHVCAQH GK	VVTWRTATLC	PQSCEERNLR	ENGYEAEWRY	NSCAPACQVT	CQHPEPLACP	300
	VQCVEGCHAH	CPPGKILDEL	LQTCVDPEDC	PVCEVAGRRF	ASGKKVTLPN	SDPEHCQICH	360
	CDVVNLTC EA	CQEP					374
Fc region	DKTHTCPPCP	APELLGGPSV	FLFPPKPKDT	LMISRTPEVT	CVVVDVSHED	PEVKFNWYVD	60
	GVEVHNAKTK	PREEQYNSTY	RVVSVLTVLH	QDWLNGKEYK	CKVSNKALPA	PIEKTISKAK	120
	GQPREPQVYT	LPPSRDELTK	NQVSLTCLVK	GFYPNSDIAVE	WESNGQPENN	YKTTTPPVLD	180
	DGSFFLYSKL	TVDKSRWQQG	NVFSCSVMHE	ALHNHYTQKS	LSLSPG		
SEQ ID NO: 217							
XTEN AE288_3	GTSESATPES	GPGSEPATSG	SETPGTSESA	TPESGPGSEP	ATSGSETPGT	SESATPESGP	60
	GTSTEPSEGS	APGSPAGSPT	STEEGTSESA	TPESGPGSEP	ATSGSETPGT	SESATPESGP	120
	GSPAGSPTST	EEGSPAGSPT	STEEGTSTEP	SEGSAPGTSE	SATPESGPGT	SESATPESGP	180
	GTSESATPES	GPGSEPATSG	SETPGSEPAT	SGSETPGSPA	GSPTSTEEGT	STEPSEGSAP	240
	GTSTEPSEGS	APGSEPATSG	SETPGTSESA	TPESGPGTST	EPSEGSAPAS	S	291

[0387] The foregoing description of the specific embodiments will so fully reveal the general nature of the disclosure that others can, by applying knowledge within the skill of the art, readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the general concept of the present disclosure. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance.

[0388] Other embodiments of the disclosure will be apparent to those skilled in the art from consideration of the specification and practice of the disclosure disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the disclosure being indicated by the following claims.

[0389] All patents and publications cited herein are incorporated by reference herein in their entirety.

[0390] It is to be understood that if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art in Australia or any other country.

[0391] In the claims which follow and in the description of the invention, except where the context requires otherwise due to express language or necessary implication, the word “comprise” or variations such as “comprises” or “comprising” is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of prophylactically treating hemophilia A in a human subject comprising administering to the subject in need thereof multiple doses of a chimeric polypeptide at a dosing interval, wherein the chimeric polypeptide comprises (i) a factor VIII (FVIII) protein comprising the amino acid sequence of SEQ ID NO: 207; and (ii) a von Willebrand factor (VWF) protein comprising the amino acid sequence of SEQ ID NO: 202; wherein the FVIII protein is covalently linked to the VWF protein by a disulfide bond,
 - wherein multiple doses of the chimeric polypeptide are administered to the subject at a dosing interval of at least 6 days to 8 days; and
 - wherein each of the multiple doses is from about 45 IU/kg to about 55 IU/kg,
 - wherein the chimeric polypeptide is administered intravenously.
2. Use of a chimeric polypeptide in the manufacture of a medicament for prophylactically treating hemophilia A in a human subject, wherein the chimeric protein is to be administered at a dosing interval, wherein the chimeric protein is to be administered in multiple doses, wherein the chimeric polypeptide comprises (i) a factor VIII (FVIII) protein comprising the amino acid sequence of SEQ ID NO: 207; and (ii) a von Willebrand factor (VWF) protein comprising the amino acid sequence of SEQ ID NO: 202; wherein the FVIII protein is covalently linked to the VWF protein by a disulfide bond,
 - wherein multiple doses of the chimeric polypeptide are to be administered to the subject at a dosing interval of at least 6 days to 8 days; and
 - wherein each of the multiple doses is from about 45 IU/kg to about 55 IU/kg,
 - wherein the chimeric polypeptide is to be administered intravenously.
3. The method of claim 1 or the use of claim 2, wherein the FVIII polypeptide is associated with the VWF polypeptide by two disulfide bonds.
4. The method of claim 1 or 3, or use of claim 2 or 3, wherein each of the multiple doses is 50 IU/kg, and the dosing interval is at least about 7 days.

5. The method of claim 1 or 3, or use of claim 2 or 3, wherein at least one of the multiple doses is 50 IU/kg.
6. The method of any one of claims 1 or 3 to 5, or use of any one of claims 2 to 5, wherein the subject has previously received treatment for hemophilia A with any recombinant FVIII, plasma-derived FVIII, or cryoprecipitate for at least 150 exposure days (ED).
7. The method of any one of claims 1 or 3 to 6, or use of any one of claims 2 to 6, wherein the subject is either:
 - (a) currently on a prophylactic treatment regimen with a marketed FVIII product and has had at least four bleeding episodes in the twelve months prior to administration of the chimeric polypeptide; or
 - (b) currently on an on-demand treatment regimen with a marketed FVIII product and has had at least twelve bleeding episodes in the twelve months prior to administration of the chimeric polypeptide.
8. The method of any one of claims 1 or 3 to 7, or use of any one of claims 2 to 7, wherein the subject has a platelet count of at least 100,000 cells/ μ L.
9. The method of any one of claims 1 or 3 to 8, or use of any one of claims 2 to 8, wherein the subject is free of other coagulation disorders in addition to hemophilia A.
10. The method of any one of claims 1 or 3 to 9, or use of any one of claims 2 to 9, wherein the subject does not have a history of developing inhibitors to a FVIII product.
11. The method of any one of claims 1 or 3 to 10, or use of any one of claims 2 to 10, wherein the chimeric polypeptide is used for routine prophylaxis to reduce bleeding episodes.
12. A method of prophylactically treating severe hemophilia A comprising administering to a human subject in need thereof a chimeric polypeptide comprising:
 - (i) a factor VIII (FVIII) protein comprising the amino acid sequence set forth in SEQ ID NO: 207; and

(ii) a von Willebrand factor (VWF) protein comprising a D' domain of VWF and a D3 domain of VWF comprising the amino acid sequence set forth in SEQ ID NO: 202,

wherein the chimeric polypeptide is administered intravenously as a once weekly dose of 45-55 IU/kg for at least about 3 months.

13. Use of a chimeric polypeptide in the manufacture of a medicament for prophylactically treating severe hemophilia A, wherein the chimeric polypeptide is to be administered to a human subject in need thereof, wherein the chimeric polypeptide comprises:

(i) a factor VIII (FVIII) protein comprising the amino acid sequence set forth in SEQ ID NO: 207; and

(ii) a von Willebrand factor (VWF) protein comprising a D' domain of VWF and a D3 domain of VWF comprising the amino acid sequence set forth in SEQ ID NO: 202,

wherein the chimeric polypeptide is to be administered intravenously as a once weekly dose of 45-55 IU/kg for at least about 3 months.

14. The method of any one of claims 1 or 3 to 12, or use of any one of claims 2 to 11 or 13, wherein the multiple doses are to be administered for at least about 6 months.

15. The method of any one of claims 1, 3 to 12, or 14, or use according to any one of claims 2 to 11, 13 or 14, wherein the multiple doses are to be administered for at least about 12 months.

FIG. 1

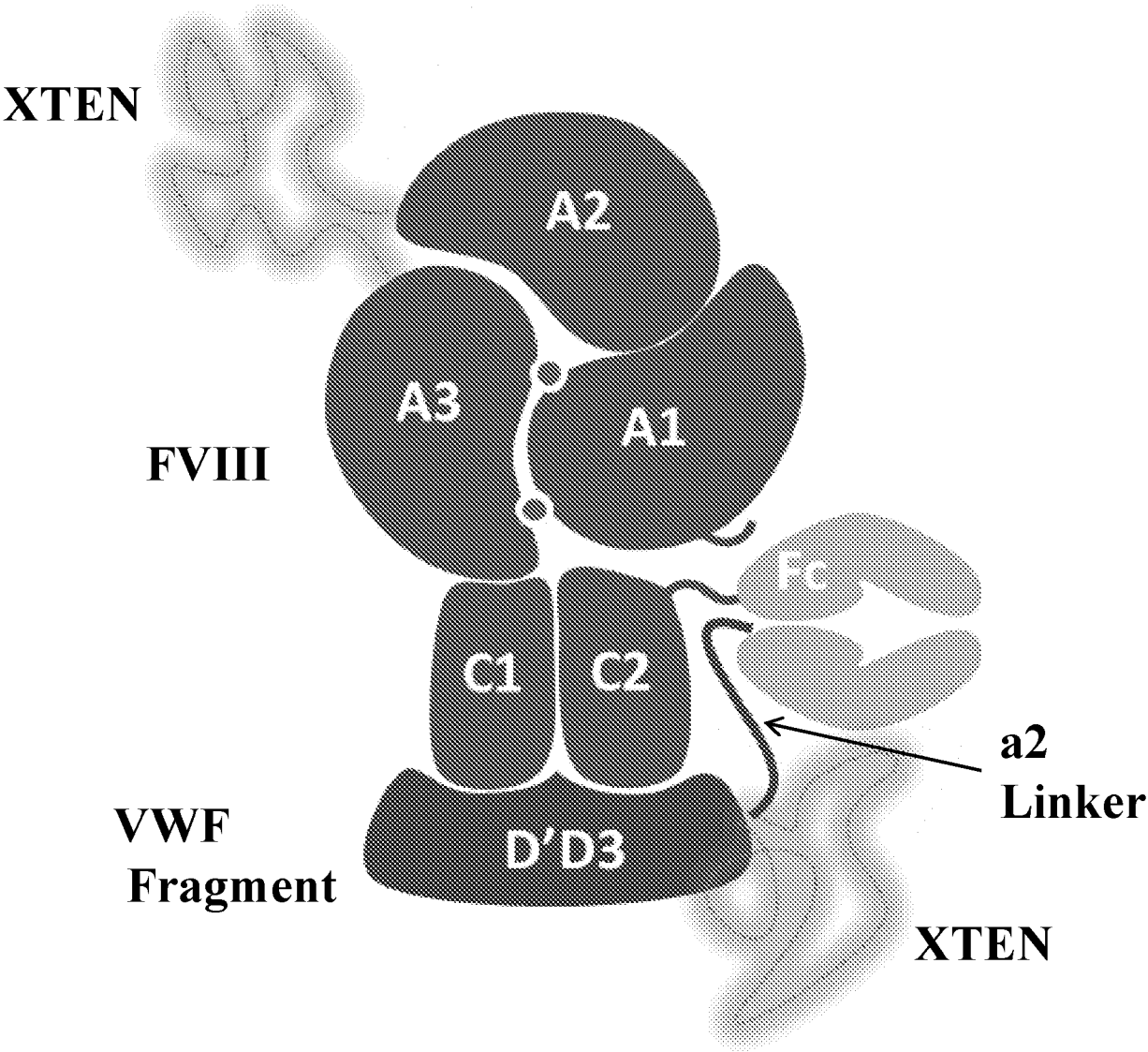


FIG. 2A

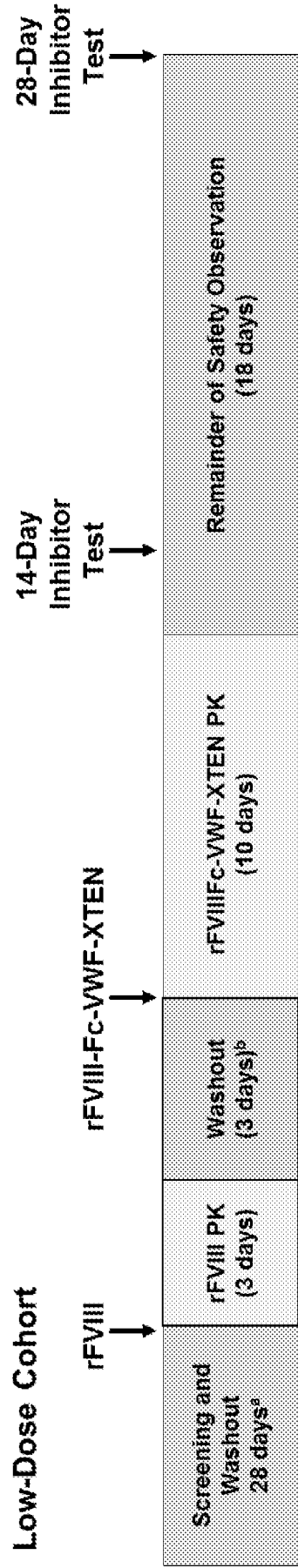


FIG. 2B

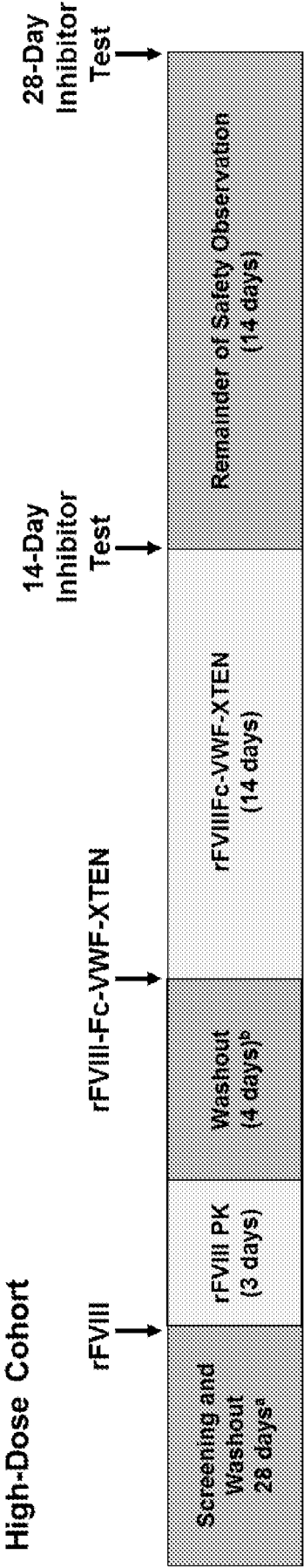


FIG. 3A

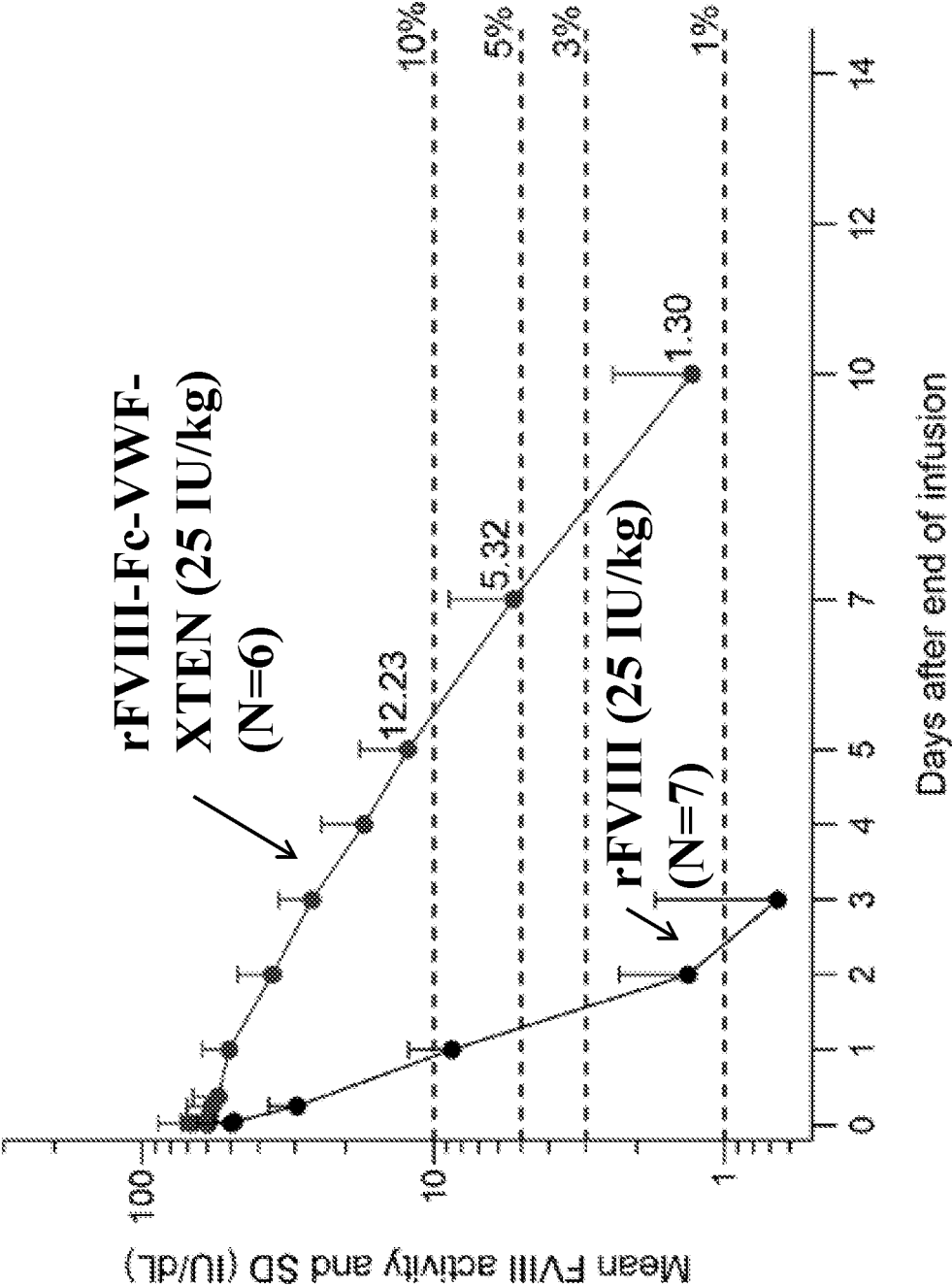


FIG. 3B

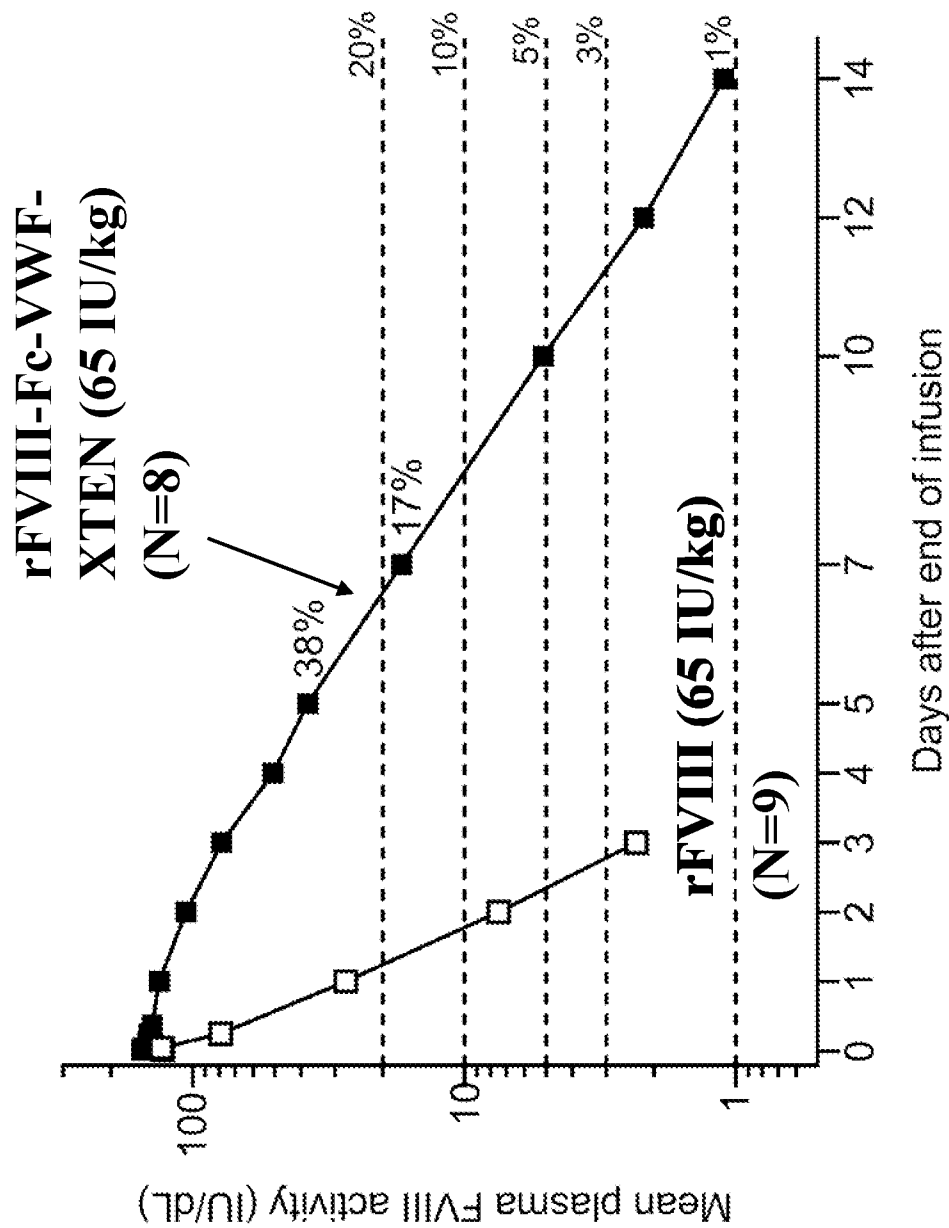
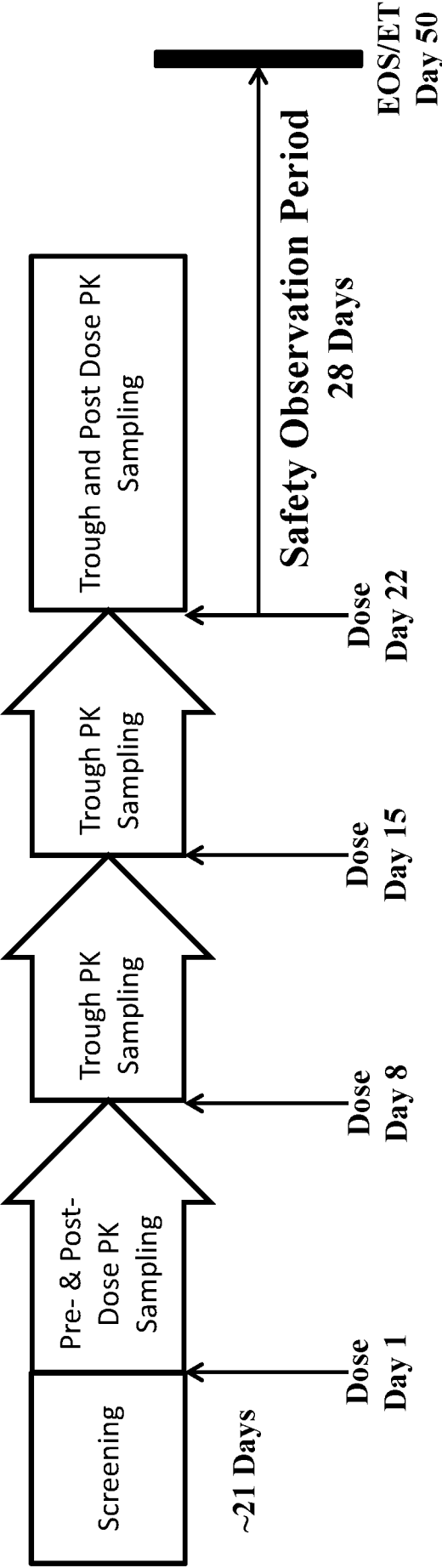


FIG. 4



SEQUENCE LISTING

<110> Bioverativ Therapeutics Inc.

<120> Methods of treating hemophilia A

<130> 612297: SA9-461PC

<150> US 62/673,670

<151> 2018-05-18

<150> US 62/712,880

<151> 2018-07-31

<150> US 62/773,785

<151> 2018-11-30

<150> US 62/801,576

<151> 2019-02-05

<160> 218

<170> PatentIn version 3.5

<210> 1

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker

<400> 1

Thr Gln Ser Phe Asn Asp Phe Thr Arg

1

5

<210> 2

<211> 302

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN FVIII 312A

<400> 2

Pro Arg Ser Phe Ser Gln Asn Gly Thr Ser Glu Ser Ala Thr Pro Glu
 1 5 10 15

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 20 25 30

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 35 40 45

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 50 55 60

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 65 70 75 80

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser
 85 90 95

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
 100 105 110

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 115 120 125

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly
 130 135 140

Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly
 145 150 155 160

Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 165 170 175

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser
180 185 190

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
195 200 205

Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
210 215 220

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu
225 230 235 240

Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly
245 250 255

Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
260 265 270

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu
275 280 285

Pro Ser Glu Gly Ser Ala Pro Ala Ser Ser Glu Ile Thr Arg
290 295 300

<210> 3

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker

<400> 3

Ser Val Ser Gln Thr Ser Lys Leu Thr Arg

1 5 10

<210> 4
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Linker

<400> 4

Asp Phe Leu Ala Glu Gly Gly Gly Val Arg
 1 5 10

<210> 5
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Linker

<400> 5

Thr Thr Lys Ile Lys Pro Arg
 1 5

<210> 6
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Linker

<400> 6

Leu Val Pro Arg Gly
 1 5

<210> 7
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Linker

<400> 7

Ala Leu Arg Pro Arg
 1 5

<210> 8
 <211> 288
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN AE288

<400> 8

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
 1 5 10 15

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
 20 25 30

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
 35 40 45

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
 50 55 60

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
 65 70 75 80

Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro

85

90

95

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu
 100 105 110

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr
 115 120 125

Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
 130 135 140

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu
 145 150 155 160

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro
 165 170 175

Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
 180 185 190

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro
 195 200 205

Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr
 210 215 220

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
 225 230 235 240

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro
 245 250 255

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
 260 265 270

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
 275 280 285

<210> 9
 <211> 42
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN AE42

<400> 9

Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
 1 5 10 15

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 20 25 30

Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser
 35 40

<210> 10
 <211> 78
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN AE72

<400> 10

Gly Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
 1 5 10 15

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala
 20 25 30

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
35 40 45

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr
50 55 60

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser
65 70 75

<210> 11

<211> 143

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN AE144

<400> 11

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu
1 5 10 15

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
20 25 30

Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
35 40 45

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro
50 55 60

Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly
65 70 75 80

Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
85 90 95

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu
 100 105 110

Ser Ala Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
 115 120 125

Glu Thr Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
 130 135 140

<210> 12
 <211> 56
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> pSYN VWF057

<400> 12

Thr Ser Thr Glu Glu Gly Ala Ser Ser Gly Gly Gly Gly Ser Gly Gly
 1 5 10 15

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 20 25 30

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

Gly Ser Gly Gly Asp Lys Thr His
 50 55

<210> 13
 <211> 46
 <212> PRT
 <213> Artificial Sequence

<220>

<223> pSYN VWF059

<400> 13

Thr	Ser	Thr	Glu	Glu	Gly	Ala	Ser	Ile	Ser	Asp	Lys	Asn	Thr	Gly	Asp
1				5					10					15	

Tyr	Tyr	Glu	Asp	Ser	Tyr	Glu	Asp	Ile	Ser	Ala	Tyr	Leu	Leu	Ser	Lys
			20					25					30		

Asn	Asn	Ala	Ile	Glu	Pro	Arg	Ser	Phe	Ser	Asp	Lys	Thr	His
		35					40					45	

<210> 14

<211> 144

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN AG144

<400> 14

Gly	Thr	Pro	Gly	Ser	Gly	Thr	Ala	Ser	Ser	Ser	Pro	Gly	Ser	Ser	Thr
1				5					10					15	

Pro	Ser	Gly	Ala	Thr	Gly	Ser	Pro	Gly	Ser	Ser	Pro	Ser	Ala	Ser	Thr
			20					25					30		

Gly	Thr	Gly	Pro	Gly	Ser	Ser	Pro	Ser	Ala	Ser	Thr	Gly	Thr	Gly	Pro
			35				40					45			

Gly	Ala	Ser	Pro	Gly	Thr	Ser	Ser	Thr	Gly	Ser	Pro	Gly	Ala	Ser	Pro
	50					55					60				

Gly	Thr	Ser	Ser	Thr	Gly	Ser	Pro	Gly	Ser	Ser	Thr	Pro	Ser	Gly	Ala
65					70				75					80	

Thr Gly Ser Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro
 85 90 95

Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ser Ser Pro
 100 105 110

Ser Ala Ser Thr Gly Thr Gly Pro Gly Thr Pro Gly Ser Gly Thr Ala
 115 120 125

Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro
 130 135 140

<210> 15
 <211> 864
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN AE864

<400> 15

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu
 1 5 10 15

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu
 20 25 30

Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
 35 40 45

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
 50 55 60

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro

65

70

75

80

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
85 90 95

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala
100 105 110

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro
115 120 125

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
130 135 140

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala
145 150 155 160

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu
165 170 175

Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
180 185 190

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
195 200 205

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
210 215 220

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
225 230 235 240

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
245 250 255

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
260 265 270

Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
275 280 285

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu
290 295 300

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
305 310 315 320

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
325 330 335

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
340 345 350

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu
355 360 365

Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
370 375 380

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
385 390 395 400

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
405 410 415

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
420 425 430

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
 435 440 445

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
 450 455 460

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
 465 470 475 480

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
 485 490 495

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
 500 505 510

Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
 515 520 525

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala
 530 535 540

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro
 545 550 555 560

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
 565 570 575

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
 580 585 590

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
 595 600 605

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
 610 615 620

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
 625 630 635 640

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
 645 650 655

Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
 660 665 670

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu
 675 680 685

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr
 690 695 700

Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
 705 710 715 720

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu
 725 730 735

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro
 740 745 750

Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
 755 760 765

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro
 770 775 780

Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr

785 790 795 800

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
805 810 815

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro
820 825 830

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
835 840 845

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
850 855 860

<210> 16
<211> 576
<212> PRT
<213> Artificial Sequence

<220>
<223> XTEN AE576

<400> 16

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu
1 5 10 15

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu
20 25 30

Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
35 40 45

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
50 55 60

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
65 70 75 80

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
85 90 95

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala
100 105 110

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro
115 120 125

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
130 135 140

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala
145 150 155 160

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu
165 170 175

Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
180 185 190

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
195 200 205

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
210 215 220

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
225 230 235 240

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
420 425 430

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
 435 440 445

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
 450 455 460

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
 465 470 475 480

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
 485 490 495

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
 500 505 510

Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
 515 520 525

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala
 530 535 540

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro
 545 550 555 560

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
 565 570 575

<210> 17

<211> 864

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN AG864

<400> 17

Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ser Ser Pro
 1 5 10 15

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser Pro Ser Ala Ser Thr
 20 25 30

Gly Thr Gly Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro
 35 40 45

Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Pro
 50 55 60

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser
 65 70 75 80

Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro
 85 90 95

Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Thr Pro Gly
 100 105 110

Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
 115 120 125

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
 130 135 140

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr
 145 150 155 160

Pro Ser Gly Ala Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
 165 170 175

Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro
 180 185 190

Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Pro
 195 200 205

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser Pro Ser Ala Ser Thr
 210 215 220

Gly Thr Gly Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro
 225 230 235 240

Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ala Ser Pro
 245 250 255

Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
 260 265 270

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
 275 280 285

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala Ser Pro
 290 295 300

Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
 305 310 315 320

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
 325 330 335

Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Thr Pro Gly
 340 345 350

Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
 355 360 365

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
 370 375 380

Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ser Ser Thr
 385 390 395 400

Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala
 405 410 415

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
 420 425 430

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr
 435 440 445

Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala
 450 455 460

Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro
 465 470 475 480

Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro
 485 490 495

Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
 500 505 510

Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro
 515 520 525

Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro
 530 535 540

Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
 545 550 555 560

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
 565 570 575

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr
 580 585 590

Pro Ser Gly Ala Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala
 595 600 605

Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro
 610 615 620

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr
 625 630 635 640

Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala
 645 650 655

Thr Gly Ser Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro
 660 665 670

Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro
 675 680 685

Gly Thr Ser Ser Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala
 690 695 700

Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro

705 710 715 720

Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser Pro
725 730 735

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser
740 745 750

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
755 760 765

Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Pro
770 775 780

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser
785 790 795 800

Thr Gly Ser Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro
805 810 815

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr
820 825 830

Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala
835 840 845

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
850 855 860

<210> 18

<211> 576

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN AG576

<400> 18

Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser
1 5 10 15

Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Pro Ser Ala Ser
20 25 30

Thr Gly Thr Gly Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly
35 40 45

Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser
50 55 60

Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser
65 70 75 80

Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser
85 90 95

Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Thr Pro
100 105 110

Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala Ser Pro Gly Thr Ser
115 120 125

Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser
130 135 140

Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ser Ser
145 150 155 160

Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Thr Pro Gly Ser Gly Thr

165

170

175

Ala Ser Ser Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser
 180 185 190

Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser
 195 200 205

Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly
 210 215 220

Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser
 225 230 235 240

Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Thr Pro
 245 250 255

Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly
 260 265 270

Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser
 275 280 285

Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser
 290 295 300

Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser
 305 310 315 320

Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser
 325 330 335

Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala Ser
 340 345 350

Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser
 355 360 365

Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser
 370 375 380

Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Thr Pro
 385 390 395 400

Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly
 405 410 415

Ala Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser
 420 425 430

Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Thr Pro
 435 440 445

Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly
 450 455 460

Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser
 465 470 475 480

Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser
 485 490 495

Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser
 500 505 510

Ser Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser
 515 520 525

Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser
 530 535 540

Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser Pro Ser Ala Ser
 545 550 555 560

Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser
 565 570 575

<210> 19
 <211> 288
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN AG288

<400> 19

Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser
 1 5 10 15

Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr
 20 25 30

Ala Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser
 35 40 45

Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser
 50 55 60

Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr
 65 70 75 80

Ala Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser
 85 90 95

Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser
 100 105 110

Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser Pro Ser Ala Ser
 115 120 125

Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser
 130 135 140

Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser
 145 150 155 160

Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Pro Ser Ala Ser
 165 170 175

Thr Gly Thr Gly Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly
 180 185 190

Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser
 195 200 205

Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly
 210 215 220

Ala Thr Gly Ser Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly
 225 230 235 240

Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ser Ser
 245 250 255

Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Thr Pro Gly Ser Gly Thr
 260 265 270

Ala Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser
 275 280 285

<210> 20
 <211> 8442
 <212> DNA
 <213> Homo sapiens

<400> 20
 atgattcctg ccagatttgc cggggtgctg cttgctctgg ccctcatttt gccagggacc
 60
 ctttgtgcag aaggaactcg cggcagggtca tccacggccc gatgcagcct tttcggaagt
 120
 gacttcgtca acacctttga tgggagcatg tacagctttg cgggatactg cagttacctc
 180
 ctggcagggg gctgccagaa acgctccttc tcgattattg gggacttcca gaatggcaag
 240
 agagtgagcc tctccgtgta tcttggggaa ttttttgaca tccatttggt tgtcaatggt
 300
 accgtgacac agggggacca aagagtctcc atgccctatg cctccaaagg gctgtatcta
 360
 gaaactgagg ctgggtacta caagctgtcc ggtgaggcct atggccttgt ggccaggatc
 420
 gatggcagcg gcaactttca agtcctgctg tcagacagat acttcaacaa gacctgcggg
 480
 ctgtgtggca actttaacat ctttgctgaa gatgacttta tgaccaaga agggaccttg
 540
 acctcggacc cttatgactt tgccaactca tgggctctga gcagtggaga acagtgggtgt
 600
 gaacgggcat ctccctcccag cagctcatgc aacatctcct ctggggaaat gcagaagggc
 660
 ctgtgggagc agtgccagct tctgaagagc acctcgggtgt ttgcccgtg ccaccctctg
 720

gtggaccccg agccttttgt ggccttgtgt gagaagactt tgtgtgagtg tgctgggggg
780

ctggagtgcg cctgccctgc cctcctggag tacgcccgga cctgtgccca ggaggggaatg
840

gtgctgtacg gctggaccga ccacagcgcg tgcagcccag tgtgccctgc tggatatggag
900

tataggcagt gtgtgtcccc ttgcgccagg acctgccaga gcctgcacat caatgaaatg
960

tgtcaggagc gatgcgtgga tggctgcagc tgccctgagg gacagctcct ggatgaaggc
1020

ctctgcgtgg agagcaccga gtgtccctgc gtgcattccg gaaagcgcta ccctcccggc
1080

acctccctct ctcgagactg caacacctgc atttgccgaa acagccagtg gatctgcagc
1140

aatgaagaat gtccagggga gtgccttgtc actggtcaat cccacttcaa gagctttgac
1200

aacagatact tcaccttcag tgggatctgc cagtacctgc tggcccggga ttgccaggac
1260

cactccttct ccattgtcat tgagactgtc cagtgtgctg atgaccgcga cgctgtgtgc
1320

accggtccg tcaccgtccg gctgcctggc ctgcacaaca gccttgtgaa actgaagcat
1380

ggggcaggag ttgccatgga tggccaggac atccagctcc ccctcctgaa aggtgacctc
1440

cgcattccagc atacagtgac ggcctccgtg cgcctcagct acggggagga cctgcagatg
1500

gactgggatg gccgcgggag gctgctggtg aagctgtccc ccgtctatgc cgggaagacc
1560

tgcggcctgt gtgggaatta caatggcaac cagggcgacg acttccttac cccctctggg
1620

ctggcrgagc cccgggtgga ggacttcggg aacgcctgga agctgcacgg ggactgccag
1680

gacctgcaga agcagcacag cgatccctgc gccctcaacc cgcgcatgac caggttctcc
1740

gaggaggcgt gcgcggtcct gacgtccccc acattcgagg cctgccatcg tgccgtcagc
1800

ccgctgccct acctgcggaa ctgccgctac gacgtgtgct cctgctcgga cggccgagag
1860

tgccctgtgcg gcgccctggc cagctatgcc gcggcctgcg cggggagagg cgtgcgcgtc
1920

gcgtggcgcg agccaggccg ctgtgagctg aactgcccga aaggccaggt gtacctgcag
1980

tgcgggaccc cctgcaacct gacctgccgc tctctctctt acccggatga ggaatgcaat
2040

gaggcctgcc tggagggctg cttctgcccc ccagggtctt acatggatga gaggggggac
2100

tgcggtgccca aggcccagtg cccctgttac tatgacggtg agatcttcca gccagaagac
2160

atcttctcag accatcacac catgtgctac tgtgaggatg gcttcatgca ctgtaccatg
2220

agtggagtcc ccggaagctt gctgcctgac gctgtcctca gcagtcccct gtctcatcgc
2280

agcaaaaagga gcctatcctg tcggcccccc atgggtcaagc tgggtgtgtcc cgctgacaac
2340

ctgcgggctg aagggtcga gtgtaccaa acgtgccaga actatgacct ggagtgcattg
2400

agcatgggct gtgtctctgg ctgcctctgc cccccgggca tgggtccggca tgagaacaga
2460

tgtgtggccc tggaaagggtg tccctgcttc catcagggca aggagtatgc ccctggagaa
2520

acagtgaaga ttggctgcaa cacttgtgtc tgtcgggacc ggaagtggaa ctgcacagac
2580

catgtgtgtg atgccacgtg ctccacgac ggcatggccc actacctcac cttcgacggg
2640

ctcaaatacc tgttccccgg ggagtgccag tacgttctgg tgcaggatta ctgcggcagt
2700

aaccctggga cctttcggat cctagtgggg aataagggat gcagccaccc ctcagtgaag
2760

tgcaagaaac gggtcaccat cctgggtggag ggaggagaga ttgagctgtt tgacggggag
2820

gtgaatgtga agaggcccat gaaggatgag actcactttg aggtgggtgga gtctggccgg
2880

tacatcattc tgctgctggg caaagccctc tccgtgggtc tggaccgcca cctgagcatc
2940

tccgtgggtc tgaagcagac ataccaggag aaagtgtgtg gcctgtgtgg gaattttgat
3000

ggcatccaga acaatgacct caccagcagc aacctccaag tggaggaaga ccctgtggac
3060

tttggggaact cctggaaagt gagctcgcag tgtgctgaca ccagaaaagt gcctctggac
3120

tcattcccctg ccacctgcca taacaacatc atgaagcaga cgatgggtgga ttctctctgt
3180

agaatcctta ccagtgacgt cttccaggac tgcaacaagc tgggtggaccc cgagccatat
3240

ctggatgtct gcatttacga cacctgctcc tgtgagtcca ttggggactg cgcttgcttc
3300

tgcgacacca ttgctgccta tgcccacgtg tgtgcccagc atggcaagggt ggtgacctgg
3360

aggacggcca cattgtgccc ccagagctgc gaggagagga atctccggga gaacgggtat
3420

gagtgtgagt ggcgctataa cagctgtgca cctgcctgtc aagtcacgtg tcagcaccct
3480

gagccactgg cctgccctgt gcagtgtgtg gagggctgcc atgcccactg ccctccaggg
3540

aaaatcctgg atgagctttt gcagacctgc gttgacctg aagactgtcc agtgtgtgag
3600

gtggctggcc ggcgttttgc ctcaggaaag aaagtcacct tgaatcccag tgacctgag
3660

cactgccaga tttgccactg tgatgttgtc aacctcacct gtgaagcctg ccaggagccg
3720

ggaggcctgg tgggtgcctcc cacagatgcc ccggtgagcc ccaccactct gtatgtggag
3780

gacatctcgg aaccgccgtt gcacgatttc tactgcagca ggctactgga cctgggtcttc
3840

ctgctggatg gctcctccag gctgtccgag gctgagtttg aagtgtgaa ggcctttgtg
3900

gtggacatga tggagcggct gcgcatctcc cagaagtggg tccgcgtggc cgtgggtggag
3960

taccacgacg gctcccacgc ctacatcggg ctcaaggacc ggaagcgacc gtcagagctg
4020

cggcgcattg ccagccaggt gaagtatgcg ggcagccagg tggcctccac cagcgaggtc
4080

ttgaaataca cactgttcca aatcttcagc aagatcgacc gccctgaagc ctcccgcatac
4140

gccctgctcc tgatggccag ccaggagccc caacggatgt cccggaactt tgtccgctac
4200

gtccagggcc tgaagaagaa gaaggtcatt gtgatcccgg tgggcattgg gccccatgcc
4260

aacctcaagc agatccgcct catcgagaag caggcccctg agaacaaggc cttcgtgctg
4320

agcagtgtgg atgagctgga gcagcaaagg gacgagatcg ttagctacct ctgtgacctt
 4380

gcccctgaag cccctcctcc tactctgccc cccgacatgg cacaagtcac tgtgggcccg
 4440

gggctcttgg gggtttcgac cctggggccc aagaggaact ccatggttct ggatgtggcg
 4500

ttcgtcctgg aaggatcgga caaaattgggt gaagccgact tcaacaggag caaggagttc
 4560

atggaggagg tgattcagcg gatggatgtg ggccaggaca gcatccacgt cacgggtgctg
 4620

cagtactcct acatggtgac cgtggagtag cccttcagcg aggcacagtc caaaggggac
 4680

atcctgcagc ggggtgcgaga gatccgctac cagggcggca acaggaccaa cactgggctg
 4740

gccctgcggg acctctctga ccacagcttc ttgggtcagcc aggggtgaccg ggagcaggcg
 4800

cccaacctgg tctacatgggt caccggaaat cctgcctctg atgagatcaa gaggctgcct
 4860

ggagacatcc aggtgggtgcc cattggagtg ggccctaata ccaacgtgca ggagctggag
 4920

aggattggct ggcccaatgc ccctatcctc atccaggact ttgagacgct cccccgagag
 4980

gctcctgacc tgggtgctgca gaggtgctgc tccggagagg ggctgcagat ccccacctc
 5040

tcccctgcac ctgactgcag ccagcccctg gacgtgatcc ttctcctgga tggctcctcc
 5100

agtttcccag cttcttattt tgatgaaatg aagagtttcg ccaaggcttt catttcaaaa
 5160

gccaatatag ggcctcgtct cactcagggt tcagtgtgctc agtatggaag catcaccacc
 5220

attgacgtgc catggaacgt ggtcccggag aaagcccatt tgctgagcct tgtggacgtc
5280

atgcagcggg agggaggccc cagccaaatc ggggatgcct tgggctttgc tgtgcgatac
5340

ttgacttcag aaatgcatgg tgccaggccg ggagcctcaa aggcggtggg catcctgggc
5400

acggacgtct ctgtggattc agtggatgca gcagctgatg ccgccaggtc caacagagtg
5460

acagtgttcc ctattggaat tggagatcgc tacgatgcag cccagctacg gatcttggca
5520

ggcccagcag gcgactccaa cgtggtgaag ctccagcgaa tcgaagacct ccctaccatg
5580

gtcaccttgg gcaattcctt cctccacaaa ctgtgctctg gatttgttag gatttgcacg
5640

gatgaggatg ggaatgagaa gagggccggg gacgtctgga ccttgccaga ccagtgccac
5700

accgtgactt gccagccaga tggccagacc ttgctgaaga gtcacgaggc caactgtgac
5760

cgggggctga ggccttcgtg ccctaacagc cagtcccctg ttaaagtgga agagacctgt
5820

ggctgccgct ggacctgccc ctgygtgtgc acaggcagct ccactcggca catcgtgacc
5880

tttgatgggc agaatttcaa gctgactggc agctgttctt atgtcctatt tcaaaacaag
5940

gagcaggacc tggaggatgat tctccataat ggtgcctgca gccctggagc aaggcagggc
6000

tgcatgaaat ccatcgaggc gaagcacagt gccctctccg tcgagstgca cagtgcacatg
6060

gaggtgacgg tgaatgggag actggtctct gtcccttacg tgggtgggaa catggaagtc
6120

aacgtttatg gtgccatcat gcatgaggtc agattcaatc accttgggtca catcttcaca
6180

ttcactccac aaaacaatga gttccaactg cagctcagcc ccaagacttt tgcttcaaag
6240

acgtatggtc tgtgtgggat ctgtgatgag aacggagcca atgacttcat gctgagggat
6300

ggcacagtca ccacagactg gaaaacactt gttcaggaat ggactgtgca gcggccaggg
6360

cagacgtgcc agcccatcct ggaggagcag tgtcttgtcc ccgacagctc ccactgccag
6420

gtcctcctct taccactggt tgctgaatgc cacaagggtcc tggctccagc cacattctat
6480

gccatctgcc agcaggacag ttgccaccag gagcaagtgt gtgaggtgat cgcctcttat
6540

gccacactct gtcggaccaa cgggggtctgc gttgactgga ggacacctga tttctgtgct
6600

atgtcatgcc caccatctct ggtctacaac cactgtgagc atggctgtcc ccggcactgt
6660

gatggcaacg tgagctcctg tggggaccat ccctccgaag gctgtttctg ccctccagat
6720

aaagtcatgt tggaaggcag ctgtgtccct gaagaggcct gcactcagtg cattggtgag
6780

gatggagtcc agcaccagtt cctggaagcc tgggtcccgg accaccagcc ctgtcagatc
6840

tgcacatgcc tcagcgggcg gaagggtcaac tgcacaacgc agccctgccc cacggccaaa
6900

gctcccacgt gtggcctgtg tgaagtagcc cgcctccgcc agaatgcaga ccagtgtgct
6960

cccgagtatg agtgtgtgtg tgaccacagt agctgtgacc tgccccagtg gcctcactgt
7020

gaacgtggcc tccagcccac actgaccaac cctggcgagt gcagacccaa cttcacctgc
7080

gcctgcagga aggaggagtg caaaagagtg tccccaccct cctgcccccc gcaccgtttg
7140

cccacccttc ggaagaccca gtgctgtgat gagtatgagt gtgcctgcaa ctgtgtcaac
7200

tccacagtga gctgtcccct tgggtacttg gcctcaaccg ccaccaatga ctgtggctgt
7260

accacaacca cctgccttcc cgacaagggt tgtgtccacc gaagcaccat ctaccctgtg
7320

ggccagtctt gggaggaggg ctgcgatgtg tgcacctgca ccgacatgga ggatgccgtg
7380

atgggcctcc gcgtggccca gtgctcccag aagccctgtg aggacagctg tcggtcgggc
7440

ttcacttacg ttctgcatga aggcgagtgc tgtggaagggt gcctgccatc tgcctgtgag
7500

gtggtgactg gctcaccgcg gggggactcc cagtcttcct ggaagagtgt cggctcccag
7560

tgggcctccc cggagaaccc ctgcctcatc aatgagtgtg tccgagtga ggaggaggtc
7620

tttatacaac aaaggaacgt ctccctgcccc cagctggagg tccctgtctg cccctcgggc
7680

tttcagctga gctgtaagac ctcagcgtgc tgcccaagct gtcgctgtga gcgcatggag
7740

gcctgcatgc tcaatggcac tgtcattggg cccgggaaga ctgtgatgat cgatgtgtgc
7800

acgacctgcc gctgcatggg gcagggtgggg gtcattctctg gattcaagct ggagtgcagg
7860

aagaccacct gcaaccctg ccccctgggt tacaaggaag aaaataacac aggtgaatgt
7920

tgtgggagat gtttgcctac ggcttgcacc attcagctaa gaggaggaca gatcatgaca
7980

ctgaagcgtg atgagacgct ccaggatggc tgtgatactc acttctgcaa ggtcaatgag
8040

agaggagagt acttctggga gaagagggtc acaggctgcc caccctttga tgaacacaag
8100

tgtcttgctg agggaggtaa aattatgaaa attccaggca cctgctgtga cacatgtgag
8160

gagcctgagt gcaacgacat cactgccagg ctgcagtatg tcaagggtggg aagctgtaag
8220

tctgaagtag aggtggatat ccactactgc cagggcaaatt gtgccagcaa agccatgtac
8280

tccattgaca tcaacgatgt gcaggaccag tgctcctgct gctctccgac acggacggag
8340

cccatgcagg tggccctgca ctgcaccaat ggctctgttg tgtaccatga ggttctcaat
8400

gccatggagt gcaaattgctc ccccaggaag tgcagcaagt ga
8442

<210> 21
<211> 2813
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (2016)..(2016)
<223> Xaa can be any naturally occurring amino acid

<400> 21

Met Ile Pro Ala Arg Phe Ala Gly Val Leu Leu Ala Leu Ala Leu Ile
1 5 10 15

Leu Pro Gly Thr Leu Cys Ala Glu Gly Thr Arg Gly Arg Ser Ser Thr
 20 25 30

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

Ser Met Tyr Ser Phe Ala Gly Tyr Cys Ser Tyr Leu Leu Ala Gly Gly
 50 55 60

Cys Gln Lys Arg Ser Phe Ser Ile Ile Gly Asp Phe Gln Asn Gly Lys
 65 70 75 80

Arg Val Ser Leu Ser Val Tyr Leu Gly Glu Phe Phe Asp Ile His Leu
 85 90 95

Phe Val Asn Gly Thr Val Thr Gln Gly Asp Gln Arg Val Ser Met Pro
 100 105 110

Tyr Ala Ser Lys Gly Leu Tyr Leu Glu Thr Glu Ala Gly Tyr Tyr Lys
 115 120 125

Leu Ser Gly Glu Ala Tyr Gly Phe Val Ala Arg Ile Asp Gly Ser Gly
 130 135 140

Asn Phe Gln Val Leu Leu Ser Asp Arg Tyr Phe Asn Lys Thr Cys Gly
 145 150 155 160

Leu Cys Gly Asn Phe Asn Ile Phe Ala Glu Asp Asp Phe Met Thr Gln
 165 170 175

Glu Gly Thr Leu Thr Ser Asp Pro Tyr Asp Phe Ala Asn Ser Trp Ala
 180 185 190

Leu Ser Ser Gly Glu Gln Trp Cys Glu Arg Ala Ser Pro Pro Ser Ser
 195 200 205

Ser Cys Asn Ile Ser Ser Gly Glu Met Gln Lys Gly Leu Trp Glu Gln
 210 215 220

Cys Gln Leu Leu Lys Ser Thr Ser Val Phe Ala Arg Cys His Pro Leu
 225 230 235 240

Val Asp Pro Glu Pro Phe Val Ala Leu Cys Glu Lys Thr Leu Cys Glu
 245 250 255

Cys Ala Gly Gly Leu Glu Cys Ala Cys Pro Ala Leu Leu Glu Tyr Ala
 260 265 270

Arg Thr Cys Ala Gln Glu Gly Met Val Leu Tyr Gly Trp Thr Asp His
 275 280 285

Ser Ala Cys Ser Pro Val Cys Pro Ala Gly Met Glu Tyr Arg Gln Cys
 290 295 300

Val Ser Pro Cys Ala Arg Thr Cys Gln Ser Leu His Ile Asn Glu Met
 305 310 315 320

Cys Gln Glu Arg Cys Val Asp Gly Cys Ser Cys Pro Glu Gly Gln Leu
 325 330 335

Leu Asp Glu Gly Leu Cys Val Glu Ser Thr Glu Cys Pro Cys Val His
 340 345 350

Ser Gly Lys Arg Tyr Pro Pro Gly Thr Ser Leu Ser Arg Asp Cys Asn
 355 360 365

Thr Cys Ile Cys Arg Asn Ser Gln Trp Ile Cys Ser Asn Glu Glu Cys

370

375

380

Pro Gly Glu Cys Leu Val Thr Gly Gln Ser His Phe Lys Ser Phe Asp
 385 390 395 400

Asn Arg Tyr Phe Thr Phe Ser Gly Ile Cys Gln Tyr Leu Leu Ala Arg
 405 410 415

Asp Cys Gln Asp His Ser Phe Ser Ile Val Ile Glu Thr Val Gln Cys
 420 425 430

Ala Asp Asp Arg Asp Ala Val Cys Thr Arg Ser Val Thr Val Arg Leu
 435 440 445

Pro Gly Leu His Asn Ser Leu Val Lys Leu Lys His Gly Ala Gly Val
 450 455 460

Ala Met Asp Gly Gln Asp Ile Gln Leu Pro Leu Leu Lys Gly Asp Leu
 465 470 475 480

Arg Ile Gln His Thr Val Thr Ala Ser Val Arg Leu Ser Tyr Gly Glu
 485 490 495

Asp Leu Gln Met Asp Trp Asp Gly Arg Gly Arg Leu Leu Val Lys Leu
 500 505 510

Ser Pro Val Tyr Ala Gly Lys Thr Cys Gly Leu Cys Gly Asn Tyr Asn
 515 520 525

Gly Asn Gln Gly Asp Asp Phe Leu Thr Pro Ser Gly Leu Ala Glu Pro
 530 535 540

Arg Val Glu Asp Phe Gly Asn Ala Trp Lys Leu His Gly Asp Cys Gln
 545 550 555 560

Asp Leu Gln Lys Gln His Ser Asp Pro Cys Ala Leu Asn Pro Arg Met
565 570 575

Thr Arg Phe Ser Glu Glu Ala Cys Ala Val Leu Thr Ser Pro Thr Phe
580 585 590

Glu Ala Cys His Arg Ala Val Ser Pro Leu Pro Tyr Leu Arg Asn Cys
595 600 605

Arg Tyr Asp Val Cys Ser Cys Ser Asp Gly Arg Glu Cys Leu Cys Gly
610 615 620

Ala Leu Ala Ser Tyr Ala Ala Ala Cys Ala Gly Arg Gly Val Arg Val
625 630 635 640

Ala Trp Arg Glu Pro Gly Arg Cys Glu Leu Asn Cys Pro Lys Gly Gln
645 650 655

Val Tyr Leu Gln Cys Gly Thr Pro Cys Asn Leu Thr Cys Arg Ser Leu
660 665 670

Ser Tyr Pro Asp Glu Glu Cys Asn Glu Ala Cys Leu Glu Gly Cys Phe
675 680 685

Cys Pro Pro Gly Leu Tyr Met Asp Glu Arg Gly Asp Cys Val Pro Lys
690 695 700

Ala Gln Cys Pro Cys Tyr Tyr Asp Gly Glu Ile Phe Gln Pro Glu Asp
705 710 715 720

Ile Phe Ser Asp His His Thr Met Cys Tyr Cys Glu Asp Gly Phe Met
725 730 735

His Cys Thr Met Ser Gly Val Pro Gly Ser Leu Leu Pro Asp Ala Val
740 745 750

Leu Ser Ser Pro Leu Ser His Arg Ser Lys Arg Ser Leu Ser Cys Arg
755 760 765

Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp Asn Leu Arg Ala Glu
770 775 780

Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr Asp Leu Glu Cys Met
785 790 795 800

Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro Pro Gly Met Val Arg
805 810 815

His Glu Asn Arg Cys Val Ala Leu Glu Arg Cys Pro Cys Phe His Gln
820 825 830

Gly Lys Glu Tyr Ala Pro Gly Glu Thr Val Lys Ile Gly Cys Asn Thr
835 840 845

Cys Val Cys Arg Asp Arg Lys Trp Asn Cys Thr Asp His Val Cys Asp
850 855 860

Ala Thr Cys Ser Thr Ile Gly Met Ala His Tyr Leu Thr Phe Asp Gly
865 870 875 880

Leu Lys Tyr Leu Phe Pro Gly Glu Cys Gln Tyr Val Leu Val Gln Asp
885 890 895

Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys
900 905 910

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

Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys
 930 935 940

Arg Pro Met Lys Asp Glu Thr His Phe Glu Val Val Glu Ser Gly Arg
 945 950 955 960

Tyr Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg
 965 970 975

His Leu Ser Ile Ser Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val
 980 985 990

Cys Gly Leu Cys Gly Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr
 995 1000 1005

Ser Ser Asn Leu Gln Val Glu Glu Asp Pro Val Asp Phe Gly Asn
 1010 1015 1020

Ser Trp Lys Val Ser Ser Gln Cys Ala Asp Thr Arg Lys Val Pro
 1025 1030 1035

Leu Asp Ser Ser Pro Ala Thr Cys His Asn Asn Ile Met Lys Gln
 1040 1045 1050

Thr Met Val Asp Ser Ser Cys Arg Ile Leu Thr Ser Asp Val Phe
 1055 1060 1065

Gln Asp Cys Asn Lys Leu Val Asp Pro Glu Pro Tyr Leu Asp Val
 1070 1075 1080

Cys Ile Tyr Asp Thr Cys Ser Cys Glu Ser Ile Gly Asp Cys Ala

1085						1090						1095			
Cys	Phe	Cys	Asp	Thr	Ile	Ala	Ala	Tyr	Ala	His	Val	Cys	Ala	Gln	
1100						1105					1110				
His	Gly	Lys	Val	Val	Thr	Trp	Arg	Thr	Ala	Thr	Leu	Cys	Pro	Gln	
1115						1120					1125				
Ser	Cys	Glu	Glu	Arg	Asn	Leu	Arg	Glu	Asn	Gly	Tyr	Glu	Cys	Glu	
1130						1135					1140				
Trp	Arg	Tyr	Asn	Ser	Cys	Ala	Pro	Ala	Cys	Gln	Val	Thr	Cys	Gln	
1145						1150					1155				
His	Pro	Glu	Pro	Leu	Ala	Cys	Pro	Val	Gln	Cys	Val	Glu	Gly	Cys	
1160						1165					1170				
His	Ala	His	Cys	Pro	Pro	Gly	Lys	Ile	Leu	Asp	Glu	Leu	Leu	Gln	
1175						1180					1185				
Thr	Cys	Val	Asp	Pro	Glu	Asp	Cys	Pro	Val	Cys	Glu	Val	Ala	Gly	
1190						1195					1200				
Arg	Arg	Phe	Ala	Ser	Gly	Lys	Lys	Val	Thr	Leu	Asn	Pro	Ser	Asp	
1205						1210					1215				
Pro	Glu	His	Cys	Gln	Ile	Cys	His	Cys	Asp	Val	Val	Asn	Leu	Thr	
1220						1225					1230				
Cys	Glu	Ala	Cys	Gln	Glu	Pro	Gly	Gly	Leu	Val	Val	Pro	Pro	Thr	
1235						1240					1245				
Asp	Ala	Pro	Val	Ser	Pro	Thr	Thr	Leu	Tyr	Val	Glu	Asp	Ile	Ser	
1250						1255					1260				

Glu Pro Pro Leu His Asp Phe Tyr Cys Ser Arg Leu Leu Asp Leu
 1265 1270 1275

Val Phe Leu Leu Asp Gly Ser Ser Arg Leu Ser Glu Ala Glu Phe
 1280 1285 1290

Glu Val Leu Lys Ala Phe Val Val Asp Met Met Glu Arg Leu Arg
 1295 1300 1305

Ile Ser Gln Lys Trp Val Arg Val Ala Val Val Glu Tyr His Asp
 1310 1315 1320

Gly Ser His Ala Tyr Ile Gly Leu Lys Asp Arg Lys Arg Pro Ser
 1325 1330 1335

Glu Leu Arg Arg Ile Ala Ser Gln Val Lys Tyr Ala Gly Ser Gln
 1340 1345 1350

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

Phe Ser Lys Ile Asp Arg Pro Glu Ala Ser Arg Ile Ala Leu Leu
 1370 1375 1380

Leu Met Ala Ser Gln Glu Pro Gln Arg Met Ser Arg Asn Phe Val
 1385 1390 1395

Arg Tyr Val Gln Gly Leu Lys Lys Lys Lys Val Ile Val Ile Pro
 1400 1405 1410

Val Gly Ile Gly Pro His Ala Asn Leu Lys Gln Ile Arg Leu Ile
 1415 1420 1425

Glu Lys Gln Ala Pro Glu Asn Lys Ala Phe Val Leu Ser Ser Val
 1430 1435 1440

Asp Glu Leu Glu Gln Gln Arg Asp Glu Ile Val Ser Tyr Leu Cys
 1445 1450 1455

Asp Leu Ala Pro Glu Ala Pro Pro Pro Thr Leu Pro Pro Asp Met
 1460 1465 1470

Ala Gln Val Thr Val Gly Pro Gly Leu Leu Gly Val Ser Thr Leu
 1475 1480 1485

Gly Pro Lys Arg Asn Ser Met Val Leu Asp Val Ala Phe Val Leu
 1490 1495 1500

Glu Gly Ser Asp Lys Ile Gly Glu Ala Asp Phe Asn Arg Ser Lys
 1505 1510 1515

Glu Phe Met Glu Glu Val Ile Gln Arg Met Asp Val Gly Gln Asp
 1520 1525 1530

Ser Ile His Val Thr Val Leu Gln Tyr Ser Tyr Met Val Thr Val
 1535 1540 1545

Glu Tyr Pro Phe Ser Glu Ala Gln Ser Lys Gly Asp Ile Leu Gln
 1550 1555 1560

Arg Val Arg Glu Ile Arg Tyr Gln Gly Gly Asn Arg Thr Asn Thr
 1565 1570 1575

Gly Leu Ala Leu Arg Tyr Leu Ser Asp His Ser Phe Leu Val Ser
 1580 1585 1590

Gln	Gly	Asp	Arg	Glu	Gln	Ala	Pro	Asn	Leu	Val	Tyr	Met	Val	Thr
	1595					1600					1605			
Gly	Asn	Pro	Ala	Ser	Asp	Glu	Ile	Lys	Arg	Leu	Pro	Gly	Asp	Ile
	1610					1615					1620			
Gln	Val	Val	Pro	Ile	Gly	Val	Gly	Pro	Asn	Ala	Asn	Val	Gln	Glu
	1625					1630					1635			
Leu	Glu	Arg	Ile	Gly	Trp	Pro	Asn	Ala	Pro	Ile	Leu	Ile	Gln	Asp
	1640					1645					1650			
Phe	Glu	Thr	Leu	Pro	Arg	Glu	Ala	Pro	Asp	Leu	Val	Leu	Gln	Arg
	1655					1660					1665			
Cys	Cys	Ser	Gly	Glu	Gly	Leu	Gln	Ile	Pro	Thr	Leu	Ser	Pro	Ala
	1670					1675					1680			
Pro	Asp	Cys	Ser	Gln	Pro	Leu	Asp	Val	Ile	Leu	Leu	Leu	Asp	Gly
	1685					1690					1695			
Ser	Ser	Ser	Phe	Pro	Ala	Ser	Tyr	Phe	Asp	Glu	Met	Lys	Ser	Phe
	1700					1705					1710			
Ala	Lys	Ala	Phe	Ile	Ser	Lys	Ala	Asn	Ile	Gly	Pro	Arg	Leu	Thr
	1715					1720					1725			
Gln	Val	Ser	Val	Leu	Gln	Tyr	Gly	Ser	Ile	Thr	Thr	Ile	Asp	Val
	1730					1735					1740			
Pro	Trp	Asn	Val	Val	Pro	Glu	Lys	Ala	His	Leu	Leu	Ser	Leu	Val
	1745					1750					1755			
Asp	Val	Met	Gln	Arg	Glu	Gly	Gly	Pro	Ser	Gln	Ile	Gly	Asp	Ala

1760

1765

1770

Leu Gly Phe Ala Val Arg Tyr Leu Thr Ser Glu Met His Gly Ala
 1775 1780 1785

Arg Pro Gly Ala Ser Lys Ala Val Val Ile Leu Val Thr Asp Val
 1790 1795 1800

Ser Val Asp Ser Val Asp Ala Ala Ala Asp Ala Ala Arg Ser Asn
 1805 1810 1815

Arg Val Thr Val Phe Pro Ile Gly Ile Gly Asp Arg Tyr Asp Ala
 1820 1825 1830

Ala Gln Leu Arg Ile Leu Ala Gly Pro Ala Gly Asp Ser Asn Val
 1835 1840 1845

Val Lys Leu Gln Arg Ile Glu Asp Leu Pro Thr Met Val Thr Leu
 1850 1855 1860

Gly Asn Ser Phe Leu His Lys Leu Cys Ser Gly Phe Val Arg Ile
 1865 1870 1875

Cys Met Asp Glu Asp Gly Asn Glu Lys Arg Pro Gly Asp Val Trp
 1880 1885 1890

Thr Leu Pro Asp Gln Cys His Thr Val Thr Cys Gln Pro Asp Gly
 1895 1900 1905

Gln Thr Leu Leu Lys Ser His Arg Val Asn Cys Asp Arg Gly Leu
 1910 1915 1920

Arg Pro Ser Cys Pro Asn Ser Gln Ser Pro Val Lys Val Glu Glu
 1925 1930 1935

Thr 1940	Cys	Gly	Cys	Arg	Trp	Thr 1945	Cys	Pro	Cys	Val	Cys 1950	Thr	Gly	Ser
Ser 1955	Thr	Arg	His	Ile	Val	Thr 1960	Phe	Asp	Gly	Gln	Asn 1965	Phe	Lys	Leu
Thr 1970	Gly	Ser	Cys	Ser	Tyr	Val 1975	Leu	Phe	Gln	Asn	Lys 1980	Glu	Gln	Asp
Leu 1985	Glu	Val	Ile	Leu	His	Asn 1990	Gly	Ala	Cys	Ser	Pro 1995	Gly	Ala	Arg
Gln 2000	Gly	Cys	Met	Lys	Ser	Ile 2005	Glu	Val	Lys	His	Ser 2010	Ala	Leu	Ser
Val 2015	Glu	Xaa	His	Ser	Asp	Met 2020	Glu	Val	Thr	Val	Asn 2025	Gly	Arg	Leu
Val 2030	Ser	Val	Pro	Tyr	Val	Gly 2035	Gly	Asn	Met	Glu	Val 2040	Asn	Val	Tyr
Gly 2045	Ala	Ile	Met	His	Glu	Val 2050	Arg	Phe	Asn	His	Leu 2055	Gly	His	Ile
Phe 2060	Thr	Phe	Thr	Pro	Gln	Asn 2065	Asn	Glu	Phe	Gln	Leu 2070	Gln	Leu	Ser
Pro 2075	Lys	Thr	Phe	Ala	Ser	Lys 2080	Thr	Tyr	Gly	Leu	Cys 2085	Gly	Ile	Cys
Asp 2090	Glu	Asn	Gly	Ala	Asn	Asp 2095	Phe	Met	Leu	Arg	Asp 2100	Gly	Thr	Val

Thr Thr Asp Trp Lys Thr Leu Val Gln Glu Trp Thr Val Gln Arg
 2105 2110 2115

Pro Gly Gln Thr Cys Gln Pro Ile Leu Glu Glu Gln Cys Leu Val
 2120 2125 2130

Pro Asp Ser Ser His Cys Gln Val Leu Leu Leu Pro Leu Phe Ala
 2135 2140 2145

Glu Cys His Lys Val Leu Ala Pro Ala Thr Phe Tyr Ala Ile Cys
 2150 2155 2160

Gln Gln Asp Ser Cys His Gln Glu Gln Val Cys Glu Val Ile Ala
 2165 2170 2175

Ser Tyr Ala His Leu Cys Arg Thr Asn Gly Val Cys Val Asp Trp
 2180 2185 2190

Arg Thr Pro Asp Phe Cys Ala Met Ser Cys Pro Pro Ser Leu Val
 2195 2200 2205

Tyr Asn His Cys Glu His Gly Cys Pro Arg His Cys Asp Gly Asn
 2210 2215 2220

Val Ser Ser Cys Gly Asp His Pro Ser Glu Gly Cys Phe Cys Pro
 2225 2230 2235

Pro Asp Lys Val Met Leu Glu Gly Ser Cys Val Pro Glu Glu Ala
 2240 2245 2250

Cys Thr Gln Cys Ile Gly Glu Asp Gly Val Gln His Gln Phe Leu
 2255 2260 2265

Glu Ala Trp Val Pro Asp His Gln Pro Cys Gln Ile Cys Thr Cys
 2270 2275 2280

Leu Ser Gly Arg Lys Val Asn Cys Thr Thr Gln Pro Cys Pro Thr
 2285 2290 2295

Ala Lys Ala Pro Thr Cys Gly Leu Cys Glu Val Ala Arg Leu Arg
 2300 2305 2310

Gln Asn Ala Asp Gln Cys Cys Pro Glu Tyr Glu Cys Val Cys Asp
 2315 2320 2325

Pro Val Ser Cys Asp Leu Pro Pro Val Pro His Cys Glu Arg Gly
 2330 2335 2340

Leu Gln Pro Thr Leu Thr Asn Pro Gly Glu Cys Arg Pro Asn Phe
 2345 2350 2355

Thr Cys Ala Cys Arg Lys Glu Glu Cys Lys Arg Val Ser Pro Pro
 2360 2365 2370

Ser Cys Pro Pro His Arg Leu Pro Thr Leu Arg Lys Thr Gln Cys
 2375 2380 2385

Cys Asp Glu Tyr Glu Cys Ala Cys Asn Cys Val Asn Ser Thr Val
 2390 2395 2400

Ser Cys Pro Leu Gly Tyr Leu Ala Ser Thr Ala Thr Asn Asp Cys
 2405 2410 2415

Gly Cys Thr Thr Thr Thr Cys Leu Pro Asp Lys Val Cys Val His
 2420 2425 2430

Arg Ser Thr Ile Tyr Pro Val Gly Gln Phe Trp Glu Glu Gly Cys

2435						2440						2445			
Asp	Val	Cys	Thr	Cys	Thr	Asp	Met	Glu	Asp	Ala	Val	Met	Gly	Leu	
2450						2455					2460				
Arg	Val	Ala	Gln	Cys	Ser	Gln	Lys	Pro	Cys	Glu	Asp	Ser	Cys	Arg	
2465						2470					2475				
Ser	Gly	Phe	Thr	Tyr	Val	Leu	His	Glu	Gly	Glu	Cys	Cys	Gly	Arg	
2480						2485					2490				
Cys	Leu	Pro	Ser	Ala	Cys	Glu	Val	Val	Thr	Gly	Ser	Pro	Arg	Gly	
2495						2500					2505				
Asp	Ser	Gln	Ser	Ser	Trp	Lys	Ser	Val	Gly	Ser	Gln	Trp	Ala	Ser	
2510						2515					2520				
Pro	Glu	Asn	Pro	Cys	Leu	Ile	Asn	Glu	Cys	Val	Arg	Val	Lys	Glu	
2525						2530					2535				
Glu	Val	Phe	Ile	Gln	Gln	Arg	Asn	Val	Ser	Cys	Pro	Gln	Leu	Glu	
2540						2545					2550				
Val	Pro	Val	Cys	Pro	Ser	Gly	Phe	Gln	Leu	Ser	Cys	Lys	Thr	Ser	
2555						2560					2565				
Ala	Cys	Cys	Pro	Ser	Cys	Arg	Cys	Glu	Arg	Met	Glu	Ala	Cys	Met	
2570						2575					2580				
Leu	Asn	Gly	Thr	Val	Ile	Gly	Pro	Gly	Lys	Thr	Val	Met	Ile	Asp	
2585						2590					2595				
Val	Cys	Thr	Thr	Cys	Arg	Cys	Met	Val	Gln	Val	Gly	Val	Ile	Ser	
2600						2605					2610				

Gly Phe Lys Leu Glu Cys Arg Lys Thr Thr Cys Asn Pro Cys Pro
 2615 2620 2625

Leu Gly Tyr Lys Glu Glu Asn Asn Thr Gly Glu Cys Cys Gly Arg
 2630 2635 2640

Cys Leu Pro Thr Ala Cys Thr Ile Gln Leu Arg Gly Gly Gln Ile
 2645 2650 2655

Met Thr Leu Lys Arg Asp Glu Thr Leu Gln Asp Gly Cys Asp Thr
 2660 2665 2670

His Phe Cys Lys Val Asn Glu Arg Gly Glu Tyr Phe Trp Glu Lys
 2675 2680 2685

Arg Val Thr Gly Cys Pro Pro Phe Asp Glu His Lys Cys Leu Ala
 2690 2695 2700

Glu Gly Gly Lys Ile Met Lys Ile Pro Gly Thr Cys Cys Asp Thr
 2705 2710 2715

Cys Glu Glu Pro Glu Cys Asn Asp Ile Thr Ala Arg Leu Gln Tyr
 2720 2725 2730

Val Lys Val Gly Ser Cys Lys Ser Glu Val Glu Val Asp Ile His
 2735 2740 2745

Tyr Cys Gln Gly Lys Cys Ala Ser Lys Ala Met Tyr Ser Ile Asp
 2750 2755 2760

Ile Asn Asp Val Gln Asp Gln Cys Ser Cys Cys Ser Pro Thr Arg
 2765 2770 2775

Thr Glu Pro Met Gln Val Ala Leu His Cys Thr Asn Gly Ser Val
 2780 2785 2790

Val Tyr His Glu Val Leu Asn Ala Met Glu Cys Lys Cys Ser Pro
 2795 2800 2805

Arg Lys Cys Ser Lys
 2810

<210> 22
 <211> 45
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> pSYN VWF059A

<400> 22

Thr Ser Thr Glu Glu Gly Ala Ser Ser Asp Lys Asn Thr Gly Asp Tyr
 1 5 10 15

Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn
 20 25 30

Asn Ala Ile Glu Pro Arg Ser Phe Ser Asp Lys Thr His
 35 40 45

<210> 23
 <211> 54
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> pSYN VWF073

<400> 23

Thr Ser Thr Glu Glu Gly Ala Ser Ser Gly Gly Gly Gly Ser Gly Gly
 1 5 10 15

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 20 25 30

Gly Ser Gly Gly Gly Gly Ser Ile Glu Pro Arg Ser Phe Ser Gly Ser
 35 40 45

Gly Gly Asp Lys Thr His
 50

<210> 24
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Family AD

<400> 24

Gly Glu Ser Pro Gly Gly Ser Ser Gly Ser Glu Ser
 1 5 10

<210> 25
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Family AD

<400> 25

Gly Ser Glu Gly Ser Ser Gly Pro Gly Glu Ser Ser
 1 5 10

<210> 26

<211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Family AD

<400> 26

Gly Ser Ser Glu Ser Gly Ser Ser Glu Gly Gly Pro
 1 5 10

<210> 27
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Family AD

<400> 27

Gly Ser Gly Gly Glu Pro Ser Glu Ser Gly Ser Ser
 1 5 10

<210> 28
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Families AE, AM

<400> 28

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
 1 5 10

<210> 29
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>

<223> XTEN Motif Families AE, AM, AQ

<400> 29

Gly	Ser	Glu	Pro	Ala	Thr	Ser	Gly	Ser	Glu	Thr	Pro
1				5					10		

<210> 30

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN Motif Families AE, AM, AQ

<400> 30

Gly	Thr	Ser	Glu	Ser	Ala	Thr	Pro	Glu	Ser	Gly	Pro
1				5					10		

<210> 31

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN Motif Families AE, AM, AQ

<400> 31

Gly	Thr	Ser	Thr	Glu	Pro	Ser	Glu	Gly	Ser	Ala	Pro
1				5					10		

<210> 32

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN Motif Families AF, AM

<400> 32

Gly Ser Thr Ser Glu Ser Pro Ser Gly Thr Ala Pro
1 5 10

<210> 33

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN Motif Families AF, AM

<400> 33

Gly Thr Ser Thr Pro Glu Ser Gly Ser Ala Ser Pro
1 5 10

<210> 34

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> AF, AM

<400> 34

Gly Thr Ser Pro Ser Gly Glu Ser Ser Thr Ala Pro
1 5 10

<210> 35

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN Motif Families AF, AM

<400> 35

Gly Ser Thr Ser Ser Thr Ala Glu Ser Pro Gly Pro
 1 5 10

<210> 36
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Families AG, AM

<400> 36

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro
 1 5 10

<210> 37
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Families AG, AM

<400> 37

Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro
 1 5 10

<210> 38
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Families AG, AM

<400> 38

Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro
 1 5 10

<210> 39
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Families AG, AM

<400> 39

Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
 1 5 10

<210> 40
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Family AQ

<400> 40

Gly Glu Pro Ala Gly Ser Pro Thr Ser Thr Ser Glu
 1 5 10

<210> 41
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Family AQ

<400> 41

Gly Thr Gly Glu Pro Ser Ser Thr Pro Ala Ser Glu
 1 5 10

<210> 42
 <211> 12

<212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Family AQ

<400> 42

Gly Ser Gly Pro Ser Thr Glu Ser Ala Pro Thr Glu
 1 5 10

<210> 43
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Family AQ

<400> 43

Gly Ser Glu Thr Pro Ser Gly Pro Ser Glu Thr Ala
 1 5 10

<210> 44
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN Motif Family AQ

<400> 44

Gly Pro Ser Glu Thr Ser Thr Ser Glu Pro Gly Ala
 1 5 10

<210> 45
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>

<223> XTEN Motif Family AQ

<400> 45

Gly	Ser	Pro	Ser	Glu	Pro	Thr	Glu	Gly	Thr	Ser	Ala
1				5					10		

<210> 46

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN Motif Family BC

<400> 46

Gly	Ser	Gly	Ala	Ser	Glu	Pro	Thr	Ser	Thr	Glu	Pro
1				5					10		

<210> 47

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN Motif Family BC

<400> 47

Gly	Ser	Glu	Pro	Ala	Thr	Ser	Gly	Thr	Glu	Pro	Ser
1				5					10		

<210> 48

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN Motif Family BC

<400> 48

Gly Thr Ser Glu Pro Ser Thr Ser Glu Pro Gly Ala
1 5 10

<210> 49

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN Family Motif BC

<400> 49

Gly Thr Ser Thr Glu Pro Ser Glu Pro Gly Ser Ala
1 5 10

<210> 50

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN Motif Family BD

<400> 50

Gly Ser Thr Ala Gly Ser Glu Thr Ser Thr Glu Ala
1 5 10

<210> 51

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN Motif Family BD

<400> 51

Gly Ser Glu Thr Ala Thr Ser Gly Ser Glu Thr Ala

1 5 10

<210> 52
 <211> 12
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> XTEN Motif Family BD

 <400> 52

Gly Thr Ser Glu Ser Ala Thr Ser Glu Ser Gly Ala
 1 5 10

<210> 53
 <211> 12
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> XTEN Motif Family BD

 <400> 53

Gly Thr Ser Thr Glu Ala Ser Glu Gly Ser Ala Ser
 1 5 10

<210> 54
 <211> 288
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> XTEN AE288_2

 <400> 54

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu
 1 5 10 15

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
 20 25 30

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
 35 40 45

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
 50 55 60

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu
 65 70 75 80

Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
 85 90 95

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
 100 105 110

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
 115 120 125

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
 130 135 140

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
 145 150 155 160

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
 165 170 175

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
 180 185 190

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr

195

200

205

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
 210 215 220

Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
 225 230 235 240

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala
 245 250 255

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro
 260 265 270

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
 275 280 285

<210> 55
 <211> 143
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN AE144_2A

<400> 55

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser
 1 5 10 15

Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
 20 25 30

Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr
 35 40 45

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro
 50 55 60

Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 65 70 75 80

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
 85 90 95

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro
 100 105 110

Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 115 120 125

Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 130 135 140

<210> 56

<211> 144

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN AE144_3B

<400> 56

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser
 1 5 10 15

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
 20 25 30

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 35 40 45

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu
 50 55 60

Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly
 65 70 75 80

Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 85 90 95

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu
 100 105 110

Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 115 120 125

Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 130 135 140

<210> 57

<211> 144

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN AE144_4A

<400> 57

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 1 5 10 15

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 20 25 30

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 35 40 45

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu
 50 55 60

Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 65 70 75 80

Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
 85 90 95

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly
 100 105 110

Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu
 115 120 125

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 130 135 140

<210> 58

<211> 144

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN AE144_5A

<400> 58

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 1 5 10 15

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 20 25 30

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly

35

40

45

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu
 50 55 60

Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 65 70 75 80

Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 85 90 95

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser
 100 105 110

Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 115 120 125

Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
 130 135 140

<210> 59

<211> 144

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN AE144_6B

<400> 59

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser
 1 5 10 15

Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 20 25 30

Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 35 40 45

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala
 50 55 60

Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 65 70 75 80

Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 85 90 95

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala
 100 105 110

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 115 120 125

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 130 135 140

<210> 60
 <211> 144
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN AG144_A

<400> 60

Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ser Ser Pro
 1 5 10 15

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser Pro Ser Ala Ser Thr
 20 25 30

Gly Thr Gly Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro
35 40 45

Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Pro
50 55 60

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser
65 70 75 80

Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro
85 90 95

Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Thr Pro Gly
100 105 110

Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
115 120 125

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
130 135 140

<210> 61

<211> 144

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN AG144_B

<400> 61

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr
1 5 10 15

Pro Ser Gly Ala Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
20 25 30

Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro
 35 40 45

Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Pro
 50 55 60

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser Pro Ser Ala Ser Thr
 65 70 75 80

Gly Thr Gly Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro
 85 90 95

Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ala Ser Pro
 100 105 110

Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
 115 120 125

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
 130 135 140

<210> 62
 <211> 144
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> XTEN AG144_C

<400> 62

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala Ser Pro
 1 5 10 15

Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser

Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser Pro
1 5 10 15

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser
20 25 30

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
35 40 45

Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Pro
50 55 60

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser
65 70 75 80

Thr Gly Ser Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro
85 90 95

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr
100 105 110

Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala
115 120 125

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
130 135 140

<210> 64

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> FVIII Signal Peptide

<400> 64

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

Cys Phe Ser

<210> 65
 <211> 2332
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Mature Factor VIII

<400> 65

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro

660

665

670

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

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

Leu Leu Lys Val Ser Ser Cys Asp Lys 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
 2300 2305 2310

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

Gln Asp Leu Tyr
 2330

<210> 66
 <211> 7053
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Full-Length FVIII

<400> 66

atgcaaatag agctctccac ctgcttcttt ctgtgccttt tgcgattctg ctttagtgcc
60

accagaagat actacctggg tgcagtggaa ctgtcatggg actatatgca aagtgatctc
120

ggtgagctgc ctgtggacgc aagatttcct cctagagtgc caaaatcttt tccattcaac
180

acctcagtcg tgtacaaaaa gactctgttt gtagaattca cggatcacct tttcaacatc
240

gctaagccaa ggccaccctg gatgggtctg ctaggtccta ccatccaggc tgaggtttat
300

gatacagtgg tcattacact taagaacatg gcttcccatc ctgtcagtct tcatgctgtt
360

ggtgtatcct actggaaagc ttctgaggga gctgaatatg atgatcagac cagtcaaagg
420

gagaaagaag atgataaagt cttccctggg ggaagccata catatgtctg gcaggctctg
480

aaagagaatg gtccaatggc ctctgaccca ctgtgcctta cctactcata tctttctcat
540

gtggacctgg taaaagactt gaattcaggc ctcattggag ccctactagt atgtagagaa
600

gggagtctgg ccaaggaaaa gacacagacc ttgcacaaat ttatactact ttttgctgta
660

tttgatgaag ggaaaagttg gcactcagaa acaaagaact ccttgatgca ggatagggat
720

gctgcatctg ctcgggcctg gcctaaaatg cacacagtca atggttatgt aaacagggtct
780

ctgccagggtc tgattggatg ccacaggaaa tcagtctatt ggcatgtgat tggaatgggc
840

accactcctg aagtgcactc aatattcctc gaaggtcaca catttcttgt gaggaaccat
900

cgccaggcgt ccttggaat ctgcgaata actttcctta ctgctcaaac actcttgatg
 960
 gaccttggac agtttctact gttttgtcat atctcttccc accaacaatga tggcatggaa
 1020
 gcttatgtca aagtagacag ctgtccagag gaacccaac tacgaatgaa aaataatgaa
 1080
 gaagcggaag actatgatga tgatcttact gattctgaaa tggatgtggt caggtttgat
 1140
 gatgacaact ctcttcctt tatccaaatt cgctcagttg ccaagaagca tcctaaaact
 1200
 tgggtacatt acattgctgc tgaagaggag gactgggact atgctccctt agtcctcgcc
 1260
 cccgatgaca gaagttataa aagtcaatat ttgaacaatg gccctcagcg gattggtagg
 1320
 aagtacaaaa aagtccgatt tatggcatac acagatgaaa cctttaagac tcgtgaagct
 1380
 attcagcatg aatcaggaat cttgggacct ttactttatg gggaagttgg agacacactg
 1440
 ttgattatat ttaagaatca agcaagcaga ccatataaca tctaccctca cggaatcact
 1500
 gatgtccgtc ctttgtattc aaggagatta ccaaaggtg taaaacattt gaaggatttt
 1560
 ccaattctgc caggagaaat attcaaatat aaatggacag tgactgtaga agatgggcca
 1620
 actaaatcag atcctcgggtg cctgaccgcg tattactcta gtttcgttaa tatggagaga
 1680
 gatctagctt caggactcat tggccctctc ctcatctgct acaaagaatc tgtagatcaa
 1740
 agaggaaacc agataatgtc agacaagagg aatgtcatcc tgttttctgt atttgatgag
 1800

aaccgaagct 1860	ggtacctcac	agagaatata	caacgctttc	tccccaatcc	agctggagtg
cagcttgagg 1920	atccagagtt	ccaagcctcc	aacatcatgc	acagcatcaa	tggtatgtt
tttgatagtt 1980	tgcagttgtc	agtttgtttg	catgaggtgg	catactggta	cattctaagc
attggagcac 2040	agactgactt	cctttctgtc	ttcttctctg	gatatacctt	caaacacaaa
atggtctatg 2100	aagacacact	caccctattc	ccattctcag	gagaaactgt	cttcatgtcg
atggaaaacc 2160	caggtctatg	gattctgggg	tgccacaact	cagactttcg	gaacagaggc
atgaccgcct 2220	tactgaaggt	ttctagttgt	gacaagaaca	ctggtgatta	ttacgaggac
agttatgaag 2280	atatttcagc	atacttgctg	agtaaaaaca	atgccattga	accaagaagc
ttctcccaga 2340	attcaagaca	ccctagcact	aggcaaaagc	aatttaatgc	caccacaatt
ccagaaaatg 2400	acatagagaa	gactgaccct	tggtttgcac	acagaacacc	tatgcctaaa
atacaaaatg 2460	tctcctctag	tgatttggtg	atgctcttgc	gacagagtcc	tactccacat
gggctatcct 2520	tatctgatct	ccaagaagcc	aaatatgaga	ctttttctga	tgatccatca
cctggagcaa 2580	tagacagtaa	taacagcctg	tctgaaatga	cacacttcag	gccacagctc
catcacagtg 2640	gggacatggg	atttaccctt	gagtcaggcc	tccaattaag	attaaatgag
aaactgggga 2700	caactgcagc	aacagagttg	aagaaacttg	atttcaaagt	ttctagtaca

tcaaataatc tgatttcaac aattccatca gacaatttgg cagcaggtac tgataataca
2760

agttccttag gacccccaag tatgccagtt cattatgata gtcaattaga taccactcta
2820

tttggcaaaa agtcatctcc ccttactgag tctggtggac ctctgagctt gagtgaagaa
2880

aataatgatt caaagttggt agaatcaggt ttaatgaata gccaagaaag ttcattggga
2940

aaaaatgtat cgtcaacaga gagtggtagg ttatttaaag ggaaaagagc tcatggacct
3000

gctttgttga ctaaagataa tgccttattc aaagtttagca tctctttggt aaagacaaac
3060

aaaacttcca ataattcagc aactaataga aagactcaca ttgatggccc atcattatta
3120

attgagaata gtccatcagt ctggcaaaat atattagaaa gtgacactga gtttaaaaaa
3180

gtgacacctt tgattcatga cagaatgctt atggacaaaa atgctacagc tttgaggcta
3240

aatcatatgt caaataaaaac tacttcatca aaaaacatgg aaatgggtcca acagaaaaaa
3300

gagggcccca ttccaccaga tgcacaaaat ccagatatgt cgttctttaa gatgctattc
3360

ttgccagaat cagcaagggt gatacaaagg actcatggaa agaactctct gaactctggg
3420

caaggcccca gtccaaagca attagtatcc ttaggaccag aaaaatctgt ggaaggtcag
3480

aatttcttgt ctgagaaaaa caaagtggta gtaggaaagg gtgaatttac aaaggacgta
3540

ggactcaaag agatgggttt tccaagcagc agaaacctat ttcttactaa cttggataat
3600

ttacatgaaa ataatacaca caatcaagaa aaaaaaattc aggaagaaat agaaaagaag
3660

gaaacattaa tccaagagaa tgtagttttg cctcagatac atacagtgac tggcactaag
3720

aatttcatga agaacctttt cttactgagc actaggcaaa atgtagaagg ttcatatgac
3780

ggggcatatg ctccagtact tcaagatttt aggtcattaa atgattcaac aaatagaaca
3840

aagaaacaca cagctcatth ctcaaaaaaa ggggaggaag aaaacttgga aggcttggga
3900

aatcaaacca agcaaattgt agagaaatat gcatgcacca caaggatatc tcctaataca
3960

agccagcaga attttgtcac gcaacgtagt aagagagctt tgaaacaatt cagactccca
4020

ctagaagaaa cagaacttga aaaaaggata attgtggatg acacctcaac ccagtgggtcc
4080

aaaaacatga aacatttgac cccgagcacc ctcacacaga tagactacaa tgagaaggag
4140

aaaggggcca ttactcagtc tcccttatca gattgcctta cgaggagtca tagcatccct
4200

caagcaaata gatctccatt acccattgca aaggtatcat catttccatc tattagacct
4260

atatatctga ccagggtcct attccaagac aactcttctc atcttccagc agcatcttat
4320

agaaagaaag attctgggggt ccaagaaagc agtcatttct tacaaggagc caaaaaaat
4380

aacctttctt tagccattct aaccttggag atgactgggtg atcaaagaga gggttggtcc
4440

ctggggacaa gtgccacaaa ttcagtcaca tacaagaaag ttgagaacac tgttctcccg
4500

aaaccagact tgcccaaac atctggcaaa gttgaattgc ttccaaaagt tcacatttat
 4560

cagaaggacc tattccctac ggaaactagc aatgggtctc ctggccatct ggatctcgtg
 4620

gaagggagcc ttcttcaggg aacagaggga gcgattaagt ggaatgaagc aaacagacct
 4680

ggaaaagttc cctttctgag agtagcaaca gaaagctctg caaagactcc ctccaagcta
 4740

ttggatcctc ttgcttgga taaccactat ggtactcaga taccaaaaga agagtggaaa
 4800

tccaagaga agtcaccaga aaaaacagct ttttaagaaaa aggataccat tttgtccctg
 4860

aacgcttggtg aaagcaatca tgcaatagca gcaataaatg aggacaaaa taagcccgaa
 4920

atagaagtca cctgggcaaa gcaaggtagg actgaaaggc tgtgctctca aaaccaccca
 4980

gtcttgaaac gccatcaacg ggaaataact cgtactactc ttcagtcaga tcaagaggaa
 5040

attgactatg atgataccat atcagttgaa atgaagaagg aagattttga catttatgat
 5100

gaggatgaaa atcagagccc ccgcagcttt caaaagaaaa cacgacacta ttttattgct
 5160

gcagtggaga ggctctggga ttatgggatg agtagctccc cacatgttct aagaaacagg
 5220

gctcagagtg gcagtgtccc tcagttcaag aaagttgttt tccaggaatt tactgatggc
 5280

tcctttactc agcccttata ccgtggagaa ctaaataaac atttgggact cctggggcca
 5340

tatataagag cagaagttga agataatatc atggtaactt tcagaaatca ggcctctcgt
 5400

ccctattcct tctattctag ccttatttct tatgaggaag atcagaggca aggagcagaa
 5460

cctagaaaaa actttgtcaa gcctaataa accaaaactt acttttggaa agtgcaacat
 5520

catatggcac ccactaaaga tgagtttgac tgcaaagcct gggcttattt ctctgatggt
 5580

gacctggaaa aagatgtgca ctcaggcctg attggacccc ttctgggtctg ccacactaac
 5640

aactgaacc ctgctcatgg gagacaagtg acagtacagg aatttgctct gtttttcacc
 5700

atctttgatg agaccaaag ctggtacttc actgaaaata tggaaagaaa ctgcagggct
 5760

ccctgcaata tccagatgga agatcccact tttaaagaga attatcgctt ccatgcaatc
 5820

aatggctaca taatggatac actacctggc ttagtaatgg ctcaggatca aaggattcga
 5880

tggatatctg tcagcatggg cagcaatgaa aacatccatt ctattcattt cagtggacat
 5940

gtgttcactg tacgaaaaaa agaggagtat aaaatggcac tgtacaatct ctatccaggt
 6000

gtttttgaga cagtggaaat gttaccatcc aaagctggaa tttggcgggt ggaatgcctt
 6060

attggcgagc atctacatgc tgggatgagc acactttttc tgggtgtacag caataagtgt
 6120

cagactcccc tgggaatggc ttctggacac attagagatt ttcagattac agcttcagga
 6180

caatatggac agtgggcccc aaagctggcc agacttcatt attccggatc aatcaatgcc
 6240

tggagcacca aggagccctt ttcttggatc aaggtggatc tgttggcacc aatgattatt
 6300

cacggcatca agaccaggg tgcccgtcag aagttctcca gcctctacat ctctcagttt
6360

atcatcatgt atagtcttga tgggaagaag tggcagactt atcgaggaaa ttccactgga
6420

accttaatgg tcttcttttg caatgtggat tcactctggga taaaacacaa tatttttaac
6480

cctccaatta ttgctcgata catccgtttg cacccaactc attatagcat tcgcagcact
6540

cttcgcatgg agttgatggg ctgtgattta aatagttgca gcatgccatt gggaatggag
6600

agtaaagcaa tatcagatgc acagattact gcttcatcct actttaccaa tatgtttgcc
6660

acctggctctc cttcaaaagc tcgacttcac ctccaaggga ggagtaatgc ctggagacct
6720

caggtgaata atccaaaaga gtggctgcaa gtggacttcc agaagacaat gaaagtcaca
6780

ggagtaacta ctcagggagt aaaatctctg cttaccagca tgtatgtgaa ggagttcctc
6840

atctccagca gtcaagatgg ccatcagtgg actctctttt ttcagaatgg caaagtaaag
6900

gtttttcagg gaaatcaaga ctccttcaca cctgtgggtga actctctaga cccaccgtta
6960

ctgactcgct accttcgaat tcacccccag agttgggtgc accagattgc cctgaggatg
7020

g a g g t t c t g g g c t g c g a g g c a c a g g a c c t c t a c
7053

<210> 67

<211> 1438

<212> PRT

<213> Artificial Sequence

<220>

<223> BDD FVIII

<400> 67

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys

515

520

525

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

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

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

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

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

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

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

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

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

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

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

Leu Leu Lys Val Ser Ser Cys Asp Lys 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 1055	Ser	Asn	Glu	Asn	Ile	His 1060	Ser	Ile	His	Phe	Ser 1065	Gly	His	Val
Phe 1070	Thr	Val	Arg	Lys	Lys	Glu 1075	Glu	Tyr	Lys	Met	Ala 1080	Leu	Tyr	Asn
Leu 1085	Tyr	Pro	Gly	Val	Phe	Glu 1090	Thr	Val	Glu	Met	Leu 1095	Pro	Ser	Lys
Ala 1100	Gly	Ile	Trp	Arg	Val	Glu 1105	Cys	Leu	Ile	Gly	Glu 1110	His	Leu	His
Ala 1115	Gly	Met	Ser	Thr	Leu	Phe 1120	Leu	Val	Tyr	Ser	Asn 1125	Lys	Cys	Gln
Thr 1130	Pro	Leu	Gly	Met	Ala	Ser 1135	Gly	His	Ile	Arg	Asp 1140	Phe	Gln	Ile
Thr 1145	Ala	Ser	Gly	Gln	Tyr	Gly 1150	Gln	Trp	Ala	Pro	Lys 1155	Leu	Ala	Arg
Leu 1160	His	Tyr	Ser	Gly	Ser	Ile 1165	Asn	Ala	Trp	Ser	Thr 1170	Lys	Glu	Pro
Phe 1175	Ser	Trp	Ile	Lys	Val	Asp 1180	Leu	Leu	Ala	Pro	Met 1185	Ile	Ile	His
Gly 1190	Ile	Lys	Thr	Gln	Gly	Ala 1195	Arg	Gln	Lys	Phe	Ser 1200	Ser	Leu	Tyr
Ile 1205	Ser	Gln	Phe	Ile	Ile	Met 1210	Tyr	Ser	Leu	Asp	Gly 1215	Lys	Lys	Trp
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

<210> 68

<211> 1429

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino Acid Sequence of B-domain Deleted Factor VIII (B-domain deletion except 5 amino acid residues)

<400> 68

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

260

265

270

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Leu Leu Lys Val Ser Ser Cys Asp Lys 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 Glu Ile Thr Arg Thr Thr Leu
740 745 750

Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu
755 760 765

Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser
770 775 780

Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val
785 790 795 800

Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg
 805 810 815

Asn Arg Ala Gln Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe
 820 825 830

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

Leu Asn Glu His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val
 850 855 860

Glu Asp Asn Ile Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr
 865 870 875 880

Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly
 885 890 895

Ala Glu Pro Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr
 900 905 910

Phe Trp Lys Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp
 915 920 925

Cys Lys Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val
 930 935 940

His Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu
 945 950 955 960

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

Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met

980

985

990

Glu Arg Asn Cys Arg Ala Pro Cys Asn Ile Gln Met Glu Asp Pro Thr
 995 1000 1005

Phe Lys Glu Asn Tyr Arg Phe His Ala Ile Asn Gly Tyr Ile Met
 1010 1015 1020

Asp Thr Leu Pro Gly Leu Val Met Ala Gln Asp Gln Arg Ile Arg
 1025 1030 1035

Trp Tyr Leu Leu Ser Met Gly Ser Asn Glu Asn Ile His Ser Ile
 1040 1045 1050

His Phe Ser Gly His Val Phe Thr Val Arg Lys Lys Glu Glu Tyr
 1055 1060 1065

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

Glu Met Leu Pro Ser Lys Ala Gly Ile Trp Arg Val Glu Cys Leu
 1085 1090 1095

Ile Gly Glu His Leu His Ala Gly Met Ser Thr Leu Phe Leu Val
 1100 1105 1110

Tyr Ser Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His
 1115 1120 1125

Ile Arg Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp
 1130 1135 1140

Ala Pro Lys Leu Ala Arg Leu His Tyr Ser Gly Ser Ile Asn Ala
 1145 1150 1155

Trp	Ser	Thr	Lys	Glu	Pro	Phe	Ser	Trp	Ile	Lys	Val	Asp	Leu	Leu
	1160					1165					1170			
Ala	Pro	Met	Ile	Ile	His	Gly	Ile	Lys	Thr	Gln	Gly	Ala	Arg	Gln
	1175					1180					1185			
Lys	Phe	Ser	Ser	Leu	Tyr	Ile	Ser	Gln	Phe	Ile	Ile	Met	Tyr	Ser
	1190					1195					1200			
Leu	Asp	Gly	Lys	Lys	Trp	Gln	Thr	Tyr	Arg	Gly	Asn	Ser	Thr	Gly
	1205					1210					1215			
Thr	Leu	Met	Val	Phe	Phe	Gly	Asn	Val	Asp	Ser	Ser	Gly	Ile	Lys
	1220					1225					1230			
His	Asn	Ile	Phe	Asn	Pro	Pro	Ile	Ile	Ala	Arg	Tyr	Ile	Arg	Leu
	1235					1240					1245			
His	Pro	Thr	His	Tyr	Ser	Ile	Arg	Ser	Thr	Leu	Arg	Met	Glu	Leu
	1250					1255					1260			
Met	Gly	Cys	Asp	Leu	Asn	Ser	Cys	Ser	Met	Pro	Leu	Gly	Met	Glu
	1265					1270					1275			
Ser	Lys	Ala	Ile	Ser	Asp	Ala	Gln	Ile	Thr	Ala	Ser	Ser	Tyr	Phe
	1280					1285					1290			
Thr	Asn	Met	Phe	Ala	Thr	Trp	Ser	Pro	Ser	Lys	Ala	Arg	Leu	His
	1295					1300					1305			
Leu	Gln	Gly	Arg	Ser	Asn	Ala	Trp	Arg	Pro	Gln	Val	Asn	Asn	Pro
	1310					1315					1320			

Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val Thr
 1325 1330 1335

Gly Val Thr Thr Gln Gly Val Lys Ser Leu Leu Thr Ser Met Tyr
 1340 1345 1350

Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Gln Trp
 1355 1360 1365

Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn
 1370 1375 1380

Gln Asp Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro Leu
 1385 1390 1395

Leu Thr Arg Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln
 1400 1405 1410

Ile Ala Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu
 1415 1420 1425

Tyr

<210> 69

<211> 2754

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN-FVIII-161

<400> 69

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

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

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
 50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
 65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
 85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
 100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
 115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
 130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
 145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
 165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
 180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
 195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
 210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
 225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
 245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
 260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
 275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
 290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
 305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
 325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
 340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
 355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
 370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
 385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
 405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
 420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
 435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
 450 455 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
 465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
 485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
 500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
 515 520 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
 530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg

545		550		555		560									
Asp	Leu	Ala	Ser	Gly	Leu	Ile	Gly	Pro	Leu	Leu	Ile	Cys	Tyr	Lys	Glu
				565					570					575	
Ser	Val	Asp	Gln	Arg	Gly	Asn	Gln	Ile	Met	Ser	Asp	Lys	Arg	Asn	Val
			580					585					590		
Ile	Leu	Phe	Ser	Val	Phe	Asp	Glu	Asn	Arg	Ser	Trp	Tyr	Leu	Thr	Glu
		595					600					605			
Asn	Ile	Gln	Arg	Phe	Leu	Pro	Asn	Pro	Ala	Gly	Val	Gln	Leu	Glu	Asp
	610					615					620				
Pro	Glu	Phe	Gln	Ala	Ser	Asn	Ile	Met	His	Ser	Ile	Asn	Gly	Tyr	Val
625					630					635					640
Phe	Asp	Ser	Leu	Gln	Leu	Ser	Val	Cys	Leu	His	Glu	Val	Ala	Tyr	Trp
				645					650					655	
Tyr	Ile	Leu	Ser	Ile	Gly	Ala	Gln	Thr	Asp	Phe	Leu	Ser	Val	Phe	Phe
			660					665					670		
Ser	Gly	Tyr	Thr	Phe	Lys	His	Lys	Met	Val	Tyr	Glu	Asp	Thr	Leu	Thr
		675					680					685			
Leu	Phe	Pro	Phe	Ser	Gly	Glu	Thr	Val	Phe	Met	Ser	Met	Glu	Asn	Pro
	690					695					700				
Gly	Leu	Trp	Ile	Leu	Gly	Cys	His	Asn	Ser	Asp	Phe	Arg	Asn	Arg	Gly
705					710					715					720
Met	Thr	Ala	Leu	Leu	Lys	Val	Ser	Ser	Cys	Asp	Lys	Asn	Thr	Gly	Asp
				725					730					735	

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu
755 760 765

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

Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu
785 790 795 800

Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe
805 810 815

Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp
820 825 830

Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln
835 840 845

Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr
850 855 860

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His
865 870 875 880

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

Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser
900 905 910

Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg
 915 920 925

Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val
 930 935 940

Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp
 945 950 955 960

Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu
 965 970 975

Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His
 980 985 990

Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe
 995 1000 1005

Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn
 1010 1015 1020

Cys Arg Ala Pro Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys
 1025 1030 1035

Glu Asn Tyr Arg Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr
 1040 1045 1050

Leu Pro Gly Leu Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr
 1055 1060 1065

Leu Leu Ser Met Gly Ser Asn Glu Asn Ile His Ser Ile His Phe
 1070 1075 1080

Ser Gly His Val Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met
 1085 1090 1095

Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met
 1100 1105 1110

Leu Pro Ser Lys Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly
 1115 1120 1125

Glu His Leu His Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser
 1130 1135 1140

Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg
 1145 1150 1155

Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro
 1160 1165 1170

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

Thr Lys Glu Pro Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro
 1190 1195 1200

Met Ile Ile His Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe
 1205 1210 1215

Ser Ser Leu Tyr Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp
 1220 1225 1230

Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu
 1235 1240 1245

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

1250						1255						1260			
Ile	Phe	Asn	Pro	Pro	Ile	Ile	Ala	Arg	Tyr	Ile	Arg	Leu	His	Pro	
1265						1270					1275				
Thr	His	Tyr	Ser	Ile	Arg	Ser	Thr	Leu	Arg	Met	Glu	Leu	Met	Gly	
1280						1285					1290				
Cys	Asp	Leu	Asn	Ser	Cys	Ser	Met	Pro	Leu	Gly	Met	Glu	Ser	Lys	
1295						1300					1305				
Ala	Ile	Ser	Asp	Ala	Gln	Ile	Thr	Ala	Ser	Ser	Tyr	Phe	Thr	Asn	
1310						1315					1320				
Met	Phe	Ala	Thr	Trp	Ser	Pro	Ser	Lys	Ala	Arg	Leu	His	Leu	Gln	
1325						1330					1335				
Gly	Arg	Ser	Asn	Ala	Trp	Arg	Pro	Gln	Val	Asn	Asn	Pro	Lys	Glu	
1340						1345					1350				
Trp	Leu	Gln	Val	Asp	Phe	Gln	Lys	Thr	Met	Lys	Val	Thr	Gly	Val	
1355						1360					1365				
Thr	Thr	Gln	Gly	Val	Lys	Ser	Leu	Leu	Thr	Ser	Met	Tyr	Val	Lys	
1370						1375					1380				
Glu	Phe	Leu	Ile	Ser	Ser	Ser	Gln	Asp	Gly	His	Gln	Trp	Thr	Leu	
1385						1390					1395				
Phe	Phe	Gln	Asn	Gly	Lys	Val	Lys	Val	Phe	Gln	Gly	Asn	Gln	Asp	
1400						1405					1410				
Ser	Phe	Thr	Pro	Val	Val	Asn	Ser	Leu	Asp	Pro	Pro	Leu	Leu	Thr	
1415						1420					1425				

Arg Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala
 1430 1435 1440

Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr Asp
 1445 1450 1455

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
 1460 1465 1470

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 1475 1480 1485

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
 1490 1495 1500

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
 1505 1510 1515

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
 1520 1525 1530

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 1535 1540 1545

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 1550 1555 1560

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 1565 1570 1575

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 1580 1585 1590

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
1595 1600 1605

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
1610 1615 1620

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
1625 1630 1635

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
1640 1645 1650

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
1655 1660 1665

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
1670 1675 1680

Lys Arg Arg Arg Arg Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
1685 1690 1695

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
1700 1705 1710

Ser Gly Gly Gly Gly Ser Arg Lys Arg Arg Lys Arg Ser Leu Ser
1715 1720 1725

Cys Arg Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp Asn Leu
1730 1735 1740

Arg Ala Glu Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr Asp
1745 1750 1755

Leu Glu Cys Met Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro
 1760 1765 1770

Pro Gly Met Val Arg His Glu Asn Arg Cys Val Ala Leu Glu Arg
 1775 1780 1785

Cys Pro Cys Phe His Gln Gly Lys Glu Tyr Ala Pro Gly Glu Thr
 1790 1795 1800

Val Lys Ile Gly Cys Asn Thr Cys Val Cys Arg Asp Arg Lys Trp
 1805 1810 1815

Asn Cys Thr Asp His Val Cys Asp Ala Thr Cys Ser Thr Ile Gly
 1820 1825 1830

Met Ala His Tyr Leu Thr Phe Asp Gly Leu Lys Tyr Leu Phe Pro
 1835 1840 1845

Gly Glu Cys Gln Tyr Val Leu Val Gln Asp Tyr Cys Gly Ser Asn
 1850 1855 1860

Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys Gly Cys Ser His
 1865 1870 1875

Pro Ser Val Lys Cys Lys Lys Arg Val Thr Ile Leu Val Glu Gly
 1880 1885 1890

Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys Arg Pro
 1895 1900 1905

Met Lys Asp Glu Thr His Phe Glu Val Val Glu Ser Gly Arg Tyr
 1910 1915 1920

Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg

1925						1930						1935					
His	Leu	Ser	Ile	Ser	Val	Val	Leu	Lys	Gln	Thr	Tyr	Gln	Glu	Lys			
1940						1945					1950						
Val	Cys	Gly	Leu	Cys	Gly	Asn	Phe	Asp	Gly	Ile	Gln	Asn	Asn	Asp			
1955						1960					1965						
Leu	Thr	Ser	Ser	Asn	Leu	Gln	Val	Glu	Glu	Asp	Pro	Val	Asp	Phe			
1970						1975					1980						
Gly	Asn	Ser	Trp	Lys	Val	Ser	Ser	Gln	Cys	Ala	Asp	Thr	Arg	Lys			
1985						1990					1995						
Val	Pro	Leu	Asp	Ser	Ser	Pro	Ala	Thr	Cys	His	Asn	Asn	Ile	Met			
2000						2005					2010						
Lys	Gln	Thr	Met	Val	Asp	Ser	Ser	Cys	Arg	Ile	Leu	Thr	Ser	Asp			
2015						2020					2025						
Val	Phe	Gln	Asp	Cys	Asn	Lys	Leu	Val	Asp	Pro	Glu	Pro	Tyr	Leu			
2030						2035					2040						
Asp	Val	Cys	Ile	Tyr	Asp	Thr	Cys	Ser	Cys	Glu	Ser	Ile	Gly	Asp			
2045						2050					2055						
Cys	Ala	Ala	Phe	Cys	Asp	Thr	Ile	Ala	Ala	Tyr	Ala	His	Val	Cys			
2060						2065					2070						
Ala	Gln	His	Gly	Lys	Val	Val	Thr	Trp	Arg	Thr	Ala	Thr	Leu	Cys			
2075						2080					2085						
Pro	Gln	Ser	Cys	Glu	Glu	Arg	Asn	Leu	Arg	Glu	Asn	Gly	Tyr	Glu			
2090						2095					2100						

Ala Glu Trp Arg Tyr Asn Ser Cys Ala Pro Ala Cys Gln Val Thr
 2105 2110 2115

Cys Gln His Pro Glu Pro Leu Ala Cys Pro Val Gln Cys Val Glu
 2120 2125 2130

Gly Cys His Ala His Cys Pro Pro Gly Lys Ile Leu Asp Glu Leu
 2135 2140 2145

Leu Gln Thr Cys Val Asp Pro Glu Asp Cys Pro Val Cys Glu Val
 2150 2155 2160

Ala Gly Arg Arg Phe Ala Ser Gly Lys Lys Val Thr Leu Asn Pro
 2165 2170 2175

Ser Asp Pro Glu His Cys Gln Ile Cys His Cys Asp Val Val Asn
 2180 2185 2190

Leu Thr Cys Glu Ala Cys Gln Glu Pro Ile Ser Gly Thr Ser Glu
 2195 2200 2205

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 2210 2215 2220

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 2225 2230 2235

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 2240 2245 2250

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
 2255 2260 2265

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro
 2270 2275 2280

Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 2285 2290 2295

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 2300 2305 2310

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala
 2315 2320 2325

Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro
 2330 2335 2340

Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
 2345 2350 2355

Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 2360 2365 2370

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu
 2375 2380 2385

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 2390 2395 2400

Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
 2405 2410 2415

Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
 2420 2425 2430

Thr 2435	Ser	Thr	Glu	Pro	Ser	Glu 2440	Gly	Ser	Ala	Pro	Gly 2445	Thr	Ser	Thr
Glu 2450	Pro	Ser	Glu	Gly	Ser	Ala 2455	Pro	Gly	Ser	Glu	Pro 2460	Ala	Thr	Ser
Gly 2465	Ser	Glu	Thr	Pro	Gly	Thr 2470	Ser	Glu	Ser	Ala	Thr 2475	Pro	Glu	Ser
Gly 2480	Pro	Gly	Thr	Ser	Thr	Glu 2485	Pro	Ser	Glu	Gly	Ser 2490	Ala	Pro	Asp
Ser 2495	Gly	Gly	Gly	Gly	Ser	Gly 2500	Gly	Gly	Gly	Ser	Gly 2505	Gly	Gly	Gly
Ser 2510	Gly	Gly	Gly	Gly	Ser	Gly 2515	Gly	Gly	Gly	Ser	Leu 2520	Val	Pro	Arg
Gly 2525	Ser	Gly	Gly	Asp	Lys	Thr 2530	His	Thr	Cys	Pro	Pro 2535	Cys	Pro	Ala
Pro 2540	Glu	Leu	Leu	Gly	Gly	Pro 2545	Ser	Val	Phe	Leu	Phe 2550	Pro	Pro	Lys
Pro 2555	Lys	Asp	Thr	Leu	Met	Ile 2560	Ser	Arg	Thr	Pro	Glu 2565	Val	Thr	Cys
Val 2570	Val	Val	Asp	Val	Ser	His 2575	Glu	Asp	Pro	Glu	Val 2580	Lys	Phe	Asn
Trp 2585	Tyr	Val	Asp	Gly	Val	Glu 2590	Val	His	Asn	Ala	Lys 2595	Thr	Lys	Pro
Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu

2600

2605

2610

Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys
	2615					2620					2625			

Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile
	2630					2635					2640			

Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
	2645					2650					2655			

Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
	2660					2665					2670			

Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
	2675					2680					2685			

Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro
	2690					2695					2700			

Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr
	2705					2710					2715			

Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser
	2720					2725					2730			

Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu
	2735					2740					2745			

Ser	Leu	Ser	Pro	Gly	Lys
	2750				

<210> 70

<211> 1978

<212> PRT

<213> Artificial Sequence

<220>

<223> FVIII 169

<400> 70

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

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

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
 50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
 65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
 85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
 100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
 115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
 130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu

145					150					155					160
Lys	Glu	Asn	Gly	Pro	Met	Ala	Ser	Asp	Pro	Leu	Cys	Leu	Thr	Tyr	Ser
				165					170					175	
Tyr	Leu	Ser	His	Val	Asp	Leu	Val	Lys	Asp	Leu	Asn	Ser	Gly	Leu	Ile
			180					185					190		
Gly	Ala	Leu	Leu	Val	Cys	Arg	Glu	Gly	Ser	Leu	Ala	Lys	Glu	Lys	Thr
		195					200					205			
Gln	Thr	Leu	His	Lys	Phe	Ile	Leu	Leu	Phe	Ala	Val	Phe	Asp	Glu	Gly
	210					215					220				
Lys	Ser	Trp	His	Ser	Glu	Thr	Lys	Asn	Ser	Leu	Met	Gln	Asp	Arg	Asp
225					230					235					240
Ala	Ala	Ser	Ala	Arg	Ala	Trp	Pro	Lys	Met	His	Thr	Val	Asn	Gly	Tyr
				245					250					255	
Val	Asn	Arg	Ser	Leu	Pro	Gly	Leu	Ile	Gly	Cys	His	Arg	Lys	Ser	Val
			260					265					270		
Tyr	Trp	His	Val	Ile	Gly	Met	Gly	Thr	Thr	Pro	Glu	Val	His	Ser	Ile
		275					280					285			
Phe	Leu	Glu	Gly	His	Thr	Phe	Leu	Val	Arg	Asn	His	Arg	Gln	Ala	Ser
	290					295					300				
Leu	Glu	Ile	Ser	Pro	Ile	Thr	Phe	Leu	Thr	Ala	Gln	Thr	Leu	Leu	Met
305					310					315					320
Asp	Leu	Gly	Gln	Phe	Leu	Leu	Phe	Cys	His	Ile	Ser	Ser	His	Gln	His
				325					330					335	

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
 340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
 355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
 370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
 385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
 405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
 420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
 435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
 450 455 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
 465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
 485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
 500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
 515 520 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
 530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
 545 550 555 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
 565 570 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
 580 585 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
 595 600 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
 610 615 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
 625 630 635 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
 645 650 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
 660 665 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
 675 680 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
 690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
 705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
 725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
 740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Gly Ala Pro Gly
 755 760 765

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 770 775 780

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 785 790 795 800

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 805 810 815

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu
 820 825 830

Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 835 840 845

Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 850 855 860

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser

865		870		875		880
Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser						
		885		890		895
Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly						
		900		905		910
Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser						
		915		920		925
Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu						
		930		935		940
Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly						
		945		950		955
						960
Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala						
		965		970		975
Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser						
		980		985		990
Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly						
		995		1000		1005
Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro						
		1010		1015		1020
Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr						
		1025		1030		1035
Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser						
		1040		1045		1050

Ala Pro Ala Ser Ser Pro Pro Val Leu Lys Arg His Gln Ala Glu
1055 1060 1065

Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr
1070 1075 1080

Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile
1085 1090 1095

Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
1100 1105 1110

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr
1115 1120 1125

Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser
1130 1135 1140

Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr
1145 1150 1155

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu
1160 1165 1170

His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp
1175 1180 1185

Asn Ile Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser
1190 1195 1200

Phe Tyr Ser Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly
1205 1210 1215

Ala Glu Pro Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr
 1220 1225 1230

Tyr Phe Trp Lys Val Gln His His Met Ala Pro Thr Lys Asp Glu
 1235 1240 1245

Phe Asp Cys Lys Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu
 1250 1255 1260

Lys Asp Val His Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His
 1265 1270 1275

Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln Val Thr Val Gln
 1280 1285 1290

Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp
 1295 1300 1305

Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro Cys Asn
 1310 1315 1320

Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg Phe His
 1325 1330 1335

Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu Val Met
 1340 1345 1350

Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met Gly Ser
 1355 1360 1365

Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val Phe Thr
 1370 1375 1380

Val	Arg	Lys	Lys	Glu	Glu	Tyr	Lys	Met	Ala	Leu	Tyr	Asn	Leu	Tyr
1385						1390					1395			
Pro	Gly	Val	Phe	Glu	Thr	Val	Glu	Met	Leu	Pro	Ser	Lys	Ala	Gly
1400						1405					1410			
Ile	Trp	Arg	Val	Glu	Cys	Leu	Ile	Gly	Glu	His	Leu	His	Ala	Gly
1415						1420					1425			
Met	Ser	Thr	Leu	Phe	Leu	Val	Tyr	Ser	Asn	Lys	Cys	Gln	Thr	Pro
1430						1435					1440			
Leu	Gly	Met	Ala	Ser	Gly	His	Ile	Arg	Asp	Phe	Gln	Ile	Thr	Ala
1445						1450					1455			
Ser	Gly	Gln	Tyr	Gly	Gln	Trp	Ala	Pro	Lys	Leu	Ala	Arg	Leu	His
1460						1465					1470			
Tyr	Ser	Gly	Ser	Ile	Asn	Ala	Trp	Ser	Thr	Lys	Glu	Pro	Phe	Ser
1475						1480					1485			
Trp	Ile	Lys	Val	Asp	Leu	Leu	Ala	Pro	Met	Ile	Ile	His	Gly	Ile
1490						1495					1500			
Lys	Thr	Gln	Gly	Ala	Arg	Gln	Lys	Phe	Ser	Ser	Leu	Tyr	Ile	Ser
1505						1510					1515			
Gln	Phe	Ile	Ile	Met	Tyr	Ser	Leu	Asp	Gly	Lys	Lys	Trp	Gln	Thr
1520						1525					1530			
Tyr	Arg	Gly	Asn	Ser	Thr	Gly	Thr	Leu	Met	Val	Phe	Phe	Gly	Asn
1535						1540					1545			
Val	Asp	Ser	Ser	Gly	Ile	Lys	His	Asn	Ile	Phe	Asn	Pro	Pro	Ile

1550

1555

1560

Ile	Ala	Arg	Tyr	Ile	Arg	Leu	His	Pro	Thr	His	Tyr	Ser	Ile	Arg
1565						1570					1575			

Ser	Thr	Leu	Arg	Met	Glu	Leu	Met	Gly	Cys	Asp	Leu	Asn	Ser	Cys
1580						1585					1590			

Ser	Met	Pro	Leu	Gly	Met	Glu	Ser	Lys	Ala	Ile	Ser	Asp	Ala	Gln
1595						1600					1605			

Ile	Thr	Ala	Ser	Ser	Tyr	Phe	Thr	Asn	Met	Phe	Ala	Thr	Trp	Ser
1610						1615					1620			

Pro	Ser	Lys	Ala	Arg	Leu	His	Leu	Gln	Gly	Arg	Ser	Asn	Ala	Trp
1625						1630					1635			

Arg	Pro	Gln	Val	Asn	Asn	Pro	Lys	Glu	Trp	Leu	Gln	Val	Asp	Phe
1640						1645					1650			

Gln	Lys	Thr	Met	Lys	Val	Thr	Gly	Val	Thr	Thr	Gln	Gly	Val	Lys
1655						1660					1665			

Ser	Leu	Leu	Thr	Ser	Met	Tyr	Val	Lys	Glu	Phe	Leu	Ile	Ser	Ser
1670						1675					1680			

Ser	Gln	Asp	Gly	His	Gln	Trp	Thr	Leu	Phe	Phe	Gln	Asn	Gly	Lys
1685						1690					1695			

Val	Lys	Val	Phe	Gln	Gly	Asn	Gln	Asp	Ser	Phe	Thr	Pro	Val	Val
1700						1705					1710			

Asn	Ser	Leu	Asp	Pro	Pro	Leu	Leu	Thr	Arg	Tyr	Leu	Arg	Ile	His
1715						1720					1725			

Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu Val Leu
1730 1735 1740

Gly Cys Glu Ala Gln Asp Leu Tyr Asp Lys Thr His Thr Cys Pro
1745 1750 1755

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
1760 1765 1770

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
1775 1780 1785

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
1790 1795 1800

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
1805 1810 1815

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
1820 1825 1830

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
1835 1840 1845

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
1850 1855 1860

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
1865 1870 1875

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
1880 1885 1890

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 1895 1900 1905

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 1910 1915 1920

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 1925 1930 1935

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
 1940 1945 1950

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 1955 1960 1965

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 1970 1975

<210> 71
 <211> 2242
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> pSYN-FVIII-170

<400> 71

Ser Leu Ser Cys Arg Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp
 1 5 10 15

Asn Leu Arg Ala Glu Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr
 20 25 30

Asp Leu Glu Cys Met Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro
 35 40 45

Pro Gly Met Val Arg His Glu Asn Arg Cys Val Ala Leu Glu Arg Cys
50 55 60

Pro Cys Phe His Gln Gly Lys Glu Tyr Ala Pro Gly Glu Thr Val Lys
65 70 75 80

Ile Gly Cys Asn Thr Cys Val Cys Arg Asp Arg Lys Trp Asn Cys Thr
85 90 95

Asp His Val Cys Asp Ala Thr Cys Ser Thr Ile Gly Met Ala His Tyr
100 105 110

Leu Thr Phe Asp Gly Leu Lys Tyr Leu Phe Pro Gly Glu Cys Gln Tyr
115 120 125

Val Leu Val Gln Asp Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile
130 135 140

Leu Val Gly Asn Lys Gly Cys Ser His Pro Ser Val Lys Cys Lys Lys
145 150 155 160

Arg Val Thr Ile Leu Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly
165 170 175

Glu Val Asn Val Lys Arg Pro Met Lys Asp Glu Thr His Phe Glu Val
180 185 190

Val Glu Ser Gly Arg Tyr Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser
195 200 205

Val Val Trp Asp Arg His Leu Ser Ile Ser Val Val Leu Lys Gln Thr
210 215 220

Tyr Gln Glu Lys Val Cys Gly Leu Cys Gly Asn Phe Asp Gly Ile Gln
225 230 235 240

Asn Asn Asp Leu Thr Ser Ser Asn Leu Gln Val Glu Glu Asp Pro Val
245 250 255

Asp Phe Gly Asn Ser Trp Lys Val Ser Ser Gln Cys Ala Asp Thr Arg
260 265 270

Lys Val Pro Leu Asp Ser Ser Pro Ala Thr Cys His Asn Asn Ile Met
275 280 285

Lys Gln Thr Met Val Asp Ser Ser Cys Arg Ile Leu Thr Ser Asp Val
290 295 300

Phe Gln Asp Cys Asn Lys Leu Val Asp Pro Glu Pro Tyr Leu Asp Val
305 310 315 320

Cys Ile Tyr Asp Thr Cys Ser Cys Glu Ser Ile Gly Asp Cys Ala Ala
325 330 335

Phe Cys Asp Thr Ile Ala Ala Tyr Ala His Val Cys Ala Gln His Gly
340 345 350

Lys Val Val Thr Trp Arg Thr Ala Thr Leu Cys Pro Gln Ser Cys Glu
355 360 365

Glu Arg Asn Leu Arg Glu Asn Gly Tyr Glu Ala Glu Trp Arg Tyr Asn
370 375 380

Ser Cys Ala Pro Ala Cys Gln Val Thr Cys Gln His Pro Glu Pro Leu
385 390 395 400

Ala Cys Pro Val Gln Cys Val Glu Gly Cys His Ala His Cys Pro Pro
 405 410 415

Gly Lys Ile Leu Asp Glu Leu Leu Gln Thr Cys Val Asp Pro Glu Asp
 420 425 430

Cys Pro Val Cys Glu Val Ala Gly Arg Arg Phe Ala Ser Gly Lys Lys
 435 440 445

Val Thr Leu Asn Pro Ser Asp Pro Glu His Cys Gln Ile Cys His Cys
 450 455 460

Asp Val Val Asn Leu Thr Cys Glu Ala Cys Gln Glu Pro Ile Ser Gly
 465 470 475 480

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 485 490 495

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 500 505 510

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 515 520 525

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu
 530 535 540

Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 545 550 555 560

Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 565 570 575

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser

580

585

590

Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 595 600 605

Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
 610 615 620

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser
 625 630 635 640

Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 645 650 655

Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 660 665 670

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala
 675 680 685

Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 690 695 700

Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 705 710 715 720

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala
 725 730 735

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 740 745 750

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Asp
 755 760 765

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
770 775 780

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Val Pro Arg Gly Ser
785 790 795 800

Gly Gly Ala Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu
805 810 815

Ser Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala
820 825 830

Arg Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val
835 840 845

Val Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn
850 855 860

Ile Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile
865 870 875 880

Gln Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala
885 890 895

Ser His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala
900 905 910

Ser Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu
915 920 925

Asp Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val
930 935 940

Leu Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr
 945 950 955 960

Ser Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu
 965 970 975

Ile Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys
 980 985 990

Thr Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu
 995 1000 1005

Gly Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp
 1010 1015 1020

Arg Asp Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val
 1025 1030 1035

Asn Gly Tyr Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His
 1040 1045 1050

Arg Lys Ser Val Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro
 1055 1060 1065

Glu Val His Ser Ile Phe Leu Glu Gly His Thr Phe Leu Val Arg
 1070 1075 1080

Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile Thr Phe Leu
 1085 1090 1095

Thr Ala Gln Thr Leu Leu Met Asp Leu Gly Gln Phe Leu Leu Phe
 1100 1105 1110

Cys	His	Ile	Ser	Ser	His	Gln	His	Asp	Gly	Met	Glu	Ala	Tyr	Val
1115						1120					1125			
Lys	Val	Asp	Ser	Cys	Pro	Glu	Glu	Pro	Gln	Leu	Arg	Met	Lys	Asn
1130						1135					1140			
Asn	Glu	Glu	Ala	Glu	Asp	Tyr	Asp	Asp	Asp	Leu	Thr	Asp	Ser	Glu
1145						1150					1155			
Met	Asp	Val	Val	Arg	Phe	Asp	Asp	Asp	Asn	Ser	Pro	Ser	Phe	Ile
1160						1165					1170			
Gln	Ile	Arg	Ser	Val	Ala	Lys	Lys	His	Pro	Lys	Thr	Trp	Val	His
1175						1180					1185			
Tyr	Ile	Ala	Ala	Glu	Glu	Glu	Asp	Trp	Asp	Tyr	Ala	Pro	Leu	Val
1190						1195					1200			
Leu	Ala	Pro	Asp	Asp	Arg	Ser	Tyr	Lys	Ser	Gln	Tyr	Leu	Asn	Asn
1205						1210					1215			
Gly	Pro	Gln	Arg	Ile	Gly	Arg	Lys	Tyr	Lys	Lys	Val	Arg	Phe	Met
1220						1225					1230			
Ala	Tyr	Thr	Asp	Glu	Thr	Phe	Lys	Thr	Arg	Glu	Ala	Ile	Gln	His
1235						1240					1245			
Glu	Ser	Gly	Ile	Leu	Gly	Pro	Leu	Leu	Tyr	Gly	Glu	Val	Gly	Asp
1250						1255					1260			
Thr	Leu	Leu	Ile	Ile	Phe	Lys	Asn	Gln	Ala	Ser	Arg	Pro	Tyr	Asn
1265						1270					1275			
Ile	Tyr	Pro	His	Gly	Ile	Thr	Asp	Val	Arg	Pro	Leu	Tyr	Ser	Arg

1280						1285						1290			
Arg	Leu	Pro	Lys	Gly	Val	Lys	His	Leu	Lys	Asp	Phe	Pro	Ile	Leu	
1295						1300					1305				
Pro	Gly	Glu	Ile	Phe	Lys	Tyr	Lys	Trp	Thr	Val	Thr	Val	Glu	Asp	
1310						1315					1320				
Gly	Pro	Thr	Lys	Ser	Asp	Pro	Arg	Cys	Leu	Thr	Arg	Tyr	Tyr	Ser	
1325						1330					1335				
Ser	Phe	Val	Asn	Met	Glu	Arg	Asp	Leu	Ala	Ser	Gly	Leu	Ile	Gly	
1340						1345					1350				
Pro	Leu	Leu	Ile	Cys	Tyr	Lys	Glu	Ser	Val	Asp	Gln	Arg	Gly	Asn	
1355						1360					1365				
Gln	Ile	Met	Ser	Asp	Lys	Arg	Asn	Val	Ile	Leu	Phe	Ser	Val	Phe	
1370						1375					1380				
Asp	Glu	Asn	Arg	Ser	Trp	Tyr	Leu	Thr	Glu	Asn	Ile	Gln	Arg	Phe	
1385						1390					1395				
Leu	Pro	Asn	Pro	Ala	Gly	Val	Gln	Leu	Glu	Asp	Pro	Glu	Phe	Gln	
1400						1405					1410				
Ala	Ser	Asn	Ile	Met	His	Ser	Ile	Asn	Gly	Tyr	Val	Phe	Asp	Ser	
1415						1420					1425				
Leu	Gln	Leu	Ser	Val	Cys	Leu	His	Glu	Val	Ala	Tyr	Trp	Tyr	Ile	
1430						1435					1440				
Leu	Ser	Ile	Gly	Ala	Gln	Thr	Asp	Phe	Leu	Ser	Val	Phe	Phe	Ser	
1445						1450					1455				

Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
 1460 1465 1470

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn
 1475 1480 1485

Pro Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn
 1490 1495 1500

Arg Gly Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn
 1505 1510 1515

Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr
 1520 1525 1530

Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln
 1535 1540 1545

Asn Pro Pro Val Leu Lys Arg His Gln Arg Glu Ile Thr Arg Thr
 1550 1555 1560

Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile
 1565 1570 1575

Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp
 1580 1585 1590

Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr
 1595 1600 1605

Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser
 1610 1615 1620

Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser Val Pro
1625 1630 1635

Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser Phe
1640 1645 1650

Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
1655 1660 1665

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val
1670 1675 1680

Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser
1685 1690 1695

Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg
1700 1705 1710

Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys
1715 1720 1725

Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys
1730 1735 1740

Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His
1745 1750 1755

Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu
1760 1765 1770

Asn Pro Ala His Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu
1775 1780 1785

Phe 1790	Phe	Thr	Ile	Phe	Asp	Glu 1795	Thr	Lys	Ser	Trp	Tyr 1800	Phe	Thr	Glu
Asn 1805	Met	Glu	Arg	Asn	Cys	Arg 1810	Ala	Pro	Cys	Asn	Ile 1815	Gln	Met	Glu
Asp 1820	Pro	Thr	Phe	Lys	Glu	Asn 1825	Tyr	Arg	Phe	His	Ala 1830	Ile	Asn	Gly
Tyr 1835	Ile	Met	Asp	Thr	Leu	Pro 1840	Gly	Leu	Val	Met	Ala 1845	Gln	Asp	Gln
Arg 1850	Ile	Arg	Trp	Tyr	Leu	Leu 1855	Ser	Met	Gly	Ser	Asn 1860	Glu	Asn	Ile
His 1865	Ser	Ile	His	Phe	Ser	Gly 1870	His	Val	Phe	Thr	Val 1875	Arg	Lys	Lys
Glu 1880	Glu	Tyr	Lys	Met	Ala	Leu 1885	Tyr	Asn	Leu	Tyr	Pro 1890	Gly	Val	Phe
Glu 1895	Thr	Val	Glu	Met	Leu	Pro 1900	Ser	Lys	Ala	Gly	Ile 1905	Trp	Arg	Val
Glu 1910	Cys	Leu	Ile	Gly	Glu	His 1915	Leu	His	Ala	Gly	Met 1920	Ser	Thr	Leu
Phe 1925	Leu	Val	Tyr	Ser	Asn	Lys 1930	Cys	Gln	Thr	Pro	Leu 1935	Gly	Met	Ala
Ser 1940	Gly	His	Ile	Arg	Asp	Phe 1945	Gln	Ile	Thr	Ala	Ser 1950	Gly	Gln	Tyr
Gly	Gln	Trp	Ala	Pro	Lys	Leu	Ala	Arg	Leu	His	Tyr	Ser	Gly	Ser

1955						1960						1965					
Ile	Asn	Ala	Trp	Ser	Thr	Lys	Glu	Pro	Phe	Ser	Trp	Ile	Lys	Val			
1970						1975					1980						
Asp	Leu	Leu	Ala	Pro	Met	Ile	Ile	His	Gly	Ile	Lys	Thr	Gln	Gly			
1985						1990					1995						
Ala	Arg	Gln	Lys	Phe	Ser	Ser	Leu	Tyr	Ile	Ser	Gln	Phe	Ile	Ile			
2000						2005					2010						
Met	Tyr	Ser	Leu	Asp	Gly	Lys	Lys	Trp	Gln	Thr	Tyr	Arg	Gly	Asn			
2015						2020					2025						
Ser	Thr	Gly	Thr	Leu	Met	Val	Phe	Phe	Gly	Asn	Val	Asp	Ser	Ser			
2030						2035					2040						
Gly	Ile	Lys	His	Asn	Ile	Phe	Asn	Pro	Pro	Ile	Ile	Ala	Arg	Tyr			
2045						2050					2055						
Ile	Arg	Leu	His	Pro	Thr	His	Tyr	Ser	Ile	Arg	Ser	Thr	Leu	Arg			
2060						2065					2070						
Met	Glu	Leu	Met	Gly	Cys	Asp	Leu	Asn	Ser	Cys	Ser	Met	Pro	Leu			
2075						2080					2085						
Gly	Met	Glu	Ser	Lys	Ala	Ile	Ser	Asp	Ala	Gln	Ile	Thr	Ala	Ser			
2090						2095					2100						
Ser	Tyr	Phe	Thr	Asn	Met	Phe	Ala	Thr	Trp	Ser	Pro	Ser	Lys	Ala			
2105						2110					2115						
Arg	Leu	His	Leu	Gln	Gly	Arg	Ser	Asn	Ala	Trp	Arg	Pro	Gln	Val			
2120						2125					2130						

Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met
 2135 2140 2145

Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu Leu Thr
 2150 2155 2160

Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly
 2165 2170 2175

His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe
 2180 2185 2190

Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val Asn Ser Leu Asp
 2195 2200 2205

Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His Pro Gln Ser Trp
 2210 2215 2220

Val His Gln Ile Ala Leu Arg Met Glu Val Leu Gly Cys Glu Ala
 2225 2230 2235

Gln Asp Leu Tyr
 2240

<210> 72

<211> 1959

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN-FVIII-173

<400> 72

Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Leu Leu Lys Val Ser Ser Cys Asp Lys 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

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
900 905 910

Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
 915 920 925

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
 930 935 940

Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly
 945 950 955 960

Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
 965 970 975

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
 980 985 990

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly
 995 1000 1005

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 1010 1015 1020

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala Ser
 1025 1030 1035

Ser Pro Pro Val Leu Lys Arg His Gln Arg Glu Ile Thr Arg Thr
 1040 1045 1050

Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile
 1055 1060 1065

Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp
 1070 1075 1080

Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr
 1085 1090 1095

Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser
 1100 1105 1110

Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser Val Pro
 1115 1120 1125

Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser Phe
 1130 1135 1140

Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu
 1145 1150 1155

Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val
 1160 1165 1170

Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser
 1175 1180 1185

Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg
 1190 1195 1200

Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys
 1205 1210 1215

Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys
 1220 1225 1230

Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His
 1235 1240 1245

Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu
 1250 1255 1260

Asn Pro Ala His Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu
 1265 1270 1275

Phe Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu
 1280 1285 1290

Asn Met Glu Arg Asn Cys Arg Ala Pro Cys Asn Ile Gln Met Glu
 1295 1300 1305

Asp Pro Thr Phe Lys Glu Asn Tyr Arg Phe His Ala Ile Asn Gly
 1310 1315 1320

Tyr Ile Met Asp Thr Leu Pro Gly Leu Val Met Ala Gln Asp Gln
 1325 1330 1335

Arg Ile Arg Trp Tyr Leu Leu Ser Met Gly Ser Asn Glu Asn Ile
 1340 1345 1350

His Ser Ile His Phe Ser Gly His Val Phe Thr Val Arg Lys Lys
 1355 1360 1365

Glu Glu Tyr Lys Met Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe
 1370 1375 1380

Glu Thr Val Glu Met Leu Pro Ser Lys Ala Gly Ile Trp Arg Val
 1385 1390 1395

Glu Cys Leu Ile Gly Glu His Leu His Ala Gly Met Ser Thr Leu
 1400 1405 1410

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

1415

1420

1425

Ser Gly His Ile Arg Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr
 1430 1435 1440

Gly Gln Trp Ala Pro Lys Leu Ala Arg Leu His Tyr Ser Gly Ser
 1445 1450 1455

Ile Asn Ala Trp Ser Thr Lys Glu Pro Phe Ser Trp Ile Lys Val
 1460 1465 1470

Asp Leu Leu Ala Pro Met Ile Ile His Gly Ile Lys Thr Gln Gly
 1475 1480 1485

Ala Arg Gln Lys Phe Ser Ser Leu Tyr Ile Ser Gln Phe Ile Ile
 1490 1495 1500

Met Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn
 1505 1510 1515

Ser Thr Gly Thr Leu Met Val Phe Phe Gly Asn Val Asp Ser Ser
 1520 1525 1530

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

Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg Ser Thr Leu Arg
 1550 1555 1560

Met Glu Leu Met Gly Cys Asp Leu Asn Ser Cys Ser Met Pro Leu
 1565 1570 1575

Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser
 1580 1585 1590

Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser Pro Ser Lys Ala
1595 1600 1605

Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln Val
1610 1615 1620

Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met
1625 1630 1635

Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu Leu Thr
1640 1645 1650

Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly
1655 1660 1665

His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe
1670 1675 1680

Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val Asn Ser Leu Asp
1685 1690 1695

Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His Pro Gln Ser Trp
1700 1705 1710

Val His Gln Ile Ala Leu Arg Met Glu Val Leu Gly Cys Glu Ala
1715 1720 1725

Gln Asp Leu Tyr Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1730 1735 1740

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1745 1750 1755

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
1760 1765 1770

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
1775 1780 1785

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
1790 1795 1800

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
1805 1810 1815

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
1820 1825 1830

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
1835 1840 1845

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
1850 1855 1860

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
1865 1870 1875

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
1880 1885 1890

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
1895 1900 1905

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
1910 1915 1920

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
 1925 1930 1935

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
 1940 1945 1950

Ser Leu Ser Pro Gly Lys
 1955

<210> 73

<211> 1984

<212> PRT

<213> Artificial Sequence

<220>

<223> FVIII 195 (dual chain FVIIIIFc with two 144 AE XTENS at amino
 acid
 1656 and 1900)

<400> 73

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

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

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
 50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
 65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln

85

90

95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
 100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
 115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
 130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
 145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
 165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
 180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
 195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
 210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
 225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
 245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
 260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
 275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
 290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
 305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
 325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
 340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
 355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
 370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
 385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
 405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
 420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
 435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
450 455 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
515 520 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
545 550 555 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
565 570 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
580 585 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
595 600 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
610 615 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625 630 635 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
645 650 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
660 665 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
675 680 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu
755 760 765

Lys Arg His Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Gly Ala Pro
770 775 780

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala Ser Pro
785 790 795 800

Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser

Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val
980 985 990

Leu Arg Asn Arg Ala Gln Ser Gly Ser Val Pro Gln Phe Lys Lys Val
 995 1000 1005

Val Phe Gln Glu Phe Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr
 1010 1015 1020

Arg Gly Glu Leu Asn Glu His Leu Gly Leu Leu Gly Pro Tyr Ile
 1025 1030 1035

Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr Phe Arg Asn Gln
 1040 1045 1050

Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Glu
 1055 1060 1065

Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys
 1070 1075 1080

Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His Met
 1085 1090 1095

Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
 1100 1105 1110

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly
 1115 1120 1125

Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly
 1130 1135 1140

Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe
 1145 1150 1155

Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn
 1160 1165 1170

Cys Arg Gly Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 1175 1180 1185

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
 1190 1195 1200

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 1205 1210 1215

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
 1220 1225 1230

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
 1235 1240 1245

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
 1250 1255 1260

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly
 1265 1270 1275

Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr
 1280 1285 1290

Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 1295 1300 1305

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala
 1310 1315 1320

Ser Ser Ala Pro Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys
1325 1330 1335

Glu Asn Tyr Arg Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr
1340 1345 1350

Leu Pro Gly Leu Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr
1355 1360 1365

Leu Leu Ser Met Gly Ser Asn Glu Asn Ile His Ser Ile His Phe
1370 1375 1380

Ser Gly His Val Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met
1385 1390 1395

Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met
1400 1405 1410

Leu Pro Ser Lys Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly
1415 1420 1425

Glu His Leu His Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser
1430 1435 1440

Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg
1445 1450 1455

Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro
1460 1465 1470

Lys Leu Ala Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser
1475 1480 1485

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

1490

1495

1500

Met Ile Ile His Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe
 1505 1510 1515

Ser Ser Leu Tyr Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp
 1520 1525 1530

Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu
 1535 1540 1545

Met Val Phe Phe Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn
 1550 1555 1560

Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro
 1565 1570 1575

Thr His Tyr Ser Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly
 1580 1585 1590

Cys Asp Leu Asn Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys
 1595 1600 1605

Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn
 1610 1615 1620

Met Phe Ala Thr Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln
 1625 1630 1635

Gly Arg Ser Asn Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu
 1640 1645 1650

Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val
 1655 1660 1665

Thr Thr Gln Gly Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys
 1670 1675 1680

Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu
 1685 1690 1695

Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp
 1700 1705 1710

Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr
 1715 1720 1725

Arg Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala
 1730 1735 1740

Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr Asp
 1745 1750 1755

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
 1760 1765 1770

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 1775 1780 1785

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
 1790 1795 1800

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
 1805 1810 1815

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
 1820 1825 1830

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 1835 1840 1845

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 1850 1855 1860

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 1865 1870 1875

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 1880 1885 1890

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 1895 1900 1905

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 1910 1915 1920

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
 1925 1930 1935

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 1940 1945 1950

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 1955 1960 1965

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 1970 1975 1980

Lys

<210> 74
 <211> 2134
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> FVIII 196 (dual chain FVIIIIFc with three 144 AE XTENS at
 amino
 acid 26, 1656 and 1900)

<400> 74

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Gly Ala Pro
 35 40 45

Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser Pro
 50 55 60

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser
 65 70 75 80

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
 85 90 95

Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Pro
 100 105 110

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser
 115 120 125

Thr Gly Ser Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro

130

135

140

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr
 145 150 155 160

Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala
 165 170 175

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
 180 185 190

Ala Ser Ser Asp Ala Arg Phe Pro Pro Arg Val Pro Lys Ser Phe Pro
 195 200 205

Phe Asn Thr Ser Val Val Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr
 210 215 220

Asp His Leu Phe Asn Ile Ala Lys Pro Arg Pro Pro Trp Met Gly Leu
 225 230 235 240

Leu Gly Pro Thr Ile Gln Ala Glu Val Tyr Asp Thr Val Val Ile Thr
 245 250 255

Leu Lys Asn Met Ala Ser His Pro Val Ser Leu His Ala Val Gly Val
 260 265 270

Ser Tyr Trp Lys Ala Ser Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser
 275 280 285

Gln Arg Glu Lys Glu Asp Asp Lys Val Phe Pro Gly Gly Ser His Thr
 290 295 300

Tyr Val Trp Gln Val Leu Lys Glu Asn Gly Pro Met Ala Ser Asp Pro
 305 310 315 320

Leu Cys Leu Thr Tyr Ser Tyr Leu Ser His Val Asp Leu Val Lys Asp
 325 330 335

Leu Asn Ser Gly Leu Ile Gly Ala Leu Leu Val Cys Arg Glu Gly Ser
 340 345 350

Leu Ala Lys Glu Lys Thr Gln Thr Leu His Lys Phe Ile Leu Leu Phe
 355 360 365

Ala Val Phe Asp Glu Gly Lys Ser Trp His Ser Glu Thr Lys Asn Ser
 370 375 380

Leu Met Gln Asp Arg Asp Ala Ala Ser Ala Arg Ala Trp Pro Lys Met
 385 390 395 400

His Thr Val Asn Gly Tyr Val Asn Arg Ser Leu Pro Gly Leu Ile Gly
 405 410 415

Cys His Arg Lys Ser Val Tyr Trp His Val Ile Gly Met Gly Thr Thr
 420 425 430

Pro Glu Val His Ser Ile Phe Leu Glu Gly His Thr Phe Leu Val Arg
 435 440 445

Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr
 450 455 460

Ala Gln Thr Leu Leu Met Asp Leu Gly Gln Phe Leu Leu Phe Cys His
 465 470 475 480

Ile Ser Ser His Gln His Asp Gly Met Glu Ala Tyr Val Lys Val Asp
 485 490 495

Ser Cys Pro Glu Glu Pro Gln Leu Arg Met Lys Asn Asn Glu Glu Ala
500 505 510

Glu Asp Tyr Asp Asp Asp Leu Thr Asp Ser Glu Met Asp Val Val Arg
515 520 525

Phe Asp Asp Asp Asn Ser Pro Ser Phe Ile Gln Ile Arg Ser Val Ala
530 535 540

Lys Lys His Pro Lys Thr Trp Val His Tyr Ile Ala Ala Glu Glu Glu
545 550 555 560

Asp Trp Asp Tyr Ala Pro Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr
565 570 575

Lys Ser Gln Tyr Leu Asn Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr
580 585 590

Lys Lys Val Arg Phe Met Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg
595 600 605

Glu Ala Ile Gln His Glu Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly
610 615 620

Glu Val Gly Asp Thr Leu Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg
625 630 635 640

Pro Tyr Asn Ile Tyr Pro His Gly Ile Thr Asp Val Arg Pro Leu Tyr
645 650 655

Ser Arg Arg Leu Pro Lys Gly Val Lys His Leu Lys Asp Phe Pro Ile
660 665 670

Leu Pro Gly Glu Ile Phe Lys Tyr Lys Trp Thr Val Thr Val Glu Asp
 675 680 685

Gly Pro Thr Lys Ser Asp Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser
 690 695 700

Phe Val Asn Met Glu Arg Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu
 705 710 715 720

Leu Ile Cys Tyr Lys Glu Ser Val Asp Gln Arg Gly Asn Gln Ile Met
 725 730 735

Ser Asp Lys Arg Asn Val Ile Leu Phe Ser Val Phe Asp Glu Asn Arg
 740 745 750

Ser Trp Tyr Leu Thr Glu Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala
 755 760 765

Gly Val Gln Leu Glu Asp Pro Glu Phe Gln Ala Ser Asn Ile Met His
 770 775 780

Ser Ile Asn Gly Tyr Val Phe Asp Ser Leu Gln Leu Ser Val Cys Leu
 785 790 795 800

His Glu Val Ala Tyr Trp Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp
 805 810 815

Phe Leu Ser Val Phe Phe Ser Gly Tyr Thr Phe Lys His Lys Met Val
 820 825 830

Tyr Glu Asp Thr Leu Thr Leu Phe Pro Phe Ser Gly Glu Thr Val Phe
 835 840 845

Met Ser Met Glu Asn Pro Gly Leu Trp Ile Leu Gly Cys His Asn Ser

850

855

860

Asp Phe Arg Asn Arg Gly Met Thr Ala Leu Leu Lys Val Ser Ser Cys
 865 870 875 880

Asp Lys Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser
 885 890 895

Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
 900 905 910

Gln Asn Pro Pro Val Leu Lys Arg His Gln Arg Glu Ile Thr Arg Thr
 915 920 925

Thr Leu Gln Gly Ala Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser
 930 935 940

Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala
 945 950 955 960

Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr
 965 970 975

Ser Ser Thr Gly Ser Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr
 980 985 990

Gly Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala
 995 1000 1005

Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly
 1010 1015 1020

Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
 1025 1030 1035

Thr	Gly	Ser	Pro	Gly	Ser	Ser	Thr	Pro	Ser	Gly	Ala	Thr	Gly	Ser
	1040					1045					1050			
Pro	Gly	Ser	Ser	Thr	Pro	Ser	Gly	Ala	Thr	Gly	Ser	Pro	Gly	Ala
	1055					1060					1065			
Ser	Pro	Gly	Thr	Ser	Ser	Thr	Gly	Ser	Pro	Ala	Ser	Ser	Ser	Asp
	1070					1075					1080			
Gln	Glu	Glu	Ile	Asp	Tyr	Asp	Asp	Thr	Ile	Ser	Val	Glu	Met	Lys
	1085					1090					1095			
Lys	Glu	Asp	Phe	Asp	Ile	Tyr	Asp	Glu	Asp	Glu	Asn	Gln	Ser	Pro
	1100					1105					1110			
Arg	Ser	Phe	Gln	Lys	Lys	Thr	Arg	His	Tyr	Phe	Ile	Ala	Ala	Val
	1115					1120					1125			
Glu	Arg	Leu	Trp	Asp	Tyr	Gly	Met	Ser	Ser	Ser	Pro	His	Val	Leu
	1130					1135					1140			
Arg	Asn	Arg	Ala	Gln	Ser	Gly	Ser	Val	Pro	Gln	Phe	Lys	Lys	Val
	1145					1150					1155			
Val	Phe	Gln	Glu	Phe	Thr	Asp	Gly	Ser	Phe	Thr	Gln	Pro	Leu	Tyr
	1160					1165					1170			
Arg	Gly	Glu	Leu	Asn	Glu	His	Leu	Gly	Leu	Leu	Gly	Pro	Tyr	Ile
	1175					1180					1185			
Arg	Ala	Glu	Val	Glu	Asp	Asn	Ile	Met	Val	Thr	Phe	Arg	Asn	Gln
	1190					1195					1200			

Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Glu
1205 1210 1215

Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys
1220 1225 1230

Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His Met
1235 1240 1245

Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
1250 1255 1260

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly
1265 1270 1275

Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly
1280 1285 1290

Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe
1295 1300 1305

Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn
1310 1315 1320

Cys Arg Gly Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
1325 1330 1335

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
1340 1345 1350

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
1355 1360 1365

Thr 1370	Ser	Gly	Ser	Glu	Thr	Pro 1375	Gly	Thr	Ser	Glu	Ser 1380	Ala	Thr	Pro
Glu 1385	Ser	Gly	Pro	Gly	Thr	Ser 1390	Thr	Glu	Pro	Ser	Glu 1395	Gly	Ser	Ala
Pro 1400	Gly	Thr	Ser	Glu	Ser	Ala 1405	Thr	Pro	Glu	Ser	Gly 1410	Pro	Gly	Ser
Pro 1415	Ala	Gly	Ser	Pro	Thr	Ser 1420	Thr	Glu	Glu	Gly	Ser 1425	Pro	Ala	Gly
Ser 1430	Pro	Thr	Ser	Thr	Glu	Glu 1435	Gly	Ser	Pro	Ala	Gly 1440	Ser	Pro	Thr
Ser 1445	Thr	Glu	Glu	Gly	Thr	Ser 1450	Glu	Ser	Ala	Thr	Pro 1455	Glu	Ser	Gly
Pro 1460	Gly	Thr	Ser	Thr	Glu	Pro 1465	Ser	Glu	Gly	Ser	Ala 1470	Pro	Gly	Ala
Ser 1475	Ser	Ala	Pro	Cys	Asn	Ile 1480	Gln	Met	Glu	Asp	Pro 1485	Thr	Phe	Lys
Glu 1490	Asn	Tyr	Arg	Phe	His	Ala 1495	Ile	Asn	Gly	Tyr	Ile 1500	Met	Asp	Thr
Leu 1505	Pro	Gly	Leu	Val	Met	Ala 1510	Gln	Asp	Gln	Arg	Ile 1515	Arg	Trp	Tyr
Leu 1520	Leu	Ser	Met	Gly	Ser	Asn 1525	Glu	Asn	Ile	His	Ser 1530	Ile	His	Phe
Ser	Gly	His	Val	Phe	Thr	Val	Arg	Lys	Lys	Glu	Glu	Tyr	Lys	Met

1535

1540

1545

Ala	Leu	Tyr	Asn	Leu	Tyr	Pro	Gly	Val	Phe	Glu	Thr	Val	Glu	Met
1550						1555					1560			

Leu	Pro	Ser	Lys	Ala	Gly	Ile	Trp	Arg	Val	Glu	Cys	Leu	Ile	Gly
1565						1570					1575			

Glu	His	Leu	His	Ala	Gly	Met	Ser	Thr	Leu	Phe	Leu	Val	Tyr	Ser
1580						1585					1590			

Asn	Lys	Cys	Gln	Thr	Pro	Leu	Gly	Met	Ala	Ser	Gly	His	Ile	Arg
1595						1600					1605			

Asp	Phe	Gln	Ile	Thr	Ala	Ser	Gly	Gln	Tyr	Gly	Gln	Trp	Ala	Pro
1610						1615					1620			

Lys	Leu	Ala	Arg	Leu	His	Tyr	Ser	Gly	Ser	Ile	Asn	Ala	Trp	Ser
1625						1630					1635			

Thr	Lys	Glu	Pro	Phe	Ser	Trp	Ile	Lys	Val	Asp	Leu	Leu	Ala	Pro
1640						1645					1650			

Met	Ile	Ile	His	Gly	Ile	Lys	Thr	Gln	Gly	Ala	Arg	Gln	Lys	Phe
1655						1660					1665			

Ser	Ser	Leu	Tyr	Ile	Ser	Gln	Phe	Ile	Ile	Met	Tyr	Ser	Leu	Asp
1670						1675					1680			

Gly	Lys	Lys	Trp	Gln	Thr	Tyr	Arg	Gly	Asn	Ser	Thr	Gly	Thr	Leu
1685						1690					1695			

Met	Val	Phe	Phe	Gly	Asn	Val	Asp	Ser	Ser	Gly	Ile	Lys	His	Asn
1700						1705					1710			

Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro
 1715 1720 1725

Thr His Tyr Ser Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly
 1730 1735 1740

Cys Asp Leu Asn Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys
 1745 1750 1755

Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn
 1760 1765 1770

Met Phe Ala Thr Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln
 1775 1780 1785

Gly Arg Ser Asn Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu
 1790 1795 1800

Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val
 1805 1810 1815

Thr Thr Gln Gly Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys
 1820 1825 1830

Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu
 1835 1840 1845

Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp
 1850 1855 1860

Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr
 1865 1870 1875

Arg Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala
1880 1885 1890

Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr Asp
1895 1900 1905

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1910 1915 1920

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
1925 1930 1935

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
1940 1945 1950

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
1955 1960 1965

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
1970 1975 1980

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
1985 1990 1995

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
2000 2005 2010

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
2015 2020 2025

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
2030 2035 2040

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 2045 2050 2055

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 2060 2065 2070

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
 2075 2080 2085

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 2090 2095 2100

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 2105 2110 2115

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 2120 2125 2130

Lys

<210> 75
 <211> 1984
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> FVIII 199 (single chain FVIIIIFc with three 144 AE XTENS at
 amino acid 1656 and 1900)

<400> 75

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser

20

25

30

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

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
 50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
 65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
 85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
 100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
 115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
 130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
 145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
 165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
 180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
 195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
 210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
 225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
 245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
 260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
 275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
 290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
 305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
 325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
 340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
 355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
 370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
 385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
 405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
 420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
 435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
 450 455 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
 465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
 485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
 500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
 515 520 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
 530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
 545 550 555 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
 565 570 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
 580 585 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
 595 600 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
 610 615 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
 625 630 635 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
 645 650 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
 660 665 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
 675 680 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
 690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
 705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
 725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys

740

745

750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu
 755 760 765

Lys Arg His Gln Ala Glu Ile Thr Arg Thr Thr Leu Gln Gly Ala Pro
 770 775 780

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala Ser Pro
 785 790 795 800

Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
 805 810 815

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
 820 825 830

Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Thr Pro Gly
 835 840 845

Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
 850 855 860

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
 865 870 875 880

Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ser Ser Thr
 885 890 895

Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala
 900 905 910

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
 915 920 925

Ala Ser Ser Ser Asp Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser
 930 935 940

Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn
 945 950 955 960

Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala
 965 970 975

Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val
 980 985 990

Leu Arg Asn Arg Ala Gln Ser Gly Ser Val Pro Gln Phe Lys Lys Val
 995 1000 1005

Val Phe Gln Glu Phe Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr
 1010 1015 1020

Arg Gly Glu Leu Asn Glu His Leu Gly Leu Leu Gly Pro Tyr Ile
 1025 1030 1035

Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr Phe Arg Asn Gln
 1040 1045 1050

Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Glu
 1055 1060 1065

Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys
 1070 1075 1080

Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His Met
 1085 1090 1095

Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
 1100 1105 1110

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly
 1115 1120 1125

Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly
 1130 1135 1140

Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe
 1145 1150 1155

Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn
 1160 1165 1170

Cys Arg Gly Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 1175 1180 1185

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
 1190 1195 1200

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 1205 1210 1215

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
 1220 1225 1230

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
 1235 1240 1245

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
 1250 1255 1260

Pro 1265	Ala	Gly	Ser	Pro	Thr	Ser 1270	Thr	Glu	Glu	Gly	Ser 1275	Pro	Ala	Gly
Ser 1280	Pro	Thr	Ser	Thr	Glu	Glu 1285	Gly	Ser	Pro	Ala	Gly 1290	Ser	Pro	Thr
Ser 1295	Thr	Glu	Glu	Gly	Thr	Ser 1300	Glu	Ser	Ala	Thr	Pro 1305	Glu	Ser	Gly
Pro 1310	Gly	Thr	Ser	Thr	Glu	Pro 1315	Ser	Glu	Gly	Ser	Ala 1320	Pro	Gly	Ala
Ser 1325	Ser	Ala	Pro	Cys	Asn	Ile 1330	Gln	Met	Glu	Asp	Pro 1335	Thr	Phe	Lys
Glu 1340	Asn	Tyr	Arg	Phe	His	Ala 1345	Ile	Asn	Gly	Tyr	Ile 1350	Met	Asp	Thr
Leu 1355	Pro	Gly	Leu	Val	Met	Ala 1360	Gln	Asp	Gln	Arg	Ile 1365	Arg	Trp	Tyr
Leu 1370	Leu	Ser	Met	Gly	Ser	Asn 1375	Glu	Asn	Ile	His	Ser 1380	Ile	His	Phe
Ser 1385	Gly	His	Val	Phe	Thr	Val 1390	Arg	Lys	Lys	Glu	Glu 1395	Tyr	Lys	Met
Ala 1400	Leu	Tyr	Asn	Leu	Tyr	Pro 1405	Gly	Val	Phe	Glu	Thr 1410	Val	Glu	Met
Leu 1415	Pro	Ser	Lys	Ala	Gly	Ile 1420	Trp	Arg	Val	Glu	Cys 1425	Leu	Ile	Gly
Glu	His	Leu	His	Ala	Gly	Met	Ser	Thr	Leu	Phe	Leu	Val	Tyr	Ser

1430						1435						1440			
Asn	Lys	Cys	Gln	Thr	Pro	Leu	Gly	Met	Ala	Ser	Gly	His	Ile	Arg	
1445						1450					1455				
Asp	Phe	Gln	Ile	Thr	Ala	Ser	Gly	Gln	Tyr	Gly	Gln	Trp	Ala	Pro	
1460						1465					1470				
Lys	Leu	Ala	Arg	Leu	His	Tyr	Ser	Gly	Ser	Ile	Asn	Ala	Trp	Ser	
1475						1480					1485				
Thr	Lys	Glu	Pro	Phe	Ser	Trp	Ile	Lys	Val	Asp	Leu	Leu	Ala	Pro	
1490						1495					1500				
Met	Ile	Ile	His	Gly	Ile	Lys	Thr	Gln	Gly	Ala	Arg	Gln	Lys	Phe	
1505						1510					1515				
Ser	Ser	Leu	Tyr	Ile	Ser	Gln	Phe	Ile	Ile	Met	Tyr	Ser	Leu	Asp	
1520						1525					1530				
Gly	Lys	Lys	Trp	Gln	Thr	Tyr	Arg	Gly	Asn	Ser	Thr	Gly	Thr	Leu	
1535						1540					1545				
Met	Val	Phe	Phe	Gly	Asn	Val	Asp	Ser	Ser	Gly	Ile	Lys	His	Asn	
1550						1555					1560				
Ile	Phe	Asn	Pro	Pro	Ile	Ile	Ala	Arg	Tyr	Ile	Arg	Leu	His	Pro	
1565						1570					1575				
Thr	His	Tyr	Ser	Ile	Arg	Ser	Thr	Leu	Arg	Met	Glu	Leu	Met	Gly	
1580						1585					1590				
Cys	Asp	Leu	Asn	Ser	Cys	Ser	Met	Pro	Leu	Gly	Met	Glu	Ser	Lys	
1595						1600					1605				

Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn
1610 1615 1620

Met Phe Ala Thr Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln
1625 1630 1635

Gly Arg Ser Asn Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu
1640 1645 1650

Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val
1655 1660 1665

Thr Thr Gln Gly Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys
1670 1675 1680

Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu
1685 1690 1695

Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp
1700 1705 1710

Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr
1715 1720 1725

Arg Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala
1730 1735 1740

Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr Asp
1745 1750 1755

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1760 1765 1770

Gly 1775	Pro	Ser	Val	Phe	Leu	Phe 1780	Pro	Pro	Lys	Pro	Lys 1785	Asp	Thr	Leu
Met 1790	Ile	Ser	Arg	Thr	Pro	Glu 1795	Val	Thr	Cys	Val	Val 1800	Val	Asp	Val
Ser 1805	His	Glu	Asp	Pro	Glu	Val 1810	Lys	Phe	Asn	Trp	Tyr 1815	Val	Asp	Gly
Val 1820	Glu	Val	His	Asn	Ala	Lys 1825	Thr	Lys	Pro	Arg	Glu 1830	Glu	Gln	Tyr
Asn 1835	Ser	Thr	Tyr	Arg	Val	Val 1840	Ser	Val	Leu	Thr	Val 1845	Leu	His	Gln
Asp 1850	Trp	Leu	Asn	Gly	Lys	Glu 1855	Tyr	Lys	Cys	Lys	Val 1860	Ser	Asn	Lys
Ala 1865	Leu	Pro	Ala	Pro	Ile	Glu 1870	Lys	Thr	Ile	Ser	Lys 1875	Ala	Lys	Gly
Gln 1880	Pro	Arg	Glu	Pro	Gln	Val 1885	Tyr	Thr	Leu	Pro	Pro 1890	Ser	Arg	Asp
Glu 1895	Leu	Thr	Lys	Asn	Gln	Val 1900	Ser	Leu	Thr	Cys	Leu 1905	Val	Lys	Gly
Phe 1910	Tyr	Pro	Ser	Asp	Ile	Ala 1915	Val	Glu	Trp	Glu	Ser 1920	Asn	Gly	Gln
Pro 1925	Glu	Asn	Asn	Tyr	Lys	Thr 1930	Thr	Pro	Pro	Val	Leu 1935	Asp	Ser	Asp

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 1940 1945 1950

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 1955 1960 1965

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 1970 1975 1980

Lys

<210> 76

<211> 2134

<212> PRT

<213> Artificial Sequence

<220>

<223> FVIII 201 (single chain FVIIIIFc with three 144 AE XTENS at
 amino acid 26, 1656 &1900)

<400> 76

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Gly Ala Pro
 35 40 45

Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser Pro
 50 55 60

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser

Leu Lys Asn Met Ala Ser His Pro Val Ser Leu His Ala Val Gly Val
 260 265 270

Ser Tyr Trp Lys Ala Ser Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser
 275 280 285

Gln Arg Glu Lys Glu Asp Asp Lys Val Phe Pro Gly Gly Ser His Thr
 290 295 300

Tyr Val Trp Gln Val Leu Lys Glu Asn Gly Pro Met Ala Ser Asp Pro
 305 310 315 320

Leu Cys Leu Thr Tyr Ser Tyr Leu Ser His Val Asp Leu Val Lys Asp
 325 330 335

Leu Asn Ser Gly Leu Ile Gly Ala Leu Leu Val Cys Arg Glu Gly Ser
 340 345 350

Leu Ala Lys Glu Lys Thr Gln Thr Leu His Lys Phe Ile Leu Leu Phe
 355 360 365

Ala Val Phe Asp Glu Gly Lys Ser Trp His Ser Glu Thr Lys Asn Ser
 370 375 380

Leu Met Gln Asp Arg Asp Ala Ala Ser Ala Arg Ala Trp Pro Lys Met
 385 390 395 400

His Thr Val Asn Gly Tyr Val Asn Arg Ser Leu Pro Gly Leu Ile Gly
 405 410 415

Cys His Arg Lys Ser Val Tyr Trp His Val Ile Gly Met Gly Thr Thr
 420 425 430

Pro Glu Val His Ser Ile Phe Leu Glu Gly His Thr Phe Leu Val Arg
 435 440 445

Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr
 450 455 460

Ala Gln Thr Leu Leu Met Asp Leu Gly Gln Phe Leu Leu Phe Cys His
 465 470 475 480

Ile Ser Ser His Gln His Asp Gly Met Glu Ala Tyr Val Lys Val Asp
 485 490 495

Ser Cys Pro Glu Glu Pro Gln Leu Arg Met Lys Asn Asn Glu Glu Ala
 500 505 510

Glu Asp Tyr Asp Asp Asp Leu Thr Asp Ser Glu Met Asp Val Val Arg
 515 520 525

Phe Asp Asp Asp Asn Ser Pro Ser Phe Ile Gln Ile Arg Ser Val Ala
 530 535 540

Lys Lys His Pro Lys Thr Trp Val His Tyr Ile Ala Ala Glu Glu Glu
 545 550 555 560

Asp Trp Asp Tyr Ala Pro Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr
 565 570 575

Lys Ser Gln Tyr Leu Asn Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr
 580 585 590

Lys Lys Val Arg Phe Met Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg
 595 600 605

Glu Ala Ile Gln His Glu Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly
 610 615 620

Glu Val Gly Asp Thr Leu Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg
 625 630 635 640

Pro Tyr Asn Ile Tyr Pro His Gly Ile Thr Asp Val Arg Pro Leu Tyr
 645 650 655

Ser Arg Arg Leu Pro Lys Gly Val Lys His Leu Lys Asp Phe Pro Ile
 660 665 670

Leu Pro Gly Glu Ile Phe Lys Tyr Lys Trp Thr Val Thr Val Glu Asp
 675 680 685

Gly Pro Thr Lys Ser Asp Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser
 690 695 700

Phe Val Asn Met Glu Arg Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu
 705 710 715 720

Leu Ile Cys Tyr Lys Glu Ser Val Asp Gln Arg Gly Asn Gln Ile Met
 725 730 735

Ser Asp Lys Arg Asn Val Ile Leu Phe Ser Val Phe Asp Glu Asn Arg
 740 745 750

Ser Trp Tyr Leu Thr Glu Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala
 755 760 765

Gly Val Gln Leu Glu Asp Pro Glu Phe Gln Ala Ser Asn Ile Met His
 770 775 780

Ser Ile Asn Gly Tyr Val Phe Asp Ser Leu Gln Leu Ser Val Cys Leu

785					790						795					800
His	Glu	Val	Ala	Tyr	Trp	Tyr	Ile	Leu	Ser	Ile	Gly	Ala	Gln	Thr	Asp	
				805					810					815		
Phe	Leu	Ser	Val	Phe	Phe	Ser	Gly	Tyr	Thr	Phe	Lys	His	Lys	Met	Val	
			820					825					830			
Tyr	Glu	Asp	Thr	Leu	Thr	Leu	Phe	Pro	Phe	Ser	Gly	Glu	Thr	Val	Phe	
		835					840					845				
Met	Ser	Met	Glu	Asn	Pro	Gly	Leu	Trp	Ile	Leu	Gly	Cys	His	Asn	Ser	
	850					855					860					
Asp	Phe	Arg	Asn	Arg	Gly	Met	Thr	Ala	Leu	Leu	Lys	Val	Ser	Ser	Cys	
865					870					875					880	
Asp	Lys	Asn	Thr	Gly	Asp	Tyr	Tyr	Glu	Asp	Ser	Tyr	Glu	Asp	Ile	Ser	
				885					890					895		
Ala	Tyr	Leu	Leu	Ser	Lys	Asn	Asn	Ala	Ile	Glu	Pro	Arg	Ser	Phe	Ser	
			900					905					910			
Gln	Asn	Pro	Pro	Val	Leu	Lys	Arg	His	Gln	Ala	Glu	Ile	Thr	Arg	Thr	
		915					920					925				
Thr	Leu	Gln	Gly	Ala	Pro	Gly	Thr	Pro	Gly	Ser	Gly	Thr	Ala	Ser	Ser	
	930					935					940					
Ser	Pro	Gly	Ala	Ser	Pro	Gly	Thr	Ser	Ser	Thr	Gly	Ser	Pro	Gly	Ala	
945					950					955					960	
Ser	Pro	Gly	Thr	Ser	Ser	Thr	Gly	Ser	Pro	Gly	Ala	Ser	Pro	Gly	Thr	
				965					970					975		

Ser Ser Thr Gly Ser Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr
 980 985 990

Gly Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala
 995 1000 1005

Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly
 1010 1015 1020

Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
 1025 1030 1035

Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser
 1040 1045 1050

Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ala
 1055 1060 1065

Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Ala Ser Ser Ser Asp
 1070 1075 1080

Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys
 1085 1090 1095

Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro
 1100 1105 1110

Arg Ser Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val
 1115 1120 1125

Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu
 1130 1135 1140

Arg Asn Arg Ala Gln Ser Gly Ser Val Pro Gln Phe Lys Lys Val
 1145 1150 1155

Val Phe Gln Glu Phe Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr
 1160 1165 1170

Arg Gly Glu Leu Asn Glu His Leu Gly Leu Leu Gly Pro Tyr Ile
 1175 1180 1185

Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr Phe Arg Asn Gln
 1190 1195 1200

Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Glu
 1205 1210 1215

Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys
 1220 1225 1230

Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His Met
 1235 1240 1245

Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
 1250 1255 1260

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly
 1265 1270 1275

Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly
 1280 1285 1290

Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe
 1295 1300 1305

Asp	Glu	Thr	Lys	Ser	Trp	Tyr	Phe	Thr	Glu	Asn	Met	Glu	Arg	Asn
1310						1315					1320			
Cys	Arg	Gly	Ala	Pro	Thr	Ser	Glu	Ser	Ala	Thr	Pro	Glu	Ser	Gly
1325						1330					1335			
Pro	Gly	Ser	Glu	Pro	Ala	Thr	Ser	Gly	Ser	Glu	Thr	Pro	Gly	Thr
1340						1345					1350			
Ser	Glu	Ser	Ala	Thr	Pro	Glu	Ser	Gly	Pro	Gly	Ser	Glu	Pro	Ala
1355						1360					1365			
Thr	Ser	Gly	Ser	Glu	Thr	Pro	Gly	Thr	Ser	Glu	Ser	Ala	Thr	Pro
1370						1375					1380			
Glu	Ser	Gly	Pro	Gly	Thr	Ser	Thr	Glu	Pro	Ser	Glu	Gly	Ser	Ala
1385						1390					1395			
Pro	Gly	Thr	Ser	Glu	Ser	Ala	Thr	Pro	Glu	Ser	Gly	Pro	Gly	Ser
1400						1405					1410			
Pro	Ala	Gly	Ser	Pro	Thr	Ser	Thr	Glu	Glu	Gly	Ser	Pro	Ala	Gly
1415						1420					1425			
Ser	Pro	Thr	Ser	Thr	Glu	Glu	Gly	Ser	Pro	Ala	Gly	Ser	Pro	Thr
1430						1435					1440			
Ser	Thr	Glu	Glu	Gly	Thr	Ser	Glu	Ser	Ala	Thr	Pro	Glu	Ser	Gly
1445						1450					1455			
Pro	Gly	Thr	Ser	Thr	Glu	Pro	Ser	Glu	Gly	Ser	Ala	Pro	Gly	Ala
1460						1465					1470			
Ser	Ser	Ala	Pro	Cys	Asn	Ile	Gln	Met	Glu	Asp	Pro	Thr	Phe	Lys

1475						1480						1485			
Glu	Asn	Tyr	Arg	Phe	His	Ala	Ile	Asn	Gly	Tyr	Ile	Met	Asp	Thr	
1490						1495					1500				
Leu	Pro	Gly	Leu	Val	Met	Ala	Gln	Asp	Gln	Arg	Ile	Arg	Trp	Tyr	
1505						1510					1515				
Leu	Leu	Ser	Met	Gly	Ser	Asn	Glu	Asn	Ile	His	Ser	Ile	His	Phe	
1520						1525					1530				
Ser	Gly	His	Val	Phe	Thr	Val	Arg	Lys	Lys	Glu	Glu	Tyr	Lys	Met	
1535						1540					1545				
Ala	Leu	Tyr	Asn	Leu	Tyr	Pro	Gly	Val	Phe	Glu	Thr	Val	Glu	Met	
1550						1555					1560				
Leu	Pro	Ser	Lys	Ala	Gly	Ile	Trp	Arg	Val	Glu	Cys	Leu	Ile	Gly	
1565						1570					1575				
Glu	His	Leu	His	Ala	Gly	Met	Ser	Thr	Leu	Phe	Leu	Val	Tyr	Ser	
1580						1585					1590				
Asn	Lys	Cys	Gln	Thr	Pro	Leu	Gly	Met	Ala	Ser	Gly	His	Ile	Arg	
1595						1600					1605				
Asp	Phe	Gln	Ile	Thr	Ala	Ser	Gly	Gln	Tyr	Gly	Gln	Trp	Ala	Pro	
1610						1615					1620				
Lys	Leu	Ala	Arg	Leu	His	Tyr	Ser	Gly	Ser	Ile	Asn	Ala	Trp	Ser	
1625						1630					1635				
Thr	Lys	Glu	Pro	Phe	Ser	Trp	Ile	Lys	Val	Asp	Leu	Leu	Ala	Pro	
1640						1645					1650				

Met Ile Ile His Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe
1655 1660 1665

Ser Ser Leu Tyr Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp
1670 1675 1680

Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu
1685 1690 1695

Met Val Phe Phe Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn
1700 1705 1710

Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro
1715 1720 1725

Thr His Tyr Ser Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly
1730 1735 1740

Cys Asp Leu Asn Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys
1745 1750 1755

Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn
1760 1765 1770

Met Phe Ala Thr Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln
1775 1780 1785

Gly Arg Ser Asn Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu
1790 1795 1800

Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val
1805 1810 1815

Thr 1820	Thr	Gln	Gly	Val	Lys	Ser 1825	Leu	Leu	Thr	Ser	Met 1830	Tyr	Val	Lys
Glu 1835	Phe	Leu	Ile	Ser	Ser	Ser 1840	Gln	Asp	Gly	His	Gln 1845	Trp	Thr	Leu
Phe 1850	Phe	Gln	Asn	Gly	Lys	Val 1855	Lys	Val	Phe	Gln	Gly 1860	Asn	Gln	Asp
Ser 1865	Phe	Thr	Pro	Val	Val	Asn 1870	Ser	Leu	Asp	Pro	Pro 1875	Leu	Leu	Thr
Arg 1880	Tyr	Leu	Arg	Ile	His	Pro 1885	Gln	Ser	Trp	Val	His 1890	Gln	Ile	Ala
Leu 1895	Arg	Met	Glu	Val	Leu	Gly 1900	Cys	Glu	Ala	Gln	Asp 1905	Leu	Tyr	Asp
Lys 1910	Thr	His	Thr	Cys	Pro	Pro 1915	Cys	Pro	Ala	Pro	Glu 1920	Leu	Leu	Gly
Gly 1925	Pro	Ser	Val	Phe	Leu	Phe 1930	Pro	Pro	Lys	Pro	Lys 1935	Asp	Thr	Leu
Met 1940	Ile	Ser	Arg	Thr	Pro	Glu 1945	Val	Thr	Cys	Val	Val 1950	Val	Asp	Val
Ser 1955	His	Glu	Asp	Pro	Glu	Val 1960	Lys	Phe	Asn	Trp	Tyr 1965	Val	Asp	Gly
Val 1970	Glu	Val	His	Asn	Ala	Lys 1975	Thr	Lys	Pro	Arg	Glu 1980	Glu	Gln	Tyr

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
1985 1990 1995

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
2000 2005 2010

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
2015 2020 2025

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
2030 2035 2040

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
2045 2050 2055

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
2060 2065 2070

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
2075 2080 2085

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
2090 2095 2100

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
2105 2110 2115

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
2120 2125 2130

Lys

<210> 77

<211> 2128

<212> PRT

<213> Artificial Sequence

<220>

<223> FVIII 203 (single chain FVIIIIFc with two AE XTENS, one 288AE XTEN in B-domain and one 144 AE XTEN at amino acid 1900)

<400> 77

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

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

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

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
 145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
 165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
 180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
 195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
 210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
 225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
 245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
 260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
 275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
 290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
 305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
450 455 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
 500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
 515 520 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
 530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
 545 550 555 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
 565 570 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
 580 585 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
 595 600 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
 610 615 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
 625 630 635 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
 645 650 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
 660 665 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr

675

680

685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
 690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
 705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
 725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
 740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Gly Ala Pro Gly
 755 760 765

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 770 775 780

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 785 790 795 800

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 805 810 815

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu
 820 825 830

Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 835 840 845

Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 850 855 860

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser
865 870 875 880

Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
885 890 895

Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
900 905 910

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser
915 920 925

Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
930 935 940

Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
945 950 955 960

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala
965 970 975

Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
980 985 990

Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
995 1000 1005

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro
1010 1015 1020

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr
1025 1030 1035

Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
 1040 1045 1050

Ala Pro Ala Ser Ser Pro Pro Val Leu Lys Arg His Gln Ala Glu
 1055 1060 1065

Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr
 1070 1075 1080

Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile
 1085 1090 1095

Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
 1100 1105 1110

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr
 1115 1120 1125

Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser
 1130 1135 1140

Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr
 1145 1150 1155

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu
 1160 1165 1170

His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp
 1175 1180 1185

Asn Ile Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser
 1190 1195 1200

Phe Tyr Ser Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly
1205 1210 1215

Ala Glu Pro Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr
1220 1225 1230

Tyr Phe Trp Lys Val Gln His His Met Ala Pro Thr Lys Asp Glu
1235 1240 1245

Phe Asp Cys Lys Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu
1250 1255 1260

Lys Asp Val His Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His
1265 1270 1275

Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln Val Thr Val Gln
1280 1285 1290

Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp
1295 1300 1305

Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Gly Ala Pro Thr
1310 1315 1320

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
1325 1330 1335

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
1340 1345 1350

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
1355 1360 1365

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr

1370

1375

1380

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser
 1385 1390 1395

Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr
 1400 1405 1410

Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu
 1415 1420 1425

Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr
 1430 1435 1440

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu
 1445 1450 1455

Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser Ala Pro Cys Asn
 1460 1465 1470

Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg Phe His
 1475 1480 1485

Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu Val Met
 1490 1495 1500

Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met Gly Ser
 1505 1510 1515

Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val Phe Thr
 1520 1525 1530

Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn Leu Tyr
 1535 1540 1545

Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys Ala Gly
 1550 1555 1560

Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His Ala Gly
 1565 1570 1575

Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln Thr Pro
 1580 1585 1590

Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile Thr Ala
 1595 1600 1605

Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg Leu His
 1610 1615 1620

Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro Phe Ser
 1625 1630 1635

Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His Gly Ile
 1640 1645 1650

Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr Ile Ser
 1655 1660 1665

Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr
 1670 1675 1680

Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe Gly Asn
 1685 1690 1695

Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro Pro Ile
 1700 1705 1710

Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg
1715 1720 1725

Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn Ser Cys
1730 1735 1740

Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln
1745 1750 1755

Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser
1760 1765 1770

Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp
1775 1780 1785

Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe
1790 1795 1800

Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys
1805 1810 1815

Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser
1820 1825 1830

Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys
1835 1840 1845

Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val
1850 1855 1860

Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His
1865 1870 1875

Pro 1880	Gln	Ser	Trp	Val	His	Gln 1885	Ile	Ala	Leu	Arg	Met 1890	Glu	Val	Leu
Gly 1895	Cys	Glu	Ala	Gln	Asp	Leu 1900	Tyr	Asp	Lys	Thr	His 1905	Thr	Cys	Pro
Pro 1910	Cys	Pro	Ala	Pro	Glu	Leu 1915	Leu	Gly	Gly	Pro	Ser 1920	Val	Phe	Leu
Phe 1925	Pro	Pro	Lys	Pro	Lys	Asp 1930	Thr	Leu	Met	Ile	Ser 1935	Arg	Thr	Pro
Glu 1940	Val	Thr	Cys	Val	Val	Val 1945	Asp	Val	Ser	His	Glu 1950	Asp	Pro	Glu
Val 1955	Lys	Phe	Asn	Trp	Tyr	Val 1960	Asp	Gly	Val	Glu	Val 1965	His	Asn	Ala
Lys 1970	Thr	Lys	Pro	Arg	Glu	Glu 1975	Gln	Tyr	Asn	Ser	Thr 1980	Tyr	Arg	Val
Val 1985	Ser	Val	Leu	Thr	Val	Leu 1990	His	Gln	Asp	Trp	Leu 1995	Asn	Gly	Lys
Glu 2000	Tyr	Lys	Cys	Lys	Val	Ser 2005	Asn	Lys	Ala	Leu	Pro 2010	Ala	Pro	Ile
Glu 2015	Lys	Thr	Ile	Ser	Lys	Ala 2020	Lys	Gly	Gln	Pro	Arg 2025	Glu	Pro	Gln
Val 2030	Tyr	Thr	Leu	Pro	Pro	Ser 2035	Arg	Asp	Glu	Leu	Thr 2040	Lys	Asn	Gln
Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile

2045

2050

2055

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 2060 2065 2070

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 2075 2080 2085

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
 2090 2095 2100

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 2105 2110 2115

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 2120 2125

<210> 78

<211> 2128

<212> PRT

<213> Artificial Sequence

<220>

<223> FVIII 204 (single chain FVIIIIFc with two AE XTENS, one 288AE XTEN

in B-domain and one 144 AE XTEN at amino acid 403)

<400> 78

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

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

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
 50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
 65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
 85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
 100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
 115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
 130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
 145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
 165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
 180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
 195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
 210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
 225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
 245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
 260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
 275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
 290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
 305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
 325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
 340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
 355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
 370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
 385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
 405 410 415

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

Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
 435 440 445

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
 450 455 460

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
 465 470 475 480

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
 485 490 495

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
 500 505 510

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Thr Glu Pro Ser Glu
 515 520 525

Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
 530 535 540

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu
 545 550 555 560

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ala Ser Ser Asp Arg Ser Tyr
 565 570 575

Lys Ser Gln Tyr Leu Asn Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr

580

585

590

Lys Lys Val Arg Phe Met Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg
 595 600 605

Glu Ala Ile Gln His Glu Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly
 610 615 620

Glu Val Gly Asp Thr Leu Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg
 625 630 635 640

Pro Tyr Asn Ile Tyr Pro His Gly Ile Thr Asp Val Arg Pro Leu Tyr
 645 650 655

Ser Arg Arg Leu Pro Lys Gly Val Lys His Leu Lys Asp Phe Pro Ile
 660 665 670

Leu Pro Gly Glu Ile Phe Lys Tyr Lys Trp Thr Val Thr Val Glu Asp
 675 680 685

Gly Pro Thr Lys Ser Asp Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser
 690 695 700

Phe Val Asn Met Glu Arg Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu
 705 710 715 720

Leu Ile Cys Tyr Lys Glu Ser Val Asp Gln Arg Gly Asn Gln Ile Met
 725 730 735

Ser Asp Lys Arg Asn Val Ile Leu Phe Ser Val Phe Asp Glu Asn Arg
 740 745 750

Ser Trp Tyr Leu Thr Glu Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala
 755 760 765

Gly Val Gln Leu Glu Asp Pro Glu Phe Gln Ala Ser Asn Ile Met His
 770 775 780

Ser Ile Asn Gly Tyr Val Phe Asp Ser Leu Gln Leu Ser Val Cys Leu
 785 790 795 800

His Glu Val Ala Tyr Trp Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp
 805 810 815

Phe Leu Ser Val Phe Phe Ser Gly Tyr Thr Phe Lys His Lys Met Val
 820 825 830

Tyr Glu Asp Thr Leu Thr Leu Phe Pro Phe Ser Gly Glu Thr Val Phe
 835 840 845

Met Ser Met Glu Asn Pro Gly Leu Trp Ile Leu Gly Cys His Asn Ser
 850 855 860

Asp Phe Arg Asn Arg Gly Met Thr Ala Leu Leu Lys Val Ser Ser Cys
 865 870 875 880

Asp Lys Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser
 885 890 895

Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
 900 905 910

Gln Asn Gly Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 915 920 925

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
 930 935 940

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 945 950 955 960

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 965 970 975

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro
 980 985 990

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr
 995 1000 1005

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
 1010 1015 1020

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 1025 1030 1035

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala
 1040 1045 1050

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser
 1055 1060 1065

Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 1070 1075 1080

Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 1085 1090 1095

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
 1100 1105 1110

Ala Thr Ser Gly Ser Glu Thr	Pro Gly Ser Glu Pro	Ala Thr Ser
1115	1120	1125
Gly Ser Glu Thr Pro Gly Ser	Pro Ala Gly Ser Pro	Thr Ser Thr
1130	1135	1140
Glu Glu Gly Thr Ser Thr Glu	Pro Ser Glu Gly Ser	Ala Pro Gly
1145	1150	1155
Thr Ser Thr Glu Pro Ser Glu	Gly Ser Ala Pro Gly	Ser Glu Pro
1160	1165	1170
Ala Thr Ser Gly Ser Glu Thr	Pro Gly Thr Ser Glu	Ser Ala Thr
1175	1180	1185
Pro Glu Ser Gly Pro Gly Thr	Ser Thr Glu Pro Ser	Glu Gly Ser
1190	1195	1200
Ala Pro Ala Ser Ser Pro Pro	Val Leu Lys Arg His	Gln Ala Glu
1205	1210	1215
Ile Thr Arg Thr Thr Leu Gln	Ser Asp Gln Glu Glu	Ile Asp Tyr
1220	1225	1230
Asp Asp Thr Ile Ser Val Glu	Met Lys Lys Glu Asp	Phe Asp Ile
1235	1240	1245
Tyr Asp Glu Asp Glu Asn Gln	Ser Pro Arg Ser Phe	Gln Lys Lys
1250	1255	1260
Thr Arg His Tyr Phe Ile Ala	Ala Val Glu Arg Leu	Trp Asp Tyr
1265	1270	1275
Gly Met Ser Ser Ser Pro His	Val Leu Arg Asn Arg	Ala Gln Ser

1280						1285						1290			
Gly	Ser	Val	Pro	Gln	Phe	Lys	Lys	Val	Val	Phe	Gln	Glu	Phe	Thr	
1295						1300					1305				
Asp	Gly	Ser	Phe	Thr	Gln	Pro	Leu	Tyr	Arg	Gly	Glu	Leu	Asn	Glu	
1310						1315					1320				
His	Leu	Gly	Leu	Leu	Gly	Pro	Tyr	Ile	Arg	Ala	Glu	Val	Glu	Asp	
1325						1330					1335				
Asn	Ile	Met	Val	Thr	Phe	Arg	Asn	Gln	Ala	Ser	Arg	Pro	Tyr	Ser	
1340						1345					1350				
Phe	Tyr	Ser	Ser	Leu	Ile	Ser	Tyr	Glu	Glu	Asp	Gln	Arg	Gln	Gly	
1355						1360					1365				
Ala	Glu	Pro	Arg	Lys	Asn	Phe	Val	Lys	Pro	Asn	Glu	Thr	Lys	Thr	
1370						1375					1380				
Tyr	Phe	Trp	Lys	Val	Gln	His	His	Met	Ala	Pro	Thr	Lys	Asp	Glu	
1385						1390					1395				
Phe	Asp	Cys	Lys	Ala	Trp	Ala	Tyr	Phe	Ser	Asp	Val	Asp	Leu	Glu	
1400						1405					1410				
Lys	Asp	Val	His	Ser	Gly	Leu	Ile	Gly	Pro	Leu	Leu	Val	Cys	His	
1415						1420					1425				
Thr	Asn	Thr	Leu	Asn	Pro	Ala	His	Gly	Arg	Gln	Val	Thr	Val	Gln	
1430						1435					1440				
Glu	Phe	Ala	Leu	Phe	Phe	Thr	Ile	Phe	Asp	Glu	Thr	Lys	Ser	Trp	
1445						1450					1455				

Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro Cys Asn
 1460 1465 1470

Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg Phe His
 1475 1480 1485

Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu Val Met
 1490 1495 1500

Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met Gly Ser
 1505 1510 1515

Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val Phe Thr
 1520 1525 1530

Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn Leu Tyr
 1535 1540 1545

Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys Ala Gly
 1550 1555 1560

Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His Ala Gly
 1565 1570 1575

Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln Thr Pro
 1580 1585 1590

Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile Thr Ala
 1595 1600 1605

Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg Leu His
 1610 1615 1620

Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro Phe Ser
1625 1630 1635

Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His Gly Ile
1640 1645 1650

Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr Ile Ser
1655 1660 1665

Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr
1670 1675 1680

Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe Gly Asn
1685 1690 1695

Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro Pro Ile
1700 1705 1710

Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg
1715 1720 1725

Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn Ser Cys
1730 1735 1740

Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln
1745 1750 1755

Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser
1760 1765 1770

Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp
1775 1780 1785

Arg	Pro	Gln	Val	Asn	Asn	Pro	Lys	Glu	Trp	Leu	Gln	Val	Asp	Phe
	1790					1795					1800			
Gln	Lys	Thr	Met	Lys	Val	Thr	Gly	Val	Thr	Thr	Gln	Gly	Val	Lys
	1805					1810					1815			
Ser	Leu	Leu	Thr	Ser	Met	Tyr	Val	Lys	Glu	Phe	Leu	Ile	Ser	Ser
	1820					1825					1830			
Ser	Gln	Asp	Gly	His	Gln	Trp	Thr	Leu	Phe	Phe	Gln	Asn	Gly	Lys
	1835					1840					1845			
Val	Lys	Val	Phe	Gln	Gly	Asn	Gln	Asp	Ser	Phe	Thr	Pro	Val	Val
	1850					1855					1860			
Asn	Ser	Leu	Asp	Pro	Pro	Leu	Leu	Thr	Arg	Tyr	Leu	Arg	Ile	His
	1865					1870					1875			
Pro	Gln	Ser	Trp	Val	His	Gln	Ile	Ala	Leu	Arg	Met	Glu	Val	Leu
	1880					1885					1890			
Gly	Cys	Glu	Ala	Gln	Asp	Leu	Tyr	Asp	Lys	Thr	His	Thr	Cys	Pro
	1895					1900					1905			
Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu
	1910					1915					1920			
Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro
	1925					1930					1935			
Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu
	1940					1945					1950			
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala

1955					1960					1965				
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
1970						1975					1980			
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys
1985						1990					1995			
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile
2000						2005					2010			
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln
2015						2020					2025			
Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln
2030						2035					2040			
Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile
2045						2050					2055			
Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys
2060						2065					2070			
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr
2075						2080					2085			
Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val
2090						2095					2100			
Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr
2105						2110					2115			
Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys					
2120						2125								

<210> 79
 <211> 2128
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> FVIII 205 (single chain FVIIIIFc with two AE XTEN, one 288AE XTEN in B-domain and one 144 AE XTEN at amino acid 18)

<400> 79

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

Trp Asp Tyr Met Gln Gly Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu
 35 40 45

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 50 55 60

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 65 70 75 80

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 85 90 95

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 100 105 110

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser
 115 120 125

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
 130 135 140

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 145 150 155 160

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly
 165 170 175

Ser Pro Thr Ser Thr Glu Glu Gly Ala Ser Ser Ser Asp Leu Gly Glu
 180 185 190

Leu Pro Val Asp Ala Arg Phe Pro Pro Arg Val Pro Lys Ser Phe Pro
 195 200 205

Phe Asn Thr Ser Val Val Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr
 210 215 220

Asp His Leu Phe Asn Ile Ala Lys Pro Arg Pro Pro Trp Met Gly Leu
 225 230 235 240

Leu Gly Pro Thr Ile Gln Ala Glu Val Tyr Asp Thr Val Val Ile Thr
 245 250 255

Leu Lys Asn Met Ala Ser His Pro Val Ser Leu His Ala Val Gly Val
 260 265 270

Ser Tyr Trp Lys Ala Ser Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser
 275 280 285

Gln Arg Glu Lys Glu Asp Asp Lys Val Phe Pro Gly Gly Ser His Thr
 290 295 300

Tyr Val Trp Gln Val Leu Lys Glu Asn Gly Pro Met Ala Ser Asp Pro
 305 310 315 320

Leu Cys Leu Thr Tyr Ser Tyr Leu Ser His Val Asp Leu Val Lys Asp
 325 330 335

Leu Asn Ser Gly Leu Ile Gly Ala Leu Leu Val Cys Arg Glu Gly Ser
 340 345 350

Leu Ala Lys Glu Lys Thr Gln Thr Leu His Lys Phe Ile Leu Leu Phe
 355 360 365

Ala Val Phe Asp Glu Gly Lys Ser Trp His Ser Glu Thr Lys Asn Ser
 370 375 380

Leu Met Gln Asp Arg Asp Ala Ala Ser Ala Arg Ala Trp Pro Lys Met
 385 390 395 400

His Thr Val Asn Gly Tyr Val Asn Arg Ser Leu Pro Gly Leu Ile Gly
 405 410 415

Cys His Arg Lys Ser Val Tyr Trp His Val Ile Gly Met Gly Thr Thr
 420 425 430

Pro Glu Val His Ser Ile Phe Leu Glu Gly His Thr Phe Leu Val Arg
 435 440 445

Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr
 450 455 460

Ala Gln Thr Leu Leu Met Asp Leu Gly Gln Phe Leu Leu Phe Cys His
 465 470 475 480

Ile Ser Ser His Gln His Asp Gly Met Glu Ala Tyr Val Lys Val Asp

485

490

495

Ser Cys Pro Glu Glu Pro Gln Leu Arg Met Lys Asn Asn Glu Glu Ala
 500 505 510

Glu Asp Tyr Asp Asp Asp Leu Thr Asp Ser Glu Met Asp Val Val Arg
 515 520 525

Phe Asp Asp Asp Asn Ser Pro Ser Phe Ile Gln Ile Arg Ser Val Ala
 530 535 540

Lys Lys His Pro Lys Thr Trp Val His Tyr Ile Ala Ala Glu Glu Glu
 545 550 555 560

Asp Trp Asp Tyr Ala Pro Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr
 565 570 575

Lys Ser Gln Tyr Leu Asn Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr
 580 585 590

Lys Lys Val Arg Phe Met Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg
 595 600 605

Glu Ala Ile Gln His Glu Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly
 610 615 620

Glu Val Gly Asp Thr Leu Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg
 625 630 635 640

Pro Tyr Asn Ile Tyr Pro His Gly Ile Thr Asp Val Arg Pro Leu Tyr
 645 650 655

Ser Arg Arg Leu Pro Lys Gly Val Lys His Leu Lys Asp Phe Pro Ile
 660 665 670

Leu Pro Gly Glu Ile Phe Lys Tyr Lys Trp Thr Val Thr Val Glu Asp
 675 680 685

Gly Pro Thr Lys Ser Asp Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser
 690 695 700

Phe Val Asn Met Glu Arg Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu
 705 710 715 720

Leu Ile Cys Tyr Lys Glu Ser Val Asp Gln Arg Gly Asn Gln Ile Met
 725 730 735

Ser Asp Lys Arg Asn Val Ile Leu Phe Ser Val Phe Asp Glu Asn Arg
 740 745 750

Ser Trp Tyr Leu Thr Glu Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala
 755 760 765

Gly Val Gln Leu Glu Asp Pro Glu Phe Gln Ala Ser Asn Ile Met His
 770 775 780

Ser Ile Asn Gly Tyr Val Phe Asp Ser Leu Gln Leu Ser Val Cys Leu
 785 790 795 800

His Glu Val Ala Tyr Trp Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp
 805 810 815

Phe Leu Ser Val Phe Phe Ser Gly Tyr Thr Phe Lys His Lys Met Val
 820 825 830

Tyr Glu Asp Thr Leu Thr Leu Phe Pro Phe Ser Gly Glu Thr Val Phe
 835 840 845

Met Ser Met Glu Asn Pro Gly Leu Trp Ile Leu Gly Cys His Asn Ser
850 855 860

Asp Phe Arg Asn Arg Gly Met Thr Ala Leu Leu Lys Val Ser Ser Cys
865 870 875 880

Asp Lys Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser
885 890 895

Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
900 905 910

Gln Asn Gly Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
915 920 925

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
930 935 940

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
945 950 955 960

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
965 970 975

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro
980 985 990

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr
995 1000 1005

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
1010 1015 1020

Thr 1025	Pro	Gly	Thr	Ser	Glu	Ser 1030	Ala	Thr	Pro	Glu	Ser 1035	Gly	Pro	Gly
Ser 1040	Pro	Ala	Gly	Ser	Pro	Thr 1045	Ser	Thr	Glu	Glu	Gly 1050	Ser	Pro	Ala
Gly 1055	Ser	Pro	Thr	Ser	Thr	Glu 1060	Glu	Gly	Thr	Ser	Thr 1065	Glu	Pro	Ser
Glu 1070	Gly	Ser	Ala	Pro	Gly	Thr 1075	Ser	Glu	Ser	Ala	Thr 1080	Pro	Glu	Ser
Gly 1085	Pro	Gly	Thr	Ser	Glu	Ser 1090	Ala	Thr	Pro	Glu	Ser 1095	Gly	Pro	Gly
Thr 1100	Ser	Glu	Ser	Ala	Thr	Pro 1105	Glu	Ser	Gly	Pro	Gly 1110	Ser	Glu	Pro
Ala 1115	Thr	Ser	Gly	Ser	Glu	Thr 1120	Pro	Gly	Ser	Glu	Pro 1125	Ala	Thr	Ser
Gly 1130	Ser	Glu	Thr	Pro	Gly	Ser 1135	Pro	Ala	Gly	Ser	Pro 1140	Thr	Ser	Thr
Glu 1145	Glu	Gly	Thr	Ser	Thr	Glu 1150	Pro	Ser	Glu	Gly	Ser 1155	Ala	Pro	Gly
Thr 1160	Ser	Thr	Glu	Pro	Ser	Glu 1165	Gly	Ser	Ala	Pro	Gly 1170	Ser	Glu	Pro
Ala 1175	Thr	Ser	Gly	Ser	Glu	Thr 1180	Pro	Gly	Thr	Ser	Glu 1185	Ser	Ala	Thr
Pro	Glu	Ser	Gly	Pro	Gly	Thr	Ser	Thr	Glu	Pro	Ser	Glu	Gly	Ser

1190						1195						1200			
Ala	Pro	Ala	Ser	Ser	Pro	Pro	Val	Leu	Lys	Arg	His	Gln	Ala	Glu	
1205						1210					1215				
Ile	Thr	Arg	Thr	Thr	Leu	Gln	Ser	Asp	Gln	Glu	Glu	Ile	Asp	Tyr	
1220						1225					1230				
Asp	Asp	Thr	Ile	Ser	Val	Glu	Met	Lys	Lys	Glu	Asp	Phe	Asp	Ile	
1235						1240					1245				
Tyr	Asp	Glu	Asp	Glu	Asn	Gln	Ser	Pro	Arg	Ser	Phe	Gln	Lys	Lys	
1250						1255					1260				
Thr	Arg	His	Tyr	Phe	Ile	Ala	Ala	Val	Glu	Arg	Leu	Trp	Asp	Tyr	
1265						1270					1275				
Gly	Met	Ser	Ser	Ser	Pro	His	Val	Leu	Arg	Asn	Arg	Ala	Gln	Ser	
1280						1285					1290				
Gly	Ser	Val	Pro	Gln	Phe	Lys	Lys	Val	Val	Phe	Gln	Glu	Phe	Thr	
1295						1300					1305				
Asp	Gly	Ser	Phe	Thr	Gln	Pro	Leu	Tyr	Arg	Gly	Glu	Leu	Asn	Glu	
1310						1315					1320				
His	Leu	Gly	Leu	Leu	Gly	Pro	Tyr	Ile	Arg	Ala	Glu	Val	Glu	Asp	
1325						1330					1335				
Asn	Ile	Met	Val	Thr	Phe	Arg	Asn	Gln	Ala	Ser	Arg	Pro	Tyr	Ser	
1340						1345					1350				
Phe	Tyr	Ser	Ser	Leu	Ile	Ser	Tyr	Glu	Glu	Asp	Gln	Arg	Gln	Gly	
1355						1360					1365				

Ala Glu Pro Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr
 1370 1375 1380

Tyr Phe Trp Lys Val Gln His His Met Ala Pro Thr Lys Asp Glu
 1385 1390 1395

Phe Asp Cys Lys Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu
 1400 1405 1410

Lys Asp Val His Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His
 1415 1420 1425

Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln Val Thr Val Gln
 1430 1435 1440

Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp
 1445 1450 1455

Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro Cys Asn
 1460 1465 1470

Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg Phe His
 1475 1480 1485

Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu Val Met
 1490 1495 1500

Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met Gly Ser
 1505 1510 1515

Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His Val Phe Thr
 1520 1525 1530

Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn Leu Tyr
 1535 1540 1545

Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys Ala Gly
 1550 1555 1560

Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His Ala Gly
 1565 1570 1575

Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln Thr Pro
 1580 1585 1590

Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile Thr Ala
 1595 1600 1605

Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg Leu His
 1610 1615 1620

Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro Phe Ser
 1625 1630 1635

Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His Gly Ile
 1640 1645 1650

Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr Ile Ser
 1655 1660 1665

Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr
 1670 1675 1680

Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe Gly Asn
 1685 1690 1695

Val	Asp	Ser	Ser	Gly	Ile	Lys	His	Asn	Ile	Phe	Asn	Pro	Pro	Ile
1700						1705					1710			
Ile	Ala	Arg	Tyr	Ile	Arg	Leu	His	Pro	Thr	His	Tyr	Ser	Ile	Arg
1715						1720					1725			
Ser	Thr	Leu	Arg	Met	Glu	Leu	Met	Gly	Cys	Asp	Leu	Asn	Ser	Cys
1730						1735					1740			
Ser	Met	Pro	Leu	Gly	Met	Glu	Ser	Lys	Ala	Ile	Ser	Asp	Ala	Gln
1745						1750					1755			
Ile	Thr	Ala	Ser	Ser	Tyr	Phe	Thr	Asn	Met	Phe	Ala	Thr	Trp	Ser
1760						1765					1770			
Pro	Ser	Lys	Ala	Arg	Leu	His	Leu	Gln	Gly	Arg	Ser	Asn	Ala	Trp
1775						1780					1785			
Arg	Pro	Gln	Val	Asn	Asn	Pro	Lys	Glu	Trp	Leu	Gln	Val	Asp	Phe
1790						1795					1800			
Gln	Lys	Thr	Met	Lys	Val	Thr	Gly	Val	Thr	Thr	Gln	Gly	Val	Lys
1805						1810					1815			
Ser	Leu	Leu	Thr	Ser	Met	Tyr	Val	Lys	Glu	Phe	Leu	Ile	Ser	Ser
1820						1825					1830			
Ser	Gln	Asp	Gly	His	Gln	Trp	Thr	Leu	Phe	Phe	Gln	Asn	Gly	Lys
1835						1840					1845			
Val	Lys	Val	Phe	Gln	Gly	Asn	Gln	Asp	Ser	Phe	Thr	Pro	Val	Val
1850						1855					1860			
Asn	Ser	Leu	Asp	Pro	Pro	Leu	Leu	Thr	Arg	Tyr	Leu	Arg	Ile	His

1865						1870						1875			
Pro	Gln	Ser	Trp	Val	His	Gln	Ile	Ala	Leu	Arg	Met	Glu	Val	Leu	
1880						1885					1890				
Gly	Cys	Glu	Ala	Gln	Asp	Leu	Tyr	Asp	Lys	Thr	His	Thr	Cys	Pro	
1895						1900					1905				
Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	
1910						1915					1920				
Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	
1925						1930					1935				
Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	
1940						1945					1950				
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	
1955						1960					1965				
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	
1970						1975					1980				
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	
1985						1990					1995				
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	
2000						2005					2010				
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	
2015						2020					2025				
Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	
2030						2035					2040				

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
2045 2050 2055

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
2060 2065 2070

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
2075 2080 2085

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
2090 2095 2100

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
2105 2110 2115

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
2120 2125

<210> 80

<211> 2020

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN FVIII 266 (FVIII Fc with 42 AE-XTEN at amino acid 18
and
288 AE XTEN in B-domain)

<400> 80

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

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

Trp Asp Tyr Met Gln Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
 35 40 45

Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
 50 55 60

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser Ser
 65 70 75 80

Asp Leu Gly Glu Leu Pro Val Asp Ala Arg Phe Pro Pro Arg Val Pro
 85 90 95

Lys Ser Phe Pro Phe Asn Thr Ser Val Val Tyr Lys Lys Thr Leu Phe
 100 105 110

Val Glu Phe Thr Asp His Leu Phe Asn Ile Ala Lys Pro Arg Pro Pro
 115 120 125

Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu Val Tyr Asp Thr
 130 135 140

Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val Ser Leu His
 145 150 155 160

Ala Val Gly Val Ser Tyr Trp Lys Ala Ser Glu Gly Ala Glu Tyr Asp
 165 170 175

Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val Phe Pro Gly
 180 185 190

Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu Asn Gly Pro Met
 195 200 205

Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu Ser His Val Asp
 210 215 220

Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala Leu Leu Val Cys
 225 230 235 240

Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr Leu His Lys Phe
 245 250 255

Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser Trp His Ser Glu
 260 265 270

Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala Ser Ala Arg Ala
 275 280 285

Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn Arg Ser Leu Pro
 290 295 300

Gly Leu Ile Gly Cys His Arg Lys Ser Val Tyr Trp His Val Ile Gly
 305 310 315 320

Met Gly Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu Gly His Thr
 325 330 335

Phe Leu Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile
 340 345 350

Thr Phe Leu Thr Ala Gln Thr Leu Leu Met Asp Leu Gly Gln Phe Leu
 355 360 365

Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met Glu Ala Tyr
 370 375 380

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

385		390		395		400									
Asn	Glu	Glu	Ala	Glu	Asp	Tyr	Asp	Asp	Asp	Leu	Thr	Asp	Ser	Glu	Met
				405					410					415	
Asp	Val	Val	Arg	Phe	Asp	Asp	Asp	Asn	Ser	Pro	Ser	Phe	Ile	Gln	Ile
			420					425					430		
Arg	Ser	Val	Ala	Lys	Lys	His	Pro	Lys	Thr	Trp	Val	His	Tyr	Ile	Ala
		435					440					445			
Ala	Glu	Glu	Glu	Asp	Trp	Asp	Tyr	Ala	Pro	Leu	Val	Leu	Ala	Pro	Asp
	450					455					460				
Asp	Arg	Ser	Tyr	Lys	Ser	Gln	Tyr	Leu	Asn	Asn	Gly	Pro	Gln	Arg	Ile
465					470					475					480
Gly	Arg	Lys	Tyr	Lys	Lys	Val	Arg	Phe	Met	Ala	Tyr	Thr	Asp	Glu	Thr
				485					490					495	
Phe	Lys	Thr	Arg	Glu	Ala	Ile	Gln	His	Glu	Ser	Gly	Ile	Leu	Gly	Pro
			500					505					510		
Leu	Leu	Tyr	Gly	Glu	Val	Gly	Asp	Thr	Leu	Leu	Ile	Ile	Phe	Lys	Asn
		515					520					525			
Gln	Ala	Ser	Arg	Pro	Tyr	Asn	Ile	Tyr	Pro	His	Gly	Ile	Thr	Asp	Val
	530					535					540				
Arg	Pro	Leu	Tyr	Ser	Arg	Arg	Leu	Pro	Lys	Gly	Val	Lys	His	Leu	Lys
545					550					555					560
Asp	Phe	Pro	Ile	Leu	Pro	Gly	Glu	Ile	Phe	Lys	Tyr	Lys	Trp	Thr	Val
				565					570					575	

Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg Cys Leu Thr Arg
 580 585 590

Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu Ala Ser Gly Leu
 595 600 605

Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Val Asp Gln Arg Gly
 610 615 620

Asn Gln Ile Met Ser Asp Lys Arg Asn Val Ile Leu Phe Ser Val Phe
 625 630 635 640

Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu Asn Ile Gln Arg Phe Leu
 645 650 655

Pro Asn Pro Ala Gly Val Gln Leu Glu Asp Pro Glu Phe Gln Ala Ser
 660 665 670

Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp Ser Leu Gln Leu
 675 680 685

Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu Ser Ile Gly
 690 695 700

Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly Tyr Thr Phe Lys
 705 710 715 720

His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro Phe Ser Gly
 725 730 735

Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp Ile Leu Gly
 740 745 750

Cys His Asn Ser Asp Phe Arg Asn Arg Gly Met Thr Ala Leu Leu Lys
 755 760 765

Val Ser Ser Cys Asp Lys Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr
 770 775 780

Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro
 785 790 795 800

Arg Ser Phe Ser Gln Asn Gly Ala Pro Gly Thr Ser Glu Ser Ala Thr
 805 810 815

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
 820 825 830

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu
 835 840 845

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr
 850 855 860

Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
 865 870 875 880

Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser
 885 890 895

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 900 905 910

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 915 920 925

Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro
 930 935 940

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser
 945 950 955 960

Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 965 970 975

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
 980 985 990

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 995 1000 1005

Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
 1010 1015 1020

Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
 1025 1030 1035

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
 1040 1045 1050

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser
 1055 1060 1065

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 1070 1075 1080

Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala
 1085 1090 1095

Ser Ser Pro Pro Val Leu Lys Arg His Gln Ala Glu Ile Thr Arg

1100					1105					1110				
Thr	Thr	Leu	Gln	Ser	Asp	Gln	Glu	Glu	Ile	Asp	Tyr	Asp	Asp	Thr
	1115					1120					1125			
Ile	Ser	Val	Glu	Met	Lys	Lys	Glu	Asp	Phe	Asp	Ile	Tyr	Asp	Glu
	1130					1135					1140			
Asp	Glu	Asn	Gln	Ser	Pro	Arg	Ser	Phe	Gln	Lys	Lys	Thr	Arg	His
	1145					1150					1155			
Tyr	Phe	Ile	Ala	Ala	Val	Glu	Arg	Leu	Trp	Asp	Tyr	Gly	Met	Ser
	1160					1165					1170			
Ser	Ser	Pro	His	Val	Leu	Arg	Asn	Arg	Ala	Gln	Ser	Gly	Ser	Val
	1175					1180					1185			
Pro	Gln	Phe	Lys	Lys	Val	Val	Phe	Gln	Glu	Phe	Thr	Asp	Gly	Ser
	1190					1195					1200			
Phe	Thr	Gln	Pro	Leu	Tyr	Arg	Gly	Glu	Leu	Asn	Glu	His	Leu	Gly
	1205					1210					1215			
Leu	Leu	Gly	Pro	Tyr	Ile	Arg	Ala	Glu	Val	Glu	Asp	Asn	Ile	Met
	1220					1225					1230			
Val	Thr	Phe	Arg	Asn	Gln	Ala	Ser	Arg	Pro	Tyr	Ser	Phe	Tyr	Ser
	1235					1240					1245			
Ser	Leu	Ile	Ser	Tyr	Glu	Glu	Asp	Gln	Arg	Gln	Gly	Ala	Glu	Pro
	1250					1255					1260			
Arg	Lys	Asn	Phe	Val	Lys	Pro	Asn	Glu	Thr	Lys	Thr	Tyr	Phe	Trp
	1265					1270					1275			

Lys Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys
 1280 1285 1290

Lys Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val
 1295 1300 1305

His Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr
 1310 1315 1320

Leu Asn Pro Ala His Gly Arg Gln Val Thr Val Gln Glu Phe Ala
 1325 1330 1335

Leu Phe Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp Tyr Phe Thr
 1340 1345 1350

Glu Asn Met Glu Arg Asn Cys Arg Ala Pro Cys Asn Ile Gln Met
 1355 1360 1365

Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg Phe His Ala Ile Asn
 1370 1375 1380

Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu Val Met Ala Gln Asp
 1385 1390 1395

Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met Gly Ser Asn Glu Asn
 1400 1405 1410

Ile His Ser Ile His Phe Ser Gly His Val Phe Thr Val Arg Lys
 1415 1420 1425

Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn Leu Tyr Pro Gly Val
 1430 1435 1440

Phe Glu Thr Val Glu Met Leu Pro Ser Lys Ala Gly Ile Trp Arg
1445 1450 1455

Val Glu Cys Leu Ile Gly Glu His Leu His Ala Gly Met Ser Thr
1460 1465 1470

Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln Thr Pro Leu Gly Met
1475 1480 1485

Ala Ser Gly His Ile Arg Asp Phe Gln Ile Thr Ala Ser Gly Gln
1490 1495 1500

Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg Leu His Tyr Ser Gly
1505 1510 1515

Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro Phe Ser Trp Ile Lys
1520 1525 1530

Val Asp Leu Leu Ala Pro Met Ile Ile His Gly Ile Lys Thr Gln
1535 1540 1545

Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr Ile Ser Gln Phe Ile
1550 1555 1560

Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr Tyr Arg Gly
1565 1570 1575

Asn Ser Thr Gly Thr Leu Met Val Phe Phe Gly Asn Val Asp Ser
1580 1585 1590

Ser Gly Ile Lys His Asn Ile Phe Asn Pro Pro Ile Ile Ala Arg
1595 1600 1605

Tyr	Ile	Arg	Leu	His	Pro	Thr	His	Tyr	Ser	Ile	Arg	Ser	Thr	Leu
1610						1615					1620			
Arg	Met	Glu	Leu	Met	Gly	Cys	Asp	Leu	Asn	Ser	Cys	Ser	Met	Pro
1625						1630					1635			
Leu	Gly	Met	Glu	Ser	Lys	Ala	Ile	Ser	Asp	Ala	Gln	Ile	Thr	Ala
1640						1645					1650			
Ser	Ser	Tyr	Phe	Thr	Asn	Met	Phe	Ala	Thr	Trp	Ser	Pro	Ser	Lys
1655						1660					1665			
Ala	Arg	Leu	His	Leu	Gln	Gly	Arg	Ser	Asn	Ala	Trp	Arg	Pro	Gln
1670						1675					1680			
Val	Asn	Asn	Pro	Lys	Glu	Trp	Leu	Gln	Val	Asp	Phe	Gln	Lys	Thr
1685						1690					1695			
Met	Lys	Val	Thr	Gly	Val	Thr	Thr	Gln	Gly	Val	Lys	Ser	Leu	Leu
1700						1705					1710			
Thr	Ser	Met	Tyr	Val	Lys	Glu	Phe	Leu	Ile	Ser	Ser	Ser	Gln	Asp
1715						1720					1725			
Gly	His	Gln	Trp	Thr	Leu	Phe	Phe	Gln	Asn	Gly	Lys	Val	Lys	Val
1730						1735					1740			
Phe	Gln	Gly	Asn	Gln	Asp	Ser	Phe	Thr	Pro	Val	Val	Asn	Ser	Leu
1745						1750					1755			
Asp	Pro	Pro	Leu	Leu	Thr	Arg	Tyr	Leu	Arg	Ile	His	Pro	Gln	Ser
1760						1765					1770			
Trp	Val	His	Gln	Ile	Ala	Leu	Arg	Met	Glu	Val	Leu	Gly	Cys	Glu

1775						1780						1785			
Ala	Gln	Asp	Leu	Tyr	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	
1790						1795					1800				
Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	
1805						1810					1815				
Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	
1820						1825					1830				
Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	
1835						1840					1845				
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	
1850						1855					1860				
Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	
1865						1870					1875				
Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	
1880						1885					1890				
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	
1895						1900					1905				
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	
1910						1915					1920				
Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	
1925						1930					1935				
Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	
1940						1945					1950				

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 1955 1960 1965

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
 1970 1975 1980

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
 1985 1990 1995

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
 2000 2005 2010

Leu Ser Leu Ser Pro Gly Lys
 2015 2020

<210> 81

<211> 2056

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN FVIII 267 (FVIII Fc with 72 AE-XTEN at amino acid 18
 and
 288 AE XTEN in B-domain)

<400> 81

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

Trp Asp Tyr Met Gln Gly Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu
 35 40 45

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 50 55 60

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 65 70 75 80

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 85 90 95

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 100 105 110

Ala Ser Ser Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg Phe Pro
 115 120 125

Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val Tyr Lys
 130 135 140

Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile Ala Lys
 145 150 155 160

Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu
 165 170 175

Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro
 180 185 190

Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser Glu Gly
 195 200 205

Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys
 210 215 220

Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu
 225 230 235 240

Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu
 245 250 255

Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala
 260 265 270

Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr
 275 280 285

Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser
 290 295 300

Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala
 305 310 315 320

Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn
 325 330 335

Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val Tyr Trp
 340 345 350

His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile Phe Leu
 355 360 365

Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser Leu Glu
 370 375 380

Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met Asp Leu
 385 390 395 400

Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly

Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys Gly Val
580 585 590

Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr
 595 600 605

Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg
 610 615 620

Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu
 625 630 635 640

Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Val
 645 650 655

Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val Ile Leu
 660 665 670

Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu Asn Ile
 675 680 685

Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp Pro Glu
 690 695 700

Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp
 705 710 715 720

Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile
 725 730 735

Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly
 740 745 750

Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe
 755 760 765

Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu
 770 775 780

Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly Met Thr
 785 790 795 800

Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp Tyr Tyr
 805 810 815

Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn
 820 825 830

Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Gly Ala Pro Gly Thr Ser
 835 840 845

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 850 855 860

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 865 870 875 880

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
 885 890 895

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser
 900 905 910

Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu
 915 920 925

Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu
 930 935 940

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr
 945 950 955 960

Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu
 965 970 975

Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser
 980 985 990

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr
 995 1000 1005

Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 1010 1015 1020

Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 1025 1030 1035

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro
 1040 1045 1050

Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro
 1055 1060 1065

Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
 1070 1075 1080

Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 1085 1090 1095

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu
 1100 1105 1110

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser

1115	1120	1125
Glu Gly Ser Ala Pro Ala Ser Ser Pro Pro Val Leu Lys Arg His 1130 1135 1140		
Gln Ala Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu 1145 1150 1155		
Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp 1160 1165 1170		
Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe 1175 1180 1185		
Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu 1190 1195 1200		
Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg 1205 1210 1215		
Ala Gln Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln 1220 1225 1230		
Glu Phe Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu 1235 1240 1245		
Leu Asn Glu His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu 1250 1255 1260		
Val Glu Asp Asn Ile Met Val Thr Phe Arg Asn Gln Ala Ser Arg 1265 1270 1275		
Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Glu Glu Asp Gln 1280 1285 1290		

Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys Pro Asn Glu
1295 1300 1305

Thr Lys Thr Tyr Phe Trp Lys Val Gln His His Met Ala Pro Thr
1310 1315 1320

Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe Ser Asp Val
1325 1330 1335

Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro Leu Leu
1340 1345 1350

Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln Val
1355 1360 1365

Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
1370 1375 1380

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala
1385 1390 1395

Pro Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr
1400 1405 1410

Arg Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly
1415 1420 1425

Leu Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser
1430 1435 1440

Met Gly Ser Asn Glu Asn Ile His Ser Ile His Phe Ser Gly His
1445 1450 1455

Val Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr
1460 1465 1470

Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser
1475 1480 1485

Lys Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu
1490 1495 1500

His Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys
1505 1510 1515

Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln
1520 1525 1530

Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala
1535 1540 1545

Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu
1550 1555 1560

Pro Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile
1565 1570 1575

His Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu
1580 1585 1590

Tyr Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys
1595 1600 1605

Trp Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe
1610 1615 1620

Phe 1625	Gly	Asn	Val	Asp	Ser	Ser 1630	Gly	Ile	Lys	His	Asn 1635	Ile	Phe	Asn
Pro 1640	Pro	Ile	Ile	Ala	Arg	Tyr 1645	Ile	Arg	Leu	His	Pro 1650	Thr	His	Tyr
Ser 1655	Ile	Arg	Ser	Thr	Leu	Arg 1660	Met	Glu	Leu	Met	Gly 1665	Cys	Asp	Leu
Asn 1670	Ser	Cys	Ser	Met	Pro	Leu 1675	Gly	Met	Glu	Ser	Lys 1680	Ala	Ile	Ser
Asp 1685	Ala	Gln	Ile	Thr	Ala	Ser 1690	Ser	Tyr	Phe	Thr	Asn 1695	Met	Phe	Ala
Thr 1700	Trp	Ser	Pro	Ser	Lys	Ala 1705	Arg	Leu	His	Leu	Gln 1710	Gly	Arg	Ser
Asn 1715	Ala	Trp	Arg	Pro	Gln	Val 1720	Asn	Asn	Pro	Lys	Glu 1725	Trp	Leu	Gln
Val 1730	Asp	Phe	Gln	Lys	Thr	Met 1735	Lys	Val	Thr	Gly	Val 1740	Thr	Thr	Gln
Gly 1745	Val	Lys	Ser	Leu	Leu	Thr 1750	Ser	Met	Tyr	Val	Lys 1755	Glu	Phe	Leu
Ile 1760	Ser	Ser	Ser	Gln	Asp	Gly 1765	His	Gln	Trp	Thr	Leu 1770	Phe	Phe	Gln
Asn 1775	Gly	Lys	Val	Lys	Val	Phe 1780	Gln	Gly	Asn	Gln	Asp 1785	Ser	Phe	Thr
Pro	Val	Val	Asn	Ser	Leu	Asp	Pro	Pro	Leu	Leu	Thr	Arg	Tyr	Leu

1790						1795						1800			
Arg	Ile	His	Pro	Gln	Ser	Trp	Val	His	Gln	Ile	Ala	Leu	Arg	Met	
1805						1810					1815				
Glu	Val	Leu	Gly	Cys	Glu	Ala	Gln	Asp	Leu	Tyr	Asp	Lys	Thr	His	
1820						1825					1830				
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	
1835						1840					1845				
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	
1850						1855					1860				
Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	
1865						1870					1875				
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	
1880						1885					1890				
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	
1895						1900					1905				
Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	
1910						1915					1920				
Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	
1925						1930					1935				
Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	
1940						1945					1950				
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	
1955						1960					1965				

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 1970 1975 1980

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 1985 1990 1995

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 2000 2005 2010

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 2015 2020 2025

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
 2030 2035 2040

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 2045 2050 2055

<210> 82

<211> 1834

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN FVIII 268 (FVIII Fc with 144 AE-XTEN at amino acid 18)

<400> 82

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

Trp Asp Tyr Met Gln Gly Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu

35

40

45

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 50 55 60

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 65 70 75 80

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 85 90 95

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 100 105 110

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser
 115 120 125

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
 130 135 140

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 145 150 155 160

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly
 165 170 175

Ser Pro Thr Ser Thr Glu Glu Gly Ala Ser Ser Ser Asp Leu Gly Glu
 180 185 190

Leu Pro Val Asp Ala Arg Phe Pro Pro Arg Val Pro Lys Ser Phe Pro
 195 200 205

Phe Asn Thr Ser Val Val Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr
 210 215 220

Asp His Leu Phe Asn Ile Ala Lys Pro Arg Pro Pro Trp Met Gly Leu
 225 230 235 240

Leu Gly Pro Thr Ile Gln Ala Glu Val Tyr Asp Thr Val Val Ile Thr
 245 250 255

Leu Lys Asn Met Ala Ser His Pro Val Ser Leu His Ala Val Gly Val
 260 265 270

Ser Tyr Trp Lys Ala Ser Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser
 275 280 285

Gln Arg Glu Lys Glu Asp Asp Lys Val Phe Pro Gly Gly Ser His Thr
 290 295 300

Tyr Val Trp Gln Val Leu Lys Glu Asn Gly Pro Met Ala Ser Asp Pro
 305 310 315 320

Leu Cys Leu Thr Tyr Ser Tyr Leu Ser His Val Asp Leu Val Lys Asp
 325 330 335

Leu Asn Ser Gly Leu Ile Gly Ala Leu Leu Val Cys Arg Glu Gly Ser
 340 345 350

Leu Ala Lys Glu Lys Thr Gln Thr Leu His Lys Phe Ile Leu Leu Phe
 355 360 365

Ala Val Phe Asp Glu Gly Lys Ser Trp His Ser Glu Thr Lys Asn Ser
 370 375 380

Leu Met Gln Asp Arg Asp Ala Ala Ser Ala Arg Ala Trp Pro Lys Met
 385 390 395 400

His Thr Val Asn Gly Tyr Val Asn Arg Ser Leu Pro Gly Leu Ile Gly
 405 410 415

Cys His Arg Lys Ser Val Tyr Trp His Val Ile Gly Met Gly Thr Thr
 420 425 430

Pro Glu Val His Ser Ile Phe Leu Glu Gly His Thr Phe Leu Val Arg
 435 440 445

Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr
 450 455 460

Ala Gln Thr Leu Leu Met Asp Leu Gly Gln Phe Leu Leu Phe Cys His
 465 470 475 480

Ile Ser Ser His Gln His Asp Gly Met Glu Ala Tyr Val Lys Val Asp
 485 490 495

Ser Cys Pro Glu Glu Pro Gln Leu Arg Met Lys Asn Asn Glu Glu Ala
 500 505 510

Glu Asp Tyr Asp Asp Asp Leu Thr Asp Ser Glu Met Asp Val Val Arg
 515 520 525

Phe Asp Asp Asp Asn Ser Pro Ser Phe Ile Gln Ile Arg Ser Val Ala
 530 535 540

Lys Lys His Pro Lys Thr Trp Val His Tyr Ile Ala Ala Glu Glu Glu
 545 550 555 560

Asp Trp Asp Tyr Ala Pro Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr
 565 570 575

Lys Ser Gln Tyr Leu Asn Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr
 580 585 590

Lys Lys Val Arg Phe Met Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg
 595 600 605

Glu Ala Ile Gln His Glu Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly
 610 615 620

Glu Val Gly Asp Thr Leu Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg
 625 630 635 640

Pro Tyr Asn Ile Tyr Pro His Gly Ile Thr Asp Val Arg Pro Leu Tyr
 645 650 655

Ser Arg Arg Leu Pro Lys Gly Val Lys His Leu Lys Asp Phe Pro Ile
 660 665 670

Leu Pro Gly Glu Ile Phe Lys Tyr Lys Trp Thr Val Thr Val Glu Asp
 675 680 685

Gly Pro Thr Lys Ser Asp Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser
 690 695 700

Phe Val Asn Met Glu Arg Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu
 705 710 715 720

Leu Ile Cys Tyr Lys Glu Ser Val Asp Gln Arg Gly Asn Gln Ile Met
 725 730 735

Ser Asp Lys Arg Asn Val Ile Leu Phe Ser Val Phe Asp Glu Asn Arg
 740 745 750

Ser Trp Tyr Leu Thr Glu Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala

755

760

765

Gly Val Gln Leu Glu Asp Pro Glu Phe Gln Ala Ser Asn Ile Met His
 770 775 780

Ser Ile Asn Gly Tyr Val Phe Asp Ser Leu Gln Leu Ser Val Cys Leu
 785 790 795 800

His Glu Val Ala Tyr Trp Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp
 805 810 815

Phe Leu Ser Val Phe Phe Ser Gly Tyr Thr Phe Lys His Lys Met Val
 820 825 830

Tyr Glu Asp Thr Leu Thr Leu Phe Pro Phe Ser Gly Glu Thr Val Phe
 835 840 845

Met Ser Met Glu Asn Pro Gly Leu Trp Ile Leu Gly Cys His Asn Ser
 850 855 860

Asp Phe Arg Asn Arg Gly Met Thr Ala Leu Leu Lys Val Ser Ser Cys
 865 870 875 880

Asp Lys Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser
 885 890 895

Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
 900 905 910

Gln Asn Pro Pro Val Leu Lys Arg His Gln Ala Glu Ile Thr Arg Thr
 915 920 925

Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser
 930 935 940

Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn
 945 950 955 960

Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala
 965 970 975

Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val
 980 985 990

Leu Arg Asn Arg Ala Gln Ser Gly Ser Val Pro Gln Phe Lys Lys Val
 995 1000 1005

Val Phe Gln Glu Phe Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr
 1010 1015 1020

Arg Gly Glu Leu Asn Glu His Leu Gly Leu Leu Gly Pro Tyr Ile
 1025 1030 1035

Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr Phe Arg Asn Gln
 1040 1045 1050

Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Glu
 1055 1060 1065

Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys
 1070 1075 1080

Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His Met
 1085 1090 1095

Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
 1100 1105 1110

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly
 1115 1120 1125

Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly
 1130 1135 1140

Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe
 1145 1150 1155

Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn
 1160 1165 1170

Cys Arg Ala Pro Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys
 1175 1180 1185

Glu Asn Tyr Arg Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr
 1190 1195 1200

Leu Pro Gly Leu Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr
 1205 1210 1215

Leu Leu Ser Met Gly Ser Asn Glu Asn Ile His Ser Ile His Phe
 1220 1225 1230

Ser Gly His Val Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met
 1235 1240 1245

Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met
 1250 1255 1260

Leu Pro Ser Lys Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly
 1265 1270 1275

Glu	His	Leu	His	Ala	Gly	Met	Ser	Thr	Leu	Phe	Leu	Val	Tyr	Ser
1280						1285					1290			
Asn	Lys	Cys	Gln	Thr	Pro	Leu	Gly	Met	Ala	Ser	Gly	His	Ile	Arg
1295						1300					1305			
Asp	Phe	Gln	Ile	Thr	Ala	Ser	Gly	Gln	Tyr	Gly	Gln	Trp	Ala	Pro
1310						1315					1320			
Lys	Leu	Ala	Arg	Leu	His	Tyr	Ser	Gly	Ser	Ile	Asn	Ala	Trp	Ser
1325						1330					1335			
Thr	Lys	Glu	Pro	Phe	Ser	Trp	Ile	Lys	Val	Asp	Leu	Leu	Ala	Pro
1340						1345					1350			
Met	Ile	Ile	His	Gly	Ile	Lys	Thr	Gln	Gly	Ala	Arg	Gln	Lys	Phe
1355						1360					1365			
Ser	Ser	Leu	Tyr	Ile	Ser	Gln	Phe	Ile	Ile	Met	Tyr	Ser	Leu	Asp
1370						1375					1380			
Gly	Lys	Lys	Trp	Gln	Thr	Tyr	Arg	Gly	Asn	Ser	Thr	Gly	Thr	Leu
1385						1390					1395			
Met	Val	Phe	Phe	Gly	Asn	Val	Asp	Ser	Ser	Gly	Ile	Lys	His	Asn
1400						1405					1410			
Ile	Phe	Asn	Pro	Pro	Ile	Ile	Ala	Arg	Tyr	Ile	Arg	Leu	His	Pro
1415						1420					1425			
Thr	His	Tyr	Ser	Ile	Arg	Ser	Thr	Leu	Arg	Met	Glu	Leu	Met	Gly
1430						1435					1440			
Cys	Asp	Leu	Asn	Ser	Cys	Ser	Met	Pro	Leu	Gly	Met	Glu	Ser	Lys

1445						1450						1455			
Ala	Ile	Ser	Asp	Ala	Gln	Ile	Thr	Ala	Ser	Ser	Tyr	Phe	Thr	Asn	
1460						1465					1470				
Met	Phe	Ala	Thr	Trp	Ser	Pro	Ser	Lys	Ala	Arg	Leu	His	Leu	Gln	
1475						1480					1485				
Gly	Arg	Ser	Asn	Ala	Trp	Arg	Pro	Gln	Val	Asn	Asn	Pro	Lys	Glu	
1490						1495					1500				
Trp	Leu	Gln	Val	Asp	Phe	Gln	Lys	Thr	Met	Lys	Val	Thr	Gly	Val	
1505						1510					1515				
Thr	Thr	Gln	Gly	Val	Lys	Ser	Leu	Leu	Thr	Ser	Met	Tyr	Val	Lys	
1520						1525					1530				
Glu	Phe	Leu	Ile	Ser	Ser	Ser	Gln	Asp	Gly	His	Gln	Trp	Thr	Leu	
1535						1540					1545				
Phe	Phe	Gln	Asn	Gly	Lys	Val	Lys	Val	Phe	Gln	Gly	Asn	Gln	Asp	
1550						1555					1560				
Ser	Phe	Thr	Pro	Val	Val	Asn	Ser	Leu	Asp	Pro	Pro	Leu	Leu	Thr	
1565						1570					1575				
Arg	Tyr	Leu	Arg	Ile	His	Pro	Gln	Ser	Trp	Val	His	Gln	Ile	Ala	
1580						1585					1590				
Leu	Arg	Met	Glu	Val	Leu	Gly	Cys	Glu	Ala	Gln	Asp	Leu	Tyr	Asp	
1595						1600					1605				
Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	
1610						1615					1620				

Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
1625						1630					1635			
Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val
1640						1645					1650			
Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly
1655						1660					1665			
Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr
1670						1675					1680			
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln
1685						1690					1695			
Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
1700						1705					1710			
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly
1715						1720					1725			
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp
1730						1735					1740			
Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly
1745						1750					1755			
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln
1760						1765					1770			
Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp
1775						1780					1785			

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 1790 1795 1800

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 1805 1810 1815

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 1820 1825 1830

Lys

<210> 83

<211> 1762

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN FVIII 269 (FVIII Fc with 72 AE-XTEN at amino acid 18)

<400> 83

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

Trp Asp Tyr Met Gln Gly Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu
 35 40 45

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 50 55 60

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 65 70 75 80

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
85 90 95

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
100 105 110

Ala Ser Ser Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg Phe Pro
115 120 125

Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val Tyr Lys
130 135 140

Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile Ala Lys
145 150 155 160

Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu
165 170 175

Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro
180 185 190

Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser Glu Gly
195 200 205

Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys
210 215 220

Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu
225 230 235 240

Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu
245 250 255

Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala
 260 265 270

Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr
 275 280 285

Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser
 290 295 300

Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala
 305 310 315 320

Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn
 325 330 335

Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val Tyr Trp
 340 345 350

His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile Phe Leu
 355 360 365

Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser Leu Glu
 370 375 380

Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met Asp Leu
 385 390 395 400

Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly
 405 410 415

Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro Gln Leu
 420 425 430

Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp Leu Thr
 435 440 445

Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser Pro Ser
 450 455 460

Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val
 465 470 475 480

His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Leu Val
 485 490 495

Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn Asn Gly
 500 505 510

Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr
 515 520 525

Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly
 530 535 540

Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile
 545 550 555 560

Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly
 565 570 575

Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys Gly Val
 580 585 590

Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe Lys Tyr
 595 600 605

Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg

610

615

620

Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg Asp Leu
 625 630 635 640

Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser Val
 645 650 655

Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val Ile Leu
 660 665 670

Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu Asn Ile
 675 680 685

Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp Pro Glu
 690 695 700

Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val Phe Asp
 705 710 715 720

Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile
 725 730 735

Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe Ser Gly
 740 745 750

Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe
 755 760 765

Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu
 770 775 780

Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly Met Thr
 785 790 795 800

Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp Tyr Tyr
805 810 815

Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn
820 825 830

Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu Lys Arg
835 840 845

His Gln Ala Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu
850 855 860

Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe
865 870 875 880

Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys
885 890 895

Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr
900 905 910

Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly
915 920 925

Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly
930 935 940

Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly
945 950 955 960

Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val
965 970 975

Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu
 980 985 990

Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn
 995 1000 1005

Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln
 1010 1015 1020

His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp
 1025 1030 1035

Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly
 1040 1045 1050

Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro
 1055 1060 1065

Ala His Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe
 1070 1075 1080

Thr Ile Phe Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met
 1085 1090 1095

Glu Arg Asn Cys Arg Ala Pro Cys Asn Ile Gln Met Glu Asp Pro
 1100 1105 1110

Thr Phe Lys Glu Asn Tyr Arg Phe His Ala Ile Asn Gly Tyr Ile
 1115 1120 1125

Met Asp Thr Leu Pro Gly Leu Val Met Ala Gln Asp Gln Arg Ile
 1130 1135 1140

Arg	Trp	Tyr	Leu	Leu	Ser	Met	Gly	Ser	Asn	Glu	Asn	Ile	His	Ser
	1145					1150					1155			
Ile	His	Phe	Ser	Gly	His	Val	Phe	Thr	Val	Arg	Lys	Lys	Glu	Glu
	1160					1165					1170			
Tyr	Lys	Met	Ala	Leu	Tyr	Asn	Leu	Tyr	Pro	Gly	Val	Phe	Glu	Thr
	1175					1180					1185			
Val	Glu	Met	Leu	Pro	Ser	Lys	Ala	Gly	Ile	Trp	Arg	Val	Glu	Cys
	1190					1195					1200			
Leu	Ile	Gly	Glu	His	Leu	His	Ala	Gly	Met	Ser	Thr	Leu	Phe	Leu
	1205					1210					1215			
Val	Tyr	Ser	Asn	Lys	Cys	Gln	Thr	Pro	Leu	Gly	Met	Ala	Ser	Gly
	1220					1225					1230			
His	Ile	Arg	Asp	Phe	Gln	Ile	Thr	Ala	Ser	Gly	Gln	Tyr	Gly	Gln
	1235					1240					1245			
Trp	Ala	Pro	Lys	Leu	Ala	Arg	Leu	His	Tyr	Ser	Gly	Ser	Ile	Asn
	1250					1255					1260			
Ala	Trp	Ser	Thr	Lys	Glu	Pro	Phe	Ser	Trp	Ile	Lys	Val	Asp	Leu
	1265					1270					1275			
Leu	Ala	Pro	Met	Ile	Ile	His	Gly	Ile	Lys	Thr	Gln	Gly	Ala	Arg
	1280					1285					1290			
Gln	Lys	Phe	Ser	Ser	Leu	Tyr	Ile	Ser	Gln	Phe	Ile	Ile	Met	Tyr
	1295					1300					1305			
Ser	Leu	Asp	Gly	Lys	Lys	Trp	Gln	Thr	Tyr	Arg	Gly	Asn	Ser	Thr

1310

1315

1320

Gly Thr Leu Met Val Phe Phe Gly Asn Val Asp Ser Ser Gly Ile
 1325 1330 1335

Lys His Asn Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr Ile Arg
 1340 1345 1350

Leu His Pro Thr His Tyr Ser Ile Arg Ser Thr Leu Arg Met Glu
 1355 1360 1365

Leu Met Gly Cys Asp Leu Asn Ser Cys Ser Met Pro Leu Gly Met
 1370 1375 1380

Glu Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr
 1385 1390 1395

Phe Thr Asn Met Phe Ala Thr Trp Ser Pro Ser Lys Ala Arg Leu
 1400 1405 1410

His Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln Val Asn Asn
 1415 1420 1425

Pro Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val
 1430 1435 1440

Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu Leu Thr Ser Met
 1445 1450 1455

Tyr Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Gln
 1460 1465 1470

Trp Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly
 1475 1480 1485

Asn Gln Asp Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro
 1490 1495 1500

Leu Leu Thr Arg Tyr Leu Arg Ile His Pro Gln Ser Trp Val His
 1505 1510 1515

Gln Ile Ala Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp
 1520 1525 1530

Leu Tyr Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
 1535 1540 1545

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 1550 1555 1560

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 1565 1570 1575

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 1580 1585 1590

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 1595 1600 1605

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
 1610 1615 1620

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 1625 1630 1635

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 1640 1645 1650

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 1655 1660 1665

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 1670 1675 1680

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
 1685 1690 1695

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 1700 1705 1710

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 1715 1720 1725

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 1730 1735 1740

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
 1745 1750 1755

Ser Pro Gly Lys
 1760

<210> 84

<211> 1726

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYNFVIII 271 (FVIII Fc with 42 AE-XTEN at amino acid 18)

<400> 84

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

Trp Asp Tyr Met Gln Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
 35 40 45

Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
 50 55 60

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser Ser
 65 70 75 80

Asp Leu Gly Glu Leu Pro Val Asp Ala Arg Phe Pro Pro Arg Val Pro
 85 90 95

Lys Ser Phe Pro Phe Asn Thr Ser Val Val Tyr Lys Lys Thr Leu Phe
 100 105 110

Val Glu Phe Thr Asp His Leu Phe Asn Ile Ala Lys Pro Arg Pro Pro
 115 120 125

Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu Val Tyr Asp Thr
 130 135 140

Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val Ser Leu His
 145 150 155 160

Ala Val Gly Val Ser Tyr Trp Lys Ala Ser Glu Gly Ala Glu Tyr Asp
 165 170 175

Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp Asp Lys Val Phe Pro Gly
 180 185 190

Gly Ser His Thr Tyr Val Trp Gln Val Leu Lys Glu Asn Gly Pro Met
 195 200 205

Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser Tyr Leu Ser His Val Asp
 210 215 220

Leu Val Lys Asp Leu Asn Ser Gly Leu Ile Gly Ala Leu Leu Val Cys
 225 230 235 240

Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr Leu His Lys Phe
 245 250 255

Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser Trp His Ser Glu
 260 265 270

Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala Ser Ala Arg Ala
 275 280 285

Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn Arg Ser Leu Pro
 290 295 300

Gly Leu Ile Gly Cys His Arg Lys Ser Val Tyr Trp His Val Ile Gly
 305 310 315 320

Met Gly Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu Gly His Thr
 325 330 335

Phe Leu Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile
 340 345 350

Thr Phe Leu Thr Ala Gln Thr Leu Leu Met Asp Leu Gly Gln Phe Leu
 355 360 365

Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met Glu Ala Tyr
 370 375 380

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

Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp Leu Thr Asp Ser Glu Met
 405 410 415

Asp Val Val Arg Phe Asp Asp Asp Asn Ser Pro Ser Phe Ile Gln Ile
 420 425 430

Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val His Tyr Ile Ala
 435 440 445

Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Leu Val Leu Ala Pro Asp
 450 455 460

Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn Asn Gly Pro Gln Arg Ile
 465 470 475 480

Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr Asp Glu Thr
 485 490 495

Phe Lys Thr Arg Glu Ala Ile Gln His Glu Ser Gly Ile Leu Gly Pro
 500 505 510

Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu Leu Ile Ile Phe Lys Asn
 515 520 525

Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro His Gly Ile Thr Asp Val
 530 535 540

Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys Gly Val Lys His Leu Lys

545		550		555		560									
Asp	Phe	Pro	Ile	Leu	Pro	Gly	Glu	Ile	Phe	Lys	Tyr	Lys	Trp	Thr	Val
				565					570					575	
Thr	Val	Glu	Asp	Gly	Pro	Thr	Lys	Ser	Asp	Pro	Arg	Cys	Leu	Thr	Arg
			580					585					590		
Tyr	Tyr	Ser	Ser	Phe	Val	Asn	Met	Glu	Arg	Asp	Leu	Ala	Ser	Gly	Leu
		595					600					605			
Ile	Gly	Pro	Leu	Leu	Ile	Cys	Tyr	Lys	Glu	Ser	Val	Asp	Gln	Arg	Gly
	610					615					620				
Asn	Gln	Ile	Met	Ser	Asp	Lys	Arg	Asn	Val	Ile	Leu	Phe	Ser	Val	Phe
625					630					635					640
Asp	Glu	Asn	Arg	Ser	Trp	Tyr	Leu	Thr	Glu	Asn	Ile	Gln	Arg	Phe	Leu
				645					650					655	
Pro	Asn	Pro	Ala	Gly	Val	Gln	Leu	Glu	Asp	Pro	Glu	Phe	Gln	Ala	Ser
			660					665					670		
Asn	Ile	Met	His	Ser	Ile	Asn	Gly	Tyr	Val	Phe	Asp	Ser	Leu	Gln	Leu
		675					680					685			
Ser	Val	Cys	Leu	His	Glu	Val	Ala	Tyr	Trp	Tyr	Ile	Leu	Ser	Ile	Gly
	690					695					700				
Ala	Gln	Thr	Asp	Phe	Leu	Ser	Val	Phe	Phe	Ser	Gly	Tyr	Thr	Phe	Lys
705					710					715					720
His	Lys	Met	Val	Tyr	Glu	Asp	Thr	Leu	Thr	Leu	Phe	Pro	Phe	Ser	Gly
				725					730					735	

Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp Ile Leu Gly
 740 745 750

Cys His Asn Ser Asp Phe Arg Asn Arg Gly Met Thr Ala Leu Leu Lys
 755 760 765

Val Ser Ser Cys Asp Lys Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr
 770 775 780

Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro
 785 790 795 800

Arg Ser Phe Ser Gln Asn Pro Pro Val Leu Lys Arg His Gln Ala Glu
 805 810 815

Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp
 820 825 830

Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp
 835 840 845

Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg His
 850 855 860

Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser
 865 870 875 880

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

Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly Ser Phe Thr Gln
 900 905 910

Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly Leu Leu Gly Pro
 915 920 925

Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val Thr Phe Arg Asn
 930 935 940

Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Glu
 945 950 955 960

Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys Pro
 965 970 975

Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His Met Ala Pro
 980 985 990

Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe Ser Asp Val
 995 1000 1005

Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro Leu Leu
 1010 1015 1020

Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln Val
 1025 1030 1035

Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr
 1040 1045 1050

Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala
 1055 1060 1065

Pro Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr
 1070 1075 1080

Arg	Phe	His	Ala	Ile	Asn	Gly	Tyr	Ile	Met	Asp	Thr	Leu	Pro	Gly
1085						1090					1095			
Leu	Val	Met	Ala	Gln	Asp	Gln	Arg	Ile	Arg	Trp	Tyr	Leu	Leu	Ser
1100						1105					1110			
Met	Gly	Ser	Asn	Glu	Asn	Ile	His	Ser	Ile	His	Phe	Ser	Gly	His
1115						1120					1125			
Val	Phe	Thr	Val	Arg	Lys	Lys	Glu	Glu	Tyr	Lys	Met	Ala	Leu	Tyr
1130						1135					1140			
Asn	Leu	Tyr	Pro	Gly	Val	Phe	Glu	Thr	Val	Glu	Met	Leu	Pro	Ser
1145						1150					1155			
Lys	Ala	Gly	Ile	Trp	Arg	Val	Glu	Cys	Leu	Ile	Gly	Glu	His	Leu
1160						1165					1170			
His	Ala	Gly	Met	Ser	Thr	Leu	Phe	Leu	Val	Tyr	Ser	Asn	Lys	Cys
1175						1180					1185			
Gln	Thr	Pro	Leu	Gly	Met	Ala	Ser	Gly	His	Ile	Arg	Asp	Phe	Gln
1190						1195					1200			
Ile	Thr	Ala	Ser	Gly	Gln	Tyr	Gly	Gln	Trp	Ala	Pro	Lys	Leu	Ala
1205						1210					1215			
Arg	Leu	His	Tyr	Ser	Gly	Ser	Ile	Asn	Ala	Trp	Ser	Thr	Lys	Glu
1220						1225					1230			
Pro	Phe	Ser	Trp	Ile	Lys	Val	Asp	Leu	Leu	Ala	Pro	Met	Ile	Ile
1235						1240					1245			
His	Gly	Ile	Lys	Thr	Gln	Gly	Ala	Arg	Gln	Lys	Phe	Ser	Ser	Leu

1250						1255						1260			
Tyr	Ile	Ser	Gln	Phe	Ile	Ile	Met	Tyr	Ser	Leu	Asp	Gly	Lys	Lys	
1265						1270					1275				
Trp	Gln	Thr	Tyr	Arg	Gly	Asn	Ser	Thr	Gly	Thr	Leu	Met	Val	Phe	
1280						1285					1290				
Phe	Gly	Asn	Val	Asp	Ser	Ser	Gly	Ile	Lys	His	Asn	Ile	Phe	Asn	
1295						1300					1305				
Pro	Pro	Ile	Ile	Ala	Arg	Tyr	Ile	Arg	Leu	His	Pro	Thr	His	Tyr	
1310						1315					1320				
Ser	Ile	Arg	Ser	Thr	Leu	Arg	Met	Glu	Leu	Met	Gly	Cys	Asp	Leu	
1325						1330					1335				
Asn	Ser	Cys	Ser	Met	Pro	Leu	Gly	Met	Glu	Ser	Lys	Ala	Ile	Ser	
1340						1345					1350				
Asp	Ala	Gln	Ile	Thr	Ala	Ser	Ser	Tyr	Phe	Thr	Asn	Met	Phe	Ala	
1355						1360					1365				
Thr	Trp	Ser	Pro	Ser	Lys	Ala	Arg	Leu	His	Leu	Gln	Gly	Arg	Ser	
1370						1375					1380				
Asn	Ala	Trp	Arg	Pro	Gln	Val	Asn	Asn	Pro	Lys	Glu	Trp	Leu	Gln	
1385						1390					1395				
Val	Asp	Phe	Gln	Lys	Thr	Met	Lys	Val	Thr	Gly	Val	Thr	Thr	Gln	
1400						1405					1410				
Gly	Val	Lys	Ser	Leu	Leu	Thr	Ser	Met	Tyr	Val	Lys	Glu	Phe	Leu	
1415						1420					1425				

Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln
 1430 1435 1440

Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr
 1445 1450 1455

Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu
 1460 1465 1470

Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met
 1475 1480 1485

Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr Asp Lys Thr His
 1490 1495 1500

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
 1505 1510 1515

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 1520 1525 1530

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 1535 1540 1545

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 1550 1555 1560

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
 1565 1570 1575

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
 1580 1585 1590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
 1595 1600 1605

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 1610 1615 1620

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
 1625 1630 1635

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 1640 1645 1650

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 1655 1660 1665

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 1670 1675 1680

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 1685 1690 1695

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
 1700 1705 1710

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 1715 1720 1725

<210> 85

<211> 1901

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN FVIII 272 (FVIII with 144 AE XTEN at amino acid 18 and 244

AE XTEN in B-domain- no Fc)

<400> 85

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

Trp Asp Tyr Met Gln Gly Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu
 35 40 45

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 50 55 60

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 65 70 75 80

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 85 90 95

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 100 105 110

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser
 115 120 125

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
 130 135 140

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 145 150 155 160

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly

165

170

175

Ser Pro Thr Ser Thr Glu Glu Gly Ala Ser Ser Ser Asp Leu Gly Glu
 180 185 190

Leu Pro Val Asp Ala Arg Phe Pro Pro Arg Val Pro Lys Ser Phe Pro
 195 200 205

Phe Asn Thr Ser Val Val Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr
 210 215 220

Asp His Leu Phe Asn Ile Ala Lys Pro Arg Pro Pro Trp Met Gly Leu
 225 230 235 240

Leu Gly Pro Thr Ile Gln Ala Glu Val Tyr Asp Thr Val Val Ile Thr
 245 250 255

Leu Lys Asn Met Ala Ser His Pro Val Ser Leu His Ala Val Gly Val
 260 265 270

Ser Tyr Trp Lys Ala Ser Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser
 275 280 285

Gln Arg Glu Lys Glu Asp Asp Lys Val Phe Pro Gly Gly Ser His Thr
 290 295 300

Tyr Val Trp Gln Val Leu Lys Glu Asn Gly Pro Met Ala Ser Asp Pro
 305 310 315 320

Leu Cys Leu Thr Tyr Ser Tyr Leu Ser His Val Asp Leu Val Lys Asp
 325 330 335

Leu Asn Ser Gly Leu Ile Gly Ala Leu Leu Val Cys Arg Glu Gly Ser
 340 345 350

Leu Ala Lys Glu Lys Thr Gln Thr Leu His Lys Phe Ile Leu Leu Phe
 355 360 365

Ala Val Phe Asp Glu Gly Lys Ser Trp His Ser Glu Thr Lys Asn Ser
 370 375 380

Leu Met Gln Asp Arg Asp Ala Ala Ser Ala Arg Ala Trp Pro Lys Met
 385 390 395 400

His Thr Val Asn Gly Tyr Val Asn Arg Ser Leu Pro Gly Leu Ile Gly
 405 410 415

Cys His Arg Lys Ser Val Tyr Trp His Val Ile Gly Met Gly Thr Thr
 420 425 430

Pro Glu Val His Ser Ile Phe Leu Glu Gly His Thr Phe Leu Val Arg
 435 440 445

Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr
 450 455 460

Ala Gln Thr Leu Leu Met Asp Leu Gly Gln Phe Leu Leu Phe Cys His
 465 470 475 480

Ile Ser Ser His Gln His Asp Gly Met Glu Ala Tyr Val Lys Val Asp
 485 490 495

Ser Cys Pro Glu Glu Pro Gln Leu Arg Met Lys Asn Asn Glu Glu Ala
 500 505 510

Glu Asp Tyr Asp Asp Asp Leu Thr Asp Ser Glu Met Asp Val Val Arg
 515 520 525

Phe Asp Asp Asp Asn Ser Pro Ser Phe Ile Gln Ile Arg Ser Val Ala
 530 535 540

Lys Lys His Pro Lys Thr Trp Val His Tyr Ile Ala Ala Glu Glu Glu
 545 550 555 560

Asp Trp Asp Tyr Ala Pro Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr
 565 570 575

Lys Ser Gln Tyr Leu Asn Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr
 580 585 590

Lys Lys Val Arg Phe Met Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg
 595 600 605

Glu Ala Ile Gln His Glu Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly
 610 615 620

Glu Val Gly Asp Thr Leu Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg
 625 630 635 640

Pro Tyr Asn Ile Tyr Pro His Gly Ile Thr Asp Val Arg Pro Leu Tyr
 645 650 655

Ser Arg Arg Leu Pro Lys Gly Val Lys His Leu Lys Asp Phe Pro Ile
 660 665 670

Leu Pro Gly Glu Ile Phe Lys Tyr Lys Trp Thr Val Thr Val Glu Asp
 675 680 685

Gly Pro Thr Lys Ser Asp Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser
 690 695 700

Phe Val Asn Met Glu Arg Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu
 705 710 715 720

Leu Ile Cys Tyr Lys Glu Ser Val Asp Gln Arg Gly Asn Gln Ile Met
 725 730 735

Ser Asp Lys Arg Asn Val Ile Leu Phe Ser Val Phe Asp Glu Asn Arg
 740 745 750

Ser Trp Tyr Leu Thr Glu Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala
 755 760 765

Gly Val Gln Leu Glu Asp Pro Glu Phe Gln Ala Ser Asn Ile Met His
 770 775 780

Ser Ile Asn Gly Tyr Val Phe Asp Ser Leu Gln Leu Ser Val Cys Leu
 785 790 795 800

His Glu Val Ala Tyr Trp Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp
 805 810 815

Phe Leu Ser Val Phe Phe Ser Gly Tyr Thr Phe Lys His Lys Met Val
 820 825 830

Tyr Glu Asp Thr Leu Thr Leu Phe Pro Phe Ser Gly Glu Thr Val Phe
 835 840 845

Met Ser Met Glu Asn Pro Gly Leu Trp Ile Leu Gly Cys His Asn Ser
 850 855 860

Asp Phe Arg Asn Arg Gly Met Thr Ala Leu Leu Lys Val Ser Ser Cys
 865 870 875 880

Asp Lys Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser

885

890

895

Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
 900 905 910

Gln Asn Gly Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 915 920 925

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
 930 935 940

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 945 950 955 960

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 965 970 975

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro
 980 985 990

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr
 995 1000 1005

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
 1010 1015 1020

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 1025 1030 1035

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala
 1040 1045 1050

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser
 1055 1060 1065

Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 1070 1075 1080

Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 1085 1090 1095

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
 1100 1105 1110

Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser
 1115 1120 1125

Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr
 1130 1135 1140

Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 1145 1150 1155

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro
 1160 1165 1170

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr
 1175 1180 1185

Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
 1190 1195 1200

Ala Pro Ala Ser Ser Pro Pro Val Leu Lys Arg His Gln Ala Glu
 1205 1210 1215

Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr
 1220 1225 1230

Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile
1235 1240 1245

Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
1250 1255 1260

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr
1265 1270 1275

Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser
1280 1285 1290

Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr
1295 1300 1305

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu
1310 1315 1320

His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp
1325 1330 1335

Asn Ile Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser
1340 1345 1350

Phe Tyr Ser Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly
1355 1360 1365

Ala Glu Pro Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr
1370 1375 1380

Tyr Phe Trp Lys Val Gln His His Met Ala Pro Thr Lys Asp Glu
1385 1390 1395

Phe	Asp	Cys	Lys	Ala	Trp	Ala	Tyr	Phe	Ser	Asp	Val	Asp	Leu	Glu
	1400					1405					1410			
Lys	Asp	Val	His	Ser	Gly	Leu	Ile	Gly	Pro	Leu	Leu	Val	Cys	His
	1415					1420					1425			
Thr	Asn	Thr	Leu	Asn	Pro	Ala	His	Gly	Arg	Gln	Val	Thr	Val	Gln
	1430					1435					1440			
Glu	Phe	Ala	Leu	Phe	Phe	Thr	Ile	Phe	Asp	Glu	Thr	Lys	Ser	Trp
	1445					1450					1455			
Tyr	Phe	Thr	Glu	Asn	Met	Glu	Arg	Asn	Cys	Arg	Ala	Pro	Cys	Asn
	1460					1465					1470			
Ile	Gln	Met	Glu	Asp	Pro	Thr	Phe	Lys	Glu	Asn	Tyr	Arg	Phe	His
	1475					1480					1485			
Ala	Ile	Asn	Gly	Tyr	Ile	Met	Asp	Thr	Leu	Pro	Gly	Leu	Val	Met
	1490					1495					1500			
Ala	Gln	Asp	Gln	Arg	Ile	Arg	Trp	Tyr	Leu	Leu	Ser	Met	Gly	Ser
	1505					1510					1515			
Asn	Glu	Asn	Ile	His	Ser	Ile	His	Phe	Ser	Gly	His	Val	Phe	Thr
	1520					1525					1530			
Val	Arg	Lys	Lys	Glu	Glu	Tyr	Lys	Met	Ala	Leu	Tyr	Asn	Leu	Tyr
	1535					1540					1545			
Pro	Gly	Val	Phe	Glu	Thr	Val	Glu	Met	Leu	Pro	Ser	Lys	Ala	Gly
	1550					1555					1560			
Ile	Trp	Arg	Val	Glu	Cys	Leu	Ile	Gly	Glu	His	Leu	His	Ala	Gly

1565						1570						1575			
Met	Ser	Thr	Leu	Phe	Leu	Val	Tyr	Ser	Asn	Lys	Cys	Gln	Thr	Pro	
1580						1585					1590				
Leu	Gly	Met	Ala	Ser	Gly	His	Ile	Arg	Asp	Phe	Gln	Ile	Thr	Ala	
1595						1600					1605				
Ser	Gly	Gln	Tyr	Gly	Gln	Trp	Ala	Pro	Lys	Leu	Ala	Arg	Leu	His	
1610						1615					1620				
Tyr	Ser	Gly	Ser	Ile	Asn	Ala	Trp	Ser	Thr	Lys	Glu	Pro	Phe	Ser	
1625						1630					1635				
Trp	Ile	Lys	Val	Asp	Leu	Leu	Ala	Pro	Met	Ile	Ile	His	Gly	Ile	
1640						1645					1650				
Lys	Thr	Gln	Gly	Ala	Arg	Gln	Lys	Phe	Ser	Ser	Leu	Tyr	Ile	Ser	
1655						1660					1665				
Gln	Phe	Ile	Ile	Met	Tyr	Ser	Leu	Asp	Gly	Lys	Lys	Trp	Gln	Thr	
1670						1675					1680				
Tyr	Arg	Gly	Asn	Ser	Thr	Gly	Thr	Leu	Met	Val	Phe	Phe	Gly	Asn	
1685						1690					1695				
Val	Asp	Ser	Ser	Gly	Ile	Lys	His	Asn	Ile	Phe	Asn	Pro	Pro	Ile	
1700						1705					1710				
Ile	Ala	Arg	Tyr	Ile	Arg	Leu	His	Pro	Thr	His	Tyr	Ser	Ile	Arg	
1715						1720					1725				
Ser	Thr	Leu	Arg	Met	Glu	Leu	Met	Gly	Cys	Asp	Leu	Asn	Ser	Cys	
1730						1735					1740				

Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln
 1745 1750 1755

Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser
 1760 1765 1770

Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp
 1775 1780 1785

Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe
 1790 1795 1800

Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys
 1805 1810 1815

Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser
 1820 1825 1830

Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys
 1835 1840 1845

Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val
 1850 1855 1860

Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His
 1865 1870 1875

Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu Val Leu
 1880 1885 1890

Gly Cys Glu Ala Gln Asp Leu Tyr
 1895 1900

<210> 86
 <211> 1515
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VWF031

<400> 86

Met Ile Pro Ala Arg Phe Ala Gly Val Leu Leu Ala Leu Ala Leu Ile
 1 5 10 15

Leu Pro Gly Thr Leu Cys Ala Glu Gly Thr Arg Gly Arg Ser Ser Thr
 20 25 30

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

Ser Met Tyr Ser Phe Ala Gly Tyr Cys Ser Tyr Leu Leu Ala Gly Gly
 50 55 60

Cys Gln Lys Arg Ser Phe Ser Ile Ile Gly Asp Phe Gln Asn Gly Lys
 65 70 75 80

Arg Val Ser Leu Ser Val Tyr Leu Gly Glu Phe Phe Asp Ile His Leu
 85 90 95

Phe Val Asn Gly Thr Val Thr Gln Gly Asp Gln Arg Val Ser Met Pro
 100 105 110

Tyr Ala Ser Lys Gly Leu Tyr Leu Glu Thr Glu Ala Gly Tyr Tyr Lys
 115 120 125

Leu Ser Gly Glu Ala Tyr Gly Phe Val Ala Arg Ile Asp Gly Ser Gly
 130 135 140

Asn Phe Gln Val Leu Leu Ser Asp Arg Tyr Phe Asn Lys Thr Cys Gly
 145 150 155 160

Leu Cys Gly Asn Phe Asn Ile Phe Ala Glu Asp Asp Phe Met Thr Gln
 165 170 175

Glu Gly Thr Leu Thr Ser Asp Pro Tyr Asp Phe Ala Asn Ser Trp Ala
 180 185 190

Leu Ser Ser Gly Glu Gln Trp Cys Glu Arg Ala Ser Pro Pro Ser Ser
 195 200 205

Ser Cys Asn Ile Ser Ser Gly Glu Met Gln Lys Gly Leu Trp Glu Gln
 210 215 220

Cys Gln Leu Leu Lys Ser Thr Ser Val Phe Ala Arg Cys His Pro Leu
 225 230 235 240

Val Asp Pro Glu Pro Phe Val Ala Leu Cys Glu Lys Thr Leu Cys Glu
 245 250 255

Cys Ala Gly Gly Leu Glu Cys Ala Cys Pro Ala Leu Leu Glu Tyr Ala
 260 265 270

Arg Thr Cys Ala Gln Glu Gly Met Val Leu Tyr Gly Trp Thr Asp His
 275 280 285

Ser Ala Cys Ser Pro Val Cys Pro Ala Gly Met Glu Tyr Arg Gln Cys
 290 295 300

Val Ser Pro Cys Ala Arg Thr Cys Gln Ser Leu His Ile Asn Glu Met
 305 310 315 320

Cys Gln Glu Arg Cys Val Asp Gly Cys Ser Cys Pro Glu Gly Gln Leu
 325 330 335

Leu Asp Glu Gly Leu Cys Val Glu Ser Thr Glu Cys Pro Cys Val His
 340 345 350

Ser Gly Lys Arg Tyr Pro Pro Gly Thr Ser Leu Ser Arg Asp Cys Asn
 355 360 365

Thr Cys Ile Cys Arg Asn Ser Gln Trp Ile Cys Ser Asn Glu Glu Cys
 370 375 380

Pro Gly Glu Cys Leu Val Thr Gly Gln Ser His Phe Lys Ser Phe Asp
 385 390 395 400

Asn Arg Tyr Phe Thr Phe Ser Gly Ile Cys Gln Tyr Leu Leu Ala Arg
 405 410 415

Asp Cys Gln Asp His Ser Phe Ser Ile Val Ile Glu Thr Val Gln Cys
 420 425 430

Ala Asp Asp Arg Asp Ala Val Cys Thr Arg Ser Val Thr Val Arg Leu
 435 440 445

Pro Gly Leu His Asn Ser Leu Val Lys Leu Lys His Gly Ala Gly Val
 450 455 460

Ala Met Asp Gly Gln Asp Ile Gln Leu Pro Leu Leu Lys Gly Asp Leu
 465 470 475 480

Arg Ile Gln His Thr Val Thr Ala Ser Val Arg Leu Ser Tyr Gly Glu
 485 490 495

Asp Leu Gln Met Asp Trp Asp Gly Arg Gly Arg Leu Leu Val Lys Leu
 500 505 510

Ser Pro Val Tyr Ala Gly Lys Thr Cys Gly Leu Cys Gly Asn Tyr Asn
 515 520 525

Gly Asn Gln Gly Asp Asp Phe Leu Thr Pro Ser Gly Leu Ala Glu Pro
 530 535 540

Arg Val Glu Asp Phe Gly Asn Ala Trp Lys Leu His Gly Asp Cys Gln
 545 550 555 560

Asp Leu Gln Lys Gln His Ser Asp Pro Cys Ala Leu Asn Pro Arg Met
 565 570 575

Thr Arg Phe Ser Glu Glu Ala Cys Ala Val Leu Thr Ser Pro Thr Phe
 580 585 590

Glu Ala Cys His Arg Ala Val Ser Pro Leu Pro Tyr Leu Arg Asn Cys
 595 600 605

Arg Tyr Asp Val Cys Ser Cys Ser Asp Gly Arg Glu Cys Leu Cys Gly
 610 615 620

Ala Leu Ala Ser Tyr Ala Ala Ala Cys Ala Gly Arg Gly Val Arg Val
 625 630 635 640

Ala Trp Arg Glu Pro Gly Arg Cys Glu Leu Asn Cys Pro Lys Gly Gln
 645 650 655

Val Tyr Leu Gln Cys Gly Thr Pro Cys Asn Leu Thr Cys Arg Ser Leu
 660 665 670

Ser Tyr Pro Asp Glu Glu Cys Asn Glu Ala Cys Leu Glu Gly Cys Phe

675

680

685

Cys Pro Pro Gly Leu Tyr Met Asp Glu Arg Gly Asp Cys Val Pro Lys
 690 695 700

Ala Gln Cys Pro Cys Tyr Tyr Asp Gly Glu Ile Phe Gln Pro Glu Asp
 705 710 715 720

Ile Phe Ser Asp His His Thr Met Cys Tyr Cys Glu Asp Gly Phe Met
 725 730 735

His Cys Thr Met Ser Gly Val Pro Gly Ser Leu Leu Pro Asp Ala Val
 740 745 750

Leu Ser Ser Pro Leu Ser His Arg Ser Lys Arg Ser Leu Ser Cys Arg
 755 760 765

Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp Asn Leu Arg Ala Glu
 770 775 780

Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr Asp Leu Glu Cys Met
 785 790 795 800

Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro Pro Gly Met Val Arg
 805 810 815

His Glu Asn Arg Cys Val Ala Leu Glu Arg Cys Pro Cys Phe His Gln
 820 825 830

Gly Lys Glu Tyr Ala Pro Gly Glu Thr Val Lys Ile Gly Cys Asn Thr
 835 840 845

Cys Val Cys Arg Asp Arg Lys Trp Asn Cys Thr Asp His Val Cys Asp
 850 855 860

Ala Thr Cys Ser Thr Ile Gly Met Ala His Tyr Leu Thr Phe Asp Gly
865 870 875 880

Leu Lys Tyr Leu Phe Pro Gly Glu Cys Gln Tyr Val Leu Val Gln Asp
885 890 895

Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys
900 905 910

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

Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys
930 935 940

Arg Pro Met Lys Asp Glu Thr His Phe Glu Val Val Glu Ser Gly Arg
945 950 955 960

Tyr Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg
965 970 975

His Leu Ser Ile Ser Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val
980 985 990

Cys Gly Leu Cys Gly Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr
995 1000 1005

Ser Ser Asn Leu Gln Val Glu Glu Asp Pro Val Asp Phe Gly Asn
1010 1015 1020

Ser Trp Lys Val Ser Ser Gln Cys Ala Asp Thr Arg Lys Val Pro
1025 1030 1035

Leu Asp Ser Ser Pro Ala Thr Cys His Asn Asn Ile Met Lys Gln
 1040 1045 1050

Thr Met Val Asp Ser Ser Cys Arg Ile Leu Thr Ser Asp Val Phe
 1055 1060 1065

Gln Asp Cys Asn Lys Leu Val Asp Pro Glu Pro Tyr Leu Asp Val
 1070 1075 1080

Cys Ile Tyr Asp Thr Cys Ser Cys Glu Ser Ile Gly Asp Cys Ala
 1085 1090 1095

Ala Phe Cys Asp Thr Ile Ala Ala Tyr Ala His Val Cys Ala Gln
 1100 1105 1110

His Gly Lys Val Val Thr Trp Arg Thr Ala Thr Leu Cys Pro Gln
 1115 1120 1125

Ser Cys Glu Glu Arg Asn Leu Arg Glu Asn Gly Tyr Glu Ala Glu
 1130 1135 1140

Trp Arg Tyr Asn Ser Cys Ala Pro Ala Cys Gln Val Thr Cys Gln
 1145 1150 1155

His Pro Glu Pro Leu Ala Cys Pro Val Gln Cys Val Glu Gly Cys
 1160 1165 1170

His Ala His Cys Pro Pro Gly Lys Ile Leu Asp Glu Leu Leu Gln
 1175 1180 1185

Thr Cys Val Asp Pro Glu Asp Cys Pro Val Cys Glu Val Ala Gly
 1190 1195 1200

Arg	Arg	Phe	Ala	Ser	Gly	Lys	Lys	Val	Thr	Leu	Asn	Pro	Ser	Asp
1205						1210					1215			
Pro	Glu	His	Cys	Gln	Ile	Cys	His	Cys	Asp	Val	Val	Asn	Leu	Thr
1220						1225					1230			
Cys	Glu	Ala	Cys	Gln	Glu	Pro	Ile	Ser	Gly	Gly	Gly	Gly	Ser	Gly
1235						1240					1245			
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly
1250						1255					1260			
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Leu	Val	Pro	Arg	Gly	Ser
1265						1270					1275			
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Asp	Lys	Thr	His	Thr
1280						1285					1290			
Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val
1295						1300					1305			
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
1310						1315					1320			
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
1325						1330					1335			
Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
1340						1345					1350			
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr
1355						1360					1365			
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn

1370

1375

1380

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
 1385 1390 1395

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
 1400 1405 1410

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
 1415 1420 1425

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
 1430 1435 1440

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 1445 1450 1455

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 1460 1465 1470

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 1475 1480 1485

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
 1490 1495 1500

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 1505 1510 1515

<210> 87

<211> 1778

<212> PRT

<213> Artificial Sequence

<220>

<223> VWF034

<400> 87

Met	Ile	Pro	Ala	Arg	Phe	Ala	Gly	Val	Leu	Leu	Ala	Leu	Ala	Leu	Ile
1				5					10					15	

Leu	Pro	Gly	Thr	Leu	Cys	Ala	Glu	Gly	Thr	Arg	Gly	Arg	Ser	Ser	Thr
			20					25					30		

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

Ser	Met	Tyr	Ser	Phe	Ala	Gly	Tyr	Cys	Ser	Tyr	Leu	Leu	Ala	Gly	Gly
	50					55					60				

Cys	Gln	Lys	Arg	Ser	Phe	Ser	Ile	Ile	Gly	Asp	Phe	Gln	Asn	Gly	Lys
65					70					75					80

Arg	Val	Ser	Leu	Ser	Val	Tyr	Leu	Gly	Glu	Phe	Phe	Asp	Ile	His	Leu
				85					90					95	

Phe	Val	Asn	Gly	Thr	Val	Thr	Gln	Gly	Asp	Gln	Arg	Val	Ser	Met	Pro
			100					105					110		

Tyr	Ala	Ser	Lys	Gly	Leu	Tyr	Leu	Glu	Thr	Glu	Ala	Gly	Tyr	Tyr	Lys
		115					120					125			

Leu	Ser	Gly	Glu	Ala	Tyr	Gly	Phe	Val	Ala	Arg	Ile	Asp	Gly	Ser	Gly
		130				135					140				

Asn	Phe	Gln	Val	Leu	Leu	Ser	Asp	Arg	Tyr	Phe	Asn	Lys	Thr	Cys	Gly
145					150					155					160

Leu	Cys	Gly	Asn	Phe	Asn	Ile	Phe	Ala	Glu	Asp	Asp	Phe	Met	Thr	Gln

165

170

175

Glu Gly Thr Leu Thr Ser Asp Pro Tyr Asp Phe Ala Asn Ser Trp Ala
 180 185 190

Leu Ser Ser Gly Glu Gln Trp Cys Glu Arg Ala Ser Pro Pro Ser Ser
 195 200 205

Ser Cys Asn Ile Ser Ser Gly Glu Met Gln Lys Gly Leu Trp Glu Gln
 210 215 220

Cys Gln Leu Leu Lys Ser Thr Ser Val Phe Ala Arg Cys His Pro Leu
 225 230 235 240

Val Asp Pro Glu Pro Phe Val Ala Leu Cys Glu Lys Thr Leu Cys Glu
 245 250 255

Cys Ala Gly Gly Leu Glu Cys Ala Cys Pro Ala Leu Leu Glu Tyr Ala
 260 265 270

Arg Thr Cys Ala Gln Glu Gly Met Val Leu Tyr Gly Trp Thr Asp His
 275 280 285

Ser Ala Cys Ser Pro Val Cys Pro Ala Gly Met Glu Tyr Arg Gln Cys
 290 295 300

Val Ser Pro Cys Ala Arg Thr Cys Gln Ser Leu His Ile Asn Glu Met
 305 310 315 320

Cys Gln Glu Arg Cys Val Asp Gly Cys Ser Cys Pro Glu Gly Gln Leu
 325 330 335

Leu Asp Glu Gly Leu Cys Val Glu Ser Thr Glu Cys Pro Cys Val His
 340 345 350

Ser Gly Lys Arg Tyr Pro Pro Gly Thr Ser Leu Ser Arg Asp Cys Asn
 355 360 365

Thr Cys Ile Cys Arg Asn Ser Gln Trp Ile Cys Ser Asn Glu Glu Cys
 370 375 380

Pro Gly Glu Cys Leu Val Thr Gly Gln Ser His Phe Lys Ser Phe Asp
 385 390 395 400

Asn Arg Tyr Phe Thr Phe Ser Gly Ile Cys Gln Tyr Leu Leu Ala Arg
 405 410 415

Asp Cys Gln Asp His Ser Phe Ser Ile Val Ile Glu Thr Val Gln Cys
 420 425 430

Ala Asp Asp Arg Asp Ala Val Cys Thr Arg Ser Val Thr Val Arg Leu
 435 440 445

Pro Gly Leu His Asn Ser Leu Val Lys Leu Lys His Gly Ala Gly Val
 450 455 460

Ala Met Asp Gly Gln Asp Ile Gln Leu Pro Leu Leu Lys Gly Asp Leu
 465 470 475 480

Arg Ile Gln His Thr Val Thr Ala Ser Val Arg Leu Ser Tyr Gly Glu
 485 490 495

Asp Leu Gln Met Asp Trp Asp Gly Arg Gly Arg Leu Leu Val Lys Leu
 500 505 510

Ser Pro Val Tyr Ala Gly Lys Thr Cys Gly Leu Cys Gly Asn Tyr Asn
 515 520 525

Gly Asn Gln Gly Asp Asp Phe Leu Thr Pro Ser Gly Leu Ala Glu Pro
 530 535 540

Arg Val Glu Asp Phe Gly Asn Ala Trp Lys Leu His Gly Asp Cys Gln
 545 550 555 560

Asp Leu Gln Lys Gln His Ser Asp Pro Cys Ala Leu Asn Pro Arg Met
 565 570 575

Thr Arg Phe Ser Glu Glu Ala Cys Ala Val Leu Thr Ser Pro Thr Phe
 580 585 590

Glu Ala Cys His Arg Ala Val Ser Pro Leu Pro Tyr Leu Arg Asn Cys
 595 600 605

Arg Tyr Asp Val Cys Ser Cys Ser Asp Gly Arg Glu Cys Leu Cys Gly
 610 615 620

Ala Leu Ala Ser Tyr Ala Ala Ala Cys Ala Gly Arg Gly Val Arg Val
 625 630 635 640

Ala Trp Arg Glu Pro Gly Arg Cys Glu Leu Asn Cys Pro Lys Gly Gln
 645 650 655

Val Tyr Leu Gln Cys Gly Thr Pro Cys Asn Leu Thr Cys Arg Ser Leu
 660 665 670

Ser Tyr Pro Asp Glu Glu Cys Asn Glu Ala Cys Leu Glu Gly Cys Phe
 675 680 685

Cys Pro Pro Gly Leu Tyr Met Asp Glu Arg Gly Asp Cys Val Pro Lys
 690 695 700

Ala	Gln	Cys	Pro	Cys	Tyr	Tyr	Asp	Gly	Glu	Ile	Phe	Gln	Pro	Glu	Asp
705					710					715					720
Ile	Phe	Ser	Asp	His	His	Thr	Met	Cys	Tyr	Cys	Glu	Asp	Gly	Phe	Met
				725					730					735	
His	Cys	Thr	Met	Ser	Gly	Val	Pro	Gly	Ser	Leu	Leu	Pro	Asp	Ala	Val
			740					745					750		
Leu	Ser	Ser	Pro	Leu	Ser	His	Arg	Ser	Lys	Arg	Ser	Leu	Ser	Cys	Arg
		755					760					765			
Pro	Pro	Met	Val	Lys	Leu	Val	Cys	Pro	Ala	Asp	Asn	Leu	Arg	Ala	Glu
		770				775					780				
Gly	Leu	Glu	Cys	Thr	Lys	Thr	Cys	Gln	Asn	Tyr	Asp	Leu	Glu	Cys	Met
785					790					795					800
Ser	Met	Gly	Cys	Val	Ser	Gly	Cys	Leu	Cys	Pro	Pro	Gly	Met	Val	Arg
				805					810					815	
His	Glu	Asn	Arg	Cys	Val	Ala	Leu	Glu	Arg	Cys	Pro	Cys	Phe	His	Gln
			820					825					830		
Gly	Lys	Glu	Tyr	Ala	Pro	Gly	Glu	Thr	Val	Lys	Ile	Gly	Cys	Asn	Thr
		835					840					845			
Cys	Val	Cys	Arg	Asp	Arg	Lys	Trp	Asn	Cys	Thr	Asp	His	Val	Cys	Asp
	850					855					860				
Ala	Thr	Cys	Ser	Thr	Ile	Gly	Met	Ala	His	Tyr	Leu	Thr	Phe	Asp	Gly
865					870					875					880
Leu	Lys	Tyr	Leu	Phe	Pro	Gly	Glu	Cys	Gln	Tyr	Val	Leu	Val	Gln	Asp

885

890

895

Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys
 900 905 910

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

Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys
 930 935 940

Arg Pro Met Lys Asp Glu Thr His Phe Glu Val Val Glu Ser Gly Arg
 945 950 955 960

Tyr Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg
 965 970 975

His Leu Ser Ile Ser Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val
 980 985 990

Cys Gly Leu Cys Gly Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr
 995 1000 1005

Ser Ser Asn Leu Gln Val Glu Glu Asp Pro Val Asp Phe Gly Asn
 1010 1015 1020

Ser Trp Lys Val Ser Ser Gln Cys Ala Asp Thr Arg Lys Val Pro
 1025 1030 1035

Leu Asp Ser Ser Pro Ala Thr Cys His Asn Asn Ile Met Lys Gln
 1040 1045 1050

Thr Met Val Asp Ser Ser Cys Arg Ile Leu Thr Ser Asp Val Phe
 1055 1060 1065

Gln Asp Cys Asn Lys Leu Val Asp Pro Glu Pro Tyr Leu Asp Val
 1070 1075 1080

Cys Ile Tyr Asp Thr Cys Ser Cys Glu Ser Ile Gly Asp Cys Ala
 1085 1090 1095

Ala Phe Cys Asp Thr Ile Ala Ala Tyr Ala His Val Cys Ala Gln
 1100 1105 1110

His Gly Lys Val Val Thr Trp Arg Thr Ala Thr Leu Cys Pro Gln
 1115 1120 1125

Ser Cys Glu Glu Arg Asn Leu Arg Glu Asn Gly Tyr Glu Ala Glu
 1130 1135 1140

Trp Arg Tyr Asn Ser Cys Ala Pro Ala Cys Gln Val Thr Cys Gln
 1145 1150 1155

His Pro Glu Pro Leu Ala Cys Pro Val Gln Cys Val Glu Gly Cys
 1160 1165 1170

His Ala His Cys Pro Pro Gly Lys Ile Leu Asp Glu Leu Leu Gln
 1175 1180 1185

Thr Cys Val Asp Pro Glu Asp Cys Pro Val Cys Glu Val Ala Gly
 1190 1195 1200

Arg Arg Phe Ala Ser Gly Lys Lys Val Thr Leu Asn Pro Ser Asp
 1205 1210 1215

Pro Glu His Cys Gln Ile Cys His Cys Asp Val Val Asn Leu Thr
 1220 1225 1230

Cys Glu Ala Cys Gln Glu Pro Ile Ser Gly Thr Ser Glu Ser Ala
 1235 1240 1245

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
 1250 1255 1260

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
 1265 1270 1275

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
 1280 1285 1290

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro
 1295 1300 1305

Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 1310 1315 1320

Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
 1325 1330 1335

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
 1340 1345 1350

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser
 1355 1360 1365

Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser
 1370 1375 1380

Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
 1385 1390 1395

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
1400 1405 1410

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala
1415 1420 1425

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
1430 1435 1440

Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
1445 1450 1455

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser
1460 1465 1470

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro
1475 1480 1485

Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
1490 1495 1500

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
1505 1510 1515

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Asp Ile Gly
1520 1525 1530

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Val Pro Arg Gly
1535 1540 1545

Ser Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
1550 1555 1560

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro

1565						1570						1575			
Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	
1580						1585					1590				
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	
1595						1600					1605				
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	
1610						1615					1620				
Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	
1625						1630					1635				
Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	
1640						1645					1650				
Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	
1655						1660					1665				
Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	
1670						1675					1680				
Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	
1685						1690					1695				
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	
1700						1705					1710				
Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	
1715						1720					1725				
Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	
1730						1735					1740				

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
 1745 1750 1755

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 1760 1765 1770

Leu Ser Pro Gly Lys
 1775

<210> 88
 <211> 32
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Cleavable linker

<400> 88

Asp Lys Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser
 1 5 10 15

Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
 20 25 30

<210> 89
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Ig constant region portion

<400> 89

Pro Lys Asn Ser Ser Met Ile Ser Asn Thr Pro
 1 5 10

<210> 90
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Ig constant region portion

<400> 90

His Gln Ser Leu Gly Thr Gln
 1 5

<210> 91
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Ig constant region portion

<400> 91

His Gln Asn Leu Ser Asp Gly Lys
 1 5

<210> 92
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Ig constant region portion

<400> 92

His Gln Asn Ile Ser Asp Gly Lys
 1 5

<210> 93
 <211> 8

<212> PRT
 <213> Artificial Sequence

<220>
 <223> Ig constant region portion

<400> 93

Val Ile Ser Ser His Leu Gly Gln
 1 5

<210> 94
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Linker, where the sequence can repeated between 1-20 times

<400> 94

Gly Gly Gly Gly Ser
 1 5

<210> 95
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Linker, where the sequence can be repeated between 1-100
 times or
 1-20 times

<400> 95

Gly Gly Ser Gly Gly Gly Gly Ser
 1 5

<210> 96
 <211> 7
 <212> PRT

<213> Artificial Sequence

<220>

<223> Linker

<400> 96

Ser Gly Gly Ser Gly Gly Ser
1 5

<210> 97

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker

<400> 97

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Gly
1 5 10 15

<210> 98

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker

<400> 98

Gly Gly Ser Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 99

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker

<400> 99

Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly
1				5					10					15	

Gly Ser

<210> 100

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker

<400> 100

Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
1				5					10					15

<210> 101

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> Linker, where the sequence can be repeated between 1-00 times
or

1-20 times

<400> 101

Gly Gly Gly Ser

1

<210> 102

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavage site

<400> 102

Arg Arg Arg Arg

1

<210> 103

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavage site

<400> 103

Arg Lys Arg Arg Lys Arg

1

5

<210> 104

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavage site

<400> 104

Arg Arg Arg Arg Ser

1

5

<210> 105

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> Thrombin cleavable site

<220>

<221> misc_feature

<222> (1)..(1)

<223> Xaa is an aliphatic amino acid

<400> 105

Xaa Val Pro Arg

1

<210> 106

<211> 34

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 106

Ile	Ser	Asp	Lys	Asn	Thr	Gly	Asp	Tyr	Tyr	Glu	Asp	Ser	Tyr	Glu	Asp
1				5					10					15	

Ile	Ser	Ala	Tyr	Leu	Leu	Ser	Lys	Asn	Asn	Ala	Ile	Glu	Pro	Arg	Ser
			20					25					30		

Phe Ser

<210> 107

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 107

Ile Ser Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp Leu
 1 5 10 15

Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser Pro
 20 25 30

Ser Phe Ile Gln Ile Arg Ser Val
 35 40

<210> 108

<211> 46

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 108

Ile Ser Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
 1 5 10 15

Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
 20 25 30

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln
 35 40 45

<210> 109

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> PAR1 exosite interaction motif

<400> 109

Ser Phe Leu Leu Arg Asn

1 5

<210> 110

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> PAR1 exosite interaction motif

<400> 110

Pro Asn Asp Lys

1

<210> 111

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> PAR1 exosite interaction motif

<400> 111

Pro Asn Asp Lys Tyr

1 5

<210> 112

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> PAR1 exosite interaction motif

<400> 112

Pro Asn Asp Lys Tyr Glu

1 5

<210> 113
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> PAR1 exosite interaction motif

<400> 113

Pro Asn Asp Lys Tyr Glu Pro
 1 5

<210> 114
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> PAR1 exosite interaction motif

<400> 114

Pro Asn Asp Lys Tyr Glu Pro Phe
 1 5

<210> 115
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> PAR1 exosite interaction motif

<400> 115

Pro Asn Asp Lys Tyr Glu Pro Phe Trp
 1 5

<210> 116
 <211> 10

<212> PRT
 <213> Artificial Sequence

<220>
 <223> PAR1 exosite interaction motif

<400> 116

Pro	Asn	Asp	Lys	Tyr	Glu	Pro	Phe	Trp	Glu
1				5					10

<210> 117
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> PAR1 exosite interaction motif

<400> 117

Pro	Asn	Asp	Lys	Tyr	Glu	Pro	Phe	Trp	Glu	Asp
1				5					10	

<210> 118
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> PAR1 exosite interaction motif

<400> 118

Pro	Asn	Asp	Lys	Tyr	Glu	Pro	Phe	Trp	Glu	Asp	Glu
1				5					10		

<210> 119
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>

<223> PAR1 exosite interaction motif

<400> 119

Pro	Asn	Asp	Lys	Tyr	Glu	Pro	Phe	Trp	Glu	Asp	Glu	Glu
1				5					10			

<210> 120

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> PAR1 exosite interaction motif

<400> 120

Pro	Asn	Asp	Lys	Tyr	Glu	Pro	Phe	Trp	Glu	Asp	Glu	Glu	Ser
1				5					10				

<210> 121

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> FXIa cleavage site

<400> 121

Lys	Leu	Thr	Arg	Ala	Glu	Thr
1				5		

<210> 122

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> FXIa cleavage site

<400> 122

Asp Phe Thr Arg Val Val Gly
1 5

<210> 123

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> FXIIa cleavage site

<400> 123

Thr Met Thr Arg Ile Val Gly Gly
1 5

<210> 124

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Kallikrein cleavage site

<400> 124

Ser Pro Phe Arg Ser Thr Gly Gly
1 5

<210> 125

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> FVIIa cleavage site

<400> 125

Leu Gln Val Arg Ile Val Gly Gly

1 5

<210> 126
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> FIXa cleavage site

<400> 126

Pro Leu Gly Arg Ile Val Gly Gly
 1 5

<210> 127
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> FXa cleavage site

<400> 127

Ile Glu Gly Arg Thr Val Gly Gly
 1 5

<210> 128
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> FIIa (thrombin) cleavage site

<400> 128

Leu Thr Pro Arg Ser Leu Leu Val
 1 5

<210> 129
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Elastase-2 cleavage site

<400> 129

Leu Gly Pro Val Ser Gly Val Pro
 1 5

<210> 130
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Granzyme-B cleavage

<400> 130

Val Ala Gly Asp Ser Leu Glu Glu
 1 5

<210> 131
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> MMP-12 cleavage site

<400> 131

Gly Pro Ala Gly Leu Gly Gly Ala
 1 5

<210> 132
 <211> 8
 <212> PRT

<213> Artificial Sequence

<220>

<223> MMP-13 cleavage site

<400> 132

Gly Pro Ala Gly Leu Arg Gly Ala
1 5

<210> 133

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> MMP-17 cleavage site

<400> 133

Ala Pro Leu Gly Leu Arg Leu Arg
1 5

<210> 134

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> MMP-20 cleavage site

<400> 134

Pro Ala Leu Pro Leu Val Ala Gln
1 5

<210> 135

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> TEV cleavage site

<400> 135

Glu Asn Leu Tyr Phe Gln Gly
1 5

<210> 136

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Enterokinase cleavage site

<400> 136

Asp Asp Asp Lys Ile Val Gly Gly
1 5

<210> 137

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Protease 3C (PRESCISSIN) cleavage site

<400> 137

Leu Glu Val Leu Phe Gln Gly Pro
1 5

<210> 138

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Sortase A cleavage site

<400> 138

Leu Pro Lys Thr Gly Ser Glu Ser
1 5

<210> 139
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> Cleavable linker

<400> 139

Lys Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala
1 5 10 15

Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
20 25 30

<210> 140
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Cleavable linker

<400> 140

Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr
1 5 10 15

Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
20 25 30

<210> 141
<211> 29
<212> PRT
<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 141

Thr	Gly	Asp	Tyr	Tyr	Glu	Asp	Ser	Tyr	Glu	Asp	Ile	Ser	Ala	Tyr	Leu
1				5					10					15	

Leu	Ser	Lys	Asn	Asn	Ala	Ile	Glu	Pro	Arg	Ser	Phe	Ser
			20					25				

<210> 142

<211> 28

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 142

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

Ser	Lys	Asn	Asn	Ala	Ile	Glu	Pro	Arg	Ser	Phe	Ser
			20					25			

<210> 143

<211> 27

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 143

Asp	Tyr	Tyr	Glu	Asp	Ser	Tyr	Glu	Asp	Ile	Ser	Ala	Tyr	Leu	Leu	Ser
1				5					10					15	

Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
 20 25

<210> 144
 <211> 26
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Cleavable linker

<400> 144

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
 1 5 10 15

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
 20 25

<210> 145
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Thrombin cleavage site

<400> 145

Ala Leu Arg Pro Arg Val Val Gly Gly Ala
 1 5 10

<210> 146
 <211> 25
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Linker

<400> 146

Thr	Leu	Asp	Pro	Arg	Ser	Phe	Leu	Leu	Arg	Asn	Pro	Asn	Asp	Lys	Tyr
1				5					10					15	

Glu	Pro	Phe	Trp	Glu	Asp	Glu	Glu	Lys
			20					25

<210> 147

<211> 4548

<212> DNA

<213> Artificial Sequence

<220>

<223> VWF031

<400> 147

atgattcctg	ccagatttgc	cgggggtgctg	cttgctcttg	ccctcatttt	gccagggacc
60					

ctttgtgcag	aaggaactcg	cggcagggtca	tccacggccc	gatgcagcct	tttcggaagt
120					

gacttcgtca	acacctttga	tgggagcatg	tacagctttg	cgggatactg	cagttacctc
180					

ctggcagggg	gctgccagaa	acgctccttc	tcgattattg	gggacttcca	gaatggcaag
240					

agagtgcagc	tctccgtgta	tcttggggaa	ttttttgaca	tccatttggt	tgtcaatggt
300					

accgtgacac	agggggacca	aagagtctcc	atgccctatg	cctccaaagg	gctgtatcta
360					

gaaactgagg	ctgggtacta	caagctgtcc	ggtgaggcct	atggctttgt	ggccaggatc
420					

gatggcagcg	gcaactttca	agtcctgctg	tcagacagat	acttcaacaa	gacctgcggg
480					

ctgtgtggca	actttaacat	ctttgctgaa	gatgacttta	tgaccaaga	agggaccttg
540					

acctcggacc cttatgactt tgccaactca tgggctctga gcagtggaga acagtgggtgt
 600
 gaacgggcat ctccctcccag cagctcatgc aacatctcct ctgggggaaat gcagaagggc
 660
 ctgtgggagc agtgccagct tctgaagagc acctcgggtgt ttgcccgctg ccaccctctg
 720
 gtggaccccg agcctttttgt ggccctgtgt gagaagactt tgtgtgagtg tgctgggggg
 780
 ctggagtgcg cctgccctgc cctcctggag tacgcccgga cctgtgcca ggagggaatg
 840
 gtgctgtacg gctggaccga ccacagcgcg tgcagcccag tgtgccctgc tggatatggag
 900
 tataggcagt gtgtgtcccc ttgcgccagg acctgccaga gcctgcacat caatgaaatg
 960
 tgtcaggagc gatgcgtgga tggctgcagc tgccctgagg gacagctcct ggatgaaggc
 1020
 ctctgcgtgg agagcaccga gtgtccctgc gtgcattccg gaaagcgcta ccctcccggc
 1080
 acctccctct ctcgagactg caacacctgc atttgccgaa acagccagtg gatctgcagc
 1140
 aatgaagaat gtccagggga gtgccttgtc actgggtcaat cccacttcaa gagctttgac
 1200
 aacagatact tcaccttcag tgggatctgc cagtacctgc tggcccggga ttgccaggac
 1260
 cactccttct ccattgtcat tgagactgtc cagtgtgctg atgaccgcga cgctgtgtgc
 1320
 acccgctccg tcaccgtccg gctgcctggc ctgcacaaca gccttgtgaa actgaagcat
 1380
 ggggcaggag ttgccatgga tggccaggac atccagctcc ccctcctgaa aggtgacctc
 1440

cgcatccagc 1500	atacagtgac	ggcctccgtg	cgccctcagct	acgggggagga	cctgcagatg
gactgggatg 1560	gccgcgggag	gctgctggtg	aagctgtccc	ccgtctatgc	cggaagacc
tgcggcctgt 1620	gtgggaatta	caatggcaac	cagggcgacg	acttccttac	cccctctggg
ctggcggagc 1680	cccgggtgga	ggacttcggg	aacgcctgga	agctgcacgg	ggactgccag
gacctgcaga 1740	agcagcacag	cgatccctgc	gccctcaacc	cgcgcatgac	caggttctcc
gaggaggcgt 1800	gcgcggtcct	gacgtccccc	acattcgagg	cctgccatcg	tgccgtcagc
ccgctgccct 1860	acctgcggaa	ctgccgctac	gacgtgtgct	cctgctcgga	cggccgag
tgctgtgcg 1920	gcgccctggc	cagctatgcc	gcggcctgcg	cggggagagg	cgtgcgcgtc
gcgtggcgcg 1980	agccaggccg	ctgtgagctg	aactgcccga	aaggccaggt	gtacctgcag
tgcgggaccc 2040	cctgcaacct	gacctgccgc	tctctctctt	acccggatga	ggaatgcaat
gaggcctgcc 2100	tggagggtg	cttctgcccc	ccagggtctt	acatggatga	gaggggggac
tgcggtgcca 2160	aggcccagtg	cccctgttac	tatgacggtg	agatcttcca	gccagaagac
atcttctcag 2220	accatcacac	catgtgctac	tgtgaggatg	gcttcatgca	ctgtaccatg
agtggagtcc 2280	ccggaagctt	gctgcctgac	gctgtcctca	gcagtcccct	gtctcatcgc
agcaaaaagga 2340	gcctatcctg	tcggcccccc	atggtcaagc	tggtgtgtcc	cgctgacaac

ctgcgggctg 2400	aagggctcga	gtgtaccaa	acgtgccaga	actatgacct	ggagtgcattg
agcatgggct 2460	gtgtctcttg	ctgcctctgc	ccccgggca	tggtccggca	tgagaacaga
tgtgtggccc 2520	tggaaagggtg	tccctgcttc	catcagggca	aggagtatgc	ccctggagaa
acagtgaaga 2580	ttggctgcaa	cacttgtgtc	tgtcgggacc	ggaagtggaa	ctgcacagac
catgtgtgtg 2640	atgccacgtg	ctccacgata	ggcatggccc	actacctcac	cttcgacggg
ctcaaatacc 2700	tgttccccgg	ggagtgccag	tacgttcttg	tgcaggatta	ctgcggcagt
aaccctggga 2760	cctttcggat	cctagtgggg	aataagggat	gcagccaccc	ctcagtgaaa
tgcaagaaac 2820	gggtcaccat	cctggtggag	ggaggagaga	ttgagctgtt	tgacggggag
gtgaatgtga 2880	agaggcccat	gaaggatgag	actcactttg	aggtggtgga	gtctggccgg
tacatcattc 2940	tgctgctggg	caaagccctc	tccgtggtct	gggaccgcca	cctgagcatc
tccgtggtcc 3000	tgaagcagac	ataccaggag	aaagtgtgtg	gcctgtgtgg	gaattttgat
ggcatccaga 3060	acaatgacct	caccagcagc	aacctccaag	tggaggaaga	ccctgtggac
tttgggaaact 3120	cctggaaagt	gagctcgcag	tgtgctgaca	ccagaaaagt	gcctctggac
tcatcccctg 3180	ccacctgcca	taacaacatc	atgaagcaga	cgatggtgga	ttcctcctgt
agaatcctta 3240	ccagtgacgt	cttccaggac	tgcaacaagc	tggtggaccc	cgagccatat

ctggatgtct gcatttacga cacctgctcc tgtgagtcca ttggggactg cgccgcattc
3300

tgcgacacca ttgctgccta tgcccacgtg tgtgcccagc atggcaaggt ggtgacctgg
3360

aggacggcca cattgtgccc ccagagctgc gaggagagga atctccggga gaacgggtat
3420

gaggctgagt ggcgctataa cagctgtgca cctgcctgtc aagtcacgtg tcagcacctt
3480

gagccactgg cctgccctgt gcagtgtgtg gagggctgcc atgccactg ccctccaggg
3540

aaaatcctgg atgagctttt gcagacctgc gttgacctg aagactgtcc agtgtgtgag
3600

gtggctggcc ggcgttttgc ctcaggaaag aaagtcacct tgaatcccag tgacctgag
3660

cactgccaga tttgccactg tgatgttgtc aacctcacct gtgaagcctg ccaggagccg
3720

atatctggcg gtggagggtc cggtgggcggg ggatccggcg gtggagggtc cggcgggtga
3780

ggttccgggtg gcggggggatc cggtgggcggg ggatccctgg tcccccgggg cagcggcgggt
3840

ggaggttccg gtggcggggg atccgacaaa actcacacat gccaccgtg cccagctcca
3900

gaactcctgg gcggaccgtc agtcttcctc tcccccccaa aaccaagga caccctcatg
3960

atctcccgga cccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag
4020

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg
4080

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac
4140

tggtgaatg gcaaggagta caagtgaag gtctccaaca aagccctccc agccccatc
4200

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacagggtgta caccctgccc
4260

ccatcccgcg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc
4320

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag
4380

accacgcctc ccgtgttgga ctccgacggc tccttcttcc tctacagcaa gctcacctg
4440

gacaagagca ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg
4500

cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtaaataga
4548

<210> 148

<211> 5379

<212> DNA

<213> Artificial Sequence

<220>

<223> VWF034

<400> 148

atgattcctg ccagatttgc cgggggtgctg cttgctctgg ccctcatttt gccagggacc
60

ctttgtgcag aaggaactcg cggcagggtca tccacggccc gatgcagcct tttcggaagt
120

gacttcgtca acacctttga tgggagcatg tacagctttg cgggatactg cagttacctc
180

ctggcagggg gctgccagaa acgctccttc tcgattattg gggacttcca gaatggcaag
240

agagtgaagc tctccgtgta tcttggggaa ttttttgaca tccatttgtt tgtcaatggt
300

accgtgacac aggggggacca aagagtctcc atgccctatg cctccaaagg gctgtatcta
360

gaaactgagg ctgggtacta caagctgtcc ggtgaggcct atggctttgt ggccaggatc
420

gatggcagcg gcaactttca agtcctgctg tcagacagat acttcaacaa gacctgcggg
480

ctgtgtggca actttaacat ctttgctgaa gatgacttta tgaccaaga agggaccttg
540

acctcggacc cttatgactt tgccaactca tgggctctga gcagtggaga acagtggtgt
600

gaacgggcat ctccctcccag cagctcatgc aacatctcct ctggggaaat gcagaagggc
660

ctgtgggagc agtgccagct tctgaagagc acctcggtgt ttgcccgtg ccacctctg
720

gtggaccccg agccttttgt ggccctgtgt gagaagactt tgtgtgagtg tgctgggggg
780

ctggagtgcg cctgccctgc cctcctggag tacgcccgga cctgtgccca ggagggaatg
840

gtgctgtacg gctggaccga ccacagcgcg tgcagcccag tgtgccctgc tggatatggag
900

tataggcagt gtgtgtcccc ttgcgccagg acctgccaga gcctgcacat caatgaaatg
960

tgtcaggagc gatgcgtgga tggctgcagc tgccctgagg gacagctcct ggatgaaggc
1020

ctctgcgtgg agagcaccga gtgtccctgc gtgcattccg gaaagcgcta ccctcccggc
1080

acctccctct ctcgagactg caacacctgc atttgccgaa acagccagtg gatctgcagc
1140

aatgaagaat gtccagggga gtgccttgtc actgggtcaat cccacttcaa gagctttgac
1200

aacagatact tcaccttcag tgggatctgc cagtacctgc tggcccggga ttgccaggac
1260

cactccttct ccattgtcat tgagactgtc cagtgtgctg atgaccgcga cgctgtgtgc
1320

acccgctccg tcaccgtccg gctgcctggc ctgcacaaca gccttgtgaa actgaagcat
1380

ggggcaggag ttgccatgga tggccaggac atccagctcc ccctcctgaa aggtgacctc
1440

cgcattccagc atacagtgc ggcctccgtg cgcctcagct acggggagga cctgcagatg
1500

gactgggatg gccgcgggag gctgctggtg aagctgtccc ccgtctatgc cgggaagacc
1560

tgcggcctgt gtgggaatta caatggcaac cagggcgacg acttccttac cccctctggg
1620

ctggcggagc cccgggtgga ggacttcggg aacgcctgga agctgcacgg ggactgccag
1680

gacctgcaga agcagcacag cgatccctgc gccctcaacc cgcgcatgac caggttctcc
1740

gaggaggcgt gcgcggtcct gacgtccccc acattcgagg cctgccatcg tgccgtcagc
1800

ccgctgccct acctgcggaa ctgccgctac gacgtgtgct cctgctcgga cggccgcgag
1860

tgcctgtgcg gcgccctggc cagctatgcc gcggcctgcg cggggagagg cgtgcgcgtc
1920

gcgtggcgcg agccaggccg ctgtgagctg aactgcccga aaggccaggt gtacctgcag
1980

tgcgggaccc cctgcaacct gacctgccgc tctctctctt acccggatga ggaatgcaat
2040

gaggcctgcc tggagggctg cttctgcccc ccagggctct acatggatga gaggggggac
2100

tgcgtgcca aggccagtg cccctgttac tatgacgggtg agatcttcca gccagaagac
 2160

atcttctcag accatcacac catgtgctac tgtgaggatg gcttcatgca ctgtaccatg
 2220

agtggagtcc ccggaagctt gctgcctgac gctgtcctca gcagtcccct gtctcatcgc
 2280

agcaaaagga gcctatcctg tcggccccc atggtcaagc tgggtgtgtcc cgctgacaac
 2340

ctgcgggctg aagggtcga gtgtaccaa acgtgccaga actatgacct ggagtgcattg
 2400

agcatgggct gtgtctctgg ctgcctctgc cccccgggca tgggtccggca tgagaacaga
 2460

tgtgtggccc tggaaagggtg tccctgcttc catcagggca aggagtatgc ccctggagaa
 2520

acagtgaaga ttggctgcaa cacttgtgtc tgctcgggacc ggaagtggaa ctgcacagac
 2580

catgtgtgtg atgccacgtg ctccacgata ggcatggccc actacctcac cttcgacggg
 2640

ctcaaatacc tgttccccgg ggagtgccag tacgttctgg tgcaggatta ctgcggcagt
 2700

aaccctggga cctttcggat cctagtgggg aataagggat gcagccaccc ctcaagtga
 2760

tgcaagaaac gggtcacat cctgggtggag ggaggagaga ttgagctgtt tgacggggag
 2820

gtgaatgtga agaggccat gaaggatgag actcactttg aggtgggtgga gtctggccgg
 2880

tacatcattc tgctgctggg caaagccctc tccgtgggtc tggaccgcca cctgagcatc
 2940

tccgtgggtc tgaagcagac ataccaggag aaagtgtgtg gcctgtgtgg gaattttgat
 3000

ggcatccaga acaatgacct caccagcagc aacctccaag tggaggaaga ccctgtggac
3060

tttggaact cctggaaagt gagctcgag tgtgctgaca ccagaaaagt gcctctggac
3120

tcatcccctg ccacctgcca taacaacatc atgaagcaga cgatggtgga ttcctcctgt
3180

agaatcctta ccagtgcgt cttccaggac tgcaacaagc tgggtggacc cgagccatat
3240

ctggatgtct gcatttacga cacctgctcc tgtgagtcca ttggggactg cgccgcattc
3300

tgcgacacca ttgctgccta tgcccacgtg tgtgcccagc atggcaaggt ggtgacctgg
3360

aggacggcca cattgtgccc ccagagctgc gaggagagga atctccggga gaacgggtat
3420

gaggctgagt ggcgtataa cagctgtgca cctgcctgtc aagtcacgtg tcagcacctt
3480

gagccactgg cctgccctgt gcagtgtgtg gagggctgcc atgcccactg ccctccaggg
3540

aaaatcctgg atgagctttt gcagacctgc gttgacctg aagactgtcc agtgtgtgag
3600

gtggctggcc ggcgttttgc ctcaggaaag aaagtcacct tgaatcccag tgacctgag
3660

cactgccaga tttgccactg tgatgttgtc aacctcacct gtgaagcctg ccaggagccg
3720

atatcgggta cctcagagtc tgctaccccc gagtcagggc caggatcaga gccagccacc
3780

tccgggtctg agacacccgg gacttccgag agtgccaccc ctgagtccgg acccgggtcc
3840

gagcccgcca cttccggctc cgaaactccc ggcacaagcg agagcgctac cccagagtca
3900

ggaccaggaa catctacaga gccctctgaa ggctccgctc cagggtcccc agccggcagt
3960

cccactagca ccgaggaggg aacctctgaa agcgccacac ccgaatcagg gccagggtct
4020

gagcctgcta ccagcggcag cgagacacca ggcacctctg agtccgccac accagagtcc
4080

ggacccggat ctcccgtgg gagccccacc tccactgagg agggatctcc tgctggctct
4140

ccaacatcta ctgaggaagg tacctcaacc gagccatccg agggatcagc tcccggcacc
4200

tcagagtcgg caaccccgga gtctggaccc ggaacttccg aaagtgccac accagagtcc
4260

gggtcccggga cttcagaatc agcaacaccc gagtccggcc ctgggtctga acccgccaca
4320

agtggtagtg agacaccagg atcagaacct gctacctcag ggtcagagac acccggtatct
4380

ccggcaggct caccaacctc cactgaggag ggcaccagca cagaaccaag cgagggtctcc
4440

gcacccggaa caagcactga acccagtgag gggtcagcac ccggctctga gccggccaca
4500

agtggcagtg agacacccgg cacttcagag agtgccaccc ccgagagtgg cccaggcact
4560

agtaccgagc cctctgaagg cagtgcgcca gattctggcg gtggagggttc cgggtggcggg
4620

ggatccggtg gcggggggatc cggtggcggg ggatccggtg gcggggggatc cctgggtcccc
4680

cggggcagcg gaggcgacaa aactcacaca tgcccaccgt gccagctcc agaactcctg
4740

ggcggaccgt cagtcttcct cttcccccca aaaccaagg acaccctcat gatctcccgg
4800

acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc
4860

aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag
4920

tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat
4980

ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagcccccat cgagaaaacc
5040

atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg
5100

gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc
5160

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct
5220

cccgtgttgg actccgacgg ctctttcttc ctctacagca agctcaccgt ggacaagagc
5280

aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac
5340

t a c a c g c a g a a g a g c c t c t c c c t g t c t c c g g g t a a a t g a
5379

<210> 149

<211> 4548

<212> DNA

<213> Artificial Sequence

<220>

<223> VWF050 (IHH triple mutant)

<400> 149

atgattcctg ccagatttgc cggggtgctg cttgctctgg ccctcatttt gccagggacc
60

ctttgtgcag aaggaactcg cggcagggtca tccacggccc gatgcagcct tttcggaagt
120

gacttcgtca acacctttga tgggagcatg tacagctttg cgggatactg cagttacctc
 180
 ctggcagggg gctgccagaa acgctccttc tcgattattg gggacttcca gaatggcaag
 240
 agagtgagcc tctccgtgta tcttggggaa ttttttgaca tccatttggt tgtcaatggg
 300
 accgtgacac agggggacca aagagtctcc atgccctatg cctccaaagg gctgtatcta
 360
 gaaactgagg ctgggtacta caagctgtcc ggtgaggcct atggctttgt ggccaggatc
 420
 gatggcagcg gcaactttca agtcctgctg tcagacagat acttcaacaa gacctgcggg
 480
 ctgtgtggca actttaacat ctttgctgaa gatgacttta tgaccaaga agggaccttg
 540
 acctcggacc cttatgactt tgccaactca tgggctctga gcagtggaga acagtgggtg
 600
 gaacgggcat ctccctccag cagctcatgc aacatctcct ctggggaaat gcagaagggc
 660
 ctgtgggagc agtgccagct tctgaagagc acctcgggtg ttgcccgtg ccaccctctg
 720
 gtggaccccg agccttttgt ggccctgtgt gagaagactt tgtgtgagtg tgctgggggg
 780
 ctggagtgcg cctgccctgc cctcctggag tacgcccga cctgtgccca ggagggaatg
 840
 gtgctgtacg gctggaccga ccacagcgcg tgcagcccag tgtgccctgc tggtatggag
 900
 tataggcagt gtgtgtcccc ttgcgccagg acctgccaga gcctgcacat caatgaaatg
 960
 tgtcaggagc gatgcgtgga tggctgcagc tgccctgagg gacagctcct ggatgaaggc
 1020

ctctgcgtgg agagcaccga gtgtccctgc gtgcattccg gaaagcgcta ccctcccggc
1080

acctccctct ctcgagactg caacacctgc atttgccgaa acagccagtg gatctgcagc
1140

aatgaagaat gtccagggga gtgccttgtc actgggtcaat cccacttcaa gagctttgac
1200

aacagatact tcaccttcag tgggatctgc cagtacctgc tggcccggga ttgccaggac
1260

cactccttct ccattgtcat tgagactgtc cagtgtgctg atgaccgcga cgctgtgtgc
1320

acccgctccg tcaccgtccg gctgcctggc ctgcacaaca gccttgtgaa actgaagcat
1380

ggggcaggag ttgccatgga tggccaggac atccagctcc ccctcctgaa aggtgacctc
1440

cgcattccagc atacagtgac ggcctccgtg cgcctcagct acggggagga cctgcagatg
1500

gactgggatg gccgcgggag gctgctggtg aagctgtccc ccgtctatgc cgggaagacc
1560

tgcggcctgt gtgggaatta caatggcaac cagggcgacg acttccttac cccctctggg
1620

ctggcggagc cccgggtgga ggacttcggg aacgcctgga agctgcacgg ggactgccag
1680

gacctgcaga agcagcacag cgatccctgc gccctcaacc cgcgcatgac caggttctcc
1740

gaggaggcgt gcgcggtcct gacgtccccc acattcgagg cctgccatcg tgccgtcagc
1800

ccgctgccct acctgcggaa ctgccgctac gacgtgtgct cctgctcgga cggccgcgag
1860

tgctgtgcg gcgccctggc cagctatgcc gcggcctgcg cggggagagg cgtgcgcgtc
1920

gcgtggcgcg agccaggccg ctgtgagctg aactgcccga aaggccaggt gtacctgcag
 1980

tgcgggaccc cctgcaacct gacctgccgc tctctctctt acccggatga ggaatgcaat
 2040

gaggcctgcc tggagggctg cttctgcccc ccagggctct acatggatga gaggggggac
 2100

tgcgtgccc aaggcccagtg cccctgttac tatgacgggtg agatcttcca gccagaagac
 2160

atcttctcag accatcacac catgtgctac tgtgaggatg gcttcatgca ctgtaccatg
 2220

agtggagtcc ccggaagctt gctgcctgac gctgtcctca gcagtcccct gtctcatcgc
 2280

agcaaaagga gcctatcctg tcggcccccc atgggtcaagc tgggtgtgtcc cgctgacaac
 2340

ctgcgggctg aagggtcga gtgtaccaa acgtgccaga actatgacct ggagtgcattg
 2400

agcatgggct gtgtctctgg ctgcctctgc cccccgggca tgggtccggca tgagaacaga
 2460

tgtgtggccc tggaaagggtg tccctgcttc catcagggca aggagtatgc ccctggagaa
 2520

acagtgaaga ttggctgcaa cacttgtgtc tgtcgggacc ggaagtggaa ctgcacagac
 2580

catgtgtgtg atgccacgtg ctccacgac ggcatggccc actacctcac cttcgacggg
 2640

ctcaaatacc tgttccccgg ggagtgccag tacgttctgg tgcaggatta ctgcggcagt
 2700

aaccctggga cctttcggat cctagtgggg aataagggat gcagccaccc ctcaagtga
 2760

tgcaagaaac gggtcaccat cctgggtggag ggaggagaga ttgagctgtt tgacggggag
 2820

gtgaatgtga agaggcccat gaaggatgag actcactttg aggtggtgga gtctggccgg
2880

tacatcattc tgctgctggg caaagccctc tccgtggtct gggaccgcca cctgagcatc
2940

tccgtggtcc tgaagcagac ataccaggag aaagtgtgtg gcctgtgtgg gaattttgat
3000

ggcatccaga acaatgacct caccagcagc aacctccaag tggaggaaga ccctgtggac
3060

tttggaact cctggaaagt gagctcgcag tgtgctgaca ccagaaaagt gcctctggac
3120

tcatcccctg ccacctgcca taacaacatc atgaagcaga cgatggtgga ttctctctgt
3180

agaatcctta ccagtgcgt cttccaggac tgcaacaagc tgggtggacc cgagccatat
3240

ctggatgtct gcatttacga cacctgctcc tgtgagtcca ttggggactg cgccgcattc
3300

tgcgacacca ttgctgccta tgcccacgtg tgtgcccagc atggcaaggt ggtgacctgg
3360

aggacggcca cattgtgccc ccagagctgc gaggagagga atctccggga gaacgggtat
3420

gaggctgagt ggcgctataa cagctgtgca cctgcctgtc aagtcacgtg tcagcacctc
3480

gagccactgg cctgccctgt gcagtgtgtg gagggctgcc atgcccactg ccctccaggg
3540

aaaatcctgg atgagctttt gcagacctgc gttgacctg aagactgtcc agtgtgtgag
3600

gtggctggcc ggcgttttgc ctcaggaaag aaagtcacct tgaatcccag tgacctgag
3660

cactgccaga ttgcccactg tgatgttgtc aacctcacct gtgaagcctg ccaggagccg
3720

atatctggcg gtggagggttc cgggtggcggg ggatccggcg gtggagggttc cggcgggtgga
3780

ggttccgggtg gcggggggatc cgggtggcggg ggatccctgg tcccccgggg cagcggcggt
3840

ggaggttccg gtggcggggg atccgacaaa actcacacat gcccaccgtg cccagctcca
3900

gaactcctgg gcggaccgtc agtcttcctc ttccccccaa aaccaagga caccctcatg
3960

gcctcccgga cccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag
4020

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg
4080

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct ggcccaggac
4140

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagccctccc agcccccatc
4200

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacagggtgta caccctgccc
4260

ccatcccgcg atgagctgac caagaaccag gtcagcctga cctgcctggg caaaggcttc
4320

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag
4380

accacgcctc ccgtgttgga ctccgacggc tccttcttcc tctacagcaa gctcaccgtg
4440

gacaagagca ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg
4500

cacaacgcct acacgcagaa gagcctctcc ctgtctccgg gtaaataga
4548

<210> 150

<211> 1515
 <212> PRT
 <213> Artificial Sequence

<220>

<223> VWF050 (IHH triple mutant)

<400> 150

Met Ile Pro Ala Arg Phe Ala Gly Val Leu Leu Ala Leu Ala Leu Ile
 1 5 10 15

Leu Pro Gly Thr Leu Cys Ala Glu Gly Thr Arg Gly Arg Ser Ser Thr
 20 25 30

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

Ser Met Tyr Ser Phe Ala Gly Tyr Cys Ser Tyr Leu Leu Ala Gly Gly
 50 55 60

Cys Gln Lys Arg Ser Phe Ser Ile Ile Gly Asp Phe Gln Asn Gly Lys
 65 70 75 80

Arg Val Ser Leu Ser Val Tyr Leu Gly Glu Phe Phe Asp Ile His Leu
 85 90 95

Phe Val Asn Gly Thr Val Thr Gln Gly Asp Gln Arg Val Ser Met Pro
 100 105 110

Tyr Ala Ser Lys Gly Leu Tyr Leu Glu Thr Glu Ala Gly Tyr Tyr Lys
 115 120 125

Leu Ser Gly Glu Ala Tyr Gly Phe Val Ala Arg Ile Asp Gly Ser Gly
 130 135 140

Asn Phe Gln Val Leu Leu Ser Asp Arg Tyr Phe Asn Lys Thr Cys Gly
 145 150 155 160

Leu Cys Gly Asn Phe Asn Ile Phe Ala Glu Asp Asp Phe Met Thr Gln
 165 170 175

Glu Gly Thr Leu Thr Ser Asp Pro Tyr Asp Phe Ala Asn Ser Trp Ala
 180 185 190

Leu Ser Ser Gly Glu Gln Trp Cys Glu Arg Ala Ser Pro Pro Ser Ser
 195 200 205

Ser Cys Asn Ile Ser Ser Gly Glu Met Gln Lys Gly Leu Trp Glu Gln
 210 215 220

Cys Gln Leu Leu Lys Ser Thr Ser Val Phe Ala Arg Cys His Pro Leu
 225 230 235 240

Val Asp Pro Glu Pro Phe Val Ala Leu Cys Glu Lys Thr Leu Cys Glu
 245 250 255

Cys Ala Gly Gly Leu Glu Cys Ala Cys Pro Ala Leu Leu Glu Tyr Ala
 260 265 270

Arg Thr Cys Ala Gln Glu Gly Met Val Leu Tyr Gly Trp Thr Asp His
 275 280 285

Ser Ala Cys Ser Pro Val Cys Pro Ala Gly Met Glu Tyr Arg Gln Cys
 290 295 300

Val Ser Pro Cys Ala Arg Thr Cys Gln Ser Leu His Ile Asn Glu Met
 305 310 315 320

Cys Gln Glu Arg Cys Val Asp Gly Cys Ser Cys Pro Glu Gly Gln Leu

325

330

335

Leu Asp Glu Gly Leu Cys Val Glu Ser Thr Glu Cys Pro Cys Val His
 340 345 350

Ser Gly Lys Arg Tyr Pro Pro Gly Thr Ser Leu Ser Arg Asp Cys Asn
 355 360 365

Thr Cys Ile Cys Arg Asn Ser Gln Trp Ile Cys Ser Asn Glu Glu Cys
 370 375 380

Pro Gly Glu Cys Leu Val Thr Gly Gln Ser His Phe Lys Ser Phe Asp
 385 390 395 400

Asn Arg Tyr Phe Thr Phe Ser Gly Ile Cys Gln Tyr Leu Leu Ala Arg
 405 410 415

Asp Cys Gln Asp His Ser Phe Ser Ile Val Ile Glu Thr Val Gln Cys
 420 425 430

Ala Asp Asp Arg Asp Ala Val Cys Thr Arg Ser Val Thr Val Arg Leu
 435 440 445

Pro Gly Leu His Asn Ser Leu Val Lys Leu Lys His Gly Ala Gly Val
 450 455 460

Ala Met Asp Gly Gln Asp Ile Gln Leu Pro Leu Leu Lys Gly Asp Leu
 465 470 475 480

Arg Ile Gln His Thr Val Thr Ala Ser Val Arg Leu Ser Tyr Gly Glu
 485 490 495

Asp Leu Gln Met Asp Trp Asp Gly Arg Gly Arg Leu Leu Val Lys Leu
 500 505 510

Ser Pro Val Tyr Ala Gly Lys Thr Cys Gly Leu Cys Gly Asn Tyr Asn
 515 520 525

Gly Asn Gln Gly Asp Asp Phe Leu Thr Pro Ser Gly Leu Ala Glu Pro
 530 535 540

Arg Val Glu Asp Phe Gly Asn Ala Trp Lys Leu His Gly Asp Cys Gln
 545 550 555 560

Asp Leu Gln Lys Gln His Ser Asp Pro Cys Ala Leu Asn Pro Arg Met
 565 570 575

Thr Arg Phe Ser Glu Glu Ala Cys Ala Val Leu Thr Ser Pro Thr Phe
 580 585 590

Glu Ala Cys His Arg Ala Val Ser Pro Leu Pro Tyr Leu Arg Asn Cys
 595 600 605

Arg Tyr Asp Val Cys Ser Cys Ser Asp Gly Arg Glu Cys Leu Cys Gly
 610 615 620

Ala Leu Ala Ser Tyr Ala Ala Ala Cys Ala Gly Arg Gly Val Arg Val
 625 630 635 640

Ala Trp Arg Glu Pro Gly Arg Cys Glu Leu Asn Cys Pro Lys Gly Gln
 645 650 655

Val Tyr Leu Gln Cys Gly Thr Pro Cys Asn Leu Thr Cys Arg Ser Leu
 660 665 670

Ser Tyr Pro Asp Glu Glu Cys Asn Glu Ala Cys Leu Glu Gly Cys Phe
 675 680 685

Cys Pro Pro Gly Leu Tyr Met Asp Glu Arg Gly Asp Cys Val Pro Lys
 690 695 700

Ala Gln Cys Pro Cys Tyr Tyr Asp Gly Glu Ile Phe Gln Pro Glu Asp
 705 710 715 720

Ile Phe Ser Asp His His Thr Met Cys Tyr Cys Glu Asp Gly Phe Met
 725 730 735

His Cys Thr Met Ser Gly Val Pro Gly Ser Leu Leu Pro Asp Ala Val
 740 745 750

Leu Ser Ser Pro Leu Ser His Arg Ser Lys Arg Ser Leu Ser Cys Arg
 755 760 765

Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp Asn Leu Arg Ala Glu
 770 775 780

Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr Asp Leu Glu Cys Met
 785 790 795 800

Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro Pro Gly Met Val Arg
 805 810 815

His Glu Asn Arg Cys Val Ala Leu Glu Arg Cys Pro Cys Phe His Gln
 820 825 830

Gly Lys Glu Tyr Ala Pro Gly Glu Thr Val Lys Ile Gly Cys Asn Thr
 835 840 845

Cys Val Cys Arg Asp Arg Lys Trp Asn Cys Thr Asp His Val Cys Asp
 850 855 860

Ala Thr Cys Ser Thr Ile Gly Met Ala His Tyr Leu Thr Phe Asp Gly
865 870 875 880

Leu Lys Tyr Leu Phe Pro Gly Glu Cys Gln Tyr Val Leu Val Gln Asp
885 890 895

Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys
900 905 910

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

Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys
930 935 940

Arg Pro Met Lys Asp Glu Thr His Phe Glu Val Val Glu Ser Gly Arg
945 950 955 960

Tyr Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg
965 970 975

His Leu Ser Ile Ser Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val
980 985 990

Cys Gly Leu Cys Gly Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr
995 1000 1005

Ser Ser Asn Leu Gln Val Glu Glu Asp Pro Val Asp Phe Gly Asn
1010 1015 1020

Ser Trp Lys Val Ser Ser Gln Cys Ala Asp Thr Arg Lys Val Pro
1025 1030 1035

Leu Asp Ser Ser Pro Ala Thr Cys His Asn Asn Ile Met Lys Gln

1040						1045						1050			
Thr	Met	Val	Asp	Ser	Ser	Cys	Arg	Ile	Leu	Thr	Ser	Asp	Val	Phe	
1055						1060					1065				
Gln	Asp	Cys	Asn	Lys	Leu	Val	Asp	Pro	Glu	Pro	Tyr	Leu	Asp	Val	
1070						1075					1080				
Cys	Ile	Tyr	Asp	Thr	Cys	Ser	Cys	Glu	Ser	Ile	Gly	Asp	Cys	Ala	
1085						1090					1095				
Ala	Phe	Cys	Asp	Thr	Ile	Ala	Ala	Tyr	Ala	His	Val	Cys	Ala	Gln	
1100						1105					1110				
His	Gly	Lys	Val	Val	Thr	Trp	Arg	Thr	Ala	Thr	Leu	Cys	Pro	Gln	
1115						1120					1125				
Ser	Cys	Glu	Glu	Arg	Asn	Leu	Arg	Glu	Asn	Gly	Tyr	Glu	Ala	Glu	
1130						1135					1140				
Trp	Arg	Tyr	Asn	Ser	Cys	Ala	Pro	Ala	Cys	Gln	Val	Thr	Cys	Gln	
1145						1150					1155				
His	Pro	Glu	Pro	Leu	Ala	Cys	Pro	Val	Gln	Cys	Val	Glu	Gly	Cys	
1160						1165					1170				
His	Ala	His	Cys	Pro	Pro	Gly	Lys	Ile	Leu	Asp	Glu	Leu	Leu	Gln	
1175						1180					1185				
Thr	Cys	Val	Asp	Pro	Glu	Asp	Cys	Pro	Val	Cys	Glu	Val	Ala	Gly	
1190						1195					1200				
Arg	Arg	Phe	Ala	Ser	Gly	Lys	Lys	Val	Thr	Leu	Asn	Pro	Ser	Asp	
1205						1210					1215				

Pro Glu His Cys Gln Ile Cys His Cys Asp Val Val Asn Leu Thr
 1220 1225 1230

Cys Glu Ala Cys Gln Glu Pro Ile Ser Gly Gly Gly Gly Ser Gly
 1235 1240 1245

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 1250 1255 1260

Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Val Pro Arg Gly Ser
 1265 1270 1275

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr
 1280 1285 1290

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
 1295 1300 1305

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ala Ser Arg
 1310 1315 1320

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
 1325 1330 1335

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 1340 1345 1350

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 1355 1360 1365

Arg Val Val Ser Val Leu Thr Val Leu Ala Gln Asp Trp Leu Asn
 1370 1375 1380

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
 1385 1390 1395

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
 1400 1405 1410

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
 1415 1420 1425

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
 1430 1435 1440

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 1445 1450 1455

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 1460 1465 1470

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
 1475 1480 1485

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Ala
 1490 1495 1500

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 1505 1510 1515

<210> 151

<211> 4959

<212> DNA

<213> Artificial Sequence

<220>

<223> VWF057

<400> 151

atgattcctg ccagatttgc cggggtgctg cttgctctgg ccctcatttt gccagggacc
60

ctttgtgcag aaggaactcg cggcagggtca tccacggccc gatgcagcct tttcggaagt
120

gacttcgtca acacctttga tgggagcatg tacagctttg cgggatactg cagttacctc
180

ctggcagggg gctgccagaa acgctccttc tcgattattg gggacttcca gaatggcaag
240

agagtgcgcc tctccgtgta tcttggggaa ttttttgaca tccatttggt tgtcaatggt
300

accgtgacac agggggacca aagagtctcc atgccctatg cctccaaagg gctgtatcta
360

gaaactgagg ctgggtacta caagctgtcc ggtgaggcct atggctttgt ggccaggatc
420

gatggcagcg gcaactttca agtcctgctg tcagacagat acttcaacaa gacctgcggg
480

ctgtgtggca actttaacat ctttgctgaa gatgacttta tgaccaaga agggaccttg
540

acctcggacc cttatgactt tgccaactca tgggctctga gcagtggaga acagtggtgt
600

gaacgggcat ctccctccag cagctcatgc aacatctcct ctggggaaat gcagaagggc
660

ctgtgggagc agtgccagct tctgaagagc acctcggtgt ttgcccgtg ccaccctctg
720

gtggaccccg agccttttgt ggccctgtgt gagaagactt tgtgtgagtg tgctgggggg
780

ctggagtgcg cctgccctgc cctcctggag tacgcccgga cctgtgccca ggagggaatg
840

gtgctgtacg gctggaccga ccacagcgcg tgcagcccag tgtgccctgc tgggtatggag
900

tataggcagt 960	gtgtgtcccc	ttgcgccagg	acctgccaga	gcctgcacat	caatgaaatg
tgtcaggagc 1020	gatgcgtgga	tggctgcagc	tgccctgagg	gacagctcct	ggatgaaggc
ctctgcgtgg 1080	agagcaccga	gtgtccctgc	gtgcattccg	gaaagcgcta	ccctcccggc
acctccctct 1140	ctcgagactg	caacacctgc	atttgccgaa	acagccagtg	gatctgcagc
aatgaagaat 1200	gtccagggga	gtgccttgtc	actgggtcaat	cccacttcaa	gagctttgac
aacagatact 1260	tcaccttcag	tgggatctgc	cagtacctgc	tggcccggga	ttgccaggac
cactccttct 1320	ccattgtcat	tgagactgtc	cagtgtgctg	atgaccgcga	cgctgtgtgc
acccgctccg 1380	tcaccgtccg	gctgcctggc	ctgcacaaca	gccttgtgaa	actgaagcat
ggggcaggag 1440	ttgccatgga	tggccaggac	atccagctcc	ccctcctgaa	aggtgacctc
cgcattccagc 1500	atacagtgac	ggcctccgtg	cgcctcagct	acggggagga	cctgcagatg
gactgggatg 1560	gccgcgggag	gctgctggtg	aagctgtccc	ccgtctatgc	cgggaagacc
tgcggcctgt 1620	gtgggaatta	caatggcaac	cagggcgacg	acttccttac	cccctctggg
ctggcggagc 1680	cccgggtgga	ggacttcggg	aacgcctgga	agctgcacgg	ggactgccag
gacctgcaga 1740	agcagcacag	cgatccctgc	gccctcaacc	cgcgcatgac	caggttctcc
gaggaggcgt 1800	gcgcggtcct	gacgtccccc	acattcgagg	cctgccatcg	tgccgtcagc

ccgctgccct acctgcggaa ctgccgctac gacgtgtgct cctgctcgga cggccgcgag
1860

tgcctgtgcg gcgccctggc cagctatgcc gcggcctgcg cggggagagg cgtgcgcgtc
1920

gcgtggcgcg agccaggccg ctgtgagctg aactgcccga aaggccaggt gtacctgcag
1980

tgcgggaccc cctgcaacct gacctgccgc tctctctctt acccggatga ggaatgcaat
2040

gaggcctgcc tggagggctg cttctgcccc ccagggtctt acatggatga gaggggggac
2100

tgcgtgcccc aggcccagtg cccctgttac tatgacggtg agatcttcca gccagaagac
2160

atcttctcag accatcacac catgtgctac tgtgaggatg gcttcatgca ctgtaccatg
2220

agtggagtcc ccggaagctt gctgcctgac gctgtcctca gcagtcccct gtctcatcgc
2280

agcaaaagga gcctatcctg tcggcccccc atgggtcaagc tgggtgtgtcc cgctgacaac
2340

ctgcgggctg aagggtcga gtgtaccaa acgtgccaga actatgacct ggagtgcattg
2400

agcatgggct gtgtctctgg ctgcctctgc cccccgggca tgggtccggca tgagaacaga
2460

tgtgtggccc tggaaggtg tccctgcttc catcagggca aggagtatgc ccctggagaa
2520

acagtgaaga ttggctgcaa cacttgtgtc tgtcgggacc ggaagtggaa ctgcacagac
2580

catgtgtgtg atgccacgtg ctccacgata ggcatggccc actacctcac cttcgacggg
2640

ctcaaatacc tgttccccgg ggagtgccag tacgttctgg tgcaggatta ctgcggcagt
2700

aaccctggga 2760	ccttttcggat	cctagtgggg	aataagggat	gcagccaccc	ctcagtgaaa
tgcaagaaac 2820	gggtcaccat	cctggtggag	ggaggagaga	ttgagctgtt	tgacggggag
gtgaatgtga 2880	agaggcccat	gaaggatgag	actcactttg	aggtggtgga	gtctggccgg
tacatcattc 2940	tgctgctggg	caaagccctc	tccgtggtct	gggaccgcca	cctgagcatc
tccgtggtcc 3000	tgaagcagac	ataccaggag	aaagtgtgtg	gcctgtgtgg	gaattttgat
ggcatccaga 3060	acaatgacct	caccagcagc	aacctccaag	tggaggaaga	ccctgtggac
tttggaact 3120	cctggaaagt	gagctcgcag	tgtgctgaca	ccagaaaagt	gcctctggac
tcatcccctg 3180	ccacctgcca	taacaacatc	atgaagcaga	cgatggtgga	ttcctcctgt
agaatcctta 3240	ccagtgacgt	cttccaggac	tgcaacaagc	tggtggaccc	cgagccatat
ctggatgtct 3300	gcattttacga	cacctgctcc	tgtgagtcca	ttggggactg	cgccgcattc
tgcgacacca 3360	ttgctgccta	tgcccacgtg	tgtgcccagc	atggcaaggt	ggtgacctgg
aggacggcca 3420	cattgtgccc	ccagagctgc	gaggagagga	atctccggga	gaacgggtat
gaggctgagt 3480	ggcgctataa	cagctgtgca	cctgcctgtc	aagtcacgtg	tcagcaccct
gagccactgg 3540	cctgccctgt	gcagtgtgtg	gagggctgcc	atgcccactg	ccctccaggg
aaaatcctgg 3600	atgagctttt	gcagacctgc	gttgaccctg	aagactgtcc	agtgtgtgag

gtggctggcc ggcgttttgc ctcaggaaag aaagtcacct tgaatcccag tgaccctgag
3660

cactgccaga tttgccactg tgatgttgtc aacctcacct gtgaagcctg ccaggagccg
3720

atatcgggcg cgccaacatc agagagcgcc acccctgaaa gtggtcccgg gagcgagcca
3780

gccacatctg ggtcggaaac gccaggcaca agtgagtctg caactcccga gtccggacct
3840

ggctccgagc ctgccactag cggctccgag actccgggaa cttccgagag cgctacacca
3900

gaaagcggac ccggaaccag taccgaacct agcgagggct ctgctccggg cagcccagcc
3960

ggctctccta catccacgga ggagggcact tccgaatccg ccaccccgga gtcagggccca
4020

ggatctgaac ccgctacctc aggcagtgag acgccaggaa cgagcgagtc cgctacaccg
4080

gagagtgggc caggagagccc tgctggatct cctacgtcca ctgaggaagg gtcaccagcg
4140

ggctcgccca ccagcactga agaaggtgcc tcgagcggcg gtggaggttc cgggtggcggg
4200

ggatccggtg gcggggggtc cgggtggcggg ggatccggtg gcggggggtc cctgggtcccc
4260

cggggcagcg gaggcgacaa aactcacaca tgcccaccgt gccagctcc agaactcctg
4320

ggcggaccgt cagtcttcct cttcccccca aaaccaagg acaccctcat gatctcccg
4380

acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc
4440

aactggtacg tggacggcgt ggaggtgcat aatgccaaaga caaagccgcg ggaggagcag
4500

tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat
4560

ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagcccccat cgagaaaacc
4620

atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg
4680

gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc
4740

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct
4800

cccggtgttg actccgacgg ctcccttcttc ctctacagca agctcaccgt ggacaagagc
4860

aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac
4920

tacacgcaga agagcctctc cctgtctccg ggtaaataga
4959

<210> 152

<211> 1652

<212> PRT

<213> Artificial Sequence

<220>

<223> VWF057

<400> 152

Met Ile Pro Ala Arg Phe Ala Gly Val Leu Leu Ala Leu Ala Leu Ile
1 5 10 15

Leu Pro Gly Thr Leu Cys Ala Glu Gly Thr Arg Gly Arg Ser Ser Thr
20 25 30

Ala Arg Cys Ser Leu Phe Gly Ser Asp Phe Val Asn Thr Phe Asp Gly

35

40

45

Ser Met Tyr Ser Phe Ala Gly Tyr Cys Ser Tyr Leu Leu Ala Gly Gly
50 55 60

Cys Gln Lys Arg Ser Phe Ser Ile Ile Gly Asp Phe Gln Asn Gly Lys
65 70 75 80

Arg Val Ser Leu Ser Val Tyr Leu Gly Glu Phe Phe Asp Ile His Leu
85 90 95

Phe Val Asn Gly Thr Val Thr Gln Gly Asp Gln Arg Val Ser Met Pro
100 105 110

Tyr Ala Ser Lys Gly Leu Tyr Leu Glu Thr Glu Ala Gly Tyr Tyr Lys
115 120 125

Leu Ser Gly Glu Ala Tyr Gly Phe Val Ala Arg Ile Asp Gly Ser Gly
130 135 140

Asn Phe Gln Val Leu Leu Ser Asp Arg Tyr Phe Asn Lys Thr Cys Gly
145 150 155 160

Leu Cys Gly Asn Phe Asn Ile Phe Ala Glu Asp Asp Phe Met Thr Gln
165 170 175

Glu Gly Thr Leu Thr Ser Asp Pro Tyr Asp Phe Ala Asn Ser Trp Ala
180 185 190

Leu Ser Ser Gly Glu Gln Trp Cys Glu Arg Ala Ser Pro Pro Ser Ser
195 200 205

Ser Cys Asn Ile Ser Ser Gly Glu Met Gln Lys Gly Leu Trp Glu Gln
210 215 220

Cys Gln Leu Leu Lys Ser Thr Ser Val Phe Ala Arg Cys His Pro Leu
225 230 235 240

Val Asp Pro Glu Pro Phe Val Ala Leu Cys Glu Lys Thr Leu Cys Glu
245 250 255

Cys Ala Gly Gly Leu Glu Cys Ala Cys Pro Ala Leu Leu Glu Tyr Ala
260 265 270

Arg Thr Cys Ala Gln Glu Gly Met Val Leu Tyr Gly Trp Thr Asp His
275 280 285

Ser Ala Cys Ser Pro Val Cys Pro Ala Gly Met Glu Tyr Arg Gln Cys
290 295 300

Val Ser Pro Cys Ala Arg Thr Cys Gln Ser Leu His Ile Asn Glu Met
305 310 315 320

Cys Gln Glu Arg Cys Val Asp Gly Cys Ser Cys Pro Glu Gly Gln Leu
325 330 335

Leu Asp Glu Gly Leu Cys Val Glu Ser Thr Glu Cys Pro Cys Val His
340 345 350

Ser Gly Lys Arg Tyr Pro Pro Gly Thr Ser Leu Ser Arg Asp Cys Asn
355 360 365

Thr Cys Ile Cys Arg Asn Ser Gln Trp Ile Cys Ser Asn Glu Glu Cys
370 375 380

Pro Gly Glu Cys Leu Val Thr Gly Gln Ser His Phe Lys Ser Phe Asp
385 390 395 400

Asn Arg Tyr Phe Thr Phe Ser Gly Ile Cys Gln Tyr Leu Leu Ala Arg
 405 410 415

Asp Cys Gln Asp His Ser Phe Ser Ile Val Ile Glu Thr Val Gln Cys
 420 425 430

Ala Asp Asp Arg Asp Ala Val Cys Thr Arg Ser Val Thr Val Arg Leu
 435 440 445

Pro Gly Leu His Asn Ser Leu Val Lys Leu Lys His Gly Ala Gly Val
 450 455 460

Ala Met Asp Gly Gln Asp Ile Gln Leu Pro Leu Leu Lys Gly Asp Leu
 465 470 475 480

Arg Ile Gln His Thr Val Thr Ala Ser Val Arg Leu Ser Tyr Gly Glu
 485 490 495

Asp Leu Gln Met Asp Trp Asp Gly Arg Gly Arg Leu Leu Val Lys Leu
 500 505 510

Ser Pro Val Tyr Ala Gly Lys Thr Cys Gly Leu Cys Gly Asn Tyr Asn
 515 520 525

Gly Asn Gln Gly Asp Asp Phe Leu Thr Pro Ser Gly Leu Ala Glu Pro
 530 535 540

Arg Val Glu Asp Phe Gly Asn Ala Trp Lys Leu His Gly Asp Cys Gln
 545 550 555 560

Asp Leu Gln Lys Gln His Ser Asp Pro Cys Ala Leu Asn Pro Arg Met
 565 570 575

Thr Arg Phe Ser Glu Glu Ala Cys Ala Val Leu Thr Ser Pro Thr Phe
 580 585 590

Glu Ala Cys His Arg Ala Val Ser Pro Leu Pro Tyr Leu Arg Asn Cys
 595 600 605

Arg Tyr Asp Val Cys Ser Cys Ser Asp Gly Arg Glu Cys Leu Cys Gly
 610 615 620

Ala Leu Ala Ser Tyr Ala Ala Ala Cys Ala Gly Arg Gly Val Arg Val
 625 630 635 640

Ala Trp Arg Glu Pro Gly Arg Cys Glu Leu Asn Cys Pro Lys Gly Gln
 645 650 655

Val Tyr Leu Gln Cys Gly Thr Pro Cys Asn Leu Thr Cys Arg Ser Leu
 660 665 670

Ser Tyr Pro Asp Glu Glu Cys Asn Glu Ala Cys Leu Glu Gly Cys Phe
 675 680 685

Cys Pro Pro Gly Leu Tyr Met Asp Glu Arg Gly Asp Cys Val Pro Lys
 690 695 700

Ala Gln Cys Pro Cys Tyr Tyr Asp Gly Glu Ile Phe Gln Pro Glu Asp
 705 710 715 720

Ile Phe Ser Asp His His Thr Met Cys Tyr Cys Glu Asp Gly Phe Met
 725 730 735

His Cys Thr Met Ser Gly Val Pro Gly Ser Leu Leu Pro Asp Ala Val
 740 745 750

Leu Ser Ser Pro Leu Ser His Arg Ser Lys Arg Ser Leu Ser Cys Arg

755

760

765

Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp Asn Leu Arg Ala Glu
 770 775 780

Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr Asp Leu Glu Cys Met
 785 790 795 800

Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro Pro Gly Met Val Arg
 805 810 815

His Glu Asn Arg Cys Val Ala Leu Glu Arg Cys Pro Cys Phe His Gln
 820 825 830

Gly Lys Glu Tyr Ala Pro Gly Glu Thr Val Lys Ile Gly Cys Asn Thr
 835 840 845

Cys Val Cys Arg Asp Arg Lys Trp Asn Cys Thr Asp His Val Cys Asp
 850 855 860

Ala Thr Cys Ser Thr Ile Gly Met Ala His Tyr Leu Thr Phe Asp Gly
 865 870 875 880

Leu Lys Tyr Leu Phe Pro Gly Glu Cys Gln Tyr Val Leu Val Gln Asp
 885 890 895

Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys
 900 905 910

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

Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys
 930 935 940

Arg Pro Met Lys Asp Glu Thr His Phe Glu Val Val Glu Ser Gly Arg
 945 950 955 960

Tyr Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg
 965 970 975

His Leu Ser Ile Ser Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val
 980 985 990

Cys Gly Leu Cys Gly Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr
 995 1000 1005

Ser Ser Asn Leu Gln Val Glu Glu Asp Pro Val Asp Phe Gly Asn
 1010 1015 1020

Ser Trp Lys Val Ser Ser Gln Cys Ala Asp Thr Arg Lys Val Pro
 1025 1030 1035

Leu Asp Ser Ser Pro Ala Thr Cys His Asn Asn Ile Met Lys Gln
 1040 1045 1050

Thr Met Val Asp Ser Ser Cys Arg Ile Leu Thr Ser Asp Val Phe
 1055 1060 1065

Gln Asp Cys Asn Lys Leu Val Asp Pro Glu Pro Tyr Leu Asp Val
 1070 1075 1080

Cys Ile Tyr Asp Thr Cys Ser Cys Glu Ser Ile Gly Asp Cys Ala
 1085 1090 1095

Ala Phe Cys Asp Thr Ile Ala Ala Tyr Ala His Val Cys Ala Gln
 1100 1105 1110

His Gly Lys Val Val Thr Trp Arg Thr Ala Thr Leu Cys Pro Gln
 1115 1120 1125

Ser Cys Glu Glu Arg Asn Leu Arg Glu Asn Gly Tyr Glu Ala Glu
 1130 1135 1140

Trp Arg Tyr Asn Ser Cys Ala Pro Ala Cys Gln Val Thr Cys Gln
 1145 1150 1155

His Pro Glu Pro Leu Ala Cys Pro Val Gln Cys Val Glu Gly Cys
 1160 1165 1170

His Ala His Cys Pro Pro Gly Lys Ile Leu Asp Glu Leu Leu Gln
 1175 1180 1185

Thr Cys Val Asp Pro Glu Asp Cys Pro Val Cys Glu Val Ala Gly
 1190 1195 1200

Arg Arg Phe Ala Ser Gly Lys Lys Val Thr Leu Asn Pro Ser Asp
 1205 1210 1215

Pro Glu His Cys Gln Ile Cys His Cys Asp Val Val Asn Leu Thr
 1220 1225 1230

Cys Glu Ala Cys Gln Glu Pro Ile Ser Gly Ala Pro Thr Ser Glu
 1235 1240 1245

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 1250 1255 1260

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 1265 1270 1275

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
1280 1285 1290

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
1295 1300 1305

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro
1310 1315 1320

Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
1325 1330 1335

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
1340 1345 1350

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala
1355 1360 1365

Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro
1370 1375 1380

Thr Ser Thr Glu Glu Gly Ala Ser Ser Gly Gly Gly Gly Ser Gly
1385 1390 1395

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1400 1405 1410

Gly Gly Gly Ser Leu Val Pro Arg Gly Ser Gly Gly Asp Lys Thr
1415 1420 1425

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
1430 1435 1440

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

1445	1450	1455
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His 1460 1465 1470		
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu 1475 1480 1485		
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser 1490 1495 1500		
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp 1505 1510 1515		
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu 1520 1525 1530		
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro 1535 1540 1545		
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu 1550 1555 1560		
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr 1565 1570 1575		
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu 1580 1585 1590		
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser 1595 1600 1605		
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln 1610 1615 1620		

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 1625 1630 1635

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 1640 1645 1650

<210> 153

<211> 5379

<212> DNA

<213> Artificial Sequence

<220>

<223> VWF058 (VWF034 with IHH mutation)

<400> 153

atgattcctg ccagatttgc cggggtgctg cttgctctgg ccctcatttt gccagggacc
 60

ctttgtgcag aaggaactcg cggcagggtca tccacggccc gatgcagcct tttcggaagt
 120

gacttcgtca acacctttga tgggagcatg tacagctttg cgggatactg cagttacctc
 180

ctggcagggg gctgccagaa acgctccttc tcgattattg gggacttcca gaatggcaag
 240

agagtgcagc tctccgtgta tcttggggaa ttttttgaca tccatttggt tgtcaatggt
 300

accgtgacac agggggacca aagagtctcc atgccctatg cctccaaagg gctgtatcta
 360

gaaactgagg ctgggtacta caagctgtcc ggtgaggcct atggctttgt ggccaggatc
 420

gatggcagcg gcaactttca agtcctgctg tcagacagat acttcaacaa gacctgcggg
 480

ctgtgtggca actttaacat ctttgctgaa gatgacttta tgaccaaga agggaccttg
 540

acctcggacc cttatgactt tgccaactca tgggctctga gcagtggaga acagtgggtgt
 600
 gaacgggcat ctccctcccag cagctcatgc aacatctcct ctgggggaaat gcagaagggc
 660
 ctgtgggagc agtgccagct tctgaagagc acctcgggtgt ttgcccgctg ccaccctctg
 720
 gtggaccccg agcctttttgt ggccctgtgt gagaagactt tgtgtgagtg tgctgggggg
 780
 ctggagtgcg cctgccctgc cctcctggag tacgcccgga cctgtgcca ggagggaatg
 840
 gtgctgtacg gctggaccga ccacagcgcg tgcagcccag tgtgccctgc tggatatggag
 900
 tataggcagt gtgtgtcccc ttgcgccagg acctgccaga gcctgcacat caatgaaatg
 960
 tgtcaggagc gatgcgtgga tggctgcagc tgccctgagg gacagctcct ggatgaaggc
 1020
 ctctgcgtgg agagcaccga gtgtccctgc gtgcattccg gaaagcgcta ccctcccggc
 1080
 acctccctct ctcgagactg caacacctgc atttgccgaa acagccagtg gatctgcagc
 1140
 aatgaagaat gtccagggga gtgccttgtc actgggtcaat cccacttcaa gagctttgac
 1200
 aacagatact tcaccttcag tgggatctgc cagtacctgc tggcccggga ttgccaggac
 1260
 cactccttct ccattgtcat tgagactgtc cagtgtgctg atgaccgcga cgctgtgtgc
 1320
 acccgctccg tcaccgtccg gctgcctggc ctgcacaaca gccttgtgaa actgaagcat
 1380
 ggggcaggag ttgccatgga tggccaggac atccagctcc ccctcctgaa aggtgacctc
 1440

cgcatccagc 1500	atacagtgac	ggcctccgtg	cgcctcagct	acggggagga	cctgcagatg
gactgggatg 1560	gccgcgggag	gctgctggtg	aagctgtccc	ccgtctatgc	cggaagacc
tgcggcctgt 1620	gtgggaatta	caatggcaac	cagggcgacg	acttccttac	cccctctggg
ctggcggagc 1680	cccgggtgga	ggacttcggg	aacgcctgga	agctgcacgg	ggactgccag
gacctgcaga 1740	agcagcacag	cgatccctgc	gccctcaacc	cgcgcatgac	caggttctcc
gaggaggcgt 1800	gcgcggtcct	gacgtccccc	acattcgagg	cctgccatcg	tgccgtcagc
ccgctgccct 1860	acctgcggaa	ctgccgctac	gacgtgtgct	cctgctcgga	cggccgag
tgctgtgcg 1920	gcgccctggc	cagctatgcc	gcggcctgcg	cggggagagg	cgtgcgcgtc
gcgtggcgcg 1980	agccaggccg	ctgtgagctg	aactgcccga	aaggccaggt	gtacctgcag
tgcgggaccc 2040	cctgcaacct	gacctgccgc	tctctctctt	acccggatga	ggaatgcaat
gaggcctgcc 2100	tggagggtg	cttctgcccc	ccagggtctt	acatggatga	gaggggggac
tgcggtgcca 2160	aggcccagtg	cccctgttac	tatgacggtg	agatcttcca	gccagaagac
atcttctcag 2220	accatcacac	catgtgctac	tgtgaggatg	gcttcatgca	ctgtaccatg
agtggagtcc 2280	ccggaagctt	gctgcctgac	gctgtcctca	gcagtcccct	gtctcatcgc
agcaaaaagga 2340	gcctatcctg	tcggccccc	atggtcaagc	tggtgtgtcc	cgctgacaac

ctgcgggctg 2400	aagggctcga	gtgtaccaa	acgtgccaga	actatgacct	ggagtgcattg
agcatgggct 2460	gtgtctcttg	ctgcctctgc	ccccgggca	tggtccggca	tgagaacaga
tgtgtggccc 2520	tggaaagggtg	tccctgcttc	catcagggca	aggagtattgc	ccctggagaa
acagtgaaga 2580	ttggctgcaa	cacttgtgtc	tgtcgggacc	ggaagtggaa	ctgcacagac
catgtgtgtg 2640	atgccacgtg	ctccacgata	ggcatggccc	actacctcac	cttcgacggg
ctcaaatacc 2700	tgttccccgg	ggagtgccag	tacgttcttg	tgcaggatta	ctgcggcagt
aaccctggga 2760	cctttcggat	cctagtgggg	aataagggat	gcagccaccc	ctcagtgaag
tgcaagaaac 2820	gggtcaccat	cctggtggag	ggaggagaga	ttgagctgtt	tgacggggag
gtgaatgtga 2880	agaggcccat	gaaggatgag	actcactttg	aggtggtgga	gtctggccgg
tacatcattc 2940	tgctgctggg	caaagccctc	tccgtggtct	gggaccgcca	cctgagcattc
tccgtggtcc 3000	tgaagcagac	ataccaggag	aaagtgtgtg	gcctgtgtgg	gaattttgat
ggcatccaga 3060	acaatgacct	caccagcagc	aacctccaag	tggaggaaga	ccctgtggac
tttgggaaact 3120	cctggaaagt	gagctcgcag	tgtgctgaca	ccagaaaagt	gcctctggac
tcatcccctg 3180	ccacctgcca	taacaacattc	atgaagcaga	cgatggtgga	ttcctcctgt
agaatcctta 3240	ccagtgacgt	cttccaggac	tgcaacaagc	tggtggaccc	cgagccatat

ctggatgtct gcatttacga cacctgctcc tgtgagtcca ttggggactg cgccgcattc
3300

tgcgacacca ttgctgccta tgcccacgtg tgtgcccagc atggcaaggt ggtgacctgg
3360

aggacggcca cattgtgccc ccagagctgc gaggagagga atctccggga gaacgggtat
3420

gaggctgagt ggcgctataa cagctgtgca cctgcctgtc aagtcacgtg tcagcaccct
3480

gagccactgg cctgccctgt gcagtgtgtg gagggctgcc atgccactg ccctccaggg
3540

aaaatcctgg atgagctttt gcagacctgc gttgaccctg aagactgtcc agtgtgtgag
3600

gtggctggcc ggcgttttgc ctcaggaaag aaagtcacct tgaatcccag tgaccctgag
3660

cactgccaga tttgccactg tgatgttgtc aacctcacct gtgaagcctg ccaggagccg
3720

atatcgggta cctcagagtc tgctaccccc gagtcagggc caggatcaga gccagccacc
3780

tccgggtctg agacacccgg gacttccgag agtgccaccc ctgagtccgg acccgggtcc
3840

gagcccgcca cttccggctc cgaaactccc ggcacaagcg agagcgctac cccagagtca
3900

ggaccaggaa catctacaga gccctctgaa ggctccgctc cagggtcccc agccggcagt
3960

cccactagca ccgaggaggg aacctctgaa agcgccacac ccgaatcagg gccagggtct
4020

gagcctgcta ccagcggcag cgagacacca ggcacctctg agtccgccac accagagtcc
4080

ggacccggat ctcccgtgg gagccccacc tccactgagg agggatctcc tgctggctct
4140

ccaacatcta ctgaggaagg tacctcaacc gagccatccg agggatcagc tcccggcacc
 4200

tcagagtcgg caaccccggg gtctggaccc ggaacttccg aaagtgccac accagagtcc
 4260

ggtcccggga cttcagaatc agcaacaccc gagtccggcc ctgggtctga acccgccaca
 4320

agtggtagtg agacaccagg atcagaacct gctacctcag ggtcagagac acccggatct
 4380

ccggcaggct caccaacctc cactgaggag ggcaccagca cagaaccaag cgagggctcc
 4440

gcacccggaa caagcactga acccagtgag gggtcagcac ccggctctga gccggccaca
 4500

agtggcagtg agacaccgga cacttcagag agtgccaccc ccgagagtgg cccaggcact
 4560

agtaccgagc cctctgaagg cagtgcgcca gattctggcg gtggaggttc cgggtggcggg
 4620

ggatccggtg gcggggggatc cgggtggcggg ggatccggtg gcggggggatc cctgggtcccc
 4680

cggggcagcg gaggcgacaa aactcacaca tgcccaccgt gcccagctcc agaactcctg
 4740

ggcggaccgt cagtcttcct cttcccccca aaaccaagg acaccctcat ggcctcccgg
 4800

acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc
 4860

aactggtacg tggacggcgt ggaggtgcat aatgccaaaga caaagccgcg ggaggagcag
 4920

tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tggcccagga ctggctgaat
 4980

ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagcccccat cgagaaaacc
 5040

atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgc
5100

gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc
5160

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct
5220

cccgtgttgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc
5280

aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaacgcc
5340

tacacgcaga agagcctctc cctgtctccg ggtaaatga
5379

<210> 154

<211> 1792

<212> PRT

<213> Artificial Sequence

<220>

<223> VWF058 (VWF034 with IHH mutation)

<400> 154

Met Ile Pro Ala Arg Phe Ala Gly Val Leu Leu Ala Leu Ala Leu Ile
1 5 10 15

Leu Pro Gly Thr Leu Cys Ala Glu Gly Thr Arg Gly Arg Ser Ser Thr
20 25 30

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

Ser Met Tyr Ser Phe Ala Gly Tyr Cys Ser Tyr Leu Leu Ala Gly Gly
50 55 60

Cys Gln Lys Arg Ser Phe Ser Ile Ile Gly Asp Phe Gln Asn Gly Lys
65 70 75 80

Arg Val Ser Leu Ser Val Tyr Leu Gly Glu Phe Phe Asp Ile His Leu
85 90 95

Phe Val Asn Gly Thr Val Thr Gln Gly Asp Gln Arg Val Ser Met Pro
100 105 110

Tyr Ala Ser Lys Gly Leu Tyr Leu Glu Thr Glu Ala Gly Tyr Tyr Lys
115 120 125

Leu Ser Gly Glu Ala Tyr Gly Phe Val Ala Arg Ile Asp Gly Ser Gly
130 135 140

Asn Phe Gln Val Leu Leu Ser Asp Arg Tyr Phe Asn Lys Thr Cys Gly
145 150 155 160

Leu Cys Gly Asn Phe Asn Ile Phe Ala Glu Asp Asp Phe Met Thr Gln
165 170 175

Glu Gly Thr Leu Thr Ser Asp Pro Tyr Asp Phe Ala Asn Ser Trp Ala
180 185 190

Leu Ser Ser Gly Glu Gln Trp Cys Glu Arg Ala Ser Pro Pro Ser Ser
195 200 205

Ser Cys Asn Ile Ser Ser Gly Glu Met Gln Lys Gly Leu Trp Glu Gln
210 215 220

Cys Gln Leu Leu Lys Ser Thr Ser Val Phe Ala Arg Cys His Pro Leu
225 230 235 240

Val	Asp	Pro	Glu	Pro	Phe	Val	Ala	Leu	Cys	Glu	Lys	Thr	Leu	Cys	Glu
245250255															
Cys	Ala	Gly	Gly	Leu	Glu	Cys	Ala	Cys	Pro	Ala	Leu	Leu	Glu	Tyr	Ala
260265270															
Arg	Thr	Cys	Ala	Gln	Glu	Gly	Met	Val	Leu	Tyr	Gly	Trp	Thr	Asp	His
275280285															
Ser	Ala	Cys	Ser	Pro	Val	Cys	Pro	Ala	Gly	Met	Glu	Tyr	Arg	Gln	Cys
290295300															
Val	Ser	Pro	Cys	Ala	Arg	Thr	Cys	Gln	Ser	Leu	His	Ile	Asn	Glu	Met
305310315320															
Cys	Gln	Glu	Arg	Cys	Val	Asp	Gly	Cys	Ser	Cys	Pro	Glu	Gly	Gln	Leu
325330335															
Leu	Asp	Glu	Gly	Leu	Cys	Val	Glu	Ser	Thr	Glu	Cys	Pro	Cys	Val	His
340345350															
Ser	Gly	Lys	Arg	Tyr	Pro	Pro	Gly	Thr	Ser	Leu	Ser	Arg	Asp	Cys	Asn
355360365															
Thr	Cys	Ile	Cys	Arg	Asn	Ser	Gln	Trp	Ile	Cys	Ser	Asn	Glu	Glu	Cys
370375380															
Pro	Gly	Glu	Cys	Leu	Val	Thr	Gly	Gln	Ser	His	Phe	Lys	Ser	Phe	Asp
385390395400															
Asn	Arg	Tyr	Phe	Thr	Phe	Ser	Gly	Ile	Cys	Gln	Tyr	Leu	Leu	Ala	Arg
405410415															
Asp	Cys	Gln	Asp	His	Ser	Phe	Ser	Ile	Val	Ile	Glu	Thr	Val	Gln	Cys

420

425

430

Ala Asp Asp Arg Asp Ala Val Cys Thr Arg Ser Val Thr Val Arg Leu
 435 440 445

Pro Gly Leu His Asn Ser Leu Val Lys Leu Lys His Gly Ala Gly Val
 450 455 460

Ala Met Asp Gly Gln Asp Ile Gln Leu Pro Leu Leu Lys Gly Asp Leu
 465 470 475 480

Arg Ile Gln His Thr Val Thr Ala Ser Val Arg Leu Ser Tyr Gly Glu
 485 490 495

Asp Leu Gln Met Asp Trp Asp Gly Arg Gly Arg Leu Leu Val Lys Leu
 500 505 510

Ser Pro Val Tyr Ala Gly Lys Thr Cys Gly Leu Cys Gly Asn Tyr Asn
 515 520 525

Gly Asn Gln Gly Asp Asp Phe Leu Thr Pro Ser Gly Leu Ala Glu Pro
 530 535 540

Arg Val Glu Asp Phe Gly Asn Ala Trp Lys Leu His Gly Asp Cys Gln
 545 550 555 560

Asp Leu Gln Lys Gln His Ser Asp Pro Cys Ala Leu Asn Pro Arg Met
 565 570 575

Thr Arg Phe Ser Glu Glu Ala Cys Ala Val Leu Thr Ser Pro Thr Phe
 580 585 590

Glu Ala Cys His Arg Ala Val Ser Pro Leu Pro Tyr Leu Arg Asn Cys
 595 600 605

Arg Tyr Asp Val Cys Ser Cys Ser Asp Gly Arg Glu Cys Leu Cys Gly
610 615 620

Ala Leu Ala Ser Tyr Ala Ala Ala Cys Ala Gly Arg Gly Val Arg Val
625 630 635 640

Ala Trp Arg Glu Pro Gly Arg Cys Glu Leu Asn Cys Pro Lys Gly Gln
645 650 655

Val Tyr Leu Gln Cys Gly Thr Pro Cys Asn Leu Thr Cys Arg Ser Leu
660 665 670

Ser Tyr Pro Asp Glu Glu Cys Asn Glu Ala Cys Leu Glu Gly Cys Phe
675 680 685

Cys Pro Pro Gly Leu Tyr Met Asp Glu Arg Gly Asp Cys Val Pro Lys
690 695 700

Ala Gln Cys Pro Cys Tyr Tyr Asp Gly Glu Ile Phe Gln Pro Glu Asp
705 710 715 720

Ile Phe Ser Asp His His Thr Met Cys Tyr Cys Glu Asp Gly Phe Met
725 730 735

His Cys Thr Met Ser Gly Val Pro Gly Ser Leu Leu Pro Asp Ala Val
740 745 750

Leu Ser Ser Pro Leu Ser His Arg Ser Lys Arg Ser Leu Ser Cys Arg
755 760 765

Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp Asn Leu Arg Ala Glu
770 775 780

Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr Asp Leu Glu Cys Met
 785 790 795 800

Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro Pro Gly Met Val Arg
 805 810 815

His Glu Asn Arg Cys Val Ala Leu Glu Arg Cys Pro Cys Phe His Gln
 820 825 830

Gly Lys Glu Tyr Ala Pro Gly Glu Thr Val Lys Ile Gly Cys Asn Thr
 835 840 845

Cys Val Cys Arg Asp Arg Lys Trp Asn Cys Thr Asp His Val Cys Asp
 850 855 860

Ala Thr Cys Ser Thr Ile Gly Met Ala His Tyr Leu Thr Phe Asp Gly
 865 870 875 880

Leu Lys Tyr Leu Phe Pro Gly Glu Cys Gln Tyr Val Leu Val Gln Asp
 885 890 895

Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys
 900 905 910

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

Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys
 930 935 940

Arg Pro Met Lys Asp Glu Thr His Phe Glu Val Val Glu Ser Gly Arg
 945 950 955 960

Tyr Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg
 965 970 975

His Leu Ser Ile Ser Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val
 980 985 990

Cys Gly Leu Cys Gly Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr
 995 1000 1005

Ser Ser Asn Leu Gln Val Glu Glu Asp Pro Val Asp Phe Gly Asn
 1010 1015 1020

Ser Trp Lys Val Ser Ser Gln Cys Ala Asp Thr Arg Lys Val Pro
 1025 1030 1035

Leu Asp Ser Ser Pro Ala Thr Cys His Asn Asn Ile Met Lys Gln
 1040 1045 1050

Thr Met Val Asp Ser Ser Cys Arg Ile Leu Thr Ser Asp Val Phe
 1055 1060 1065

Gln Asp Cys Asn Lys Leu Val Asp Pro Glu Pro Tyr Leu Asp Val
 1070 1075 1080

Cys Ile Tyr Asp Thr Cys Ser Cys Glu Ser Ile Gly Asp Cys Ala
 1085 1090 1095

Ala Phe Cys Asp Thr Ile Ala Ala Tyr Ala His Val Cys Ala Gln
 1100 1105 1110

His Gly Lys Val Val Thr Trp Arg Thr Ala Thr Leu Cys Pro Gln
 1115 1120 1125

Ser Cys Glu Glu Arg Asn Leu Arg Glu Asn Gly Tyr Glu Ala Glu

1130						1135						1140			
Trp	Arg	Tyr	Asn	Ser	Cys	Ala	Pro	Ala	Cys	Gln	Val	Thr	Cys	Gln	
1145						1150					1155				
His	Pro	Glu	Pro	Leu	Ala	Cys	Pro	Val	Gln	Cys	Val	Glu	Gly	Cys	
1160						1165					1170				
His	Ala	His	Cys	Pro	Pro	Gly	Lys	Ile	Leu	Asp	Glu	Leu	Leu	Gln	
1175						1180					1185				
Thr	Cys	Val	Asp	Pro	Glu	Asp	Cys	Pro	Val	Cys	Glu	Val	Ala	Gly	
1190						1195					1200				
Arg	Arg	Phe	Ala	Ser	Gly	Lys	Lys	Val	Thr	Leu	Asn	Pro	Ser	Asp	
1205						1210					1215				
Pro	Glu	His	Cys	Gln	Ile	Cys	His	Cys	Asp	Val	Val	Asn	Leu	Thr	
1220						1225					1230				
Cys	Glu	Ala	Cys	Gln	Glu	Pro	Ile	Ser	Gly	Thr	Ser	Glu	Ser	Ala	
1235						1240					1245				
Thr	Pro	Glu	Ser	Gly	Pro	Gly	Ser	Glu	Pro	Ala	Thr	Ser	Gly	Ser	
1250						1255					1260				
Glu	Thr	Pro	Gly	Thr	Ser	Glu	Ser	Ala	Thr	Pro	Glu	Ser	Gly	Pro	
1265						1270					1275				
Gly	Ser	Glu	Pro	Ala	Thr	Ser	Gly	Ser	Glu	Thr	Pro	Gly	Thr	Ser	
1280						1285					1290				
Glu	Ser	Ala	Thr	Pro	Glu	Ser	Gly	Pro	Gly	Thr	Ser	Thr	Glu	Pro	
1295						1300					1305				

Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 1310 1315 1320

Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
 1325 1330 1335

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
 1340 1345 1350

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser
 1355 1360 1365

Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser
 1370 1375 1380

Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
 1385 1390 1395

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
 1400 1405 1410

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala
 1415 1420 1425

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
 1430 1435 1440

Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
 1445 1450 1455

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser
 1460 1465 1470

Thr	Glu	Pro	Ser	Glu	Gly	Ser	Ala	Pro	Gly	Thr	Ser	Thr	Glu	Pro
	1475					1480					1485			
Ser	Glu	Gly	Ser	Ala	Pro	Gly	Ser	Glu	Pro	Ala	Thr	Ser	Gly	Ser
	1490					1495					1500			
Glu	Thr	Pro	Gly	Thr	Ser	Glu	Ser	Ala	Thr	Pro	Glu	Ser	Gly	Pro
	1505					1510					1515			
Gly	Thr	Ser	Thr	Glu	Pro	Ser	Glu	Gly	Ser	Ala	Pro	Asp	Ser	Gly
	1520					1525					1530			
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly
	1535					1540					1545			
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Leu	Val	Pro	Arg	Gly	Ser
	1550					1555					1560			
Gly	Gly	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu
	1565					1570					1575			
Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys
	1580					1585					1590			
Asp	Thr	Leu	Met	Ala	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val
	1595					1600					1605			
Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr
	1610					1615					1620			
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu
	1625					1630					1635			

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
 1640 1645 1650

Leu Ala Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
 1655 1660 1665

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 1670 1675 1680

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 1685 1690 1695

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 1700 1705 1710

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
 1715 1720 1725

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 1730 1735 1740

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 1745 1750 1755

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 1760 1765 1770

His Glu Ala Leu His Asn Ala Tyr Thr Gln Lys Ser Leu Ser Leu
 1775 1780 1785

Ser Pro Gly Lys
 1790

<210> 155

<211> 5937
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> FVIII 169

<400> 155
 atgcaaatag agctctccac ctgcttcttt ctgtgccttt tgcgattctg ctttagtgcc
 60
 accagaagat actacctggg tgcagtggaa ctgtcatggg actatatgca aagtgatctc
 120
 ggtgagctgc ctgtggacgc aagatttcct cctagagtgc caaaatcttt tccattcaac
 180
 acctcagtcg tgtacaaaaa gactctgttt gtagaattca cggatcacct tttcaacatc
 240
 gctaagccaa ggccaccctg gatgggtctg ctaggtccta ccatccaggc tgaggtttat
 300
 gatacagtgg tcattacact taagaacatg gcttcccatc ctgtcagtct tcatgctgtt
 360
 ggtgtatcct actggaaagc ttctgaggga gctgaatatg atgatcagac cagtcaaagg
 420
 gagaaagaag atgataaagt cttccctggg ggaagccata catatgtctg gcaggctctg
 480
 aaagagaatg gtccaatggc ctctgaccca ctgtgcctta cctactcata tctttctcat
 540
 gtggacctgg taaaagactt gaattcaggc ctcatggag ccctactagt atgtagagaa
 600
 gggagtctgg ccaaggaaaa gacacagacc ttgcacaaat ttatactact ttttgctgta
 660
 tttgatgaag ggaaaagttg gcactcagaa acaaagaact cttgatgca ggatagggat
 720
 gctgcatctg ctcgggcctg gcctaaaatg cacacagtca atggttatgt aaacaggctc
 780

ctgccaggtc tgattggatg ccacaggaaa tcagtctatt ggcatgtgat tggaatgggc
840

accactcctg aagtgcactc aatattcctc gaaggtcaca catttcttgt gaggaacccat
900

cgccaggcta gcttggaaat ctcgccaata actttcctta ctgctcaaac actcttgatg
960

gaccttggac agtttctact gttttgtcat atctcttccc accaacaatga tggcatggaa
1020

gcttatgtca aagtagacag ctgtccagag gaaccccaac tacgaatgaa aaataatgaa
1080

gaagcggaag actatgatga tgatcttact gattctgaaa tggatgtggt caggtttgat
1140

gatgacaact ctcccttcctt tatccaaatt cgctcagttg ccaagaagca tcctaaaact
1200

tgggtacatt acattgctgc tgaagaggag gactgggact atgctccctt agtcctcgcc
1260

cccgatgaca gaagttataa aagtcaatat ttgaacaatg gccctcagcg gattggtagg
1320

aagtacaaaa aagtccgatt tatggcatac acagatgaaa cctttaagac tcgtgaagct
1380

attcagcatg aatcaggaat cttgggacct ttactttatg ggggaagttgg agacacactg
1440

ttgattatat ttaagaatca agcaagcaga ccatataaca tctaccctca cggaatcact
1500

gatgtccgtc ctttgtattc aaggagatta ccaaaagggtg taaaacattt gaaggatttt
1560

ccaattctgc caggagaaat attcaaatat aaatggacag tgactgtaga agatgggcca
1620

actaaatcag atcctcgggtg cctgaccgcg tattactcta gtttcgtaa tatggagaga
1680

gatctagctt caggactcat tggccctctc ctcattctgct acaaagaatc tgtagatcaa
1740

agaggaaacc agataatgtc agacaagagg aatgtcatcc tgttttctgt atttgatgag
1800

aaccgaagct ggtacctcac agagaatata caacgctttc tccccaatcc agctggagtg
1860

cagcttgagg atccagagtt ccaagcctcc aacatcatgc acagcatcaa tggctatgtt
1920

tttgatagtt tgcagttgtc agtttgtttg catgagggtgg catactggta cattctaagc
1980

attggagcac agactgactt cctttctgtc ttcttctctg gatatacctt caaacacaaa
2040

atggtctatg aagacacact caccctattc ccattctcag gagaaactgt cttcatgtcg
2100

atggaaaacc caggtctatg gattctgggg tgccacaact cagactttcg gaacagagggc
2160

atgaccgcct tactgaaggt ttctagttgt gacaagaaca ctggtgatta ttacgaggac
2220

agttatgaag atatttcagc atacttgctg agtaaaaaca atgccattga accaagaagc
2280

ttctctcaaa acggcgcgcc aggtacctca gagtctgcta cccccgagtc agggccagga
2340

tcagagccag ccacctccgg gtctgagaca cccgggactt ccgagagtgc caccctgag
2400

tccggacccg ggtccgagcc cgccacttcc ggctccgaaa ctcccggcac aagcgagagc
2460

gctaccccag agtcaggacc aggaacatct acagagccct ctgaaggctc cgctccaggg
2520

tccccagccg gcagtcccac tagcaccgag gagggaacct ctgaaagcgc cacacccgaa
2580

tcagggccag ggtctgagcc tgctaccagc ggcagcgaga caccaggcac ctctgagtcc
2640

gccacaccag agtccggacc cggatctccc gctgggagcc ccacctccac tgaggaggga
2700

tctcctgctg gctctccaac atctactgag gaagggtacct caaccgagcc atccgaggga
2760

tcagctcccg gcacctcaga gtcggcaacc ccggagtctg gacccggaac ttccgaaagt
2820

gccacaccag agtccgggtcc cgggacttca gaatcagcaa cacccgagtc cggccctggg
2880

tctgaacccg ccacaagtgg tagtgagaca ccaggatcag aacctgctac ctcagggtca
2940

gagacacccg gatctccggc aggctcacca acctccactg aggagggcac cagcacagaa
3000

ccaagcgagg gctccgcacc cggaacaagc actgaaccca gtgaggggttc agcacccggc
3060

tctgagccgg ccacaagtgg cagtgagaca cccggcactt cagagagtgc ccccccgag
3120

agtggcccag gcactagtag cgagccctct gaaggcagtg cgccagcctc gagcccacca
3180

gtcttgaaac gccatcaagc tgaaataact cgtactactc ttcagtcaga tcaagaggaa
3240

atcgattatg atgataccat atcagttgaa atgaagaagg aagattttga catttatgat
3300

gaggatgaaa atcagagccc ccgcagcttt caaaagaaaa cacgacacta ttttattgct
3360

gcagtggaga ggctctggga ttatgggatg agtagctccc cacatgttct aagaaacagg
3420

gctcagagtg gcagtgtccc tcagttcaag aaagttgttt tccaggaatt tactgatggc
3480

tcctttactc agcccttata ccgtggagaa ctaaataaac atttgggact cctggggcca
3540

tatataagag cagaagttga agataatatc atggtaactt tcagaaatca ggcctctcgt
3600

ccctattcct tctattctag ccttatttct tatgaggaag atcagaggca aggagcagaa
3660

cctagaaaaa actttgtcaa gcctaataaa accaaaactt acttttggaa agtgcaacat
3720

catatggcac ccactaaaga tgagtttgac tgcaaagcct gggcttattt ctctgatgtt
3780

gacctggaaa aagatgtgca ctcaggcctg attggacccc ttctgggtctg ccacactaac
3840

acactgaacc ctgctcatgg gagacaagtg acagtacagg aatttgctct gtttttcacc
3900

atctttgatg agaccaaag ctggtacttc actgaaaata tggaaagaaa ctgcagggct
3960

ccctgcaata tccagatgga agatcccact tttaaagaga attatcgctt ccatgcaatc
4020

aatggctaca taatggatac actacctggc ttagtaatgg ctcaggatca aaggattcga
4080

tggtatctgc tcagcatggg cagcaatgaa aacatccatt ctattcattt cagtggacat
4140

gtgttcactg tacgaaaaaa agaggagtat aaaatggcac tgtacaatct ctatccaggc
4200

gtttttgaga cagtggaaat gttaccatcc aaagctggaa tttggcgggt ggaatgcctt
4260

attggcgagc atctacatgc tgggatgagc acactttttc tgggtgtacag caataagtgt
4320

cagactcccc tgggaatggc ttctggacac attagagatt ttcagattac agcttcagga
4380

caatatggac agtgggcccc aaagctggcc agacttcatt attccggatc aatcaatgcc
4440

tggagcacca aggagccctt ttcttggatc aaggtggatc tgttggcacc aatgattatt
4500

cacggcatca agaccaggg tgcccgtcag aagttctcca gcctctacat ctctcagttt
4560

atcatcatgt atagtcttga tgggaagaag tggcagactt atcgaggaaa ttccactgga
4620

accttaatgg tcttcttttg caatgtggat tcatctggga taaaacacaa tatttttaac
4680

cctccaatta ttgctcgata catccgtttg cacccaactc attatagcat tcgcagcact
4740

cttcgcatgg agttgatggg ctgtgattta aatagttgca gcatgccatt gggaatggag
4800

agtaaagcaa tatcagatgc acagattact gcttcatcct actttaccaa tatgtttgcc
4860

acctggtctc cttcaaaagc tcgacttcac ctccaaggga ggagtaatgc ctggagacct
4920

caggtgaata atccaaaaga gtggctgcaa gtggacttcc agaagacaat gaaagtcaca
4980

ggagtaacta ctcagggagt aaaatctctg cttaccagca tgtatgtgaa ggagttcctc
5040

atctccagca gtcaagatgg ccatcagtgg actctctttt ttcagaatgg caaagtaaag
5100

gtttttcagg gaaatcaaga ctccttcaca cctgtggtga actctctaga cccaccgtta
5160

ctgactcgct accttcgaat tcacccccag agttgggtgc accagattgc cctgaggatg
5220

gaggttctgg gctgcgaggc acaggacctc tacgacaaaa ctcacacatg cccaccgtgc
5280

ccagctccag aactcctggg cggaccgtca gtcttcctct tccccccaaa acccaaggac
5340

accctcatga tctcccggac ccctgaggtc acatgcgtgg tggaggacgt gagccacgaa
5400

gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca
5460

aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg
5520

caccaggact ggctgaatgg caaggagtac aagtgcagg tctccaacaa agccctccca
5580

gcccccatcg agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acagggtgtac
5640

accctgcccc catcccggga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc
5700

aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagAAC
5760

aactacaaga ccacgcctcc cgtgttggac tccgacggct ctttcttctt ctacagcaag
5820

ctcacctgtg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat
5880

gaggctctgc acaaccacta cacgcagaag agcctctccc tgtctccggg taaatga
5937

<210> 156

<211> 6387

<212> DNA

<213> Artificial Sequence

<220>

<223> FVIII 263 (IHH triple mutant)

<400> 156

atgcaaatag agctctccac ctgcttcttt ctgtgccttt tgcgattctg ctttagtgcc
60

accagaagat actacctggg tgcagtggaa ctgtcatggg actatatgca aggcgcgcca
120

acatcagaga gcgccacccc tgaaagtggg cccgggagcg agccagccac atctgggtcg
180

gaaacgccag gcacaagtga gtctgcaact cccgagtccg gacctggctc cgagcctgcc
240

actagcggct ccgagactcc gggaaacttc gagagcgcta caccagaaag cggacccgga
300

accagtaccg aacctagcga gggctctgct ccgggcagcc cagccggctc tcctacatcc
360

acggaggagg gcacttccga atccgccacc ccggagtcag ggccaggatc tgaaccgcgt
420

acctcaggca gtgagacgcc aggaacgagc gagtccgcta caccggagag tgggccaggg
480

agccctgctg gatctcctac gtccactgag gaaggggtcac cagcgggctc gccaccagc
540

actgaagaag gtgcctcgag cagtgatctc ggtgagctgc ctgtggacgc aagatttcct
600

cctagagtgc caaaatcttt tccattcaac acctcagtcg tgtacaaaaa gactctgttt
660

gtagaattca cggatcacct tttcaacatc gctaagccaa ggccaccctg gatgggtctg
720

ctaggtccta ccatccaggc tgaggtttat gatacagtgg tcattacact taagaacatg
780

gcttcccatc ctgtcagtct tcatgctgtt ggtgtatcct actggaaagc ttctgagggg
840

gctgaatatg atgatcagac cagtcaaagg gagaaagaag atgataaagt cttccctggg
900

ggaagccata catatgtctg gcaggtcctg aaagagaatg gtccaatggc ctctgaccca
960

ctgtgcctta cctactcata tctttctcat gtggacctgg taaaagactt gaattcaggc
1020

ctcattggag ccctactagt atgtagagaa gggagtctgg ccaaggaaaa gacacagacc
1080

ttgcacaaat ttatactact ttttgctgta tttgatgaag ggaaaagttg gcactcagaa
1140

acaaagaact ccttgatgca ggatagggat gctgcatctg ctcgggcctg gcctaaaatg
1200

cacacagtca atggttatgt aaacagggtc ctgccaggtc tgattggatg ccacaggaaa
1260

tcagtctatt ggcatgtgat tggaatgggc accactcctg aagtgcactc aatattcctc
1320

gaaggtcaca catttcttgt gaggaacat cgccaggcta gcttggaat ctcgccaata
1380

actttcctta ctgctcaaac actcttgatg gaccttggac agtttctact gttttgtcat
1440

atctcttccc accaacaatga tggcatggaa gcttatgtca aagtagacag ctgtccagag
1500

gaacccaac tacgaatgaa aaataatgaa gaagcggaag actatgatga tgatcttact
1560

gattctgaaa tggatgtggt caggtttgat gatgacaact ctccttcctt tatccaaatt
1620

cgctcagttg ccaagaagca tcctaaaact tgggtacatt acattgctgc tgaagaggag
1680

gactgggact atgctccctt agtcctcgcc cccgatgaca gaagttataa aagtcaatat
1740

ttgaacaatg gccctcagcg gattggtagg aagtacaaaa aagtccgatt tatggcatac
1800

acagatgaaa cctttaagac tcgtgaagct attcagcatg aatcaggaat cttgggacct
1860

ttacttttatg gggaagttgg agacacactg ttgattatat ttaagaatca agcaagcaga
1920

ccatataaca tctaccctca cggaatcact gatgtccgtc ctttgtattc aaggagatta
1980

ccaaaagggtg taaaacattt gaaggatttt ccaattctgc caggagaaat attcaaatat
2040

aatgggacag tgactgtaga agatgggccca actaaatcag atcctcgggtg cctgaccgcg
2100

tattactcta gtttcgttaa tatggagaga gatctagctt caggactcat tggccctctc
2160

ctcatctgct acaaagaatc tgtagatcaa agaggaaacc agataatgtc agacaagagg
2220

aatgtcatcc tgttttctgt atttgatgag aaccgaagct ggtacctcac agagaatata
2280

caacgctttc tccccaatcc agctggagtg cagcttgagg atccagagtt ccaagcctcc
2340

aacatcatgc acagcatcaa tggctatggt tttgatagtt tgcagttgtc agtttgtttg
2400

catgaggtgg catactggta cattctaagc attggagcac agactgactt cctttctgtc
2460

ttctttctctg gatatacctt caaacacaaa atgggtctatg aagacacact caccctattc
2520

ccattctcag gagaaactgt cttcatgtcg atggaaaacc caggtctatg gattctgggg
2580

tgccacaact cagactttcg gaacagaggc atgaccgcct tactgaaggt ttctagttgt
2640

gacaagaaca ctggtgatta ttacgaggac agttatgaag atatttcagc atacttgctg
2700

agtaaaaaca atgccattga accaagaagc ttctctcaaa acggcgcgcc aggtacctca
2760

gagtctgcta cccccgagtc agggccagga tcagagccag ccacctccgg gtctgagaca
2820

cccgggactt ccgagagtgc caccctgag tccggaccg ggtccgagcc cgccacttcc
2880

ggctccgaaa ctcccggcac aagcgagagc gctaccccag agtcaggacc aggaacatct
2940

acagagccct ctgaaggctc cgctccaggg tccccagccg gcagtccac tagcaccgag
3000

gagggaaacct ctgaaagcgc cacacccgaa tcagggccag ggtctgagcc tgctaccagc
3060

ggcagcgaga caccaggcac ctctgagtcc gccacaccag agtccggacc cggatctccc
3120

gctgggagcc ccacctccac tgaggaggga tctcctgctg gctctccaac atctactgag
3180

gaaggtacct caaccgagcc atccgaggga tcagctcccg gcacctcaga gtcggcaacc
3240

ccggagtctg gacccggaac ttccgaaagt gccacaccag agtccgggtcc cgggacttca
3300

gaatcagcaa caccgagtc cggccctggg tctgaaccg ccacaagtgg tagtgagaca
3360

ccaggatcag aacctgctac ctcagggtca gagacaccg gatctccggc aggctcacca
3420

acctccactg aggagggcac cagcacagaa ccaagcgagg gctccgcacc cggaacaagc
3480

actgaacca gtgagggttc agcaccggc tctgagccg ccacaagtgg cagtgagaca
3540

cccggcactt cagagagtgc ccccccgag agtggcccag gcactagtag cgagccctct
3600

gaaggcagtg cgccagcctc gagcccacca gtcttgaaac gccatcaagc tgaaataact
3660

cgtactactc ttcagtcaga tcaagaggaa atcgattatg atgataccat atcagttgaa
3720

atgaagaagg aagattttga catttatgat gaggatgaaa atcagagccc ccgcagcttt
3780

caaaagaaaa cacgacacta ttttattgct gcagtggaga ggctctggga ttatgggatg
3840

agtagctccc cacatgttct aagaaacagg gctcagagtg gcagtgtccc tcagttcaag
3900

aaagttgttt tccaggaatt tactgatggc tcctttactc agcccttata ccgtggagaa
3960

ctaaatgaac atttgggact cctggggcca tatataagag cagaagttga agataatatc
4020

atggtaactt tcagaaatca ggcctctcgt ccctattcct tctattctag ccttatttct
4080

tatgaggaag atcagaggca aggagcagaa cctagaaaaa actttgtcaa gcctaataaa
4140

acaaaaactt acttttggaa agtgcaacat catatggcac ccactaaaga tgagtttgac
4200

tgcaaagcct gggcttattt ctctgatggt gacctggaaa aagatgtgca ctcaggcctg
4260

attggacccc ttctggtctg ccacactaac acactgaacc ctgctcatgg gagacaagtg
4320

acagtacagg aatttgctct gtttttcacc atctttgatg agaccaaaag ctggtacttc
4380

actgaaaata tggaaagaaa ctgcagggct ccctgcaata tccagatgga agatcccact
4440

tttaaagaga attatcgctt ccatgcaatc aatggctaca taatggatac actacctggc
4500

ttagtaatgg ctcaggatca aaggattcga tggatatctgc tcagcatggg cagcaatgaa
4560

aacatccatt ctattcattt cagtggacat gtgttcactg tacgaaaaaa agaggagtat
 4620

aaaatggcac tgtacaatct ctatccaggt gtttttgaga cagtggaaat gttaccatcc
 4680

aaagctggaa tttggcgggt ggaatgcctt attggcgagc atctacatgc tgggatgagc
 4740

acactttttc tgggtgtacag caataagtgt cagactcccc tgggaatggc ttctggacac
 4800

attagagatt ttcagattac agcttcagga caatatggac agtgggcccc aaagctggcc
 4860

agacttcatt attccggatc aatcaatgcc tggagcacca aggagccctt ttcttggatc
 4920

aaggtggatc tgttggcacc aatgattatt cacggcatca agaccaggg tgcccgtcag
 4980

aagtctcca gcctctacat ctctcagttt atcatcatgt atagtcttga tgggaagaag
 5040

tggcagactt atcgaggaaa ttccactgga accttaatgg tcttctttgg caatgtggat
 5100

tcatctggga taaaacacaa tatttttaac cctccaatta ttgctcgata catccgtttg
 5160

caccaactc attatagcat tcgcagcact cttcgcatgg agttgatggg ctgtgattta
 5220

aatagttgca gcatgccatt gggaatggag agtaaagcaa tatcagatgc acagattact
 5280

gcttcaccc tctttaccaa tatgtttgcc acctggtctc cttcaaaagc tcgacttcac
 5340

ctccaaggga ggagtaatgc ctggagacct caggtgaata atccaaaaga gtggctgcaa
 5400

gtggacttcc agaagacaat gaaagtcaca ggagtaacta ctcagggagt aaaatctctg
 5460

cttaccagca tgtatgtgaa ggagttcctc atctccagca gtcaagatgg ccatcagtgg
5520

actctctttt ttcagaatgg caaagtaaag gtttttcagg gaaatcaaga ctccttcaca
5580

cctgtggtga actctctaga cccaccgtta ctgactcgct accttcgaat tcacccccag
5640

agttgggtgc accagattgc cctgaggatg gaggttctgg gctgcgaggc acaggacctc
5700

tacgacaaaa ctcacacatg cccaccgtgc ccagctccag aactcctggg cggaccgtca
5760

gtcttcctct tcccccaaa acccaaggac accctcatgg cctcccggac ccctgaggtc
5820

acatgcgtgg tgggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg
5880

gacggcgtgg aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg
5940

taccgtgtgg tcagcgtcct caccgtcctg gcccaggact ggctgaatgg caaggagtac
6000

aagtgcaagg tctccaacaa agccctccca gcccccatcg agaaaaccat ctccaaagcc
6060

aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccgcga tgagctgacc
6120

aagaaccagg tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg
6180

gagtgggaga gcaatgggca gccggagAAC aactacaaga ccacgcctcc cgtgttggac
6240

tccgacggct ccttcttcct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag
6300

gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaacgccta cacgcagaag
6360

a g c c t c t c c c
6387

t g t c t c c g g g

t a a a t g a

<210> 157

<211> 2128

<212> PRT

<213> Artificial Sequence

<220>

<223> FVIII 263 (IHH triple mutant)

<400> 157

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

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

Trp Asp Tyr Met Gln Gly Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu
35 40 45

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
50 55 60

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
65 70 75 80

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
85 90 95

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
100 105 110

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser
115 120 125

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
 130 135 140

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 145 150 155 160

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly
 165 170 175

Ser Pro Thr Ser Thr Glu Glu Gly Ala Ser Ser Ser Asp Leu Gly Glu
 180 185 190

Leu Pro Val Asp Ala Arg Phe Pro Pro Arg Val Pro Lys Ser Phe Pro
 195 200 205

Phe Asn Thr Ser Val Val Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr
 210 215 220

Asp His Leu Phe Asn Ile Ala Lys Pro Arg Pro Pro Trp Met Gly Leu
 225 230 235 240

Leu Gly Pro Thr Ile Gln Ala Glu Val Tyr Asp Thr Val Val Ile Thr
 245 250 255

Leu Lys Asn Met Ala Ser His Pro Val Ser Leu His Ala Val Gly Val
 260 265 270

Ser Tyr Trp Lys Ala Ser Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser
 275 280 285

Gln Arg Glu Lys Glu Asp Asp Lys Val Phe Pro Gly Gly Ser His Thr
 290 295 300

Tyr Val Trp Gln Val Leu Lys Glu Asn Gly Pro Met Ala Ser Asp Pro
 305 310 315 320

Leu Cys Leu Thr Tyr Ser Tyr Leu Ser His Val Asp Leu Val Lys Asp
 325 330 335

Leu Asn Ser Gly Leu Ile Gly Ala Leu Leu Val Cys Arg Glu Gly Ser
 340 345 350

Leu Ala Lys Glu Lys Thr Gln Thr Leu His Lys Phe Ile Leu Leu Phe
 355 360 365

Ala Val Phe Asp Glu Gly Lys Ser Trp His Ser Glu Thr Lys Asn Ser
 370 375 380

Leu Met Gln Asp Arg Asp Ala Ala Ser Ala Arg Ala Trp Pro Lys Met
 385 390 395 400

His Thr Val Asn Gly Tyr Val Asn Arg Ser Leu Pro Gly Leu Ile Gly
 405 410 415

Cys His Arg Lys Ser Val Tyr Trp His Val Ile Gly Met Gly Thr Thr
 420 425 430

Pro Glu Val His Ser Ile Phe Leu Glu Gly His Thr Phe Leu Val Arg
 435 440 445

Asn His Arg Gln Ala Ser Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr
 450 455 460

Ala Gln Thr Leu Leu Met Asp Leu Gly Gln Phe Leu Leu Phe Cys His
 465 470 475 480

Ile	Ser	Ser	His	Gln	His	Asp	Gly	Met	Glu	Ala	Tyr	Val	Lys	Val	Asp
				485					490					495	
Ser	Cys	Pro	Glu	Glu	Pro	Gln	Leu	Arg	Met	Lys	Asn	Asn	Glu	Glu	Ala
			500					505					510		
Glu	Asp	Tyr	Asp	Asp	Asp	Leu	Thr	Asp	Ser	Glu	Met	Asp	Val	Val	Arg
		515					520					525			
Phe	Asp	Asp	Asp	Asn	Ser	Pro	Ser	Phe	Ile	Gln	Ile	Arg	Ser	Val	Ala
	530					535					540				
Lys	Lys	His	Pro	Lys	Thr	Trp	Val	His	Tyr	Ile	Ala	Ala	Glu	Glu	Glu
545					550					555					560
Asp	Trp	Asp	Tyr	Ala	Pro	Leu	Val	Leu	Ala	Pro	Asp	Asp	Arg	Ser	Tyr
				565					570					575	
Lys	Ser	Gln	Tyr	Leu	Asn	Asn	Gly	Pro	Gln	Arg	Ile	Gly	Arg	Lys	Tyr
			580					585					590		
Lys	Lys	Val	Arg	Phe	Met	Ala	Tyr	Thr	Asp	Glu	Thr	Phe	Lys	Thr	Arg
		595					600					605			
Glu	Ala	Ile	Gln	His	Glu	Ser	Gly	Ile	Leu	Gly	Pro	Leu	Leu	Tyr	Gly
	610					615					620				
Glu	Val	Gly	Asp	Thr	Leu	Leu	Ile	Ile	Phe	Lys	Asn	Gln	Ala	Ser	Arg
625					630					635					640
Pro	Tyr	Asn	Ile	Tyr	Pro	His	Gly	Ile	Thr	Asp	Val	Arg	Pro	Leu	Tyr
				645					650					655	
Ser	Arg	Arg	Leu	Pro	Lys	Gly	Val	Lys	His	Leu	Lys	Asp	Phe	Pro	Ile

660

665

670

Leu Pro Gly Glu Ile Phe Lys Tyr Lys Trp Thr Val Thr Val Glu Asp
675 680 685

Gly Pro Thr Lys Ser Asp Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser
690 695 700

Phe Val Asn Met Glu Arg Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu
705 710 715 720

Leu Ile Cys Tyr Lys Glu Ser Val Asp Gln Arg Gly Asn Gln Ile Met
725 730 735

Ser Asp Lys Arg Asn Val Ile Leu Phe Ser Val Phe Asp Glu Asn Arg
740 745 750

Ser Trp Tyr Leu Thr Glu Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala
755 760 765

Gly Val Gln Leu Glu Asp Pro Glu Phe Gln Ala Ser Asn Ile Met His
770 775 780

Ser Ile Asn Gly Tyr Val Phe Asp Ser Leu Gln Leu Ser Val Cys Leu
785 790 795 800

His Glu Val Ala Tyr Trp Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp
805 810 815

Phe Leu Ser Val Phe Phe Ser Gly Tyr Thr Phe Lys His Lys Met Val
820 825 830

Tyr Glu Asp Thr Leu Thr Leu Phe Pro Phe Ser Gly Glu Thr Val Phe
835 840 845

Met Ser Met Glu Asn Pro Gly Leu Trp Ile Leu Gly Cys His Asn Ser
 850 855 860

Asp Phe Arg Asn Arg Gly Met Thr Ala Leu Leu Lys Val Ser Ser Cys
 865 870 875 880

Asp Lys Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser
 885 890 895

Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
 900 905 910

Gln Asn Gly Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 915 920 925

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
 930 935 940

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 945 950 955 960

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 965 970 975

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro
 980 985 990

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr
 995 1000 1005

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
 1010 1015 1020

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 1025 1030 1035

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala
 1040 1045 1050

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser
 1055 1060 1065

Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 1070 1075 1080

Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 1085 1090 1095

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
 1100 1105 1110

Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser
 1115 1120 1125

Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr
 1130 1135 1140

Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 1145 1150 1155

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro
 1160 1165 1170

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr
 1175 1180 1185

Pro	Glu	Ser	Gly	Pro	Gly	Thr	Ser	Thr	Glu	Pro	Ser	Glu	Gly	Ser
1190						1195					1200			
Ala	Pro	Ala	Ser	Ser	Pro	Pro	Val	Leu	Lys	Arg	His	Gln	Ala	Glu
1205						1210					1215			
Ile	Thr	Arg	Thr	Thr	Leu	Gln	Ser	Asp	Gln	Glu	Glu	Ile	Asp	Tyr
1220						1225					1230			
Asp	Asp	Thr	Ile	Ser	Val	Glu	Met	Lys	Lys	Glu	Asp	Phe	Asp	Ile
1235						1240					1245			
Tyr	Asp	Glu	Asp	Glu	Asn	Gln	Ser	Pro	Arg	Ser	Phe	Gln	Lys	Lys
1250						1255					1260			
Thr	Arg	His	Tyr	Phe	Ile	Ala	Ala	Val	Glu	Arg	Leu	Trp	Asp	Tyr
1265						1270					1275			
Gly	Met	Ser	Ser	Ser	Pro	His	Val	Leu	Arg	Asn	Arg	Ala	Gln	Ser
1280						1285					1290			
Gly	Ser	Val	Pro	Gln	Phe	Lys	Lys	Val	Val	Phe	Gln	Glu	Phe	Thr
1295						1300					1305			
Asp	Gly	Ser	Phe	Thr	Gln	Pro	Leu	Tyr	Arg	Gly	Glu	Leu	Asn	Glu
1310						1315					1320			
His	Leu	Gly	Leu	Leu	Gly	Pro	Tyr	Ile	Arg	Ala	Glu	Val	Glu	Asp
1325						1330					1335			
Asn	Ile	Met	Val	Thr	Phe	Arg	Asn	Gln	Ala	Ser	Arg	Pro	Tyr	Ser
1340						1345					1350			
Phe	Tyr	Ser	Ser	Leu	Ile	Ser	Tyr	Glu	Glu	Asp	Gln	Arg	Gln	Gly

1355

1360

1365

Ala	Glu	Pro	Arg	Lys	Asn	Phe	Val	Lys	Pro	Asn	Glu	Thr	Lys	Thr
1370						1375					1380			

Tyr	Phe	Trp	Lys	Val	Gln	His	His	Met	Ala	Pro	Thr	Lys	Asp	Glu
1385						1390					1395			

Phe	Asp	Cys	Lys	Ala	Trp	Ala	Tyr	Phe	Ser	Asp	Val	Asp	Leu	Glu
1400						1405					1410			

Lys	Asp	Val	His	Ser	Gly	Leu	Ile	Gly	Pro	Leu	Leu	Val	Cys	His
1415						1420					1425			

Thr	Asn	Thr	Leu	Asn	Pro	Ala	His	Gly	Arg	Gln	Val	Thr	Val	Gln
1430						1435					1440			

Glu	Phe	Ala	Leu	Phe	Phe	Thr	Ile	Phe	Asp	Glu	Thr	Lys	Ser	Trp
1445						1450					1455			

Tyr	Phe	Thr	Glu	Asn	Met	Glu	Arg	Asn	Cys	Arg	Ala	Pro	Cys	Asn
1460						1465					1470			

Ile	Gln	Met	Glu	Asp	Pro	Thr	Phe	Lys	Glu	Asn	Tyr	Arg	Phe	His
1475						1480					1485			

Ala	Ile	Asn	Gly	Tyr	Ile	Met	Asp	Thr	Leu	Pro	Gly	Leu	Val	Met
1490						1495					1500			

Ala	Gln	Asp	Gln	Arg	Ile	Arg	Trp	Tyr	Leu	Leu	Ser	Met	Gly	Ser
1505						1510					1515			

Asn	Glu	Asn	Ile	His	Ser	Ile	His	Phe	Ser	Gly	His	Val	Phe	Thr
1520						1525					1530			

Val Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn Leu Tyr
 1535 1540 1545

Pro Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys Ala Gly
 1550 1555 1560

Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His Ala Gly
 1565 1570 1575

Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln Thr Pro
 1580 1585 1590

Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile Thr Ala
 1595 1600 1605

Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg Leu His
 1610 1615 1620

Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro Phe Ser
 1625 1630 1635

Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His Gly Ile
 1640 1645 1650

Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr Ile Ser
 1655 1660 1665

Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr
 1670 1675 1680

Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe Gly Asn
 1685 1690 1695

Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro Pro Ile
1700 1705 1710

Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg
1715 1720 1725

Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn Ser Cys
1730 1735 1740

Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln
1745 1750 1755

Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser
1760 1765 1770

Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp
1775 1780 1785

Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe
1790 1795 1800

Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys
1805 1810 1815

Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser
1820 1825 1830

Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys
1835 1840 1845

Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val
1850 1855 1860

Asn 1865	Ser	Leu	Asp	Pro	Pro	Leu 1870	Leu	Thr	Arg	Tyr	Leu 1875	Arg	Ile	His
Pro 1880	Gln	Ser	Trp	Val	His	Gln 1885	Ile	Ala	Leu	Arg	Met 1890	Glu	Val	Leu
Gly 1895	Cys	Glu	Ala	Gln	Asp	Leu 1900	Tyr	Asp	Lys	Thr	His 1905	Thr	Cys	Pro
Pro 1910	Cys	Pro	Ala	Pro	Glu	Leu 1915	Leu	Gly	Gly	Pro	Ser 1920	Val	Phe	Leu
Phe 1925	Pro	Pro	Lys	Pro	Lys	Asp 1930	Thr	Leu	Met	Ala	Ser 1935	Arg	Thr	Pro
Glu 1940	Val	Thr	Cys	Val	Val	Val 1945	Asp	Val	Ser	His	Glu 1950	Asp	Pro	Glu
Val 1955	Lys	Phe	Asn	Trp	Tyr	Val 1960	Asp	Gly	Val	Glu	Val 1965	His	Asn	Ala
Lys 1970	Thr	Lys	Pro	Arg	Glu	Glu 1975	Gln	Tyr	Asn	Ser	Thr 1980	Tyr	Arg	Val
Val 1985	Ser	Val	Leu	Thr	Val	Leu 1990	Ala	Gln	Asp	Trp	Leu 1995	Asn	Gly	Lys
Glu 2000	Tyr	Lys	Cys	Lys	Val	Ser 2005	Asn	Lys	Ala	Leu	Pro 2010	Ala	Pro	Ile
Glu 2015	Lys	Thr	Ile	Ser	Lys	Ala 2020	Lys	Gly	Gln	Pro	Arg 2025	Glu	Pro	Gln
Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln

2030

2035

2040

Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile
2045						2050					2055			

Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys
2060						2065					2070			

Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr
2075						2080					2085			

Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val
2090						2095					2100			

Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	Ala	Tyr	Thr
2105						2110					2115			

Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys
2120						2125			

<210> 158

<211> 5505

<212> DNA

<213> Artificial Sequence

<220>

<223> FVIII 282

<400> 158

atgcaaatag agctctccac ctgcttcttt ctgtgccttt tgcgattctg ctttagtgcc
60

accagaagat actacctggg tgcagtggaa ctgtcatggg actatatgca aagtgatctc
120

ggtgagctgc ctgtggacgc aagatttcct cctagagtgc caaaatcttt tccattcaac
180

acctcagtcg tgtacaaaaa gactctgttt gtagaattca cggatcacct tttcaacatc
240

gctaagccaa ggccaccctg gatgggtctg ctaggtccta ccatccaggc tgaggtttat
300

gatacagtgg tcattacact taagaacatg gcttcccatc ctgtcagtct tcatgctggt
360

gggtgtatcct actggaaagc ttctgaggga gctgaatatg atgatcagac cagtcaaagg
420

gagaaagaag atgataaagt cttccctggt ggaagccata catatgtctg gcaggtcctg
480

aaagagaatg gtccaatggc ctctgaccca ctgtgcctta cctactcata tctttctcat
540

gtggacctgg taaaagactt gaattcaggc ctcattggag ccctactagt atgtagagaa
600

gggagtctgg ccaaggaaaa gacacagacc ttgcacaaat ttatactact ttttgctgta
660

tttgatgaag ggaaaagttg gcactcagaa acaaagaact ccttgatgca ggatagggat
720

gctgcatctg ctcgggcctg gcctaaaatg cacacagtca atggttatgt aaacaggctct
780

ctgccaggtc tgattggatg ccacaggaaa tcagtctatt ggcatgtgat tggaatgggc
840

accactcctg aagtgcactc aatattcctc gaaggtcaca catttcttgt gaggaaccat
900

cgccaggcta gcttggaat ctcgccaata actttcctta ctgctcaaac actcttgatg
960

gaccttggac agtttctact gttttgtcat atctcttccc accaacaatga tggcatggaa
1020

gcttatgtca aagtagacag ctgtccagag gaacccaac tacgaatgaa aaataatgaa
1080

gaagcggaag actatgatga tgatcttact gattctgaaa tggatgtggt caggtttgat
1140

gatgacaact ctcccttcctt tatccaaatt cgctcagttg ccaagaagca tcctaaaact
1200

tgggtacatt acattgctgc tgaagaggag gactgggact atgctccctt agtcctcgcc
1260

cccgatgaca gaagttataa aagtcaatat ttgaacaatg gccctcagcg gattggtagg
1320

aagtacaaaa aagtccgatt tatggcatac acagatgaaa cctttaagac tcgtgaagct
1380

attcagcatg aatcaggaat cttgggacct ttactttatg gggaagttgg agacacactg
1440

ttgattatat ttaagaatca agcaagcaga ccatataaca tctaccctca cggaatcact
1500

gatgtccgtc ctttgtattc aaggagatta ccaaaagggtg taaaacattt gaaggatttt
1560

ccaattctgc caggagaaat attcaaatat aaatggacag tgactgtaga agatgggcca
1620

actaaatcag atcctcgggtg cctgaccgcg tattactcta gtttcgttaa tatggagaga
1680

gatctagctt caggactcat tggccctctc ctcatctgct acaaagaatc tgtagatcaa
1740

agaggaaacc agataatgtc agacaagagg aatgtcatcc tgttttctgt atttgatgag
1800

aaccgaagct ggtacctcac agagaatata caacgctttc tccccaatcc agctggagtg
1860

cagcttgagg atccagagtt ccaagcctcc aacatcatgc acagcatcaa tggctatggt
1920

tttgatagtt tgcagttgtc agtttgtttg catgagggtgg catactggta cattctaagc
1980

attggagcac agactgactt cctttctgtc ttcttctctg gatatacctt caaacacaaa
2040

atgggtctatg aagacacact caccctattc ccattctcag gagaaactgt cttcatgtcg
2100

atggaaaacc caggtctatg gattctgggg tgccacaact cagactttcg gaacagaggc
2160

atgaccgcct tactgaaggt ttctagttgt gacaagaaca ctggtgatta ttacgaggac
2220

agttatgaag atatttcagc atacttgctg agtaaaaaca atgccattga accaagaagc
2280

ttctctcaaa acggcgcgcc aacatcagag agcgccaccc ctgaaagtgg tcccgggagc
2340

gagccagcca catctgggtc ggaaacgcca ggcacaagtg agtctgcaac tcccgagtcc
2400

ggacctggct ccgagcctgc cactagcggc tccgagactc cgggaacttc cgagagcgct
2460

acaccagaaa gcggacccgg aaccagtacc gaacctagcg agggctctgc tccgggcagc
2520

ccagccggct ctcttacatc cacggaggag ggcacttccg aatccgccac cccggagtca
2580

gggccaggat ctgaaccgcg tacctcaggc agtgagacgc caggaacgag cgagtccgct
2640

acaccggaga gtgggcccagg gagccctgct ggatctccta cgtccactga ggaaggggtca
2700

ccagcgggct cgcccaccag cactgaagaa ggtgcctcga gccaccagt cttgaaacgc
2760

catcaagctg aaataactcg tactactctt cagtcagatc aagaggaaat cgattatgat
2820

gataccatat cagttgaaat gaagaaggaa gattttgaca tttatgatga ggatgaaaat
2880

cagagccccc gcagctttca aaagaaaaca cgacactatt ttattgctgc agtggagagg
2940

ctctgggatt atgggatgag tagctcccca catgtttctaa gaaacagggc tcagagtggc
3000

agtgtccctc agttcaagaa agttgttttc caggaattta ctgatggctc ctttactcag
3060

cccttatacc gtggagaact aaatgaacat ttgggactcc tggggccata tataagagca
3120

gaagttgaag ataatatcat ggtaactttc agaaatcagg cctctcgtcc ctattccttc
3180

tattctagcc ttattttctta tgaggaagat cagaggcaag gagcagaacc tagaaaaaac
3240

tttgtcaagc ctaatgaaac caaaacttac ttttggaag tgcaacatca tatggcaccc
3300

actaaagatg agtttgactg caaagcctgg gcttatttct ctgatgttga cctggaaaaa
3360

gatgtgcact caggcctgat tggacccctt ctgggtctgcc acactaacac actgaaccct
3420

gctcatggga gacaagtgac agtacaggaa tttgctctgt ttttcacat ctttgatgag
3480

acaaaagct ggtacttcac tgaaaatatg gaaagaaact gcagggctcc ctgcaatatc
3540

cagatggaag atcccacttt taaagagaat tatcgcttcc atgcaatcaa tggctacata
3600

atggatacac tacctggctt agtaatggct caggatcaaa ggattcgatg gtatctgctc
3660

agcatgggca gcaatgaaaa catccattct attcatttca gtggacatgt gttcactgta
3720

cgaaaaaaag aggagtataa aatggcactg tacaatctct atccaggtgt ttttgagaca
3780

gtggaaatgt taccatccaa agctggaatt tggcgggtgg aatgccttat tggcgagcat
3840

ctacatgctg ggatgagcac actttttctg gtgtacagca ataagtgtca gactcccctg
3900

ggaatggctt ctggacacat tagagatttt cagattacag cttcaggaca atatggacag
3960

tgggccccaa agctggccag acttcattat tccggatcaa tcaatgcctg gagcaccaag
4020

gagccctttt cttggatcaa ggtggatctg ttggcaccaa tgattattca cggcatcaag
4080

accaggggtg cccgtcagaa gttctccagc ctctacatct ctcagtttat catcatgtat
4140

agtcttgatg ggaagaagtg gcagacttat cgaggaaatt ccactggaac cttaatggtc
4200

ttctttggca atgtggattc atctgggata aaacacaata tttttaaccc tccaattatt
4260

gctcgataca tccgtttgca cccaactcat tatagcattc gcagcactct tcgcatggag
4320

ttgatgggct gtgatttaaa tagttgcagc atgccattgg gaatggagag taaagcaata
4380

tcagatgcac agattactgc ttcatcctac tttaccaata tgtttgccac ctggtctcct
4440

tcaaaagctc gacttcacct ccaagggagg agtaatgcct ggagacctca ggtgaataat
4500

ccaaaagagt ggctgcaagt ggacttccag aagacaatga aagtcacagg agtaactact
4560

cagggagtaa aatctctgct taccagcatg tatgtgaagg agttcctcat ctccagcagt
4620

caagatggcc atcagtggac tctctttttt cagaatggca aagtaaaggt ttttcaggga
4680

aatcaagact ccttcacacc tgtggtgaac tctctagacc caccgttact gactcgctac
4740

cttcgaattc acccccagag ttgggtgcac cagattgccc tgaggatgga ggttctgggc
4800

tgcgaggcac aggacctcta cgacaaaact cacacatgcc caccgtgccc agctccagaa
4860

ctcctgggcg gaccgtcagt cttcctcttc cccccaaaac ccaaggacac cctcatgac
4920

tcccggaccc ctgaggtcac atgctgtggtg gtggacgtga gccacgaaga ccctgaggtc
4980

aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa gccgcgggag
5040

gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca ccaggactgg
5100

ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc ccccatcgag
5160

aaaaccatct ccaaagccaa agggcagccc cgagaaccac aggtgtacac cctgccccca
5220

tcccgggatg agctgaccaa gaaccaggtc agcctgacct gcctgggtcaa aggtttctat
5280

cccagcgaca tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc
5340

acgcctcccg tgttggactc cgacggctcc ttcttcctct acagcaagct caccgtggac
5400

aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg tgatgcatga ggctctgcac
5460

aaccactaca cgcagaagag cctctccctg tctccgggta aatga
5505

<210> 159

<211> 1834

<212> PRT

<213> Artificial Sequence

<220>

<223> FVIII 282

<400> 159

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

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

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
 50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
 65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
 85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
 100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
 115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
 130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu

145					150					155					160
Lys	Glu	Asn	Gly	Pro	Met	Ala	Ser	Asp	Pro	Leu	Cys	Leu	Thr	Tyr	Ser
				165					170					175	
Tyr	Leu	Ser	His	Val	Asp	Leu	Val	Lys	Asp	Leu	Asn	Ser	Gly	Leu	Ile
			180					185					190		
Gly	Ala	Leu	Leu	Val	Cys	Arg	Glu	Gly	Ser	Leu	Ala	Lys	Glu	Lys	Thr
		195					200					205			
Gln	Thr	Leu	His	Lys	Phe	Ile	Leu	Leu	Phe	Ala	Val	Phe	Asp	Glu	Gly
	210					215					220				
Lys	Ser	Trp	His	Ser	Glu	Thr	Lys	Asn	Ser	Leu	Met	Gln	Asp	Arg	Asp
225					230					235					240
Ala	Ala	Ser	Ala	Arg	Ala	Trp	Pro	Lys	Met	His	Thr	Val	Asn	Gly	Tyr
				245					250					255	
Val	Asn	Arg	Ser	Leu	Pro	Gly	Leu	Ile	Gly	Cys	His	Arg	Lys	Ser	Val
			260					265					270		
Tyr	Trp	His	Val	Ile	Gly	Met	Gly	Thr	Thr	Pro	Glu	Val	His	Ser	Ile
		275					280					285			
Phe	Leu	Glu	Gly	His	Thr	Phe	Leu	Val	Arg	Asn	His	Arg	Gln	Ala	Ser
	290					295					300				
Leu	Glu	Ile	Ser	Pro	Ile	Thr	Phe	Leu	Thr	Ala	Gln	Thr	Leu	Leu	Met
305					310					315					320
Asp	Leu	Gly	Gln	Phe	Leu	Leu	Phe	Cys	His	Ile	Ser	Ser	His	Gln	His
				325					330					335	

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
 340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
 355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
 370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
 385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
 405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
 420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
 435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
 450 455 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
 465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
 485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
 500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
 515 520 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
 530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
 545 550 555 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
 565 570 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
 580 585 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
 595 600 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
 610 615 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
 625 630 635 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
 645 650 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
 660 665 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
 675 680 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
 690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
 705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
 725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
 740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Gly Ala Pro Thr
 755 760 765

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr
 770 775 780

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 785 790 795 800

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
 805 810 815

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro
 820 825 830

Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr
 835 840 845

Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
 850 855 860

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala

865		870		875		880									
Thr	Pro	Glu	Ser	Gly	Pro	Gly	Ser	Pro	Ala	Gly	Ser	Pro	Thr	Ser	Thr
				885					890					895	
Glu	Glu	Gly	Ser	Pro	Ala	Gly	Ser	Pro	Thr	Ser	Thr	Glu	Glu	Gly	Ala
			900					905					910		
Ser	Ser	Pro	Pro	Val	Leu	Lys	Arg	His	Gln	Ala	Glu	Ile	Thr	Arg	Thr
		915					920					925			
Thr	Leu	Gln	Ser	Asp	Gln	Glu	Glu	Ile	Asp	Tyr	Asp	Asp	Thr	Ile	Ser
	930					935					940				
Val	Glu	Met	Lys	Lys	Glu	Asp	Phe	Asp	Ile	Tyr	Asp	Glu	Asp	Glu	Asn
945					950					955					960
Gln	Ser	Pro	Arg	Ser	Phe	Gln	Lys	Lys	Thr	Arg	His	Tyr	Phe	Ile	Ala
				965					970					975	
Ala	Val	Glu	Arg	Leu	Trp	Asp	Tyr	Gly	Met	Ser	Ser	Ser	Pro	His	Val
			980					985					990		
Leu	Arg	Asn	Arg	Ala	Gln	Ser	Gly	Ser	Val	Pro	Gln	Phe	Lys	Lys	Val
		995					1000					1005			
Val	Phe	Gln	Glu	Phe	Thr	Asp	Gly	Ser	Phe	Thr	Gln	Pro	Leu	Tyr	
	1010					1015					1020				
Arg	Gly	Glu	Leu	Asn	Glu	His	Leu	Gly	Leu	Leu	Gly	Pro	Tyr	Ile	
	1025					1030					1035				
Arg	Ala	Glu	Val	Glu	Asp	Asn	Ile	Met	Val	Thr	Phe	Arg	Asn	Gln	
	1040					1045					1050				

Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser Tyr Glu
1055 1060 1065

Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys
1070 1075 1080

Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His Met
1085 1090 1095

Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
1100 1105 1110

Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly
1115 1120 1125

Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly
1130 1135 1140

Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe
1145 1150 1155

Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn
1160 1165 1170

Cys Arg Ala Pro Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys
1175 1180 1185

Glu Asn Tyr Arg Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr
1190 1195 1200

Leu Pro Gly Leu Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr
1205 1210 1215

Leu 1220	Leu	Ser	Met	Gly	Ser	Asn 1225	Glu	Asn	Ile	His	Ser 1230	Ile	His	Phe
Ser 1235	Gly	His	Val	Phe	Thr	Val 1240	Arg	Lys	Lys	Glu	Glu 1245	Tyr	Lys	Met
Ala 1250	Leu	Tyr	Asn	Leu	Tyr	Pro 1255	Gly	Val	Phe	Glu	Thr 1260	Val	Glu	Met
Leu 1265	Pro	Ser	Lys	Ala	Gly	Ile 1270	Trp	Arg	Val	Glu	Cys 1275	Leu	Ile	Gly
Glu 1280	His	Leu	His	Ala	Gly	Met 1285	Ser	Thr	Leu	Phe	Leu 1290	Val	Tyr	Ser
Asn 1295	Lys	Cys	Gln	Thr	Pro	Leu 1300	Gly	Met	Ala	Ser	Gly 1305	His	Ile	Arg
Asp 1310	Phe	Gln	Ile	Thr	Ala	Ser 1315	Gly	Gln	Tyr	Gly	Gln 1320	Trp	Ala	Pro
Lys 1325	Leu	Ala	Arg	Leu	His	Tyr 1330	Ser	Gly	Ser	Ile	Asn 1335	Ala	Trp	Ser
Thr 1340	Lys	Glu	Pro	Phe	Ser	Trp 1345	Ile	Lys	Val	Asp	Leu 1350	Leu	Ala	Pro
Met 1355	Ile	Ile	His	Gly	Ile	Lys 1360	Thr	Gln	Gly	Ala	Arg 1365	Gln	Lys	Phe
Ser 1370	Ser	Leu	Tyr	Ile	Ser	Gln 1375	Phe	Ile	Ile	Met	Tyr 1380	Ser	Leu	Asp

Gly	Lys	Lys	Trp	Gln	Thr	Tyr	Arg	Gly	Asn	Ser	Thr	Gly	Thr	Leu
	1385					1390					1395			
Met	Val	Phe	Phe	Gly	Asn	Val	Asp	Ser	Ser	Gly	Ile	Lys	His	Asn
	1400					1405					1410			
Ile	Phe	Asn	Pro	Pro	Ile	Ile	Ala	Arg	Tyr	Ile	Arg	Leu	His	Pro
	1415					1420					1425			
Thr	His	Tyr	Ser	Ile	Arg	Ser	Thr	Leu	Arg	Met	Glu	Leu	Met	Gly
	1430					1435					1440			
Cys	Asp	Leu	Asn	Ser	Cys	Ser	Met	Pro	Leu	Gly	Met	Glu	Ser	Lys
	1445					1450					1455			
Ala	Ile	Ser	Asp	Ala	Gln	Ile	Thr	Ala	Ser	Ser	Tyr	Phe	Thr	Asn
	1460					1465					1470			
Met	Phe	Ala	Thr	Trp	Ser	Pro	Ser	Lys	Ala	Arg	Leu	His	Leu	Gln
	1475					1480					1485			
Gly	Arg	Ser	Asn	Ala	Trp	Arg	Pro	Gln	Val	Asn	Asn	Pro	Lys	Glu
	1490					1495					1500			
Trp	Leu	Gln	Val	Asp	Phe	Gln	Lys	Thr	Met	Lys	Val	Thr	Gly	Val
	1505					1510					1515			
Thr	Thr	Gln	Gly	Val	Lys	Ser	Leu	Leu	Thr	Ser	Met	Tyr	Val	Lys
	1520					1525					1530			
Glu	Phe	Leu	Ile	Ser	Ser	Ser	Gln	Asp	Gly	His	Gln	Trp	Thr	Leu
	1535					1540					1545			
Phe	Phe	Gln	Asn	Gly	Lys	Val	Lys	Val	Phe	Gln	Gly	Asn	Gln	Asp

1550		1555		1560
Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr				
1565		1570		1575
Arg Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala				
1580		1585		1590
Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr Asp				
1595		1600		1605
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly				
1610		1615		1620
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu				
1625		1630		1635
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val				
1640		1645		1650
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly				
1655		1660		1665
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr				
1670		1675		1680
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln				
1685		1690		1695
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys				
1700		1705		1710
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly				
1715		1720		1725

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
 1730 1735 1740

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
 1745 1750 1755

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 1760 1765 1770

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
 1775 1780 1785

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 1790 1795 1800

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 1805 1810 1815

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 1820 1825 1830

Lys

<210> 160

<211> 5937

<212> DNA

<213> Artificial Sequence

<220>

<223> FVIII 283 (FVIII 169 with IHH triple mutation)

<400> 160

atgcaaata agctctccac ctgcttcttt ctgtgccttt tgcgattctg ctttagtgcc
 60

accagaagat actacctggg tgcagtggaa ctgtcatggg actatatgca aagtgatctc
120

ggtgagctgc ctgtggacgc aagatttcct cctagagtgc caaaatcttt tccattcaac
180

acctcagtcg tgtacaaaaa gactctgttt gtagaattca cggatcacct tttcaacatc
240

gctaagccaa ggccaccctg gatgggtctg ctaggtccta ccatccaggc tgaggtttat
300

gatacagtgg tcattacact taagaacatg gcttcccatc ctgtcagtct tcatgctgtt
360

ggtgtatcct actggaaagc ttctgaggga gctgaatatg atgatcagac cagtcaaagg
420

gagaaagaag atgataaagt cttccctggg ggaagccata catatgtctg gcaggctcctg
480

aaagagaatg gtccaatggc ctctgaccca ctgtgcctta cctactcata tctttctcat
540

gtggacctgg taaaagactt gaattcaggc ctcatggag ccctactagt atgtagagaa
600

gggagtctgg ccaaggaaaa gacacagacc ttgcacaaat ttatactact ttttgctgta
660

tttgatgaag ggaaaagttg gcactcagaa acaaagaact ccttgatgca ggatagggat
720

gctgcatctg ctcgggcctg gcctaaaatg cacacagtca atggttatgt aaacaggctc
780

ctgccaggtc tgattggatg ccacaggaaa tcagtctatt ggcatgtgat tggaatgggc
840

accactcctg aagtgcactc aatattcctc gaaggtcaca catttcttgt gaggaaccat
900

cgccaggcta gcttggaat ctcgccaata actttcctta ctgctcaaac actcttgatg
960

gaccttggac agtttctact gttttgtcat atctcttccc accaacaatga tggcatggaa
1020

gcttatgtca aagtagacag ctgtccagag gaaccccaac tacgaatgaa aaataatgaa
1080

gaagcggaag actatgatga tgatcttact gattctgaaa tggatgtggt caggtttgat
1140

gatgacaact ctccttcctt tatccaaatt cgctcagttg ccaagaagca tcctaaaact
1200

tgggtacatt acattgctgc tgaagaggag gactgggact atgctccctt agtcctcgcc
1260

cccgatgaca gaagttataa aagtcaatat ttgaacaatg gccctcagcg gattggtagg
1320

aagtacaaaa aagtcgatt tatggcatat acagatgaaa cctttaagac tcgtgaagct
1380

attcagcatg aatcaggaat cttgggacct ttactttatg gggaagttgg agacacactg
1440

ttgattatat ttaagaatca agcaagcaga ccatataaca tctaccctca cggaatcact
1500

gatgtccgtc ctttgtattc aaggagatta ccaaaagggtg taaaacattt gaaggatttt
1560

ccaattctgc caggagaaat attcaaatat aaatggacag tgactgtaga agatgggccca
1620

actaaatcag atcctcgggtg cctgaccgcg tattactcta gtttcgttaa tatggagaga
1680

gatctagctt caggactcat tggccctctc ctcatctgct acaaagaatc tgtagatcaa
1740

agaggaaacc agataatgtc agacaagagg aatgtcatcc tgttttctgt atttgatgag
1800

aaccgaagct ggtacctcac agagaatata caacgctttc tccccaatcc agctggagtg
1860

cagcttgagg atccagagtt ccaagcctcc aacatcatgc acagcatcaa tggctatggt
1920

tttgatagtt tgcagttgtc agtttgtttg catgagggtgg catactggta cattctaagc
1980

attggagcac agactgactt cctttctgtc ttcttctctg gatatacctt caaacacaaa
2040

atgggtctatg aagacacact caccctattc ccattctcag gagaaactgt cttcatgtcg
2100

atggaaaacc cagggtctatg gattctgggg tgccacaact cagactttcg gaacagaggc
2160

atgaccgcct tactgaaggt ttctagttgt gacaagaaca ctggtgatta ttacgaggac
2220

agttatgaag atatttcagc atacttgctg agtaaaaaca atgccattga accaagaagc
2280

ttctctcaaa acggcgcgcc aggtacctca gagtctgcta ccccgagtc agggccagga
2340

tcagagccag ccacctccgg gtctgagaca cccgggactt ccgagagtgc caccctgag
2400

tccggacccg ggtccgagcc cgccacttcc ggctccgaaa ctcccggcac aagcgagagc
2460

gctaccccag agtcaggacc aggaacatct acagagccct ctgaaggctc cgctccaggg
2520

tccccagccg gcagtccac tagcaccgag gagggaacct ctgaaagcgc cacacccgaa
2580

tcagggccag ggtctgagcc tgctaccagc ggcagcgaga caccaggcac ctctgagtcc
2640

gccacaccag agtccggacc cggatctccc gctgggagcc ccacctccac tgaggagggga
2700

tctcctgctg gctctccaac atctactgag gaagggtacct caaccgagcc atccgagggga
2760

tcagctcccg gcacctcaga gtcggcaacc ccggagtctg gacccggaac ttccgaaagt
2820

gccacaccag agtccggtcc cgggacttca gaatcagcaa cacccgagtc cggccctggg
2880

tctgaacccg ccacaagtgg tagtgagaca ccaggatcag aacctgctac ctcaggggtca
2940

gagacacccg gatctccggc aggctcacca acctccactg aggagggcac cagcacagaa
3000

ccaagcgagg gctccgcacc cggaacaagc actgaaccca gtgaggggttc agcaccggc
3060

tctgagccgg ccacaagtgg cagtgagaca cccggcactt cagagagtgc ccccccgag
3120

agtggcccag gcactagtag cgagccctct gaaggcagtg cgccagcctc gagcccacca
3180

gtcttgaaac gccatcaagc tgaaataact cgtactactc ttcagtcaga tcaagaggaa
3240

atcgattatg atgataccat atcagttgaa atgaagaagg aagattttga catttatgat
3300

gaggatgaaa atcagagccc ccgcagcttt caaaagaaaa cacgacacta ttttattgct
3360

gcagtggaga ggctctggga ttatgggatg agtagctccc cacatgttct aagaaacagg
3420

gctcagagtg gcagtgtccc tcagttcaag aaagttgttt tccaggaatt tactgatggc
3480

tcctttactc agcccttata ccgtggagaa ctaaataaac atttgggact cctggggcca
3540

tatataagag cagaagttga agataatatc atggtaactt tcagaaatca ggcctctcgt
3600

ccctattcct tctattctag ccttatttct tatgaggaag atcagaggca aggagcagaa
3660

cctagaaaaa actttgtcaa gcctaatagaa accaaaactt acttttggaa agtgcaacat
3720

catatggcac ccactaaaga tgagtttgac tgcaaagcct gggcttattt ctctgatgtt
3780

gacctggaaa aagatgtgca ctcaggcctg attggacccc ttctggctctg ccacactaac
3840

acactgaacc ctgctcatgg gagacaagtg acagtacagg aatttgctct gtttttcacc
3900

atctttgatg agaccaaag ctggtacttc actgaaaata tggaaagaaa ctgcagggct
3960

ccctgcaata tccagatgga agatcccact tttaaagaga attatcgctt ccatgcaatc
4020

aatggctaca taatggatac actacctggc ttagtaatgg ctcaggatca aaggattcga
4080

tggtatctgc tcagcatggg cagcaatgaa aacatccatt ctattcattt cagtggacat
4140

gtgttcactg tacgaaaaaa agaggagtat aaaatggcac tgtacaatct ctatccaggt
4200

gtttttgaga cagtggaaat gttaccatcc aaagctggaa tttggcgggt ggaatgcctt
4260

attggcgagc atctacatgc tgggatgagc acactttttc tgggtgtacag caataagtgt
4320

cagactcccc tgggaatggc ttctggacac attagagatt ttcagattac agcttcagga
4380

caatatggac agtgggcccc aaagctggcc agacttcatt attccggatc aatcaatgcc
4440

tggagcacca aggagccctt ttcttggatc aaggtggatc tgttggcacc aatgattatt
4500

cacggcatca agaccaggg tgcccgtcag aagttctcca gcctctacat ctctcagttt
4560

atcatcatgt atagtcttga tgggaagaag tggcagactt atcgaggaaa ttccactgga
4620

accttaatgg tcttcttttg caatgtggat tcatctggga taaaacacaa tatttttaac
4680

cctccaatta ttgctcgata catccgtttg cacccaactc attatagcat tcgcagcact
4740

cttcgcatgg agttgatggg ctgtgattta aatagttgca gcatgccatt gggaatggag
4800

agtaaagcaa tatcagatgc acagattact gcttcatcct actttaccaa tatgtttgcc
4860

acctggtctc cttcaaaagc tcgacttcac ctccaaggga ggagtaatgc ctggagacct
4920

caggtgaata atccaaaaga gtggctgcaa gtggacttcc agaagacaat gaaagtcaca
4980

ggagtaacta ctcagggagt aaaatctctg cttaccagca tgtatgtgaa ggagttcctc
5040

atctccagca gtcaagatgg ccatcagtggt actctctttt ttcagaatgg caaagtaaag
5100

gtttttcagg gaaatcaaga ctccttcaca cctgtgggtga actctctaga cccaccgtta
5160

ctgactcgct accttcgaat tcacccccag agttgggtgc accagattgc cctgaggatg
5220

gaggttctgg gctgcgaggc acaggacctc tacgacaaaa ctcacacatg cccaccgtgc
5280

ccagctccag aactcctggg cggaccgtca gtcttcctct tccccccaaa acccaaggac
5340

accctcatgg cctcccggac ccctgaggtc acatgcgtgg tgggtggacgt gagccacgaa
5400

gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca
5460

aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg
5520

gcccaggact ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca
5580

gcccccatcg agaaaacat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac
5640

accctgcccc catcccggga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc
5700

aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagAAC
5760

aactacaaga ccacgcctcc cgtgttggac tccgacggct ccttcttctt ctacagcaag
5820

ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat
5880

gaggctctgc acaacgccta cacgcagaag agcctctccc tgtctccggg taaatga
5937

<210> 161

<211> 1978

<212> PRT

<213> Artificial Sequence

<220>

<223> FVIII 283 (FVIII 169 with IHH triple mutation)

<400> 161

Met	Gln	Ile	Glu	Leu	Ser	Thr	Cys	Phe	Phe	Leu	Cys	Leu	Leu	Arg	Phe
1				5					10					15	

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

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg

35

40

45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
 50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
 65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
 85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
 100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
 115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
 130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
 145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
 165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
 180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
 195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
 210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
 225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
 245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
 260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
 275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
 290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
 305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
 325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
 340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
 355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
 370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
 385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
 405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
 420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
 435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
 450 455 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
 465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
 485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
 500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
 515 520 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
 530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
 545 550 555 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
 565 570 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
 580 585 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
 595 600 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
 610 615 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
 625 630 635 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
 645 650 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
 660 665 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
 675 680 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
 690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
 705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
 725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
 740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Gly Ala Pro Gly

755

760

765

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 770 775 780

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 785 790 795 800

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 805 810 815

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu
 820 825 830

Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 835 840 845

Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 850 855 860

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser
 865 870 875 880

Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 885 890 895

Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
 900 905 910

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser
 915 920 925

Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 930 935 940

Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 945 950 955 960

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala
 965 970 975

Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
 980 985 990

Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 995 1000 1005

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro
 1010 1015 1020

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr
 1025 1030 1035

Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
 1040 1045 1050

Ala Pro Ala Ser Ser Pro Pro Val Leu Lys Arg His Gln Ala Glu
 1055 1060 1065

Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr
 1070 1075 1080

Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile
 1085 1090 1095

Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys
 1100 1105 1110

Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr
 1115 1120 1125

Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser
 1130 1135 1140

Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr
 1145 1150 1155

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu
 1160 1165 1170

His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp
 1175 1180 1185

Asn Ile Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser
 1190 1195 1200

Phe Tyr Ser Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly
 1205 1210 1215

Ala Glu Pro Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr
 1220 1225 1230

Tyr Phe Trp Lys Val Gln His His Met Ala Pro Thr Lys Asp Glu
 1235 1240 1245

Phe Asp Cys Lys Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu
 1250 1255 1260

Lys Asp Val His Ser Gly Leu Ile Gly Pro Leu Leu Val Cys His
 1265 1270 1275

Thr	Asn	Thr	Leu	Asn	Pro	Ala	His	Gly	Arg	Gln	Val	Thr	Val	Gln
1280						1285					1290			
Glu	Phe	Ala	Leu	Phe	Phe	Thr	Ile	Phe	Asp	Glu	Thr	Lys	Ser	Trp
1295						1300					1305			
Tyr	Phe	Thr	Glu	Asn	Met	Glu	Arg	Asn	Cys	Arg	Ala	Pro	Cys	Asn
1310						1315					1320			
Ile	Gln	Met	Glu	Asp	Pro	Thr	Phe	Lys	Glu	Asn	Tyr	Arg	Phe	His
1325						1330					1335			
Ala	Ile	Asn	Gly	Tyr	Ile	Met	Asp	Thr	Leu	Pro	Gly	Leu	Val	Met
1340						1345					1350			
Ala	Gln	Asp	Gln	Arg	Ile	Arg	Trp	Tyr	Leu	Leu	Ser	Met	Gly	Ser
1355						1360					1365			
Asn	Glu	Asn	Ile	His	Ser	Ile	His	Phe	Ser	Gly	His	Val	Phe	Thr
1370						1375					1380			
Val	Arg	Lys	Lys	Glu	Glu	Tyr	Lys	Met	Ala	Leu	Tyr	Asn	Leu	Tyr
1385						1390					1395			
Pro	Gly	Val	Phe	Glu	Thr	Val	Glu	Met	Leu	Pro	Ser	Lys	Ala	Gly
1400						1405					1410			
Ile	Trp	Arg	Val	Glu	Cys	Leu	Ile	Gly	Glu	His	Leu	His	Ala	Gly
1415						1420					1425			
Met	Ser	Thr	Leu	Phe	Leu	Val	Tyr	Ser	Asn	Lys	Cys	Gln	Thr	Pro
1430						1435					1440			
Leu	Gly	Met	Ala	Ser	Gly	His	Ile	Arg	Asp	Phe	Gln	Ile	Thr	Ala

1445						1450						1455			
Ser	Gly	Gln	Tyr	Gly	Gln	Trp	Ala	Pro	Lys	Leu	Ala	Arg	Leu	His	
1460						1465					1470				
Tyr	Ser	Gly	Ser	Ile	Asn	Ala	Trp	Ser	Thr	Lys	Glu	Pro	Phe	Ser	
1475						1480					1485				
Trp	Ile	Lys	Val	Asp	Leu	Leu	Ala	Pro	Met	Ile	Ile	His	Gly	Ile	
1490						1495					1500				
Lys	Thr	Gln	Gly	Ala	Arg	Gln	Lys	Phe	Ser	Ser	Leu	Tyr	Ile	Ser	
1505						1510					1515				
Gln	Phe	Ile	Ile	Met	Tyr	Ser	Leu	Asp	Gly	Lys	Lys	Trp	Gln	Thr	
1520						1525					1530				
Tyr	Arg	Gly	Asn	Ser	Thr	Gly	Thr	Leu	Met	Val	Phe	Phe	Gly	Asn	
1535						1540					1545				
Val	Asp	Ser	Ser	Gly	Ile	Lys	His	Asn	Ile	Phe	Asn	Pro	Pro	Ile	
1550						1555					1560				
Ile	Ala	Arg	Tyr	Ile	Arg	Leu	His	Pro	Thr	His	Tyr	Ser	Ile	Arg	
1565						1570					1575				
Ser	Thr	Leu	Arg	Met	Glu	Leu	Met	Gly	Cys	Asp	Leu	Asn	Ser	Cys	
1580						1585					1590				
Ser	Met	Pro	Leu	Gly	Met	Glu	Ser	Lys	Ala	Ile	Ser	Asp	Ala	Gln	
1595						1600					1605				
Ile	Thr	Ala	Ser	Ser	Tyr	Phe	Thr	Asn	Met	Phe	Ala	Thr	Trp	Ser	
1610						1615					1620				

Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp
 1625 1630 1635

Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe
 1640 1645 1650

Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys
 1655 1660 1665

Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser
 1670 1675 1680

Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys
 1685 1690 1695

Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val
 1700 1705 1710

Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His
 1715 1720 1725

Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu Val Leu
 1730 1735 1740

Gly Cys Glu Ala Gln Asp Leu Tyr Asp Lys Thr His Thr Cys Pro
 1745 1750 1755

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
 1760 1765 1770

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ala Ser Arg Thr Pro
 1775 1780 1785

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
1790 1795 1800

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
1805 1810 1815

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
1820 1825 1830

Val Ser Val Leu Thr Val Leu Ala Gln Asp Trp Leu Asn Gly Lys
1835 1840 1845

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
1850 1855 1860

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
1865 1870 1875

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
1880 1885 1890

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
1895 1900 1905

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
1910 1915 1920

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
1925 1930 1935

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
1940 1945 1950

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Ala Tyr Thr
 1955 1960 1965

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 1970 1975

<210> 162

<211> 5055

<212> DNA

<213> Artificial Sequence

<220>

<223> pSYNFVIII 010 (Dual chain FVIIIIFc)

<400> 162

atgcaaatag agctctccac ctgcttcttt ctgtgccttt tgcgattctg ctttagtgcc
 60

accagaagat actacctggg tgcagtggaa ctgtcatggg actatatgca aagtgatctc
 120

ggtgagctgc ctgtggacgc aagatttcct cctagagtgc caaaatcttt tccattcaac
 180

acctcagtcg tgtacaaaaa gactctgttt gtagaattca cggatcacct tttcaacatc
 240

gctaagccaa ggccaccctg gatgggtctg ctaggtccta ccatccaggc tgagggtttat
 300

gatacagtgg tcattacact taagaacatg gcttcccatc ctgtcagtct tcatgctgtt
 360

ggtgtatcct actggaaagc ttctgaggga gctgaatatg atgatcagac cagtcaaagg
 420

gagaaagaag atgataaagt cttccctggg ggaagccata catatgtctg gcaggctctg
 480

aaagagaatg gtccaatggc ctctgaccca ctgtgcctta cctactcata tctttctcat
 540

gtggacctgg taaaagactt gaattcaggc ctcattggag ccctactagt atgtagagaa
 600

gggagtcttg ccaaggaaaa gacacagacc ttgcacaaat ttatactact ttttgctgta
660

tttgatgaag ggaaaagttg gcactcagaa acaaagaact ccttgatgca ggatagggat
720

gctgcatctg ctcgggcctg gcctaaaatg cacacagtca atggttatgt aaacaggtct
780

ctgccaggtc tgattggatg ccacaggaaa tcagtctatt ggcatgtgat tggaatgggc
840

accactcctg aagtgcactc aatattcctc gaaggtcaca catttcttgt gaggaacat
900

cgccaggcgt ccttggaat ctcgccaata actttcctta ctgctcaaac actccttgatg
960

gaccttggac agtttctact gttttgtcat atctcttccc accaacaatga tggcatggaa
1020

gcttatgtca aagtagacag ctgtccagag gaacccaac tacgaatgaa aaataatgaa
1080

gaagcggaag actatgatga tgatcttact gattctgaaa tggatgtggg caggtttgat
1140

gatgacaact ctccttcctt tatccaaatt cgctcagttg ccaagaagca tcctaaaact
1200

tgggtacatt acattgctgc tgaagaggag gactgggact atgctccctt agtcctcgcc
1260

cccgatgaca gaagttataa aagtcaatat ttgaacaatg gccctcagcg gattggtagg
1320

aagtacaaaa aagtccgatt tatggcatac acagatgaaa cctttaagac tcgtgaagct
1380

attcagcatg aatcaggaat cttgggacct ttactttatg gggaagttgg agacacactg
1440

ttgattatat ttaagaatca agcaagcaga ccatataaca tctaccctca cggaatcact
1500

gatgtccgtc ctttgtattc aaggagatta ccaaaagggtg taaaacattt gaaggatttt
1560

ccaattctgc caggagaaat attcaaatat aaatggacag tgactgtaga agatgggcca
1620

actaaatcag atcctcgggtg cctgaccgcg tattactcta gtttcgttaa tatggagaga
1680

gatctagctt caggactcat tggccctctc ctcatctgct acaaagaatc tgtagatcaa
1740

agaggaaacc agataatgtc agacaagagg aatgtcatcc tgttttctgt atttgatgag
1800

aaccgaagct ggtacctcac agagaatata caacgctttc tccccaatcc agctggagtg
1860

cagcttgagg atccagagtt ccaagcctcc aacatcatgc acagcatcaa tggctatggt
1920

tttgatagtt tgcagttgtc agtttgtttg catgagggtgg catactggta cattctaagc
1980

attggagcac agactgactt cctttctgtc ttcttctctg gatatacctt caaacacaaa
2040

atgggtctatg aagacacact caccctattc ccattctcag gagaaactgt cttcatgtcg
2100

atggaaaacc cagggtctatg gattctgggg tgccacaact cagactttcg gaacagaggc
2160

atgaccgcct tactgaaggt ttctagttgt gacaagaaca ctgggtgatta ttacgaggac
2220

agttatgaag atatttcagc atacttgctg agtaaaaaca atgccattga accaagaagc
2280

ttctctcaaa acccaccagt cttgaaacgc catcaacggg aaataactcg tactactctt
2340

cagtcagatc aagaggaaat tgactatgat gataccatat cagttgaaat gaagaaggaa
2400

gatttttgaca	tttatgatga	ggatgaaaat	cagagcccc	gcagctttca	aaagaaaaca
2460					
cgacactatt	ttattgctgc	agtggagagg	ctctgggatt	atgggatgag	tagctcccca
2520					
catgttctaa	gaaacagggc	tcagagtggc	agtgtccctc	agttcaagaa	agttgttttc
2580					
caggaattta	ctgatggctc	ctttactcag	cccttatacc	gtggagaact	aatgaacat
2640					
ttgggactcc	tggggccata	tataagagca	gaagttgaag	ataatatcat	ggtaactttc
2700					
agaaatcagg	cctctcgtcc	ctattccttc	tattctagcc	ttattttcta	tgaggaagat
2760					
cagaggcaag	gagcagaacc	tagaaaaaac	tttgtcaagc	ctaataaac	caaaacttac
2820					
ttttggaaag	tgcaacatca	tatggcaccc	actaaagatg	agtttgactg	caaagcctgg
2880					
gcttattttct	ctgatgttga	cctggaaaaa	gatgtgcact	caggcctgat	tggaccctt
2940					
ctggtctgcc	acactaacac	actgaaccct	gctcatggga	gacaagtgac	agtacaggaa
3000					
tttgctctgt	ttttcaccat	ctttgatgag	accaaaagct	ggtacttcac	tgaaaatatg
3060					
gaaagaaact	gcagggctcc	ctgcaatatc	cagatggaag	atcccacttt	taaagagaat
3120					
tatcgcttcc	atgcaatcaa	tggctacata	atggatacac	tacctggctt	agtaatggct
3180					
caggatcaaa	ggattcgatg	gtatctgctc	agcatgggca	gcaatgaaaa	catccattct
3240					
attcattttca	gtggacatgt	gttcactgta	cgaaaaaaag	aggagtataa	aatggcactg
3300					

tacaatctct atccagggtgt ttttgagaca gtggaaatgt taccatccaa agctggaatt
3360

tggcgggtgg aatgccttat tggcgagcat ctacatgctg ggatgagcac actttttctg
3420

gtgtacagca ataagtgtca gactcccctg ggaatggctt ctggacacat tagagatttt
3480

cagattacag cttcaggaca atatggacag tgggccccaa agctggccag acttcattat
3540

tccggatcaa tcaatgcctg gagcaccaag gagccctttt cttggatcaa ggtggatctg
3600

ttggcaccaa tgattattca cggcatcaag acccaggggtg cccgtcagaa gttctccagc
3660

ctctacatct ctcagtttat catcatgtat agtcttgatg ggaagaagtg gcagacttat
3720

cgaggaaatt ccactggaac cttaatggtc ttctttggca atgtggattc atctgggata
3780

aaacacaata tttttaaccc tccaattatt gctcgataca tccgtttgca cccaactcat
3840

tatagcattc gcagcactct tcgcatggag ttgatgggct gtgattttaa tagttgcagc
3900

atgccattgg gaatggagag taaagcaata tcagatgcac agattactgc ttcacctac
3960

tttaccaata tgtttgccac ctggtctcct tcaaaagctc gacttcacct ccaagggagg
4020

agtaatgcct ggagacctca ggtgaataat ccaaaagagt ggctgcaagt ggacttccag
4080

aagacaatga aagtcacagg agtaactact cagggagtaa aatctctgct taccagcatg
4140

tatgtgaagg agttcctcat ctccagcagt caagatggcc atcagtggac tctctttttt
4200

cagaatggca aagtaaaggt ttttcaggga aatcaagact ccttcacacc tgtggtgaac
4260

tctctagacc caccgttact gactcgctac cttcgaattc acccccagag ttgggtgcac
4320

cagattgccc tgaggatgga ggttctgggc tgcgaggcac aggacctcta cgacaaaact
4380

cacacatgcc caccgtgccc agctccagaa ctcttgggcg gaccgtcagt cttcctcttc
4440

cccccaaac ccaaggacac cctcatgata tcccggaccc ctgaggtcac atgcgtggtg
4500

gtggacgtga gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag
4560

gtgcataatg ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc
4620

agcgtcctca ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc
4680

tccaacaaag ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc
4740

cgagaaccac aggtgtacac cctgccccca tcccgggatg agctgaccaa gaaccaggtc
4800

agcctgacct gcctgggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc
4860

aatgggcagc cggagaacaa ctacaagacc acgcctcccg tgttggactc cgacggctcc
4920

ttcttcctct acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc
4980

tcatgctccg tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg
5040

t c t c c g g g t a a a t g a
5055

<210> 163
 <211> 1684
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> pSYNFVIII 010 (Dual chain FVIIIIFc)

<400> 163

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
 1 5 10 15

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

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

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
 50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
 65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
 85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
 100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
 115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp

130

135

140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
 145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
 165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
 180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
 195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
 210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
 225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
 245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
 260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
 275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
 290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
 305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
 325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
 340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
 355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
 370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
 385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
 405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
 420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
 435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
 450 455 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
 465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
 485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
 500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
 515 520 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
 530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
 545 550 555 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
 565 570 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
 580 585 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
 595 600 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
 610 615 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
 625 630 635 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
 645 650 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
 660 665 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
 675 680 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
 690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
 705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
 725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
 740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu
 755 760 765

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

Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu
 785 790 795 800

Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe
 805 810 815

Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp
 820 825 830

Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln
 835 840 845

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

850

855

860

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His
 865 870 875 880

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

Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser
 900 905 910

Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg
 915 920 925

Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val
 930 935 940

Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp
 945 950 955 960

Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu
 965 970 975

Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His
 980 985 990

Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe
 995 1000 1005

Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn
 1010 1015 1020

Cys Arg Ala Pro Cys Asn Ile Gln Met Glu Asp Pro Thr Phe Lys
 1025 1030 1035

Glu Asn Tyr Arg Phe His Ala Ile Asn Gly Tyr Ile Met Asp Thr
 1040 1045 1050

Leu Pro Gly Leu Val Met Ala Gln Asp Gln Arg Ile Arg Trp Tyr
 1055 1060 1065

Leu Leu Ser Met Gly Ser Asn Glu Asn Ile His Ser Ile His Phe
 1070 1075 1080

Ser Gly His Val Phe Thr Val Arg Lys Lys Glu Glu Tyr Lys Met
 1085 1090 1095

Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe Glu Thr Val Glu Met
 1100 1105 1110

Leu Pro Ser Lys Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly
 1115 1120 1125

Glu His Leu His Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser
 1130 1135 1140

Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg
 1145 1150 1155

Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro
 1160 1165 1170

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

Thr Lys Glu Pro Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro
 1190 1195 1200

Met Ile Ile His Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe
1205 1210 1215

Ser Ser Leu Tyr Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp
1220 1225 1230

Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu
1235 1240 1245

Met Val Phe Phe Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn
1250 1255 1260

Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro
1265 1270 1275

Thr His Tyr Ser Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly
1280 1285 1290

Cys Asp Leu Asn Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys
1295 1300 1305

Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn
1310 1315 1320

Met Phe Ala Thr Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln
1325 1330 1335

Gly Arg Ser Asn Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu
1340 1345 1350

Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val
1355 1360 1365

Thr	Thr	Gln	Gly	Val	Lys	Ser	Leu	Leu	Thr	Ser	Met	Tyr	Val	Lys
1370						1375					1380			
Glu	Phe	Leu	Ile	Ser	Ser	Ser	Gln	Asp	Gly	His	Gln	Trp	Thr	Leu
1385						1390					1395			
Phe	Phe	Gln	Asn	Gly	Lys	Val	Lys	Val	Phe	Gln	Gly	Asn	Gln	Asp
1400						1405					1410			
Ser	Phe	Thr	Pro	Val	Val	Asn	Ser	Leu	Asp	Pro	Pro	Leu	Leu	Thr
1415						1420					1425			
Arg	Tyr	Leu	Arg	Ile	His	Pro	Gln	Ser	Trp	Val	His	Gln	Ile	Ala
1430						1435					1440			
Leu	Arg	Met	Glu	Val	Leu	Gly	Cys	Glu	Ala	Gln	Asp	Leu	Tyr	Asp
1445						1450					1455			
Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly
1460						1465					1470			
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
1475						1480					1485			
Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val
1490						1495					1500			
Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly
1505						1510					1515			
Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr
1520						1525					1530			
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln

1535

1540

1545

Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
1550						1555					1560			

Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly
1565						1570					1575			

Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp
1580						1585					1590			

Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly
1595						1600					1605			

Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln
1610						1615					1620			

Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp
1625						1630					1635			

Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg
1640						1645					1650			

Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
1655						1660					1665			

Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
1670						1675					1680			

Lys

<210> 164

<211> 6

<212> PRT
 <213> Artificial Sequence

<220>
 <223> Linker, where the sequence can be repeated between 1-10 times

<400> 164

Ser Gly Gly Gly Gly Ser
 1 5

<210> 165
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Linker

<400> 165

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 1 5 10 15

Gly Gly Gly Ser
 20

<210> 166
 <211> 34
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Linker

<400> 166

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 1 5 10 15

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Val Pro Arg Gly Ser
 20 25 30

Gly Gly

<210> 167
 <211> 314
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> pSYN FVIII 169

<400> 167

Pro Arg Ser Phe Ser Gln Asn Gly Ala Pro Gly Thr Ser Glu Ser Ala
 1 5 10 15

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
 20 25 30

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
 35 40 45

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala
 50 55 60

Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
 65 70 75 80

Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr
 85 90 95

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr
 100 105 110

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 115 120 125

Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser
 130 135 140

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
 145 150 155 160

Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 165 170 175

Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr
 180 185 190

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr
 195 200 205

Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
 210 215 220

Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr
 225 230 235 240

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro
 245 250 255

Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
 260 265 270

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr
 275 280 285

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala Ser Ser Pro Pro Val
 290 295 300

Leu Lys Arg His Gln Ala Glu Ile Thr Arg
 305 310

<210> 168

<211> 302

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN FVIII 310

<400> 168

Pro Arg Ser Phe Gly Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 1 5 10 15

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 20 25 30

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
 35 40 45

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
 50 55 60

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
 65 70 75 80

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser
 85 90 95

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
 100 105 110

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 115 120 125

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly
 130 135 140

Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly
 145 150 155 160

Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
 165 170 175

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser
 180 185 190

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
 195 200 205

Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 210 215 220

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu
 225 230 235 240

Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly
 245 250 255

Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 260 265 270

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu
 275 280 285

Pro Ser Glu Gly Ser Ala Pro Ala Ser Ser Glu Ile Thr Arg
 290 295 300

<210> 169

<211> 305

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN FVIII 312

<400> 169

Pro Arg Ser Phe Ser Gln Asn Gly Ala Pro Gly Thr Ser Glu Ser Ala
 1 5 10 15

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
 20 25 30

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
 35 40 45

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala
 50 55 60

Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
 65 70 75 80

Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr
 85 90 95

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr
 100 105 110

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 115 120 125

Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser
 130 135 140

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
 145 150 155 160

Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 165 170 175

Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr
 180 185 190

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr
 195 200 205

Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
 210 215 220

Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr
 225 230 235 240

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro
 245 250 255

Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
 260 265 270

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr
 275 280 285

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala Ser Ser Glu Ile Thr
 290 295 300

Arg
305

<210> 170
<211> 5892
<212> DNA
<213> Artificial Sequence

<220>

<223> pSYN FVIII 310 (encoding FVIII with complete B-domain deletion

except 2 amino acid residues and 288 AE-XTEN inserted after
aa
742)

<400> 170

atgcaaatag agctctccac ctgcttcttt ctgtgccttt tgcgattctg ctttagtgcc
60

accagaagat actacctggg tgcagtggaa ctgtcatggg actatatgca aagtgatctc
120

ggtgagctgc ctgtggacgc aagatttcct cctagagtgc caaaatcttt tccattcaac
180

acctcagtcg tgtacaaaaa gactctgttt gtagaattca cggatcacct tttcaacatc
240

gctaagccaa ggccaccctg gatgggtctg ctaggtccta ccatccaggc tgagggtttat
300

gatacagtgg tcattacact taagaacatg gcttcccatc ctgtcagtct tcatgctgtt
360

ggtgtatcct actggaaagc ttctgaggga gctgaatatg atgatcagac cagtcaaagg
420

gagaaagaag atgataaagt cttccctggg ggaagccata catatgtctg gcagggtcctg
480

aaagagaatg gtccaatggc ctctgaccca ctgtgcctta cctactcata tctttctcat
540

gtggacctgg taaaagactt gaattcaggc ctcattggag ccctactagt atgtagagaa
600

gggagtcttg ccaaggaaaa gacacagacc ttgcacaaat ttatactact ttttgctgta
660

tttgatgaag ggaaaagttg gcactcagaa acaaagaact ccttgatgca ggatagggat
720

gctgcatctg ctcgggcctg gcctaaaatg cacacagtca atggttatgt aaacaggtct
780

ctgccaggtc tgattggatg ccacaggaaa tcagtctatt ggcatgtgat tggaatgggc
840

accactcctg aagtgcactc aatattcctc gaaggtcaca catttcttgt gaggaacat
900

cgccaggcgt ccttggaat ctcgccaata actttcctta ctgctcaaac actccttgatg
960

gaccttggac agtttctact gttttgtcat atctcttccc accaacaatga tggcatggaa
1020

gcttatgtca aagtagacag ctgtccagag gaacccaac tacgaatgaa aaataatgaa
1080

gaagcggaag actatgatga tgatcttact gattctgaaa tggatgtggg caggtttgat
1140

gatgacaact ctcccttcctt tatccaaatt cgctcagttg ccaagaagca tcctaaaact
1200

tgggtacatt acattgctgc tgaagaggag gactgggact atgctccctt agtcctcgcc
1260

cccgatgaca gaagttataa aagtcaatat ttgaacaatg gccctcagcg gattggtagg
1320

aagtacaaaa aagtccgatt tatggcatac acagatgaaa cctttaagac tcgtgaagct
1380

attcagcatg aatcaggaat cttgggacct ttactttatg gggaagttgg agacacactg
1440

ttgattatat ttaagaatca agcaagcaga ccatataaca tctaccctca cggaatcact
1500

gatgtccgtc ctttgtattc aaggagatta ccaaaaggtg taaaacattt gaaggatttt
1560

ccaattctgc caggagaaat attcaaatat aaatggacag tgactgtaga agatgggcca
1620

actaaatcag atcctcgggtg cctgaccgcg tattactcta gtttcgttaa tatggagaga
1680

gatctagctt caggactcat tggccctctc ctcatctgct acaaagaatc tgtagatcaa
1740

agaggaaacc agataatgtc agacaagagg aatgtcatcc tgttttctgt atttgatgag
1800

aaccgaagct ggtacctcac agagaatata caacgctttc tccccaatcc agctggagtg
1860

cagcttgagg atccagagtt ccaagcctcc aacatcatgc acagcatcaa tggctatggt
1920

tttgatagtt tgcagttgtc agtttgtttg catgagggtgg catactggta cattctaagc
1980

attggagcac agactgactt cctttctgtc ttcttctctg gatatacctt caaacacaaa
2040

atgggtctatg aagacacact caccctattc ccattctcag gagaaactgt cttcatgtcg
2100

atggaaaacc cagggtctatg gattctgggg tgccacaact cagactttcg gaacagaggc
2160

atgaccgcct tactgaaggt ttctagttgt gacaagaaca ctgggtgatta ttacgaggac
2220

agttatgaag atatttcagc atacttgctg agtaaaaaca atgccattga accaagaagc
2280

ttcgggtacct cagagtctgc taccctcgag tcagggccag gatcagagcc agccacctcc
2340

gggtctgaga caccggggac ttccgagagt gccaccctg agtccggacc cgggtccgag
2400

cccgccactt ccggctccga aactcccggc acaagcgaga gcgctacccc agagtcagga
 2460

ccaggaacat ctacagagcc ctctgaaggc tccgctccag ggtccccagc cggcagtccc
 2520

actagcaccg aggaggggaac ctctgaaagc gccacacccg aatcagggcc aggggtctgag
 2580

cctgctacca gcggcagcga gacaccaggc acctctgagt ccgccacacc agagtccgga
 2640

cccggatctc ccgctgggag ccccacctcc actgaggagg gatctcctgc tggctctcca
 2700

acatctactg aggaaggtag ctcaaccgag ccatccgagg gatcagctcc cggcacctca
 2760

gagtcggcaa ccccgaggatc tggacccgga acttccgaaa gtgccacacc agagtccggt
 2820

cccgggactt cagaatcagc aacacccgag tccggccctg ggtctgaacc cgccacaagt
 2880

ggtagtgaga caccaggatc agaacctgct acctcagggg cagagacacc cggatctccg
 2940

gcaggctcac caacctccac tgaggagggc accagcacag aaccaagcga gggctccgca
 3000

cccggaacaa gcactgaacc cagtgagggg tcagcacccg gctctgagcc ggccacaagt
 3060

ggcagtgaga cacccggcac ttcagagagt gccacccccg agagtggccc aggcactagt
 3120

accgagccct ctgaaggcag tgcgccagcc tcgagcgaaa taactcgtac tactcttcag
 3180

tcagatcaag aggaaatcga ttatgatgat accatatcag ttgaaatgaa gaaggaagat
 3240

tttgacattt atgatgagga tgaaaatcag agcccccgca gctttcaaaa gaaaacacga
 3300

cactatttta ttgctgcagt ggagaggctc tgggattatg ggatgagtag ctccccacat
3360

gttctaagaa acagggctca gagtggcagt gtccctcagt tcaagaaagt tgttttccag
3420

gaatttactg atggctcctt tactcagccc ttataccgtg gagaactaaa tgaacatttg
3480

ggactcctgg ggccatatat aagagcagaa gttgaagata atatcatggg aactttcaga
3540

aatcaggcct ctcgctcccta ttccttctat tctagcctta tttcttatga ggaagatcag
3600

aggcaaggag cagaacctag aaaaaacttt gtcaagccta atgaaaccaa aacttacttt
3660

tggaaagtgc aacatcatat ggcacccact aaagatgagt ttgactgcaa agcctgggct
3720

tattttctctg atgttgacct ggaaaaagat gtgcactcag gcctgattgg accccttctg
3780

gtctgccaca ctaacacact gaaccctgct catgggagac aagtgacagt acaggaattt
3840

gctctgtttt tcaccatctt tgatgagacc aaaagctggg acttcactga aaatatggaa
3900

agaaactgca gggctccctg caatatccag atggaagatc ccacttttaa agagaattat
3960

cgcttccatg caatcaatgg ctacataatg gatacactac ctggcttagt aatggctcag
4020

gatcaaagga ttcgatggta tctgctcagc atgggcagca atgaaaacat ccattctatt
4080

catttcagtg gacatgtggt cactgtacga aaaaaagagg agtataaaat ggcactgtac
4140

aatctctatc cagggtgtttt tgagacagtg gaaatgttac catccaaagc tggaatttgg
4200

cggggtggaat gccttattgg cgagcatcta catgctggga tgagcacact ttttctggtg
4260

tacagcaata agtgtcagac tcccctggga atggcttctg gacacattag agattttcag
4320

attacagctt caggacaata tggacagtgg gcccctaaagc tggccagact tcattattcc
4380

ggatcaatca atgcctggag caccaaggag cccttttctt ggatcaaggt ggatctgttg
4440

gcaccaatga ttattcacgg catcaagacc cagggtgccc gtcagaagtt ctccagcctc
4500

tacatctctc agtttatcat catgtatagt cttgatggga agaagtggca gacttatcga
4560

ggaaattcca ctggaacctt aatggctctt tttggcaatg tggattcatc tgggataaaa
4620

cacaatattt ttaaccctcc aattattgct cgatacatcc gtttgcaccc aactcattat
4680

agcattcgca gcactcttcg catggagttg atgggctgtg atttaaatag ttgcagcatg
4740

ccattgggaa tggagagtaa agcaatatca gatgcacaga ttactgcttc atcctacttt
4800

accaatatgt ttgccacctg gtctccttca aaagctcgac ttcacctcca agggaggagt
4860

aatgcctgga gacctcaggt gaataatcca aaagagtggc tgcaagtgga cttccagaag
4920

acaatgaaag tcacaggagt aactactcag ggagtaaaat ctctgcttac cagcatgtat
4980

gtgaaggagt tcctcatctc cagcagtcaa gatggccatc agtggactct cttttttcag
5040

aatggcaaag taaagggtttt tcagggaat caagactcct tcacacctgt ggtgaactct
5100

ctagacccac cgttactgac tcgctacctt cgaattcacc cccagagttg ggtgcaccag
5160

attgccctga ggatggaggt tctgggctgc gaggcacagg acctctacga caaaactcac
5220

acatgcccac cgtgcccagc tccagaactc ctgggcggac cgtcagtctt cctcttcccc
5280

ccaaaaccca aggacaccct catgatctcc cggacccttg aggtcacatg cgtgggtggtg
5340

gacgtgagcc acgaagaccc tgagggtcaag ttcaactggt acgtggacgg cgtggaggtg
5400

cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtgggtcagc
5460

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc
5520

aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
5580

gaaccacagg tgtacaccct gcccccatcc cgggatgagc tgaccaagaa ccagggtcagc
5640

ctgacctgcc tgggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat
5700

gggcagccgg agaacaacta caagaccacg cctcccgtgt tggactccga cggctccttc
5760

ttcctctaca gcaagctcac cgtggacaag agcagggtggc agcaggggaa cgtcttctca
5820

tgctccgtga tgcattgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
5880

c c g g g t a a a t g a
5892

<210> 171

<211> 1944

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN FVIII 310 (FVIII with complete B-domain deletion except
2 amino acid residues and 288 AE-XTEN inserted after aa 742)

<400> 171

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp

675

680

685

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

Leu Leu Lys Val Ser Ser Cys Asp Lys 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 Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 740 745 750

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
 755 760 765

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr
 770 775 780

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 785 790 795 800

Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
 805 810 815

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala
 820 825 830

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
 835 840 845

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
 850 855 860

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser
865 870 875 880

Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
885 890 895

Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr
900 905 910

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala
915 920 925

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
930 935 940

Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser
945 950 955 960

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
965 970 975

Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
980 985 990

Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
995 1000 1005

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu
1010 1015 1020

Pro Ser Glu Gly Ser Ala Pro Ala Ser Ser Glu Ile Thr Arg Thr
1025 1030 1035

Thr	Leu	Gln	Ser	Asp	Gln	Glu	Glu	Ile	Asp	Tyr	Asp	Asp	Thr	Ile
1040						1045					1050			
Ser	Val	Glu	Met	Lys	Lys	Glu	Asp	Phe	Asp	Ile	Tyr	Asp	Glu	Asp
1055						1060					1065			
Glu	Asn	Gln	Ser	Pro	Arg	Ser	Phe	Gln	Lys	Lys	Thr	Arg	His	Tyr
1070						1075					1080			
Phe	Ile	Ala	Ala	Val	Glu	Arg	Leu	Trp	Asp	Tyr	Gly	Met	Ser	Ser
1085						1090					1095			
Ser	Pro	His	Val	Leu	Arg	Asn	Arg	Ala	Gln	Ser	Gly	Ser	Val	Pro
1100						1105					1110			
Gln	Phe	Lys	Lys	Val	Val	Phe	Gln	Glu	Phe	Thr	Asp	Gly	Ser	Phe
1115						1120					1125			
Thr	Gln	Pro	Leu	Tyr	Arg	Gly	Glu	Leu	Asn	Glu	His	Leu	Gly	Leu
1130						1135					1140			
Leu	Gly	Pro	Tyr	Ile	Arg	Ala	Glu	Val	Glu	Asp	Asn	Ile	Met	Val
1145						1150					1155			
Thr	Phe	Arg	Asn	Gln	Ala	Ser	Arg	Pro	Tyr	Ser	Phe	Tyr	Ser	Ser
1160						1165					1170			
Leu	Ile	Ser	Tyr	Glu	Glu	Asp	Gln	Arg	Gln	Gly	Ala	Glu	Pro	Arg
1175						1180					1185			
Lys	Asn	Phe	Val	Lys	Pro	Asn	Glu	Thr	Lys	Thr	Tyr	Phe	Trp	Lys
1190						1195					1200			

Val	Gln	His	His	Met	Ala	Pro	Thr	Lys	Asp	Glu	Phe	Asp	Cys	Lys
1205						1210					1215			
Ala	Trp	Ala	Tyr	Phe	Ser	Asp	Val	Asp	Leu	Glu	Lys	Asp	Val	His
1220						1225					1230			
Ser	Gly	Leu	Ile	Gly	Pro	Leu	Leu	Val	Cys	His	Thr	Asn	Thr	Leu
1235						1240					1245			
Asn	Pro	Ala	His	Gly	Arg	Gln	Val	Thr	Val	Gln	Glu	Phe	Ala	Leu
1250						1255					1260			
Phe	Phe	Thr	Ile	Phe	Asp	Glu	Thr	Lys	Ser	Trp	Tyr	Phe	Thr	Glu
1265						1270					1275			
Asn	Met	Glu	Arg	Asn	Cys	Arg	Ala	Pro	Cys	Asn	Ile	Gln	Met	Glu
1280						1285					1290			
Asp	Pro	Thr	Phe	Lys	Glu	Asn	Tyr	Arg	Phe	His	Ala	Ile	Asn	Gly
1295						1300					1305			
Tyr	Ile	Met	Asp	Thr	Leu	Pro	Gly	Leu	Val	Met	Ala	Gln	Asp	Gln
1310						1315					1320			
Arg	Ile	Arg	Trp	Tyr	Leu	Leu	Ser	Met	Gly	Ser	Asn	Glu	Asn	Ile
1325						1330					1335			
His	Ser	Ile	His	Phe	Ser	Gly	His	Val	Phe	Thr	Val	Arg	Lys	Lys
1340						1345					1350			
Glu	Glu	Tyr	Lys	Met	Ala	Leu	Tyr	Asn	Leu	Tyr	Pro	Gly	Val	Phe
1355						1360					1365			
Glu	Thr	Val	Glu	Met	Leu	Pro	Ser	Lys	Ala	Gly	Ile	Trp	Arg	Val

1370

1375

1380

Glu Cys Leu Ile Gly Glu His Leu His Ala Gly Met Ser Thr Leu
 1385 1390 1395

Phe Leu Val Tyr Ser Asn Lys Cys Gln Thr Pro Leu Gly Met Ala
 1400 1405 1410

Ser Gly His Ile Arg Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr
 1415 1420 1425

Gly Gln Trp Ala Pro Lys Leu Ala Arg Leu His Tyr Ser Gly Ser
 1430 1435 1440

Ile Asn Ala Trp Ser Thr Lys Glu Pro Phe Ser Trp Ile Lys Val
 1445 1450 1455

Asp Leu Leu Ala Pro Met Ile Ile His Gly Ile Lys Thr Gln Gly
 1460 1465 1470

Ala Arg Gln Lys Phe Ser Ser Leu Tyr Ile Ser Gln Phe Ile Ile
 1475 1480 1485

Met Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn
 1490 1495 1500

Ser Thr Gly Thr Leu Met Val Phe Phe Gly Asn Val Asp Ser Ser
 1505 1510 1515

Gly Ile Lys His Asn Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr
 1520 1525 1530

Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg Ser Thr Leu Arg
 1535 1540 1545

Met Glu Leu Met Gly Cys Asp Leu Asn Ser Cys Ser Met Pro Leu
 1550 1555 1560

Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala Ser
 1565 1570 1575

Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser Pro Ser Lys Ala
 1580 1585 1590

Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln Val
 1595 1600 1605

Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met
 1610 1615 1620

Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu Leu Thr
 1625 1630 1635

Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly
 1640 1645 1650

His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe
 1655 1660 1665

Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val Asn Ser Leu Asp
 1670 1675 1680

Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His Pro Gln Ser Trp
 1685 1690 1695

Val His Gln Ile Ala Leu Arg Met Glu Val Leu Gly Cys Glu Ala
 1700 1705 1710

Gln	Asp	Leu	Tyr	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala
1715						1720					1725			
Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys
1730						1735					1740			
Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys
1745						1750					1755			
Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn
1760						1765					1770			
Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro
1775						1780					1785			
Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu
1790						1795					1800			
Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys
1805						1810					1815			
Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile
1820						1825					1830			
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
1835						1840					1845			
Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
1850						1855					1860			
Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
1865						1870					1875			

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 1880 1885 1890

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
 1895 1900 1905

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
 1910 1915 1920

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
 1925 1930 1935

Ser Leu Ser Pro Gly Lys
 1940

<210> 172

<211> 5900

<212> DNA

<213> Artificial Sequence

<220>

<223> pSYN FVIII 312 (FVIII with complete B-domain deletion except
 5 amino acid residues and 288 AE-XTEN inserted after aa 745-
 FVIII B5 version)

<400> 172

atgcaaatag agctctccac ctgcttcttt ctgtgccttt tgcgattctg ctttagtgcc
 60

accagaagat actacctggg tgcagtggaa ctgtcatggg actatatgca aagtgatctc
 120

ggtgagctgc ctgtggacgc aagatttcct cctagagtgc caaaatcttt tccattcaac
 180

acctcagtcg tgtacaaaaa gactctgttt gtagaattca cggatcacct tttcaacatc
 240

gctaagccaa ggccaccctg gatgggtctg ctaggtccta ccatccaggc tgaggtttat
 300

gatacagtgg tcattacact taagaacatg gcttcccatc ctgtcagtct tcatgctggt
 360

ggtgtatcct actggaaagc ttctgaggga gctgaatatg atgatcagac cagtcaaagg
 420

gagaaagaag atgataaagt cttccctggg ggaagccata catatgtctg gcaggtcctg
 480

aaagagaatg gtccaatggc ctctgaccca ctgtgcctta cctactcata tctttctcat
 540

gtggacctgg taaaagactt gaattcaggc ctcattggag ccctactagt atgtagagaa
 600

gggagtctgg ccaaggaaaa gacacagacc ttgcacaaat ttatactact ttttgctgta
 660

tttgatgaag ggaaaagttg gcactcagaa acaaagaact ccttgatgca ggatagggat
 720

gctgcatctg ctcgggcctg gcctaaaatg cacacagtca atggttatgt aaacaggctct
 780

ctgccaggtc tgattggatg ccacaggaaa tcagtctatt ggcatgtgat tggaatgggc
 840

accactcctg aagtgcactc aatattcctc gaaggtcaca catttcttgt gaggaaccat
 900

cgccaggcgt ccttggaat ctcgccaata actttcctta ctgctcaaac actcttgatg
 960

gaccttgac agtttctact gttttgtcat atctcttccc accaacaatga tggcatggaa
 1020

gcttatgtca aagtagacag ctgtccagag gaacccaac tacgaatgaa aaataatgaa
 1080

gaagcggaag actatgatga tgatcttact gattctgaaa tggatgtggg caggtttgat
 1140

gatgacaact ctccttcctt tatccaaatt cgctcagttg ccaagaagca tcctaaaact
1200

tgggtacatt acattgctgc tgaagaggag gactgggact atgctccctt agtcctcgcc
1260

cccgatgaca gaagttataa aagtcaatat ttgaacaatg gccctcagcg gattggtagg
1320

aagtacaaaa aagtccgatt tatggcatac acagatgaaa cctttaagac tcgtgaagct
1380

attcagcatg aatcaggaat cttgggacct ttactttatg gggaagttgg agacacactg
1440

ttgattatat ttaagaatca agcaagcaga ccatataaca tctaccctca cggaatcact
1500

gatgtccgtc ctttgtattc aaggagatta ccaaaagggtg taaaacattt gaaggatttt
1560

ccaattctgc caggagaaat attcaaatat aaatggacag tgactgtaga agatgggccca
1620

actaaatcag atcctcgggtg cctgaccgcg tattactcta gtttcgttaa tatggagaga
1680

gatctagctt caggactcat tggccctctc ctcatctgct acaaagaatc tgtagatcaa
1740

agaggaaacc agataatgtc agacaagagg aatgtcatcc tgttttctgt atttgatgag
1800

aaccgaagct ggtacctcac agagaatata caacgctttc tccccaatcc agctggagtg
1860

cagcttgagg atccagagtt ccaagcctcc aacatcatgc acagcatcaa tggctatggt
1920

tttgatagtt tgcagttgtc agtttgtttg catgagggtgg catactggta cattctaagc
1980

attggagcac agactgactt cctttctgtc ttcttctctg gatatacctt caaacacaaa
2040

atggtctatg aagacacact caccctattc ccattctcag gagaaactgt cttcatgtcg
2100

atggaaaacc caggtctatg gattctgggg tgccacaact cagactttcg gaacagagggc
2160

atgaccgcct tactgaaggt ttctagttgt gacaagaaca ctggtgatta ttacgaggac
2220

agttatgaag atatttcagc atacttgctg agtaaaaaca atgccattga accaagaagc
2280

ttctctcaaa acggtacctc agagtctgct acccccaggt cagggccagg atcagagcca
2340

gccacctccg ggtctgagac acccgggact tccgagagtg ccaccctga gtccggaccc
2400

gggtccgagc ccgccacttc cggctccgaa actcccggca caagcgagag cgctacccca
2460

gagtcaggac caggaacatc tacagagccc tctgaaggct ccgctccagg gtccccagcc
2520

ggcagtccca ctagcaccga ggagggaacc tctgaaagcg ccacaccga atcagggcca
2580

gggtctgagc ctgctaccag cggcagcgag acaccaggca cctctgagtc cgccacacca
2640

gagtcgggac ccggatctcc cgctgggagc cccacctcca ctgaggaggg atctcctgct
2700

ggctctccaa catctactga ggaaggtacc tcaaccgagc catccgaggg atcagctccc
2760

ggcacctcag agtcggcaac cccggagtct ggaccgggaa cttccgaaag tgccacacca
2820

gagtcgggtc ccgggacttc agaatacagc acacccgagt ccggccctgg gtctgaaccc
2880

gccacaagtg gtagtgagac accaggatca gaacctgcta cctcagggtc agagacaccc
2940

ggatctccgg caggctcacc aacctccact gaggagggca ccagcacaga accaagcgag
3000

ggctccgcac ccggaacaag cactgaaccc agtgagggtt cagcaccgg ctctgagccg
3060

gccacaagtg gcagtgagac acccggcact tcagagagtg ccacccccga gagtggccca
3120

ggcactagta ccgagccctc tgaaggcagt gcgccagcct cgagcgaaat aactcgtact
3180

actcttcagt cagatcaaga ggaaatcgat tatgatgata ccatatcagt tgaaatgaag
3240

aaggaagatt ttgacattta tgatgaggat gaaaatcaga gccccgcag ctttcaaag
3300

aaaacacgac actattttat tgctgcagtg gagaggctct gggattatgg gatgagtagc
3360

tccccacatg ttctaagaaa cagggtcag agtggcagt tccctcagtt caagaaagtt
3420

gttttccagg aatttactga tggctccttt actcagccct tataccgtgg agaactaat
3480

gaacatttgg gactcctggg gccatatata agagcagaag ttgaagataa tatcatggta
3540

actttcagaa atcaggcctc tcgtccctat tccttctatt ctagccttat ttcttatgag
3600

gaagatcaga ggcaaggagc agaacctaga aaaaactttg tcaagcctaa tgaaaccaa
3660

acttactttt ggaaagtgca acatcatatg gcaccacta aagatgagtt tgactgcaaa
3720

gcctgggctt atttctctga tgttgacctg gaaaaagatg tgcactcagg cctgattgga
3780

ccccttctgg tctgccacac taacacactg aaccctgctc atgggagaca agtgacagta
3840

caggaatttg ctctgttttt caccatcttt gatgagacca aaagctggta cttcactgaa
3900

aatatggaaa gaaactgcag ggctccctgc aatatccaga tggaagatcc cacttttaaa
3960

gagaattatc gcttccatgc aatcaatggc tacataatgg atacactacc tggcttagta
4020

atggctcagg atcaaaggat tcgatgggat ctgctcagca tgggcagcaa tgaaaacatc
4080

cattctattc atttcagtgg acatgtgttc actgtacgaa aaaaagagga gtataaaatg
4140

gcactgtaca atctctatcc aggtgttttt gagacagtgg aaatggtacc atccaaagct
4200

ggaatttggc ggggtggaatg ccttattggc gagcatctac atgctgggat gagcacactt
4260

tttctggtgt acagcaataa gtgtcagact cccctgggaa tggcttcttg acacattaga
4320

gattttcaga ttacagcttc aggacaatat ggacagtggg ccccaaagct ggccagactt
4380

cattattccg gatcaatcaa tgcctggagc accaaggagc ccttttcttg gatcaagggtg
4440

gatctgttgg caccaatgat tattcacggc atcaagaccc aggggtgcccg tcagaagttc
4500

tccagcctct acatctctca gtttatcatc atgtatagtc ttgatgggaa gaagtggcag
4560

acttatcgag gaaattccac tggaacctta atgggtcttct ttggcaatgt ggattcatct
4620

gggataaaac acaatatattt taaccctcca attattgctc gatacatccg tttgcaccca
4680

actcattata gcattcgcag cactcttcgc atggagttga tgggctgtga tttaaatagt
4740

tgcagcatgc cattgggaat ggagagtaaa gcaatatcag atgcacagat tactgcttca
4800

tcctacttta ccaatatggt tgccacctgg tctccttcaa aagctcgact tcacctcaa
4860

gggaggagta atgcctggag acctcaggtg aataatccaa aagagtggct gcaagtggac
4920

ttccagaaga caatgaaagt cacaggagta actactcagg gagtaaaatc tctgcttacc
4980

agcatgtatg tgaaggagtt cctcatctcc agcagtcaag atggccatca gtggactctc
5040

ttttttcaga atggcaaagt aaagggttttt cagggaaatc aagactcctt cacacctgtg
5100

gtgaactctc tagaccacc gttactgact cgctaccttc gaattcacc ccagagttgg
5160

gtgcaccaga ttgccctgag gatggaggtt ctgggctgcg aggcacagga cctctacgac
5220

aaaactcaca catgcccacc gtgcccagct ccagaactcc tgggcggacc gtcagtcttc
5280

ctcttcccc caaaacccaa ggacaccctc atgatctccc ggaccctga ggtcacatgc
5340

gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc
5400

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgt
5460

gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc
5520

aagggtctcca acaaagccct cccagcccc atcgagaaaa ccatctccaa agccaaaggg
5580

cagccccgag aaccacaggt gtacaccctg ccccatccc gggatgagct gaccaagaac
5640

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg
5700

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgtt ggactccgac
5760

ggctccttct tcctctacag caagctcacc gtggacaaga gcagggtggca gcaggggaac
5820

gtctttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc
5880

t c c c t g t c t c c g g g t a a a t g
5900

<210> 173

<211> 1947

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN FVIII 312 (FVIII with complete B-domain deletion except
5

amino acid residues and 288 AE-XTEN inserted after aa 745-
FVIII
B5 version)

<400> 173

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met Ala Tyr Thr

420

425

430

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Leu Leu Lys Val Ser Ser Cys Asp Lys 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 Gly Thr Ser Glu Ser Ala Thr
 740 745 750

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
 755 760 765

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu
 770 775 780

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr
 785 790 795 800

Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
 805 810 815

Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser
 820 825 830

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 835 840 845

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 850 855 860

Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro
 865 870 875 880

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser
 885 890 895

Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 900 905 910

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
 915 920 925

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 930 935 940

Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
 945 950 955 960

Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser
 965 970 975

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser
 980 985 990

Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
 995 1000 1005

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr
 1010 1015 1020

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala Ser Ser Glu Ile
 1025 1030 1035

Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp
 1040 1045 1050

Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr
 1055 1060 1065

Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr
 1070 1075 1080

Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
 1085 1090 1095

Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly
 1100 1105 1110

Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp
 1115 1120 1125

Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His

1130						1135						1140					
Leu	Gly	Leu	Leu	Gly	Pro	Tyr	Ile	Arg	Ala	Glu	Val	Glu	Asp	Asn			
1145						1150					1155						
Ile	Met	Val	Thr	Phe	Arg	Asn	Gln	Ala	Ser	Arg	Pro	Tyr	Ser	Phe			
1160						1165					1170						
Tyr	Ser	Ser	Leu	Ile	Ser	Tyr	Glu	Glu	Asp	Gln	Arg	Gln	Gly	Ala			
1175						1180					1185						
Glu	Pro	Arg	Lys	Asn	Phe	Val	Lys	Pro	Asn	Glu	Thr	Lys	Thr	Tyr			
1190						1195					1200						
Phe	Trp	Lys	Val	Gln	His	His	Met	Ala	Pro	Thr	Lys	Asp	Glu	Phe			
1205						1210					1215						
Asp	Cys	Lys	Ala	Trp	Ala	Tyr	Phe	Ser	Asp	Val	Asp	Leu	Glu	Lys			
1220						1225					1230						
Asp	Val	His	Ser	Gly	Leu	Ile	Gly	Pro	Leu	Leu	Val	Cys	His	Thr			
1235						1240					1245						
Asn	Thr	Leu	Asn	Pro	Ala	His	Gly	Arg	Gln	Val	Thr	Val	Gln	Glu			
1250						1255					1260						
Phe	Ala	Leu	Phe	Phe	Thr	Ile	Phe	Asp	Glu	Thr	Lys	Ser	Trp	Tyr			
1265						1270					1275						
Phe	Thr	Glu	Asn	Met	Glu	Arg	Asn	Cys	Arg	Ala	Pro	Cys	Asn	Ile			
1280						1285					1290						
Gln	Met	Glu	Asp	Pro	Thr	Phe	Lys	Glu	Asn	Tyr	Arg	Phe	His	Ala			
1295						1300					1305						

Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu Val Met Ala
 1310 1315 1320

Gln Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met Gly Ser Asn
 1325 1330 1335

Glu Asn Ile His Ser Ile His Phe Ser Gly His Val Phe Thr Val
 1340 1345 1350

Arg Lys Lys Glu Glu Tyr Lys Met Ala Leu Tyr Asn Leu Tyr Pro
 1355 1360 1365

Gly Val Phe Glu Thr Val Glu Met Leu Pro Ser Lys Ala Gly Ile
 1370 1375 1380

Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu His Ala Gly Met
 1385 1390 1395

Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys Gln Thr Pro Leu
 1400 1405 1410

Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln Ile Thr Ala Ser
 1415 1420 1425

Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala Arg Leu His Tyr
 1430 1435 1440

Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro Phe Ser Trp
 1445 1450 1455

Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His Gly Ile Lys
 1460 1465 1470

Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr Ile Ser Gln
1475 1480 1485

Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr Tyr
1490 1495 1500

Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe Gly Asn Val
1505 1510 1515

Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro Pro Ile Ile
1520 1525 1530

Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg Ser
1535 1540 1545

Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn Ser Cys Ser
1550 1555 1560

Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln Ile
1565 1570 1575

Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser Pro
1580 1585 1590

Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg
1595 1600 1605

Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe Gln
1610 1615 1620

Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln Gly Val Lys Ser
1625 1630 1635

Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser Ser
 1640 1645 1650

Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys Val
 1655 1660 1665

Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val Asn
 1670 1675 1680

Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His Pro
 1685 1690 1695

Gln Ser Trp Val His Gln Ile Ala Leu Arg Met Glu Val Leu Gly
 1700 1705 1710

Cys Glu Ala Gln Asp Leu Tyr Asp Lys Thr His Thr Cys Pro Pro
 1715 1720 1725

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 1730 1735 1740

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 1745 1750 1755

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 1760 1765 1770

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 1775 1780 1785

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
 1790 1795 1800

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

1805

1810

1815

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 1820 1825 1830

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 1835 1840 1845

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
 1850 1855 1860

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
 1865 1870 1875

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 1880 1885 1890

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 1895 1900 1905

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
 1910 1915 1920

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 1925 1930 1935

Lys Ser Leu Ser Leu Ser Pro Gly Lys
 1940 1945

<210> 174

<211> 4977

<212> DNA

<213> Artificial Sequence

<220>

<223> pSYN VWF073 (VWFD1D2D'D3- 144 AE XTEN- FVIII truncated a2
thrombin site-Fc)

<400> 174

atgattcctg ccagatttgc cgggggtgctg cttgctctgg ccctcatttt gccagggacc
60

ctttgtgcag aaggaactcg cggcagggtca tccacggccc gatgcagcct tttcggaagt
120

gacttcgtca acacctttga tgggagcatg tacagctttg cgggatactg cagttacctc
180

ctggcagggg gctgccagaa acgctccttc tcgattattg gggacttcca gaatggcaag
240

agagtgcgcc tctccgtgta tcttggggaa ttttttgaca tccatttggt tgtcaatggt
300

accgtgacac agggggacca aagagtctcc atgccctatg cctccaaagg gctgtatcta
360

gaaactgagg ctgggtacta caagctgtcc ggtgaggcct atggctttgt ggccaggatc
420

gatggcagcg gcaactttca agtcctgctg tcagacagat acttcaacaa gacctgcggg
480

ctgtgtggca actttaacat ctttgcgtgaa gatgacttta tgaccaaga agggaccttg
540

acctcggacc cttatgactt tgccaactca tgggctctga gcagtggaga acagtgggtg
600

gaacgggcat ctccctcccag cagctcatgc aacatctcct ctggggaaat gcagaagggc
660

ctgtgggagc agtgccagct tctgaagagc acctcgggtg ttgcccgtg ccaccctctg
720

gtggaccccg agccttttgt ggccctgtgt gagaagactt tgtgtgagtg tgctgggggg
780

ctggagtgcg cctgccctgc cctcctggag tacgcccgga cctgtgccca ggaggggaatg
840

gtgctgtacg gctggaccga ccacagcgcg tgcagcccag tgtgccctgc tggatatggag
 900
 tataggcagt gtgtgtcccc ttgcgccagg acctgccaga gcctgcacat caatgaaatg
 960
 tgtcaggagc gatgcgtgga tggctgcagc tgccctgagg gacagctcct ggatgaaggc
 1020
 ctctgcgtgg agagcaccga gtgtccctgc gtgcattccg gaaagcgcta ccctcccggc
 1080
 acctccctct ctcgagactg caacacctgc atttgccgaa acagccagtg gatctgcagc
 1140
 aatgaagaat gtccagggga gtgccttgtc actgggtcaat cccacttcaa gagctttgac
 1200
 aacagatact tcaccttcag tgggatctgc cagtacctgc tggcccggga ttgccaggac
 1260
 cactccttct ccattgtcat tgagactgtc cagtgtgctg atgaccgcga cgctgtgtgc
 1320
 acccgctccg tcaccgtccg gctgcctggc ctgcacaaca gccttgtgaa actgaagcat
 1380
 ggggcaggag ttgccatgga tggccaggac atccagctcc ccctcctgaa aggtgacctc
 1440
 cgcattccagc atacagtgac ggcctccgtg cgcctcagct acgggggagga cctgcagatg
 1500
 gactgggatg gccgcgggag gctgctggtg aagctgtccc ccgtctatgc cgggaagacc
 1560
 tgcggcctgt gtgggaatta caatggcaac cagggcgacg acttccttac cccctctggg
 1620
 ctggcggagc cccgggtgga ggacttcggg aacgcctgga agctgcacgg ggactgccag
 1680
 gacctgcaga agcagcacag cgatccctgc gccctcaacc cgcgcatgac caggttctcc
 1740

gaggaggcgt gcgcggtcct gacgtccccc acattcgagg cctgccatcg tgccgtcagc
1800

ccgctgccct acctgcggaa ctgccgctac gacgtgtgct cctgctcgga cggccgagag
1860

tgctgtgcg gcgccctggc cagctatgcc gcggcctgcg cggggagagg cgtgcgcgtc
1920

gcgtggcgcg agccaggccg ctgtgagctg aactgcccga aaggccagggt gtacctgcag
1980

tgcgggaccc cctgcaacct gacctgccgc tctctctctt acccggatga ggaatgcaat
2040

gaggcctgcc tggagggtg cttctgcccc ccagggtctt acatggatga gaggggggac
2100

tgcgtgccca aggccagtg cccctgttac tatgacggtg agatcttcca gccagaagac
2160

atcttctcag accatcacac catgtgctac tgtgaggatg gcttcatgca ctgtaccatg
2220

agtggagtcc ccggaagctt gctgcctgac gctgtcctca gcagtcccct gtctcatcgc
2280

agcaaaagga gcctatcctg tcggcccccc atggtcaagc tgggtgtgtcc cgctgacaac
2340

ctgcgggctg aagggtcga gtgtaccaa acgtgccaga actatgacct ggagtgcattg
2400

agcatgggct gtgtctctgg ctgcctctgc cccccgggca tgggtccggca tgagaacaga
2460

tgtgtggccc tggaaagggtg tccctgcttc catcagggca aggagtatgc ccctggagaa
2520

acagtgaaga ttggctgcaa cacttgtgtc tgtcgggacc ggaagtggaa ctgcacagac
2580

catgtgtgtg atgccacgtg ctccacgata ggcatggccc actacctcac cttcgacggg
2640

ctcaaatacc tggtccccgg ggagtgccag tacgtttctgg tgcaggatta ctgcggcagt
 2700
 aaccctggga ccttttcggat cctagtgggg aataagggat gcagccaccc ctccagtga
 2760
 tgcaagaaac gggtcaccat cctgggtggag ggaggagaga ttgagctgtt tgacggggag
 2820
 gtgaatgtga agaggcccat gaaggatgag actcactttg aggtgggtgga gtctggccgg
 2880
 tacatcattc tgctgctggg caaagccctc tccgtgggtct gggaccgcca cctgagcatc
 2940
 tccgtgggtcc tgaagcagac ataccaggag aaagtgtgtg gcctgtgtgg gaattttgat
 3000
 ggcattccaga acaatgacct caccagcagc aacctccaag tggaggaaga ccctgtggac
 3060
 tttgggaact cctggaaagt gagctcgcag tgtgctgaca ccagaaaagt gcctctggac
 3120
 tcatcccctg ccacctgcca taacaacatc atgaagcaga cgatgggtgga ttctctctgt
 3180
 agaatcctta ccagtgcagt cttccaggac tgcaacaagc tgggtggaccc cgagccatat
 3240
 ctggatgtct gcatttacga cacctgctcc tgtgagtcca ttgggggactg cgccgcattc
 3300
 tgcgacacca ttgctgccta tgcccacgtg tgtgcccagc atggcaaggt ggtgacctgg
 3360
 aggacggcca cattgtgccc ccagagctgc gaggagagga atctccggga gaacgggtat
 3420
 gaggctgagt ggcgctataa cagctgtgca cctgcctgtc aagtcacgtg tcagcaccct
 3480
 gagccactgg cctgccctgt gcagtgtgtg gagggctgcc atgcccactg ccctccaggg
 3540

aaaatcctgg atgagctttt gcagacctgc gttgaccctg aagactgtcc agtgtgtgag
 3600

gtggctggcc ggcgttttgc ctcaggaaag aaagtcacct tgaatcccag tgaccctgag
 3660

cactgccaga tttgccactg tgatgtttgtc aacctcacct gtgaagcctg ccaggagccg
 3720

ggcgcgccaa catcagagag cgccaccctt gaaagtggtc ccgggagcga gccagccaca
 3780

tctgggtcgg aaacgccagg cacaagtgag tctgcaactc ccgagtccgg acctggctcc
 3840

gagcctgcc a ctagcggctc cgagactccg ggaacttccg agagcgctac accagaaagc
 3900

ggacccggaa ccagtaccga acctagcgag ggctctgctc cgggcagccc agccggctct
 3960

cctacatcca cggaggaggg cacttccgaa tccgccacc cggagtcagg gccaggatct
 4020

gaacccgcta cctcaggcag tgagacgcc a ggaacgagcg agtccgctac accggagagt
 4080

gggccaggga gccctgctgg atctcctacg tccactgagg aagggtcacc agcgggctcg
 4140

cccaccagca ctgaagaagg tgcctcgagc ggcggtggag gatccggtgg cgggggatcc
 4200

ggtggcgggg gatccggtgg cgggggatcc ggtggcgggg gatccggtgg cgggggatcc
 4260

attgaaccaa gaagcttctc tggcagcgga ggcgacaaaa ctcacacatg cccaccgtgc
 4320

ccagctccag aactcctggg cggaaccgtca gtcttcctct tcccccaaaa acccaaggac
 4380

accctcatga tctcccggac ccctgaggtc acatgcgtgg tgggtggacgt gagccacgaa
 4440

gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca
4500

aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg
4560

caccaggact ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca
4620

gcccccatcg agaaaacccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac
4680

accctgcccc catcccggga tgagctgacc aagaaccagg tcagcctgac ctgcctgggc
4740

aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagAAC
4800

aactacaaga ccacgcctcc cgtgttggac tccgacggct ctttcttctt ctacagcaag
4860

ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat
4920

gaggctctgc acaaccacta cacgcagaag agcctctccc tgtctccggg taaatga
4977

<210> 175

<211> 1658

<212> PRT

<213> Artificial Sequence

<220>

**<223> pSYN VWF073 (VWFD1D2D'D3- 144 AE XTEN- truncated a2 thrombin
 site-Fc)**

<400> 175

Met Ile Pro Ala Arg Phe Ala Gly Val Leu Leu Ala Leu Ala Leu Ile
1 5 10 15

Leu Pro Gly Thr Leu Cys Ala Glu Gly Thr Arg Gly Arg Ser Ser Thr

Leu Ser Ser Gly Glu Gln Trp Cys Glu Arg Ala Ser Pro Pro Ser Ser
195 200 205

Ser Cys Asn Ile Ser Ser Gly Glu Met Gln Lys Gly Leu Trp Glu Gln
 210 215 220

Cys Gln Leu Leu Lys Ser Thr Ser Val Phe Ala Arg Cys His Pro Leu
 225 230 235 240

Val Asp Pro Glu Pro Phe Val Ala Leu Cys Glu Lys Thr Leu Cys Glu
 245 250 255

Cys Ala Gly Gly Leu Glu Cys Ala Cys Pro Ala Leu Leu Glu Tyr Ala
 260 265 270

Arg Thr Cys Ala Gln Glu Gly Met Val Leu Tyr Gly Trp Thr Asp His
 275 280 285

Ser Ala Cys Ser Pro Val Cys Pro Ala Gly Met Glu Tyr Arg Gln Cys
 290 295 300

Val Ser Pro Cys Ala Arg Thr Cys Gln Ser Leu His Ile Asn Glu Met
 305 310 315 320

Cys Gln Glu Arg Cys Val Asp Gly Cys Ser Cys Pro Glu Gly Gln Leu
 325 330 335

Leu Asp Glu Gly Leu Cys Val Glu Ser Thr Glu Cys Pro Cys Val His
 340 345 350

Ser Gly Lys Arg Tyr Pro Pro Gly Thr Ser Leu Ser Arg Asp Cys Asn
 355 360 365

Thr Cys Ile Cys Arg Asn Ser Gln Trp Ile Cys Ser Asn Glu Glu Cys
 370 375 380

Pro Gly Glu Cys Leu Val Thr Gly Gln Ser His Phe Lys Ser Phe Asp
 385 390 395 400

Asn Arg Tyr Phe Thr Phe Ser Gly Ile Cys Gln Tyr Leu Leu Ala Arg
 405 410 415

Asp Cys Gln Asp His Ser Phe Ser Ile Val Ile Glu Thr Val Gln Cys
 420 425 430

Ala Asp Asp Arg Asp Ala Val Cys Thr Arg Ser Val Thr Val Arg Leu
 435 440 445

Pro Gly Leu His Asn Ser Leu Val Lys Leu Lys His Gly Ala Gly Val
 450 455 460

Ala Met Asp Gly Gln Asp Ile Gln Leu Pro Leu Leu Lys Gly Asp Leu
 465 470 475 480

Arg Ile Gln His Thr Val Thr Ala Ser Val Arg Leu Ser Tyr Gly Glu
 485 490 495

Asp Leu Gln Met Asp Trp Asp Gly Arg Gly Arg Leu Leu Val Lys Leu
 500 505 510

Ser Pro Val Tyr Ala Gly Lys Thr Cys Gly Leu Cys Gly Asn Tyr Asn
 515 520 525

Gly Asn Gln Gly Asp Asp Phe Leu Thr Pro Ser Gly Leu Ala Glu Pro
 530 535 540

Arg Val Glu Asp Phe Gly Asn Ala Trp Lys Leu His Gly Asp Cys Gln
 545 550 555 560

Asp Leu Gln Lys Gln His Ser Asp Pro Cys Ala Leu Asn Pro Arg Met
 565 570 575

Thr Arg Phe Ser Glu Glu Ala Cys Ala Val Leu Thr Ser Pro Thr Phe
 580 585 590

Glu Ala Cys His Arg Ala Val Ser Pro Leu Pro Tyr Leu Arg Asn Cys
 595 600 605

Arg Tyr Asp Val Cys Ser Cys Ser Asp Gly Arg Glu Cys Leu Cys Gly
 610 615 620

Ala Leu Ala Ser Tyr Ala Ala Ala Cys Ala Gly Arg Gly Val Arg Val
 625 630 635 640

Ala Trp Arg Glu Pro Gly Arg Cys Glu Leu Asn Cys Pro Lys Gly Gln
 645 650 655

Val Tyr Leu Gln Cys Gly Thr Pro Cys Asn Leu Thr Cys Arg Ser Leu
 660 665 670

Ser Tyr Pro Asp Glu Glu Cys Asn Glu Ala Cys Leu Glu Gly Cys Phe
 675 680 685

Cys Pro Pro Gly Leu Tyr Met Asp Glu Arg Gly Asp Cys Val Pro Lys
 690 695 700

Ala Gln Cys Pro Cys Tyr Tyr Asp Gly Glu Ile Phe Gln Pro Glu Asp
 705 710 715 720

Ile Phe Ser Asp His His Thr Met Cys Tyr Cys Glu Asp Gly Phe Met
 725 730 735

His Cys Thr Met Ser Gly Val Pro Gly Ser Leu Leu Pro Asp Ala Val

740

745

750

Leu Ser Ser Pro Leu Ser His Arg Ser Lys Arg Ser Leu Ser Cys Arg
 755 760 765

Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp Asn Leu Arg Ala Glu
 770 775 780

Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr Asp Leu Glu Cys Met
 785 790 795 800

Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro Pro Gly Met Val Arg
 805 810 815

His Glu Asn Arg Cys Val Ala Leu Glu Arg Cys Pro Cys Phe His Gln
 820 825 830

Gly Lys Glu Tyr Ala Pro Gly Glu Thr Val Lys Ile Gly Cys Asn Thr
 835 840 845

Cys Val Cys Arg Asp Arg Lys Trp Asn Cys Thr Asp His Val Cys Asp
 850 855 860

Ala Thr Cys Ser Thr Ile Gly Met Ala His Tyr Leu Thr Phe Asp Gly
 865 870 875 880

Leu Lys Tyr Leu Phe Pro Gly Glu Cys Gln Tyr Val Leu Val Gln Asp
 885 890 895

Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys
 900 905 910

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

Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys
 930 935 940

Arg Pro Met Lys Asp Glu Thr His Phe Glu Val Val Glu Ser Gly Arg
 945 950 955 960

Tyr Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg
 965 970 975

His Leu Ser Ile Ser Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val
 980 985 990

Cys Gly Leu Cys Gly Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr
 995 1000 1005

Ser Ser Asn Leu Gln Val Glu Glu Asp Pro Val Asp Phe Gly Asn
 1010 1015 1020

Ser Trp Lys Val Ser Ser Gln Cys Ala Asp Thr Arg Lys Val Pro
 1025 1030 1035

Leu Asp Ser Ser Pro Ala Thr Cys His Asn Asn Ile Met Lys Gln
 1040 1045 1050

Thr Met Val Asp Ser Ser Cys Arg Ile Leu Thr Ser Asp Val Phe
 1055 1060 1065

Gln Asp Cys Asn Lys Leu Val Asp Pro Glu Pro Tyr Leu Asp Val
 1070 1075 1080

Cys Ile Tyr Asp Thr Cys Ser Cys Glu Ser Ile Gly Asp Cys Ala
 1085 1090 1095

Ala Phe Cys Asp Thr Ile Ala Ala Tyr Ala His Val Cys Ala Gln
 1100 1105 1110

His Gly Lys Val Val Thr Trp Arg Thr Ala Thr Leu Cys Pro Gln
 1115 1120 1125

Ser Cys Glu Glu Arg Asn Leu Arg Glu Asn Gly Tyr Glu Ala Glu
 1130 1135 1140

Trp Arg Tyr Asn Ser Cys Ala Pro Ala Cys Gln Val Thr Cys Gln
 1145 1150 1155

His Pro Glu Pro Leu Ala Cys Pro Val Gln Cys Val Glu Gly Cys
 1160 1165 1170

His Ala His Cys Pro Pro Gly Lys Ile Leu Asp Glu Leu Leu Gln
 1175 1180 1185

Thr Cys Val Asp Pro Glu Asp Cys Pro Val Cys Glu Val Ala Gly
 1190 1195 1200

Arg Arg Phe Ala Ser Gly Lys Lys Val Thr Leu Asn Pro Ser Asp
 1205 1210 1215

Pro Glu His Cys Gln Ile Cys His Cys Asp Val Val Asn Leu Thr
 1220 1225 1230

Cys Glu Ala Cys Gln Glu Pro Gly Ala Pro Thr Ser Glu Ser Ala
 1235 1240 1245

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
 1250 1255 1260

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
1265 1270 1275

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
1280 1285 1290

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro
1295 1300 1305

Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
1310 1315 1320

Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
1325 1330 1335

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
1340 1345 1350

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser
1355 1360 1365

Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser
1370 1375 1380

Thr Glu Glu Gly Ala Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
1385 1390 1395

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
1400 1405 1410

Gly Ser Gly Gly Gly Gly Ser Ile Glu Pro Arg Ser Phe Ser Gly
1415 1420 1425

Ser Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro

1430						1435						1440			
Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	
1445						1450					1455				
Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	
1460						1465					1470				
Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	
1475						1480					1485				
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	
1490						1495					1500				
Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	
1505						1510					1515				
Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	
1520						1525					1530				
Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	
1535						1540					1545				
Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	
1550						1555					1560				
Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	
1565						1570					1575				
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	
1580						1585					1590				
Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	
1595						1600					1605				

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 1610 1615 1620

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
 1625 1630 1635

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 1640 1645 1650

Leu Ser Pro Gly Lys
 1655

<210> 176
 <211> 25
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Cleavable linker

<400> 176

Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn
 1 5 10 15

Asn Ala Ile Glu Pro Arg Ser Phe Ser
 20 25

<210> 177
 <211> 24
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Cleavable linker

<400> 177

Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn
 1 5 10 15

Ala Ile Glu Pro Arg Ser Phe Ser
 20

<210> 178

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 178

Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala
 1 5 10 15

Ile Glu Pro Arg Ser Phe Ser
 20

<210> 179

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 179

Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile
 1 5 10 15

Glu Pro Arg Ser Phe Ser
 20

<210> 180
 <211> 21
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Cleavable linker

<400> 180

Tyr	Glu	Asp	Ile	Ser	Ala	Tyr	Leu	Leu	Ser	Lys	Asn	Asn	Ala	Ile	Glu
1				5					10					15	

Pro	Arg	Ser	Phe	Ser
			20	

<210> 181
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Cleavable linker

<400> 181

Glu	Asp	Ile	Ser	Ala	Tyr	Leu	Leu	Ser	Lys	Asn	Asn	Ala	Ile	Glu	Pro
1				5					10					15	

Arg	Ser	Phe	Ser
			20

<210> 182
 <211> 19
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Cleavable linker

<400> 182

Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg
 1 5 10 15

Ser Phe Ser

<210> 183
 <211> 18
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Cleavable linker

<400> 183

Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser
 1 5 10 15

Phe Ser

<210> 184
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Cleavable linker

<400> 184

Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe
 1 5 10 15

Ser

<210> 185
 <211> 16
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Cleavable linker

<400> 185

Ala	Tyr	Leu	Leu	Ser	Lys	Asn	Asn	Ala	Ile	Glu	Pro	Arg	Ser	Phe	Ser
1				5					10					15	

<210> 186
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Cleavable linker

<400> 186

Tyr	Leu	Leu	Ser	Lys	Asn	Asn	Ala	Ile	Glu	Pro	Arg	Ser	Phe	Ser
1				5					10					15

<210> 187
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Cleavable linker

<400> 187

Leu	Leu	Ser	Lys	Asn	Asn	Ala	Ile	Glu	Pro	Arg	Ser	Phe	Ser
1				5					10				

<210> 188
 <211> 13
 <212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 188

Leu	Ser	Lys	Asn	Asn	Ala	Ile	Glu	Pro	Arg	Ser	Phe	Ser
1				5					10			

<210> 189

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 189

Ser	Lys	Asn	Asn	Ala	Ile	Glu	Pro	Arg	Ser	Phe	Ser
1				5					10		

<210> 190

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 190

Lys	Asn	Asn	Ala	Ile	Glu	Pro	Arg	Ser	Phe	Ser
1				5					10	

<210> 191

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 191

Asn	Asn	Ala	Ile	Glu	Pro	Arg	Ser	Phe	Ser
1				5					10

<210> 192

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 192

Asn	Ala	Ile	Glu	Pro	Arg	Ser	Phe	Ser
1				5				

<210> 193

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 193

Ala	Ile	Glu	Pro	Arg	Ser	Phe	Ser
1				5			

<210> 194

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Cleavable linker

<400> 194

Ile Glu Pro Arg Ser Phe Ser
1 5

<210> 195
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Cleavable linker

<400> 195

Glu Pro Arg Ser Phe Ser
1 5

<210> 196
<211> 4959
<212> DNA
<213> Artificial Sequence

<220>
<223> pSYN VWF059 (VWF D'D3-Fc with acidic region 2 (a2) thrombin
site
in the linker)

<400> 196
atgattcctg ccagatttgc cgggggtgctg cttgctctgg ccctcatttt gccagggacc
60

ctttgtgcag aaggaactcg cggcagggtca tccacggccc gatgcagcct tttcggaagt
120

gacttcgtca acacctttga tgggagcatg tacagctttg cgggatactg cagttacctc
180

ctggcagggg gctgccagaa acgctccttc tcgattattg gggacttcca gaatggcaag
240

agagtgagcc tctccgtgta tcttggggaa ttttttgaca tccatttggt tgtcaatggt
300

accgtgacac aggggggacca aagagtctcc atgccctatg cctccaaagg gctgtatcta
360

gaaactgagg ctgggtacta caagctgtcc ggtgaggcct atggctttgt ggccaggatc
420

gatggcagcg gcaactttca agtcctgctg tcagacagat acttcaacaa gacctgcggg
480

ctgtgtggca actttaacat ctttgctgaa gatgacttta tgaccaaga agggaccttg
540

acctcggacc cttatgactt tgccaactca tgggctctga gcagtggaga acagtggtgt
600

gaacgggcat ctcctcccag cagctcatgc aacatctcct ctggggaaat gcagaagggc
660

ctgtgggagc agtgccagct tctgaagagc acctcggtgt ttgcccgctg ccaccctctg
720

gtggaccccg agccttttgt ggccctgtgt gagaagactt tgtgtgagtg tgctgggggg
780

ctggagtgcg cctgccctgc ctcctggag tacgcccga cctgtgccca ggagggaatg
840

gtgctgtacg gctggaccga ccacagcgcg tgcagcccag tgtgccctgc tggatatggag
900

tataggcagt gtgtgtcccc ttgcgccagg acctgccaga gcctgcacat caatgaaatg
960

tgtcaggagc gatgcgtgga tggctgcagc tgccctgagg gacagctcct ggatgaaggc
1020

ctctgcgtgg agagcaccga gtgtccctgc gtgcattccg gaaagcgcta ccctcccggc
1080

acctccctct ctcgagactg caacacctgc atttgccgaa acagccagtg gatctgcagc
1140

aatgaagaat gtccagggga gtgccttgtc actgggtcaat cccacttcaa gagctttgac
1200

aacagatact 1260	tcaccttcag	tgggatctgc	cagtacctgc	tggcccggga	ttgccaggac
cactccttct 1320	ccattgtcat	tgagactgtc	cagtgtgctg	atgaccgcga	cgctgtgtgc
acccgctccg 1380	tcaccgtccg	gctgcctggc	ctgcacaaca	gccttgtgaa	actgaagcat
ggggcaggag 1440	ttgccatgga	tggccaggac	atccagctcc	ccctcctgaa	aggtgacctc
cgcattccagc 1500	atacagtgc	ggcctccgtg	cgcctcagct	acggggagga	cctgcagatg
gactgggatg 1560	gccgcgggag	gctgctggtg	aagctgtccc	ccgtctatgc	cggaagacc
tgcggcctgt 1620	gtgggaatta	caatggcaac	cagggcgacg	acttccttac	cccctctggg
ctggcggagc 1680	cccgggtgga	ggacttcggg	aacgcctgga	agctgcacgg	ggactgccag
gacctgcaga 1740	agcagcacag	cgatccctgc	gccctcaacc	cgcgcatgac	caggttctcc
gaggaggcgt 1800	gcgcggtcct	gacgtccccc	acattcgagg	cctgccatcg	tgccgtcagc
ccgctgccct 1860	acctgcggaa	ctgccgctac	gacgtgtgct	cctgctcgga	cggccgcgag
tgcctgtgcg 1920	gcgccctggc	cagctatgcc	gcggcctgcg	cggggagagg	cgtgcgcgtc
gcgtggcgcg 1980	agccaggccg	ctgtgagctg	aactgcccga	aaggccaggt	gtacctgcag
tgcgggaccc 2040	cctgcaacct	gacctgccgc	tctctctctt	acccggatga	ggaatgcaat
gaggcctgcc 2100	tggagggtg	cttctgcccc	ccagggtctt	acatggatga	gaggggggac

tgcggtgcca aggcccagtg cccctgttac tatgacggtg agatcttcca gccagaagac
2160

atctttctcag accatcacac catgtgctac tgtgaggatg gcttcatgca ctgtaccatg
2220

agtggagtcc ccggaagctt gctgcctgac gctgtcctca gcagtcccct gtctcatcgc
2280

agcaaaagga gcctatcctg tcggccccc atggtcaagc tgggtgtgtcc cgctgacaac
2340

ctgcgggctg aagggtcga gtgtaccaa acgtgccaga actatgacct ggagtgcattg
2400

agcatgggct gtgtctcttg ctgcctctgc cccccgggca tgggtccggca tgagaacaga
2460

tgtgtggccc tggaaagggtg tccctgcttc catcagggca aggagtatgc ccctggagaa
2520

acagtgaaga ttggctgcaa cacttgtgtc tgtcgggacc ggaagtggaa ctgcacagac
2580

catgtgtgtg atgccacgtg ctccacgac gccatggccc actacctcac cttcgacggg
2640

ctcaaatacc tgttccccgg ggagtgccag tacgttcttg tgcaggatta ctgcggcagt
2700

aaccctggga cctttcggat cctagtgggg aataagggat gcagccaccc ctcaagtga
2760

tgcaagaaac gggtcaccat cctgggtggag ggaggagaga ttgagctgtt tgacggggag
2820

gtgaatgtga agaggcccat gaaggatgag actcactttg aggtgggtgga gtctggccgg
2880

tacatcattc tgctgctggg caaagccctc tccgtgggtc gggaccgcca cctgagcatc
2940

tccgtgggtc tgaagcagac ataccaggag aaagtgtgtg gcctgtgtgg gaattttgat
3000

ggcatccaga acaatgacct caccagcagc aacctccaag tggaggaaga ccctgtggac
3060

tttggaact cctggaaagt gagctcgagc tgtgctgaca ccagaaaagt gcctctggac
3120

tcatcccctg ccacctgcca taacaacatc atgaagcaga cgatggtgga ttcctcctgt
3180

agaatcctta ccagtgcagt cttccaggac tgcaacaagc tgggtggacc cgagccatat
3240

ctggatgtct gcatttacga cacctgctcc tgtgagtcca ttggggactg cgccgcattc
3300

tgcgacacca ttgctgccta tgcccacgtg tgtgcccagc atggcaaggt ggtgacctgg
3360

aggacggcca cattgtgccc ccagagctgc gaggagagga atctccggga gaacgggtat
3420

gaggctgagt ggcgctataa cagctgtgca cctgcctgtc aagtcacgtg tcagcacctt
3480

gagccactgg cctgccctgt gcagtgtgtg gagggctgcc atgcccactg ccctccaggg
3540

aaaatcctgg atgagctttt gcagacctgc gttgacctg aagactgtcc agtgtgtgag
3600

gtggctggcc ggcgttttgc ctcaggaaag aaagtcacct tgaatcccag tgacctgag
3660

cactgccaga ttgcccactg tgatgttgtc aacctcacct gtgaagcctg ccaggagccg
3720

atatcgggcg cgccaacatc agagagcgcc acccctgaaa gtggtcccgg gagcgagcca
3780

gccacatctg ggtcggaaac gccaggcaca agtgagtctg caactcccga gtccggacct
3840

ggctccgagc ctgccactag cggctccgag actccgggaa cttccgagag cgctacacca
3900

gaaagcggac ccggaaccag taccgaacct agcgagggct ctgctccggg cagcccagcc
3960

ggctctccta catccacgga ggagggcact tccgaatccg ccaccccgga gtcagggcca
4020

ggatctgaac ccgctacctc aggcagtgag acgccaggaa cgagcgagtc cgctacaccg
4080

gagagtgggc cagggagccc tgctggatct cctacgtcca ctgaggaagg gtcaccagcg
4140

ggctcgccca ccagcactga agaaggtgcc tcgatatctg acaagaacac tgggtgattat
4200

tacgaggaca gttatgaaga tatttcagca tacttgctga gtaaaaacaa tgccattgaa
4260

ccaagaagct tctctgacaa aactcacaca tgcccaccgt gccagctcc agaactcctg
4320

ggcggaccgt cagtcttcct ctcccccca aaaccaagg acaccctcat gatctcccg
4380

accctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc
4440

aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag
4500

tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat
4560

ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagcccccat cgagaaaacc
4620

atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccg
4680

gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc
4740

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct
4800

cccggtgttg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc
4860

aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac
4920

tacacgcaga agagcctctc cctgtctccg ggtaaatga
4959

<210> 197

<211> 1652

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN VWF059 (VWF D'D3-Fc with LVPR thrombin site in the linker)

<400> 197

Met	Ile	Pro	Ala	Arg	Phe	Ala	Gly	Val	Leu	Leu	Ala	Leu	Ala	Leu	Ile
1				5					10					15	

Leu	Pro	Gly	Thr	Leu	Cys	Ala	Glu	Gly	Thr	Arg	Gly	Arg	Ser	Ser	Thr
			20					25					30		

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

Ser	Met	Tyr	Ser	Phe	Ala	Gly	Tyr	Cys	Ser	Tyr	Leu	Leu	Ala	Gly	Gly
	50					55					60				

Cys	Gln	Lys	Arg	Ser	Phe	Ser	Ile	Ile	Gly	Asp	Phe	Gln	Asn	Gly	Lys
65					70					75				80	

Arg	Val	Ser	Leu	Ser	Val	Tyr	Leu	Gly	Glu	Phe	Phe	Asp	Ile	His	Leu
				85					90					95	

Phe Val Asn Gly Thr Val Thr Gln Gly Asp Gln Arg Val Ser Met Pro
 100 105 110

Tyr Ala Ser Lys Gly Leu Tyr Leu Glu Thr Glu Ala Gly Tyr Tyr Lys
 115 120 125

Leu Ser Gly Glu Ala Tyr Gly Phe Val Ala Arg Ile Asp Gly Ser Gly
 130 135 140

Asn Phe Gln Val Leu Leu Ser Asp Arg Tyr Phe Asn Lys Thr Cys Gly
 145 150 155 160

Leu Cys Gly Asn Phe Asn Ile Phe Ala Glu Asp Asp Phe Met Thr Gln
 165 170 175

Glu Gly Thr Leu Thr Ser Asp Pro Tyr Asp Phe Ala Asn Ser Trp Ala
 180 185 190

Leu Ser Ser Gly Glu Gln Trp Cys Glu Arg Ala Ser Pro Pro Ser Ser
 195 200 205

Ser Cys Asn Ile Ser Ser Gly Glu Met Gln Lys Gly Leu Trp Glu Gln
 210 215 220

Cys Gln Leu Leu Lys Ser Thr Ser Val Phe Ala Arg Cys His Pro Leu
 225 230 235 240

Val Asp Pro Glu Pro Phe Val Ala Leu Cys Glu Lys Thr Leu Cys Glu
 245 250 255

Cys Ala Gly Gly Leu Glu Cys Ala Cys Pro Ala Leu Leu Glu Tyr Ala
 260 265 270

Arg Thr Cys Ala Gln Glu Gly Met Val Leu Tyr Gly Trp Thr Asp His

275

280

285

Ser Ala Cys Ser Pro Val Cys Pro Ala Gly Met Glu Tyr Arg Gln Cys
 290 295 300

Val Ser Pro Cys Ala Arg Thr Cys Gln Ser Leu His Ile Asn Glu Met
 305 310 315 320

Cys Gln Glu Arg Cys Val Asp Gly Cys Ser Cys Pro Glu Gly Gln Leu
 325 330 335

Leu Asp Glu Gly Leu Cys Val Glu Ser Thr Glu Cys Pro Cys Val His
 340 345 350

Ser Gly Lys Arg Tyr Pro Pro Gly Thr Ser Leu Ser Arg Asp Cys Asn
 355 360 365

Thr Cys Ile Cys Arg Asn Ser Gln Trp Ile Cys Ser Asn Glu Glu Cys
 370 375 380

Pro Gly Glu Cys Leu Val Thr Gly Gln Ser His Phe Lys Ser Phe Asp
 385 390 395 400

Asn Arg Tyr Phe Thr Phe Ser Gly Ile Cys Gln Tyr Leu Leu Ala Arg
 405 410 415

Asp Cys Gln Asp His Ser Phe Ser Ile Val Ile Glu Thr Val Gln Cys
 420 425 430

Ala Asp Asp Arg Asp Ala Val Cys Thr Arg Ser Val Thr Val Arg Leu
 435 440 445

Pro Gly Leu His Asn Ser Leu Val Lys Leu Lys His Gly Ala Gly Val
 450 455 460

Ala Met Asp Gly Gln Asp Ile Gln Leu Pro Leu Leu Lys Gly Asp Leu
 465 470 475 480

Arg Ile Gln His Thr Val Thr Ala Ser Val Arg Leu Ser Tyr Gly Glu
 485 490 495

Asp Leu Gln Met Asp Trp Asp Gly Arg Gly Arg Leu Leu Val Lys Leu
 500 505 510

Ser Pro Val Tyr Ala Gly Lys Thr Cys Gly Leu Cys Gly Asn Tyr Asn
 515 520 525

Gly Asn Gln Gly Asp Asp Phe Leu Thr Pro Ser Gly Leu Ala Glu Pro
 530 535 540

Arg Val Glu Asp Phe Gly Asn Ala Trp Lys Leu His Gly Asp Cys Gln
 545 550 555 560

Asp Leu Gln Lys Gln His Ser Asp Pro Cys Ala Leu Asn Pro Arg Met
 565 570 575

Thr Arg Phe Ser Glu Glu Ala Cys Ala Val Leu Thr Ser Pro Thr Phe
 580 585 590

Glu Ala Cys His Arg Ala Val Ser Pro Leu Pro Tyr Leu Arg Asn Cys
 595 600 605

Arg Tyr Asp Val Cys Ser Cys Ser Asp Gly Arg Glu Cys Leu Cys Gly
 610 615 620

Ala Leu Ala Ser Tyr Ala Ala Ala Cys Ala Gly Arg Gly Val Arg Val
 625 630 635 640

Ala Trp Arg Glu Pro Gly Arg Cys Glu Leu Asn Cys Pro Lys Gly Gln
645 650 655

Val Tyr Leu Gln Cys Gly Thr Pro Cys Asn Leu Thr Cys Arg Ser Leu
660 665 670

Ser Tyr Pro Asp Glu Glu Cys Asn Glu Ala Cys Leu Glu Gly Cys Phe
675 680 685

Cys Pro Pro Gly Leu Tyr Met Asp Glu Arg Gly Asp Cys Val Pro Lys
690 695 700

Ala Gln Cys Pro Cys Tyr Tyr Asp Gly Glu Ile Phe Gln Pro Glu Asp
705 710 715 720

Ile Phe Ser Asp His His Thr Met Cys Tyr Cys Glu Asp Gly Phe Met
725 730 735

His Cys Thr Met Ser Gly Val Pro Gly Ser Leu Leu Pro Asp Ala Val
740 745 750

Leu Ser Ser Pro Leu Ser His Arg Ser Lys Arg Ser Leu Ser Cys Arg
755 760 765

Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp Asn Leu Arg Ala Glu
770 775 780

Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr Asp Leu Glu Cys Met
785 790 795 800

Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro Pro Gly Met Val Arg
805 810 815

His Glu Asn Arg Cys Val Ala Leu Glu Arg Cys Pro Cys Phe His Gln
 820 825 830

Gly Lys Glu Tyr Ala Pro Gly Glu Thr Val Lys Ile Gly Cys Asn Thr
 835 840 845

Cys Val Cys Arg Asp Arg Lys Trp Asn Cys Thr Asp His Val Cys Asp
 850 855 860

Ala Thr Cys Ser Thr Ile Gly Met Ala His Tyr Leu Thr Phe Asp Gly
 865 870 875 880

Leu Lys Tyr Leu Phe Pro Gly Glu Cys Gln Tyr Val Leu Val Gln Asp
 885 890 895

Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys
 900 905 910

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

Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys
 930 935 940

Arg Pro Met Lys Asp Glu Thr His Phe Glu Val Val Glu Ser Gly Arg
 945 950 955 960

Tyr Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg
 965 970 975

His Leu Ser Ile Ser Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val
 980 985 990

Cys Gly Leu Cys Gly Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr

995						1000						1005					
Ser	Ser	Asn	Leu	Gln	Val	Glu	Glu	Asp	Pro	Val	Asp	Phe	Gly	Asn			
	1010					1015					1020						
Ser	Trp	Lys	Val	Ser	Ser	Gln	Cys	Ala	Asp	Thr	Arg	Lys	Val	Pro			
	1025					1030					1035						
Leu	Asp	Ser	Ser	Pro	Ala	Thr	Cys	His	Asn	Asn	Ile	Met	Lys	Gln			
	1040					1045					1050						
Thr	Met	Val	Asp	Ser	Ser	Cys	Arg	Ile	Leu	Thr	Ser	Asp	Val	Phe			
	1055					1060					1065						
Gln	Asp	Cys	Asn	Lys	Leu	Val	Asp	Pro	Glu	Pro	Tyr	Leu	Asp	Val			
	1070					1075					1080						
Cys	Ile	Tyr	Asp	Thr	Cys	Ser	Cys	Glu	Ser	Ile	Gly	Asp	Cys	Ala			
	1085					1090					1095						
Ala	Phe	Cys	Asp	Thr	Ile	Ala	Ala	Tyr	Ala	His	Val	Cys	Ala	Gln			
	1100					1105					1110						
His	Gly	Lys	Val	Val	Thr	Trp	Arg	Thr	Ala	Thr	Leu	Cys	Pro	Gln			
	1115					1120					1125						
Ser	Cys	Glu	Glu	Arg	Asn	Leu	Arg	Glu	Asn	Gly	Tyr	Glu	Ala	Glu			
	1130					1135					1140						
Trp	Arg	Tyr	Asn	Ser	Cys	Ala	Pro	Ala	Cys	Gln	Val	Thr	Cys	Gln			
	1145					1150					1155						
His	Pro	Glu	Pro	Leu	Ala	Cys	Pro	Val	Gln	Cys	Val	Glu	Gly	Cys			
	1160					1165					1170						

His Ala His Cys Pro Pro Gly Lys Ile Leu Asp Glu Leu Leu Gln
 1175 1180 1185

Thr Cys Val Asp Pro Glu Asp Cys Pro Val Cys Glu Val Ala Gly
 1190 1195 1200

Arg Arg Phe Ala Ser Gly Lys Lys Val Thr Leu Asn Pro Ser Asp
 1205 1210 1215

Pro Glu His Cys Gln Ile Cys His Cys Asp Val Val Asn Leu Thr
 1220 1225 1230

Cys Glu Ala Cys Gln Glu Pro Ile Ser Gly Ala Pro Thr Ser Glu
 1235 1240 1245

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 1250 1255 1260

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 1265 1270 1275

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 1280 1285 1290

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
 1295 1300 1305

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro
 1310 1315 1320

Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 1325 1330 1335

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 1340 1345 1350

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala
 1355 1360 1365

Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro
 1370 1375 1380

Thr Ser Thr Glu Glu Gly Ala Ser Ile Ser Asp Lys Asn Thr Gly
 1385 1390 1395

Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu
 1400 1405 1410

Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Asp Lys Thr
 1415 1420 1425

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
 1430 1435 1440

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 1445 1450 1455

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 1460 1465 1470

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
 1475 1480 1485

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
 1490 1495 1500

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
1505 1510 1515

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
1520 1525 1530

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
1535 1540 1545

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
1550 1555 1560

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
1565 1570 1575

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
1580 1585 1590

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
1595 1600 1605

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
1610 1615 1620

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
1625 1630 1635

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
1640 1645 1650

<210> 198

<211> 4860

<212> DNA

<213> Artificial Sequence

<220>

<223> pSYN VWF062 (VWF D'D3-Fc with no thrombin site in the linker)

<400> 198

atgattcctg ccagatttgc cgggggtgctg cttgctctgg ccctcatttt gccagggacc
60

ctttgtgcag aaggaactcg cggcagggtca tccacggccc gatgcagcct tttcggaagt
120

gacttcgtca acacctttga tgggagcatg tacagctttg cgggatactg cagttacctc
180

ctggcagggg gctgccagaa acgctccttc tcgattattg gggacttcca gaatggcaag
240

agagtgcgcc tctccgtgta tcttggggaa ttttttgaca tccatttggt tgtcaatggt
300

accgtgacac agggggacca aagagtctcc atgccctatg cctccaaagg gctgtatcta
360

gaaactgagg ctgggtacta caagctgtcc ggtgaggcct atggctttgt ggccaggatc
420

gatggcagcg gcaactttca agtcctgctg tcagacagat acttcaacaa gacctgcggg
480

ctgtgtggca actttaacat ctttgcgtgaa gatgacttta tgaccaaga agggaccttg
540

acctcggacc cttatgactt tgccaactca tgggctctga gcagtggaga acagtgggtg
600

gaacgggcat ctccctcccag cagctcatgc aacatctcct ctggggaaat gcagaagggc
660

ctgtgggagc agtgccagct tctgaagagc acctcgggtg ttgcccgtg ccaccctctg
720

gtggaccccg agccttttgt ggccctgtgt gagaagactt tgtgtgagtg tgctgggggg
780

ctggagtgcg cctgccctgc cctcctggag tacgcccgga cctgtgccca ggagggaatg
840

gtgctgtacg gctggaccga ccacagcgcg tgcagcccag tgtgccctgc tggatatggag
 900
 tataggcagt gtgtgtcccc ttgcgccagg acctgccaga gcctgcacat caatgaaatg
 960
 tgtcaggagc gatgcgtgga tggctgcagc tgccctgagg gacagctcct ggatgaaggc
 1020
 ctctgcgtgg agagcaccga gtgtccctgc gtgcattccg gaaagcgcta ccctcccggc
 1080
 acctccctct ctcgagactg caacacctgc atttgccgaa acagccagtg gatctgcagc
 1140
 aatgaagaat gtccagggga gtgccttgtc actgggtcaat cccacttcaa gagctttgac
 1200
 aacagatact tcaccttcag tgggatctgc cagtacctgc tggcccggga ttgccaggac
 1260
 cactccttct ccattgtcat tgagactgtc cagtgtgctg atgaccgcga cgctgtgtgc
 1320
 acccgctccg tcaccgtccg gctgcctggc ctgcacaaca gccttgtgaa actgaagcat
 1380
 ggggcaggag ttgccatgga tggccaggac atccagctcc ccctcctgaa aggtgacctc
 1440
 cgcattccagc atacagtgac ggcctccgtg cgcctcagct acggggagga cctgcagatg
 1500
 gactgggatg gccgcgggag gctgctggtg aagctgtccc ccgtctatgc cgggaagacc
 1560
 tgcggcctgt gtgggaatta caatggcaac cagggcgacg acttccttac cccctctggg
 1620
 ctggcggagc cccgggtgga ggacttcggg aacgcctgga agctgcacgg ggactgccag
 1680
 gacctgcaga agcagcacag cgatccctgc gccctcaacc cgcgcatgac caggttctcc
 1740

gaggaggcgt gcgcggtcct gacgtccccc acattcgagg cctgccatcg tgccgtcagc
1800

ccgctgccct acctgcggaa ctgccgctac gacgtgtgct cctgctcgga cggccgag
1860

tgctgtgcg gcgccctggc cagctatgcc gcggcctgcg cggggagagg cgtgcgcgtc
1920

gcgtggcgcg agccaggccg ctgtgagctg aactgcccga aaggccagggt gtacctgcag
1980

tgcgggaccc cctgcaacct gacctgccgc tctctctctt acccgatga ggaatgcaat
2040

gaggcctgcc tggagggtg cttctgcccc ccagggtctt acatggatga gaggggggac
2100

tgcgtgcca aggccagtg cccctgttac tatgacggtg agatcttcca gccagaagac
2160

atcttctcag accatcacac catgtgctac tgtgaggatg gcttcatgca ctgtaccatg
2220

agtggagtcc ccggaagctt gctgcctgac gctgtcctca gcagtcccct gtctcatcgc
2280

agcaaaagga gcctatcctg tcggcccccc atggtcaagc tgggtgtgtcc cgctgacaac
2340

ctgcgggctg aagggtcga gtgtaccaa acgtgccaga actatgacct ggagtgcattg
2400

agcatgggct gtgtctctgg ctgcctctgc cccccgggca tgggtccggca tgagaacaga
2460

tgtgtggccc tggaaagggtg tccctgcttc catcagggca aggagtatgc ccctggagaa
2520

acagtgaaga ttggctgcaa cacttgtgtc tgtcgggacc ggaagtggaa ctgcacagac
2580

catgtgtgtg atgccacgtg ctccacgac gccatggccc actacctcac cttcgacggg
2640

ctcaaatacc 2700	tgttccccgg	ggagtgccag	tacgtttctgg	tgaggatta	ctgcggcagt
aaccctggga 2760	cctttcggat	cctagtgggg	aataagggat	gcagccaccc	ctcagtga
tgcaagaaac 2820	gggtcaccat	cctggtggag	ggaggagaga	ttgagctgtt	tgacggggag
gtgaatgtga 2880	agaggcccat	gaaggatgag	actcactttg	aggtggtgga	gtctggccgg
tacatcattc 2940	tgctgctggg	caaagccctc	tccgtggtct	gggaccgcca	cctgagcatc
tccgtggtcc 3000	tgaagcagac	ataccaggag	aaagtgtgtg	gcctgtgtgg	gaattttgat
ggcatccaga 3060	acaatgacct	caccagcagc	aacctccaag	tggaggaaga	ccctgtggac
tttgggaaact 3120	cctggaaagt	gagctcgcag	tgtgctgaca	ccagaaaagt	gcctctggac
tcatcccctg 3180	ccacctgcca	taacaacatc	atgaagcaga	cgatggtgga	ttcctcctgt
agaatcctta 3240	ccagtgacgt	cttccaggac	tgcaacaagc	tggtggaccc	cgagccatat
ctggatgtct 3300	gcatttacga	cacctgctcc	tgtgagtcca	ttggggactg	cgccgcattc
tgcgacacca 3360	ttgctgccta	tgcccacgtg	tgtgcccagc	atggcaaggt	ggtgacctgg
aggacggcca 3420	cattgtgccc	ccagagctgc	gaggagagga	atctccggga	gaacgggtat
gaggctgagt 3480	ggcgctataa	cagctgtgca	cctgcctgtc	aagtcacgtg	tcagcaccct
gagccactgg 3540	cctgccctgt	gcagtgtgtg	gagggctgcc	atgccactg	ccctccaggg

aaaatcctgg atgagctttt gcagacctgc gttgaccctg aagactgtcc agtgtgtgag
3600

gtggctggcc ggcgttttgc ctcaggaaag aaagtcacct tgaatcccag tgaccctgag
3660

cactgccaga tttgccactg tgatgtttgtc aacctcacct gtgaagcctg ccaggagccg
3720

atatcgggcg cgccaacatc agagagcgcc acccctgaaa gtgggtcccgg gagcgagcca
3780

gccacatctg ggtcggaaac gccaggcaca agtgagtctg caactcccga gtccggacct
3840

ggctccgagc ctgccactag cggctccgag actccgggaa cttccgagag cgctacacca
3900

gaaagcggac ccggaaccag taccgaacct agcgagggct ctgctccggg cagcccagcc
3960

ggctctccta catccacgga ggagggcact tccgaatccg ccaccccgga gtcagggcca
4020

ggatctgaac ccgctacctc aggcagtgag acgccaggaa cgagcgagtc cgctacaccg
4080

gagagtgggc cagggagccc tgctggatct cctacgtcca ctgaggaagg gtcaccagcg
4140

ggctcgccca ccagcactga agaaggtgcc tcgagcgaca aaactcacac atgcccaccg
4200

tgcccagctc cagaactcct gggcggaccg tcagtcttcc tcttcccccc aaaacccaag
4260

gacaccctca tgatctcccg gaccctgag gtcacatgcg tggtggtgga cgtgagccac
4320

gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaaag
4380

acaaagccgc gggaggagca gtacaacagc acgtaccgtg tggtcagcgt cctcaccgtc
4440

ctgcaccagg actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc
4500

ccagccccc a tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg
4560

tacaccctgc ccccatcccc ggatgagctg accaagaacc aggtcagcct gacctgcctg
4620

gtcaaaggct tctatcccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag
4680

aacaactaca agaccacgcc tcccgtgttg gactccgacg gctccttctt cctctacagc
4740

aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg
4800

catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaata
4860

<210> 199

<211> 1619

<212> PRT

<213> Artificial Sequence

<220>

<223> pSYN VWF062 (VWF D'D3-Fc with no thrombin site in the linker)

<400> 199

Met	Ile	Pro	Ala	Arg	Phe	Ala	Gly	Val	Leu	Leu	Ala	Leu	Ala	Leu	Ile
1				5					10					15	

Leu	Pro	Gly	Thr	Leu	Cys	Ala	Glu	Gly	Thr	Arg	Gly	Arg	Ser	Ser	Thr
			20					25					30		

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

Ser Met Tyr Ser Phe Ala Gly Tyr Cys Ser Tyr Leu Leu Ala Gly Gly
 50 55 60

Cys Gln Lys Arg Ser Phe Ser Ile Ile Gly Asp Phe Gln Asn Gly Lys
 65 70 75 80

Arg Val Ser Leu Ser Val Tyr Leu Gly Glu Phe Phe Asp Ile His Leu
 85 90 95

Phe Val Asn Gly Thr Val Thr Gln Gly Asp Gln Arg Val Ser Met Pro
 100 105 110

Tyr Ala Ser Lys Gly Leu Tyr Leu Glu Thr Glu Ala Gly Tyr Tyr Lys
 115 120 125

Leu Ser Gly Glu Ala Tyr Gly Phe Val Ala Arg Ile Asp Gly Ser Gly
 130 135 140

Asn Phe Gln Val Leu Leu Ser Asp Arg Tyr Phe Asn Lys Thr Cys Gly
 145 150 155 160

Leu Cys Gly Asn Phe Asn Ile Phe Ala Glu Asp Asp Phe Met Thr Gln
 165 170 175

Glu Gly Thr Leu Thr Ser Asp Pro Tyr Asp Phe Ala Asn Ser Trp Ala
 180 185 190

Leu Ser Ser Gly Glu Gln Trp Cys Glu Arg Ala Ser Pro Pro Ser Ser
 195 200 205

Ser Cys Asn Ile Ser Ser Gly Glu Met Gln Lys Gly Leu Trp Glu Gln
 210 215 220

Cys Gln Leu Leu Lys Ser Thr Ser Val Phe Ala Arg Cys His Pro Leu

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

Asp Cys Gln Asp His Ser Phe Ser Ile Val Ile Glu Thr Val Gln Cys
 420 425 430

Ala Asp Asp Arg Asp Ala Val Cys Thr Arg Ser Val Thr Val Arg Leu
 435 440 445

Pro Gly Leu His Asn Ser Leu Val Lys Leu Lys His Gly Ala Gly Val
 450 455 460

Ala Met Asp Gly Gln Asp Ile Gln Leu Pro Leu Leu Lys Gly Asp Leu
 465 470 475 480

Arg Ile Gln His Thr Val Thr Ala Ser Val Arg Leu Ser Tyr Gly Glu
 485 490 495

Asp Leu Gln Met Asp Trp Asp Gly Arg Gly Arg Leu Leu Val Lys Leu
 500 505 510

Ser Pro Val Tyr Ala Gly Lys Thr Cys Gly Leu Cys Gly Asn Tyr Asn
 515 520 525

Gly Asn Gln Gly Asp Asp Phe Leu Thr Pro Ser Gly Leu Ala Glu Pro
 530 535 540

Arg Val Glu Asp Phe Gly Asn Ala Trp Lys Leu His Gly Asp Cys Gln
 545 550 555 560

Asp Leu Gln Lys Gln His Ser Asp Pro Cys Ala Leu Asn Pro Arg Met
 565 570 575

Thr Arg Phe Ser Glu Glu Ala Cys Ala Val Leu Thr Ser Pro Thr Phe
 580 585 590

Glu Ala Cys His Arg Ala Val Ser Pro Leu Pro Tyr Leu Arg Asn Cys
 595 600 605

Arg Tyr Asp Val Cys Ser Cys Ser Asp Gly Arg Glu Cys Leu Cys Gly
 610 615 620

Ala Leu Ala Ser Tyr Ala Ala Ala Cys Ala Gly Arg Gly Val Arg Val
 625 630 635 640

Ala Trp Arg Glu Pro Gly Arg Cys Glu Leu Asn Cys Pro Lys Gly Gln
 645 650 655

Val Tyr Leu Gln Cys Gly Thr Pro Cys Asn Leu Thr Cys Arg Ser Leu
 660 665 670

Ser Tyr Pro Asp Glu Glu Cys Asn Glu Ala Cys Leu Glu Gly Cys Phe
 675 680 685

Cys Pro Pro Gly Leu Tyr Met Asp Glu Arg Gly Asp Cys Val Pro Lys
 690 695 700

Ala Gln Cys Pro Cys Tyr Tyr Asp Gly Glu Ile Phe Gln Pro Glu Asp
 705 710 715 720

Ile Phe Ser Asp His His Thr Met Cys Tyr Cys Glu Asp Gly Phe Met
 725 730 735

His Cys Thr Met Ser Gly Val Pro Gly Ser Leu Leu Pro Asp Ala Val
 740 745 750

Leu Ser Ser Pro Leu Ser His Arg Ser Lys Arg Ser Leu Ser Cys Arg
 755 760 765

Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp Asn Leu Arg Ala Glu
770 775 780

Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr Asp Leu Glu Cys Met
785 790 795 800

Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro Pro Gly Met Val Arg
805 810 815

His Glu Asn Arg Cys Val Ala Leu Glu Arg Cys Pro Cys Phe His Gln
820 825 830

Gly Lys Glu Tyr Ala Pro Gly Glu Thr Val Lys Ile Gly Cys Asn Thr
835 840 845

Cys Val Cys Arg Asp Arg Lys Trp Asn Cys Thr Asp His Val Cys Asp
850 855 860

Ala Thr Cys Ser Thr Ile Gly Met Ala His Tyr Leu Thr Phe Asp Gly
865 870 875 880

Leu Lys Tyr Leu Phe Pro Gly Glu Cys Gln Tyr Val Leu Val Gln Asp
885 890 895

Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys
900 905 910

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

Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys
930 935 940

Arg Pro Met Lys Asp Glu Thr His Phe Glu Val Val Glu Ser Gly Arg

945		950		955		960									
Tyr	Ile	Ile	Leu	Leu	Leu	Gly	Lys	Ala	Leu	Ser	Val	Val	Trp	Asp	Arg
			965						970					975	
His	Leu	Ser	Ile	Ser	Val	Val	Leu	Lys	Gln	Thr	Tyr	Gln	Glu	Lys	Val
			980					985					990		
Cys	Gly	Leu	Cys	Gly	Asn	Phe	Asp	Gly	Ile	Gln	Asn	Asn	Asp	Leu	Thr
		995					1000					1005			
Ser	Ser	Asn	Leu	Gln	Val	Glu	Glu	Asp	Pro	Val	Asp	Phe	Gly	Asn	
	1010					1015					1020				
Ser	Trp	Lys	Val	Ser	Ser	Gln	Cys	Ala	Asp	Thr	Arg	Lys	Val	Pro	
	1025					1030					1035				
Leu	Asp	Ser	Ser	Pro	Ala	Thr	Cys	His	Asn	Asn	Ile	Met	Lys	Gln	
	1040					1045					1050				
Thr	Met	Val	Asp	Ser	Ser	Cys	Arg	Ile	Leu	Thr	Ser	Asp	Val	Phe	
	1055					1060					1065				
Gln	Asp	Cys	Asn	Lys	Leu	Val	Asp	Pro	Glu	Pro	Tyr	Leu	Asp	Val	
	1070					1075					1080				
Cys	Ile	Tyr	Asp	Thr	Cys	Ser	Cys	Glu	Ser	Ile	Gly	Asp	Cys	Ala	
	1085					1090					1095				
Ala	Phe	Cys	Asp	Thr	Ile	Ala	Ala	Tyr	Ala	His	Val	Cys	Ala	Gln	
	1100					1105					1110				
His	Gly	Lys	Val	Val	Thr	Trp	Arg	Thr	Ala	Thr	Leu	Cys	Pro	Gln	
	1115					1120					1125				

Ser Cys Glu Glu Arg Asn Leu Arg Glu Asn Gly Tyr Glu Ala Glu
 1130 1135 1140

Trp Arg Tyr Asn Ser Cys Ala Pro Ala Cys Gln Val Thr Cys Gln
 1145 1150 1155

His Pro Glu Pro Leu Ala Cys Pro Val Gln Cys Val Glu Gly Cys
 1160 1165 1170

His Ala His Cys Pro Pro Gly Lys Ile Leu Asp Glu Leu Leu Gln
 1175 1180 1185

Thr Cys Val Asp Pro Glu Asp Cys Pro Val Cys Glu Val Ala Gly
 1190 1195 1200

Arg Arg Phe Ala Ser Gly Lys Lys Val Thr Leu Asn Pro Ser Asp
 1205 1210 1215

Pro Glu His Cys Gln Ile Cys His Cys Asp Val Val Asn Leu Thr
 1220 1225 1230

Cys Glu Ala Cys Gln Glu Pro Ile Ser Gly Ala Pro Thr Ser Glu
 1235 1240 1245

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 1250 1255 1260

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 1265 1270 1275

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 1280 1285 1290

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
 1295 1300 1305

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro
 1310 1315 1320

Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 1325 1330 1335

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
 1340 1345 1350

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala
 1355 1360 1365

Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro
 1370 1375 1380

Thr Ser Thr Glu Glu Gly Ala Ser Ser Asp Lys Thr His Thr Cys
 1385 1390 1395

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
 1400 1405 1410

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 1415 1420 1425

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
 1430 1435 1440

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 1445 1450 1455

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
1460 1465 1470

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
1475 1480 1485

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
1490 1495 1500

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
1505 1510 1515

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
1520 1525 1530

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
1535 1540 1545

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
1550 1555 1560

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
1565 1570 1575

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
1580 1585 1590

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
1595 1600 1605

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
1610 1615

<210> 200

<211> 4
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Cleavable linker

<400> 200

Ile Glu Pro Arg
 1

<210> 201
 <211> 1945
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> FVIII(XTEN) -Fc

<400> 201

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp Tyr Ile Leu Ser

625					630						635				640
Ile	Gly	Ala	Gln	Thr	Asp	Phe	Leu	Ser	Val	Phe	Phe	Ser	Gly	Tyr	Thr
				645					650					655	
Phe	Lys	His	Lys	Met	Val	Tyr	Glu	Asp	Thr	Leu	Thr	Leu	Phe	Pro	Phe
			660					665					670		
Ser	Gly	Glu	Thr	Val	Phe	Met	Ser	Met	Glu	Asn	Pro	Gly	Leu	Trp	Ile
		675					680					685			
Leu	Gly	Cys	His	Asn	Ser	Asp	Phe	Arg	Asn	Arg	Gly	Met	Thr	Ala	Leu
	690					695					700				
Leu	Lys	Val	Ser	Ser	Cys	Asp	Lys	Asn	Thr	Gly	Asp	Tyr	Tyr	Glu	Asp
705					710					715					720
Ser	Tyr	Glu	Asp	Ile	Ser	Ala	Tyr	Leu	Leu	Ser	Lys	Asn	Asn	Ala	Ile
				725					730					735	
Glu	Pro	Arg	Ser	Phe	Ser	Gln	Asn	Gly	Thr	Ser	Glu	Ser	Ala	Thr	Pro
			740					745					750		
Glu	Ser	Gly	Pro	Gly	Ser	Glu	Pro	Ala	Thr	Ser	Gly	Ser	Glu	Thr	Pro
		755					760					765			
Gly	Thr	Ser	Glu	Ser	Ala	Thr	Pro	Glu	Ser	Gly	Pro	Gly	Ser	Glu	Pro
	770					775					780				
Ala	Thr	Ser	Gly	Ser	Glu	Thr	Pro	Gly	Thr	Ser	Glu	Ser	Ala	Thr	Pro
785					790					795					800
Glu	Ser	Gly	Pro	Gly	Thr	Ser	Thr	Glu	Pro	Ser	Glu	Gly	Ser	Ala	Pro
				805					810					815	

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu
820 825 830

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
835 840 845

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
850 855 860

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala
865 870 875 880

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu
885 890 895

Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
900 905 910

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu
915 920 925

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
930 935 940

Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
945 950 955 960

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr
965 970 975

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu
980 985 990

Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
 995 1000 1005

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
 1010 1015 1020

Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala Ser Ser Glu Ile Thr
 1025 1030 1035

Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp Asp
 1040 1045 1050

Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr Asp
 1055 1060 1065

Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg
 1070 1075 1080

His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly Met
 1085 1090 1095

Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly Ser
 1100 1105 1110

Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly
 1115 1120 1125

Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu
 1130 1135 1140

Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile
 1145 1150 1155

Met	Val	Thr	Phe	Arg	Asn	Gln	Ala	Ser	Arg	Pro	Tyr	Ser	Phe	Tyr
	1160					1165					1170			
Ser	Ser	Leu	Ile	Ser	Tyr	Glu	Glu	Asp	Gln	Arg	Gln	Gly	Ala	Glu
	1175					1180					1185			
Pro	Arg	Lys	Asn	Phe	Val	Lys	Pro	Asn	Glu	Thr	Lys	Thr	Tyr	Phe
	1190					1195					1200			
Trp	Lys	Val	Gln	His	His	Met	Ala	Pro	Thr	Lys	Asp	Glu	Phe	Asp
	1205					1210					1215			
Cys	Lys	Ala	Trp	Ala	Tyr	Phe	Ser	Asp	Val	Asp	Leu	Glu	Lys	Asp
	1220					1225					1230			
Val	His	Ser	Gly	Leu	Ile	Gly	Pro	Leu	Leu	Val	Cys	His	Thr	Asn
	1235					1240					1245			
Thr	Leu	Asn	Pro	Ala	His	Gly	Arg	Gln	Val	Thr	Val	Gln	Glu	Phe
	1250					1255					1260			
Ala	Leu	Phe	Phe	Thr	Ile	Phe	Asp	Glu	Thr	Lys	Ser	Trp	Tyr	Phe
	1265					1270					1275			
Thr	Glu	Asn	Met	Glu	Arg	Asn	Cys	Arg	Ala	Pro	Cys	Asn	Ile	Gln
	1280					1285					1290			
Met	Glu	Asp	Pro	Thr	Phe	Lys	Glu	Asn	Tyr	Arg	Phe	His	Ala	Ile
	1295					1300					1305			
Asn	Gly	Tyr	Ile	Met	Asp	Thr	Leu	Pro	Gly	Leu	Val	Met	Ala	Gln
	1310					1315					1320			
Asp	Gln	Arg	Ile	Arg	Trp	Tyr	Leu	Leu	Ser	Met	Gly	Ser	Asn	Glu

1325						1330						1335			
Asn	Ile	His	Ser	Ile	His	Phe	Ser	Gly	His	Val	Phe	Thr	Val	Arg	
1340						1345					1350				
Lys	Lys	Glu	Glu	Tyr	Lys	Met	Ala	Leu	Tyr	Asn	Leu	Tyr	Pro	Gly	
1355						1360					1365				
Val	Phe	Glu	Thr	Val	Glu	Met	Leu	Pro	Ser	Lys	Ala	Gly	Ile	Trp	
1370						1375					1380				
Arg	Val	Glu	Cys	Leu	Ile	Gly	Glu	His	Leu	His	Ala	Gly	Met	Ser	
1385						1390					1395				
Thr	Leu	Phe	Leu	Val	Tyr	Ser	Asn	Lys	Cys	Gln	Thr	Pro	Leu	Gly	
1400						1405					1410				
Met	Ala	Ser	Gly	His	Ile	Arg	Asp	Phe	Gln	Ile	Thr	Ala	Ser	Gly	
1415						1420					1425				
Gln	Tyr	Gly	Gln	Trp	Ala	Pro	Lys	Leu	Ala	Arg	Leu	His	Tyr	Ser	
1430						1435					1440				
Gly	Ser	Ile	Asn	Ala	Trp	Ser	Thr	Lys	Glu	Pro	Phe	Ser	Trp	Ile	
1445						1450					1455				
Lys	Val	Asp	Leu	Leu	Ala	Pro	Met	Ile	Ile	His	Gly	Ile	Lys	Thr	
1460						1465					1470				
Gln	Gly	Ala	Arg	Gln	Lys	Phe	Ser	Ser	Leu	Tyr	Ile	Ser	Gln	Phe	
1475						1480					1485				
Ile	Ile	Met	Tyr	Ser	Leu	Asp	Gly	Lys	Lys	Trp	Gln	Thr	Tyr	Arg	
1490						1495					1500				

Gly	Asn	Ser	Thr	Gly	Thr	Leu	Met	Val	Phe	Phe	Gly	Asn	Val	Asp
1505						1510					1515			
Ser	Ser	Gly	Ile	Lys	His	Asn	Ile	Phe	Asn	Pro	Pro	Ile	Ile	Ala
1520						1525					1530			
Arg	Tyr	Ile	Arg	Leu	His	Pro	Thr	His	Tyr	Ser	Ile	Arg	Ser	Thr
1535						1540					1545			
Leu	Arg	Met	Glu	Leu	Met	Gly	Cys	Asp	Leu	Asn	Ser	Cys	Ser	Met
1550						1555					1560			
Pro	Leu	Gly	Met	Glu	Ser	Lys	Ala	Ile	Ser	Asp	Ala	Gln	Ile	Thr
1565						1570					1575			
Ala	Ser	Ser	Tyr	Phe	Thr	Asn	Met	Phe	Ala	Thr	Trp	Ser	Pro	Ser
1580						1585					1590			
Lys	Ala	Arg	Leu	His	Leu	Gln	Gly	Arg	Ser	Asn	Ala	Trp	Arg	Pro
1595						1600					1605			
Gln	Val	Asn	Asn	Pro	Lys	Glu	Trp	Leu	Gln	Val	Asp	Phe	Gln	Lys
1610						1615					1620			
Thr	Met	Lys	Val	Thr	Gly	Val	Thr	Thr	Gln	Gly	Val	Lys	Ser	Leu
1625						1630					1635			
Leu	Thr	Ser	Met	Tyr	Val	Lys	Glu	Phe	Leu	Ile	Ser	Ser	Ser	Gln
1640						1645					1650			
Asp	Gly	His	Gln	Trp	Thr	Leu	Phe	Phe	Gln	Asn	Gly	Lys	Val	Lys
1655						1660					1665			

Val Phe Gln Gly Asn Gln Asp Ser Phe Thr Pro Val Val Asn Ser
 1670 1675 1680

Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu Arg Ile His Pro Gln
 1685 1690 1695

Ser Trp Val His Gln Ile Ala Leu Arg Met Glu Val Leu Gly Cys
 1700 1705 1710

Glu Ala Gln Asp Leu Tyr Asp Lys Thr His Thr Cys Pro Pro Cys
 1715 1720 1725

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
 1730 1735 1740

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 1745 1750 1755

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
 1760 1765 1770

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 1775 1780 1785

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
 1790 1795 1800

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 1805 1810 1815

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
 1820 1825 1830

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 1835 1840 1845

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
 1850 1855 1860

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 1865 1870 1875

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 1880 1885 1890

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
 1895 1900 1905

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
 1910 1915 1920

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 1925 1930 1935

Ser Leu Ser Leu Ser Pro Gly
 1940 1945

<210> 202

<211> 883

<212> PRT

<213> Artificial Sequence

<220>

<223> VWF(D'D3)-XTEN-a2 Linker-Fc

<400> 202

Ser Leu Ser Cys Arg Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp
 1 5 10 15

Asn Leu Arg Ala Glu Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr
 20 25 30

Asp Leu Glu Cys Met Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro
 35 40 45

Pro Gly Met Val Arg His Glu Asn Arg Cys Val Ala Leu Glu Arg Cys
 50 55 60

Pro Cys Phe His Gln Gly Lys Glu Tyr Ala Pro Gly Glu Thr Val Lys
 65 70 75 80

Ile Gly Cys Asn Thr Cys Val Cys Arg Asp Arg Lys Trp Asn Cys Thr
 85 90 95

Asp His Val Cys Asp Ala Thr Cys Ser Thr Ile Gly Met Ala His Tyr
 100 105 110

Leu Thr Phe Asp Gly Leu Lys Tyr Leu Phe Pro Gly Glu Cys Gln Tyr
 115 120 125

Val Leu Val Gln Asp Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile
 130 135 140

Leu Val Gly Asn Lys Gly Cys Ser His Pro Ser Val Lys Cys Lys Lys
 145 150 155 160

Arg Val Thr Ile Leu Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly
 165 170 175

Glu Val Asn Val Lys Arg Pro Met Lys Asp Glu Thr His Phe Glu Val
 180 185 190

Val Glu Ser Gly Arg Tyr Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser
 195 200 205

Val Val Trp Asp Arg His Leu Ser Ile Ser Val Val Leu Lys Gln Thr
 210 215 220

Tyr Gln Glu Lys Val Cys Gly Leu Cys Gly Asn Phe Asp Gly Ile Gln
 225 230 235 240

Asn Asn Asp Leu Thr Ser Ser Asn Leu Gln Val Glu Glu Asp Pro Val
 245 250 255

Asp Phe Gly Asn Ser Trp Lys Val Ser Ser Gln Cys Ala Asp Thr Arg
 260 265 270

Lys Val Pro Leu Asp Ser Ser Pro Ala Thr Cys His Asn Asn Ile Met
 275 280 285

Lys Gln Thr Met Val Asp Ser Ser Cys Arg Ile Leu Thr Ser Asp Val
 290 295 300

Phe Gln Asp Cys Asn Lys Leu Val Asp Pro Glu Pro Tyr Leu Asp Val
 305 310 315 320

Cys Ile Tyr Asp Thr Cys Ser Cys Glu Ser Ile Gly Asp Cys Ala Ala
 325 330 335

Phe Cys Asp Thr Ile Ala Ala Tyr Ala His Val Cys Ala Gln His Gly
 340 345 350

Lys Val Val Thr Trp Arg Thr Ala Thr Leu Cys Pro Gln Ser Cys Glu
 355 360 365

Glu Arg Asn Leu Arg Glu Asn Gly Tyr Glu Ala Glu Trp Arg Tyr Asn

370

375

380

Ser Cys Ala Pro Ala Cys Gln Val Thr Cys Gln His Pro Glu Pro Leu
 385 390 395 400

Ala Cys Pro Val Gln Cys Val Glu Gly Cys His Ala His Cys Pro Pro
 405 410 415

Gly Lys Ile Leu Asp Glu Leu Leu Gln Thr Cys Val Asp Pro Glu Asp
 420 425 430

Cys Pro Val Cys Glu Val Ala Gly Arg Arg Phe Ala Ser Gly Lys Lys
 435 440 445

Val Thr Leu Asn Pro Ser Asp Pro Glu His Cys Gln Ile Cys His Cys
 450 455 460

Asp Val Val Asn Leu Thr Cys Glu Ala Cys Gln Glu Pro Gly Thr Ser
 465 470 475 480

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 485 490 495

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 500 505 510

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
 515 520 525

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser
 530 535 540

Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu
 545 550 555 560

Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu
565 570 575

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr
580 585 590

Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu
595 600 605

Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ala Ser
610 615 620

Ser Asp Lys Asn Thr Gly Asp Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile
625 630 635 640

Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe
645 650 655

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
660 665 670

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
675 680 685

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
690 695 700

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
705 710 715 720

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
725 730 735

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
 740 745 750

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
 755 760 765

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
 770 775 780

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
 785 790 795 800

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 805 810 815

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 820 825 830

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
 835 840 845

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
 850 855 860

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
 865 870 875 880

Ser Pro Gly

<210> 203

<211> 1965

<212> PRT

<213> Artificial Sequence

<220>

<223> Final amino acid sequence of FVIII 312A

<400> 203

Met	Gln	Ile	Glu	Leu	Ser	Thr	Cys	Phe	Phe	Leu	Cys	Leu	Leu	Arg	Phe
1				5					10					15	

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

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

Phe	Pro	Pro	Arg	Val	Pro	Lys	Ser	Phe	Pro	Phe	Asn	Thr	Ser	Val	Val
	50					55					60				

Tyr	Lys	Lys	Thr	Leu	Phe	Val	Glu	Phe	Thr	Asp	His	Leu	Phe	Asn	Ile
65					70					75					80

Ala	Lys	Pro	Arg	Pro	Pro	Trp	Met	Gly	Leu	Leu	Gly	Pro	Thr	Ile	Gln
				85					90					95	

Ala	Glu	Val	Tyr	Asp	Thr	Val	Val	Ile	Thr	Leu	Lys	Asn	Met	Ala	Ser
			100					105					110		

His	Pro	Val	Ser	Leu	His	Ala	Val	Gly	Val	Ser	Tyr	Trp	Lys	Ala	Ser
		115					120					125			

Glu	Gly	Ala	Glu	Tyr	Asp	Asp	Gln	Thr	Ser	Gln	Arg	Glu	Lys	Glu	Asp
	130					135					140				

Asp	Lys	Val	Phe	Pro	Gly	Gly	Ser	His	Thr	Tyr	Val	Trp	Gln	Val	Leu
145					150					155					160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
 165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
 180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
 195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
 210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
 225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
 245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
 260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
 275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
 290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
 305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
 325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
 340 345 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
 355 360 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
 370 375 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
 385 390 395 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
 405 410 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
 420 425 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
 435 440 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
 450 455 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
 465 470 475 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
 485 490 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
 500 505 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe

515

520

525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
 530 535 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
 545 550 555 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
 565 570 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
 580 585 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
 595 600 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
 610 615 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
 625 630 635 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
 645 650 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
 660 665 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
 675 680 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
 690 695 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705 710 715 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
725 730 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
740 745 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Gly Thr Ser Glu
755 760 765

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
770 775 780

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
785 790 795 800

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu
805 810 815

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu
820 825 830

Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
835 840 845

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
850 855 860

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
865 870 875 880

Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
 885 890 895

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr
 900 905 910

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
 915 920 925

Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
 930 935 940

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
 945 950 955 960

Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly
 965 970 975

Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
 980 985 990

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
 995 1000 1005

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser
 1010 1015 1020

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
 1025 1030 1035

Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala
 1040 1045 1050

Ser	Ser	Glu	Ile	Thr	Arg	Thr	Thr	Leu	Gln	Ser	Asp	Gln	Glu	Glu
	1055					1060					1065			
Ile	Asp	Tyr	Asp	Asp	Thr	Ile	Ser	Val	Glu	Met	Lys	Lys	Glu	Asp
	1070					1075					1080			
Phe	Asp	Ile	Tyr	Asp	Glu	Asp	Glu	Asn	Gln	Ser	Pro	Arg	Ser	Phe
	1085					1090					1095			
Gln	Lys	Lys	Thr	Arg	His	Tyr	Phe	Ile	Ala	Ala	Val	Glu	Arg	Leu
	1100					1105					1110			
Trp	Asp	Tyr	Gly	Met	Ser	Ser	Ser	Pro	His	Val	Leu	Arg	Asn	Arg
	1115					1120					1125			
Ala	Gln	Ser	Gly	Ser	Val	Pro	Gln	Phe	Lys	Lys	Val	Val	Phe	Gln
	1130					1135					1140			
Glu	Phe	Thr	Asp	Gly	Ser	Phe	Thr	Gln	Pro	Leu	Tyr	Arg	Gly	Glu
	1145					1150					1155			
Leu	Asn	Glu	His	Leu	Gly	Leu	Leu	Gly	Pro	Tyr	Ile	Arg	Ala	Glu
	1160					1165					1170			
Val	Glu	Asp	Asn	Ile	Met	Val	Thr	Phe	Arg	Asn	Gln	Ala	Ser	Arg
	1175					1180					1185			
Pro	Tyr	Ser	Phe	Tyr	Ser	Ser	Leu	Ile	Ser	Tyr	Glu	Glu	Asp	Gln
	1190					1195					1200			
Arg	Gln	Gly	Ala	Glu	Pro	Arg	Lys	Asn	Phe	Val	Lys	Pro	Asn	Glu
	1205					1210					1215			
Thr	Lys	Thr	Tyr	Phe	Trp	Lys	Val	Gln	His	His	Met	Ala	Pro	Thr

1220						1225						1230			
Lys	Asp	Glu	Phe	Asp	Cys	Lys	Ala	Trp	Ala	Tyr	Phe	Ser	Asp	Val	
1235						1240					1245				
Asp	Leu	Glu	Lys	Asp	Val	His	Ser	Gly	Leu	Ile	Gly	Pro	Leu	Leu	
1250						1255					1260				
Val	Cys	His	Thr	Asn	Thr	Leu	Asn	Pro	Ala	His	Gly	Arg	Gln	Val	
1265						1270					1275				
Thr	Val	Gln	Glu	Phe	Ala	Leu	Phe	Phe	Thr	Ile	Phe	Asp	Glu	Thr	
1280						1285					1290				
Lys	Ser	Trp	Tyr	Phe	Thr	Glu	Asn	Met	Glu	Arg	Asn	Cys	Arg	Ala	
1295						1300					1305				
Pro	Cys	Asn	Ile	Gln	Met	Glu	Asp	Pro	Thr	Phe	Lys	Glu	Asn	Tyr	
1310						1315					1320				
Arg	Phe	His	Ala	Ile	Asn	Gly	Tyr	Ile	Met	Asp	Thr	Leu	Pro	Gly	
1325						1330					1335				
Leu	Val	Met	Ala	Gln	Asp	Gln	Arg	Ile	Arg	Trp	Tyr	Leu	Leu	Ser	
1340						1345					1350				
Met	Gly	Ser	Asn	Glu	Asn	Ile	His	Ser	Ile	His	Phe	Ser	Gly	His	
1355						1360					1365				
Val	Phe	Thr	Val	Arg	Lys	Lys	Glu	Glu	Tyr	Lys	Met	Ala	Leu	Tyr	
1370						1375					1380				
Asn	Leu	Tyr	Pro	Gly	Val	Phe	Glu	Thr	Val	Glu	Met	Leu	Pro	Ser	
1385						1390					1395				

Lys Ala Gly Ile Trp Arg Val Glu Cys Leu Ile Gly Glu His Leu
 1400 1405 1410

His Ala Gly Met Ser Thr Leu Phe Leu Val Tyr Ser Asn Lys Cys
 1415 1420 1425

Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe Gln
 1430 1435 1440

Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala
 1445 1450 1455

Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu
 1460 1465 1470

Pro Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile
 1475 1480 1485

His Gly Ile Lys Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu
 1490 1495 1500

Tyr Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys
 1505 1510 1515

Trp Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe
 1520 1525 1530

Phe Gly Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn
 1535 1540 1545

Pro Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr
 1550 1555 1560

Ser Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu
1565 1570 1575

Asn Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser
1580 1585 1590

Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala
1595 1600 1605

Thr Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser
1610 1615 1620

Asn Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln
1625 1630 1635

Val Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln
1640 1645 1650

Gly Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu
1655 1660 1665

Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln
1670 1675 1680

Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr
1685 1690 1695

Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg Tyr Leu
1700 1705 1710

Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg Met
1715 1720 1725

Glu	Val	Leu	Gly	Cys	Glu	Ala	Gln	Asp	Leu	Tyr	Asp	Lys	Thr	His
1730						1735					1740			
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
1745						1750					1755			
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
1760						1765					1770			
Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
1775						1780					1785			
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val
1790						1795					1800			
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr
1805						1810					1815			
Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu
1820						1825					1830			
Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro
1835						1840					1845			
Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg
1850						1855					1860			
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr
1865						1870					1875			
Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro
1880						1885					1890			
Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn

1895

1900

1905

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 1910 1915 1920

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
 1925 1930 1935

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
 1940 1945 1950

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 1955 1960 1965

<210> 204

<211> 5898

<212> DNA

<213> Artificial Sequence

<220>

<223> Final nucleotide sequence of FVIII 312A (SEQ ID NO: 204)

<400> 204

atgcaaatag agctctccac ctgcttcttt ctgtgccttt tgcgattctg ctttagtgcc
 60

accagaagat actacctggg tgcagtggaa ctgtcatggg actatatgca aagtgatctc
 120

ggtgagctgc ctgtggacgc aagatttcct cctagagtgc caaaatcttt tccattcaac
 180

acctcagtcg tgtacaaaaa gactctgttt gtagaattca cggatcacct tttcaacatc
 240

gctaagccaa ggccaccctg gatgggtctg ctaggtccta ccatccaggc tgaggtttat
 300

gatacagtgg tcattacact taagaacatg gcttcccatc ctgtcagtct tcatgctgtt
 360

ggtgtatcct actggaaagc ttctgagggg gctgaatatg atgatcagac cagtcaaagg
 420

gagaaagaag atgataaagt cttccctggg ggaagccata catatgtctg gcaggtcctg
 480

aaagagaatg gtccaatggc ctctgaccca ctgtgcctta cctactcata tctttctcat
 540

gtggacctgg taaaagactt gaattcaggc ctcattggag ccctactagt atgtagagaa
 600

gggagtctgg ccaaggaaaa gacacagacc ttgcacaaat ttatactact ttttgctgta
 660

tttgatgaag ggaaaagttg gcactcagaa acaaagaact ccttgatgca ggatagggat
 720

gctgcatctg ctcgggcctg gcctaaaatg cacacagtca atggttatgt aaacaggtct
 780

ctgccaggtc tgattggatg ccacaggaaa tcagtctatt ggcatgtgat tggaatgggc
 840

accactcctg aagtgcactc aatattcctc gaaggtcaca catttcttgt gaggaaccat
 900

cgccaggcgt ccttggaat ctcgccaata actttcctta ctgctcaaac actcttgatg
 960

gaccttggac agtttctact gttttgtcat atctcttccc accaacaatga tggcatggaa
 1020

gcttatgtca aagtagacag ctgtccagag gaacccaac tacgaatgaa aaataatgaa
 1080

gaagcggaag actatgatga tgatcttact gattctgaaa tggatgtggg caggtttgat
 1140

gatgacaact ctccttcctt tatccaaatt cgctcagttg ccaagaagca tcctaaaact
 1200

tgggtacatt acattgctgc tgaagaggag gactgggact atgctccctt agtcctcgcc
 1260

cccgatgaca gaagttataa aagtcaatat ttgaacaatg gccctcagcg gattggtagg
1320

aagtacaaaa aagtccgatt tatggcatac acagatgaaa cctttaagac tcgtgaagct
1380

attcagcatg aatcaggaat cttgggacct ttactttatg gggaagttgg agacacactg
1440

ttgattatat ttaagaatca agcaagcaga ccatataaca tctaccctca cggaatcact
1500

gatgtccgtc ctttgtattc aaggagatta ccaaaagggtg taaaacattt gaaggatttt
1560

ccaattctgc caggagaaat attcaaatat aaatggacag tgactgtaga agatgggccca
1620

actaaatcag atcctcgggtg cctgaccgcg tattactcta gtttcgtaa tatggagaga
1680

gatctagctt caggactcat tggccctctc ctcatctgct acaaagaatc tgtagatcaa
1740

agaggaaacc agataatgtc agacaagagg aatgtcatcc tgttttctgt atttgatgag
1800

aaccgaagct ggtacctcac agagaatata caacgctttc tccccaatcc agctggagtg
1860

cagcttgagg atccagagtt ccaagcctcc aacatcatgc acagcatcaa tggctatggt
1920

tttgatagtt tgcagttgtc agtttgtttg catgagggtg catactggta cattctaagc
1980

attggagcac agactgactt cctttctgtc ttcttctctg gatatacctt caaacacaaa
2040

atgggtctatg aagacacact caccctattc ccattctcag gagaaactgt cttcatgtcg
2100

atggaaaacc caggtctatg gattctgggg tgccacaact cagactttcg gaacagaggc
2160

atgaccgcct tactgaaggt ttctagttgt gacaagaaca ctggtgatta ttacgaggac
2220

agttatgaag atatttcagc atacttgctg agtaaaaaca atgccattga accaagaagc
2280

ttctctcaaa acggtacctc agagtctgct acccccgagt cagggccagg atcagagcca
2340

gccacctccg ggtctgagac acccgggact tccgagagtg ccaccctga gtccggaccc
2400

gggtccgagc ccgccacttc cggctccgaa actcccggca caagcgagag cgctacccca
2460

gagtcaggac caggaacatc tacagagccc tctgaaggct ccgctccagg gtccccagcc
2520

ggcagtccca ctagcaccga ggagggaacc tctgaaagcg ccacaccga atcagggcca
2580

gggtctgagc ctgctaccag cggcagcgag acaccaggca cctctgagtc cgccacacca
2640

gagtcgggac ccggatctcc cgctgggagc cccacctcca ctgaggaggg atctcctgct
2700

ggctctccaa catctactga ggaaggaacc tcaaccgagc catccgaggg atcagctccc
2760

ggcacctcag agtcggcaac cccggagtct ggacccggaa cttccgaaag tgccacacca
2820

gagtcgggtc ccgggacttc agaatcagca acacccgagt ccggccctgg gtctgaaccc
2880

gccacaagtg gtagtgagac accaggatca gaacctgcta cctcagggtc agagacaccc
2940

ggatctccgg caggctcacc aacctccact gaggagggca ccagcacaga accaagcgag
3000

ggctccgcac ccggaacaag cactgaaccc agtgagggtt cagcaccggg ctctgagccg
3060

gccacaagtg gcagtgagac acccggcact tcagagagtg ccacccccga gagtggccca
3120

ggcactagta ccgagccctc tgaaggcagt gcgccagcct cgagcgaaat aactcgtact
3180

actcttcagt cagatcaaga ggaaattgac tatgatgata ccatatcagt tgaaatgaag
3240

aaggaagatt ttgacattta tgatgaggat gaaaatcaga gccccgcag ctttcaaaag
3300

aaaacacgac actatTTTTat tgctgcagtg gagaggctct gggattatgg gatgagtagc
3360

tccccacatg ttctaagaaa cagggtcag agtggcagtg tccctcagtt caagaaagtt
3420

gttttccagg aatttactga tggctccttt actcagccct tataccgtgg agaactaaat
3480

gaacatttgg gactcctggg gccatatata agagcagaag ttgaagataa tatcatggta
3540

actttcagaa atcaggcctc tcgtccctat tccttctatt ctagccttat ttcttatgag
3600

gaagatcaga ggcaaggagc agaacctaga aaaaactttg tcaagcctaa tgaaaccaaa
3660

acttactttt ggaaagtgca acatcatatg gcaccacta aagatgagtt tgactgcaaa
3720

gcctgggctt atttctctga tgttgacctg gaaaaagatg tgcactcagg cctgattgga
3780

ccccttctgg tctgccacac taacacactg aaccctgctc atgggagaca agtgacagta
3840

caggaatttg ctctgttttt caccatcttt gatgagacca aaagctggta cttcactgaa
3900

aatatggaaa gaaactgcag ggctccctgc aatatccaga tggaagatcc cacttttaaa
3960

gagaattatc gcttccatgc aatcaatggc tacataatgg atacactacc tggcttagta
4020

atggctcagg atcaaaggat tcgatgggat ctgctcagca tgggcagcaa tgaaaacatc
4080

cattctattc atttcagtgg acatgtgttc actgtacgaa aaaaagagga gtataaaatg
4140

gcactgtaca atctctatcc aggtgttttt gagacagtgg aaatggttacc atccaaagct
4200

ggaatttggc ggggtggaatg ccttattggc gagcatctac atgctgggat gagcacactt
4260

tttctggtgt acagcaataa gtgtcagact cccctgggaa tggcttctgg acacattaga
4320

gattttcaga ttacagcttc aggacaatat ggacagtggg ccccaaagct ggccagactt
4380

cattattccg gatcaatcaa tgcctggagc accaaggagc ccttttcttg gatcaagggtg
4440

gatctgttgg caccaatgat tattcacggc atcaagaccc aggggtgcccg tcagaagttc
4500

tccagcctct acatctctca gtttatcatc atgtatagtc ttgatgggaa gaagtggcag
4560

acttatcgag gaaattccac tggaacctta atgggtcttct ttggcaatgt ggattcatct
4620

gggataaaac acaatatattt taaccctcca attattgctc gatacatccg tttgcaccca
4680

actcattata gcattcgcag cactcttcgc atggagttga tgggctgtga tttaaatagt
4740

tgcagcatgc cattgggaat ggagagtaaa gcaatatcag atgcacagat tactgcttca
4800

tcctacttta ccaatatggt tgccacctgg tctccttcaa aagctcgact tcacctccaa
4860

gggaggagta 4920	atgcctggag	acctcaggtg	aataatccaa	aagagtggct	gcaagtggac
ttccagaaga 4980	caatgaaagt	cacaggagta	actactcagg	gagtaaaatc	tctgcttacc
agcatgtatg 5040	tgaaggagtt	cctcatctcc	agcagtcaag	atggccatca	gtggactctc
ttttttcaga 5100	atggcaaagt	aaagggtttt	cagggaaatc	aagactcctt	cacacctgtg
gtgaactctc 5160	tagaccacc	gttactgact	cgctaccttc	gaattcaccc	ccagagttgg
gtgcaccaga 5220	ttgccctgag	gatggaggtt	ctgggctgcg	aggcacagga	cctctacgac
aaaactcaca 5280	catgcccacc	gtgcccagct	ccagaactcc	tgggcggacc	gtcagtcttc
ctcttcccc	caaaacccaa	ggacaccctc	atgatctccc	ggaccctga	ggtcacatgc
gtggtggtgg 5400	acgtgagcca	cgaagaccct	gaggtcaagt	tcaactggta	tgtggacggc
gtggaagtgc 5460	ataatgccaa	gacaaagccg	cgggaggagc	agtacaacag	cacgtaccgt
gtggtcagcg 5520	tcctcaccgt	cctgcaccaa	gactggctga	atggcaagga	gtacaagtgc
aaggtctcca 5580	acaaagccct	cccagcccc	atcgagaaaa	ccatctccaa	agccaaaggg
cagccccgag 5640	aaccacaggt	gtacaccctg	cccccatccc	gggatgagct	gaccaagaac
caagttagcc 5700	tgacctgcct	ggtcaaaggc	ttctatccca	gcgacatcgc	cgtggagtgg
gagagcaatg 5760	ggcagccgga	gaacaactac	aagaccacgc	ctcccgtgtt	ggactccgac

ggctccttct tcctctactc caagctcacc gtggacaaga gcaggtggca gcaggggaac
5820

gtctttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc
5880

t c c c t g t c t c c g g g t t g a
5898

<210> 205

<211> 1646

<212> PRT

<213> Artificial Sequence

<220>

<223> Final amino acid sequence of VWF059A polypeptide

<400> 205

Met Ile Pro Ala Arg Phe Ala Gly Val Leu Leu Ala Leu Ala Leu Ile
1 5 10 15

Leu Pro Gly Thr Leu Cys Ala Glu Gly Thr Arg Gly Arg Ser Ser Thr
20 25 30

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

Ser Met Tyr Ser Phe Ala Gly Tyr Cys Ser Tyr Leu Leu Ala Gly Gly
50 55 60

Cys Gln Lys Arg Ser Phe Ser Ile Ile Gly Asp Phe Gln Asn Gly Lys
65 70 75 80

Arg Val Ser Leu Ser Val Tyr Leu Gly Glu Phe Phe Asp Ile His Leu
85 90 95

Phe Val Asn Gly Thr Val Thr Gln Gly Asp Gln Arg Val Ser Met Pro
 100 105 110

Tyr Ala Ser Lys Gly Leu Tyr Leu Glu Thr Glu Ala Gly Tyr Tyr Lys
 115 120 125

Leu Ser Gly Glu Ala Tyr Gly Phe Val Ala Arg Ile Asp Gly Ser Gly
 130 135 140

Asn Phe Gln Val Leu Leu Ser Asp Arg Tyr Phe Asn Lys Thr Cys Gly
 145 150 155 160

Leu Cys Gly Asn Phe Asn Ile Phe Ala Glu Asp Asp Phe Met Thr Gln
 165 170 175

Glu Gly Thr Leu Thr Ser Asp Pro Tyr Asp Phe Ala Asn Ser Trp Ala
 180 185 190

Leu Ser Ser Gly Glu Gln Trp Cys Glu Arg Ala Ser Pro Pro Ser Ser
 195 200 205

Ser Cys Asn Ile Ser Ser Gly Glu Met Gln Lys Gly Leu Trp Glu Gln
 210 215 220

Cys Gln Leu Leu Lys Ser Thr Ser Val Phe Ala Arg Cys His Pro Leu
 225 230 235 240

Val Asp Pro Glu Pro Phe Val Ala Leu Cys Glu Lys Thr Leu Cys Glu
 245 250 255

Cys Ala Gly Gly Leu Glu Cys Ala Cys Pro Ala Leu Leu Glu Tyr Ala
 260 265 270

Arg Thr Cys Ala Gln Glu Gly Met Val Leu Tyr Gly Trp Thr Asp His

275

280

285

Ser Ala Cys Ser Pro Val Cys Pro Ala Gly Met Glu Tyr Arg Gln Cys
 290 295 300

Val Ser Pro Cys Ala Arg Thr Cys Gln Ser Leu His Ile Asn Glu Met
 305 310 315 320

Cys Gln Glu Arg Cys Val Asp Gly Cys Ser Cys Pro Glu Gly Gln Leu
 325 330 335

Leu Asp Glu Gly Leu Cys Val Glu Ser Thr Glu Cys Pro Cys Val His
 340 345 350

Ser Gly Lys Arg Tyr Pro Pro Gly Thr Ser Leu Ser Arg Asp Cys Asn
 355 360 365

Thr Cys Ile Cys Arg Asn Ser Gln Trp Ile Cys Ser Asn Glu Glu Cys
 370 375 380

Pro Gly Glu Cys Leu Val Thr Gly Gln Ser His Phe Lys Ser Phe Asp
 385 390 395 400

Asn Arg Tyr Phe Thr Phe Ser Gly Ile Cys Gln Tyr Leu Leu Ala Arg
 405 410 415

Asp Cys Gln Asp His Ser Phe Ser Ile Val Ile Glu Thr Val Gln Cys
 420 425 430

Ala Asp Asp Arg Asp Ala Val Cys Thr Arg Ser Val Thr Val Arg Leu
 435 440 445

Pro Gly Leu His Asn Ser Leu Val Lys Leu Lys His Gly Ala Gly Val
 450 455 460

Ala Met Asp Gly Gln Asp Ile Gln Leu Pro Leu Leu Lys Gly Asp Leu
 465 470 475 480

Arg Ile Gln His Thr Val Thr Ala Ser Val Arg Leu Ser Tyr Gly Glu
 485 490 495

Asp Leu Gln Met Asp Trp Asp Gly Arg Gly Arg Leu Leu Val Lys Leu
 500 505 510

Ser Pro Val Tyr Ala Gly Lys Thr Cys Gly Leu Cys Gly Asn Tyr Asn
 515 520 525

Gly Asn Gln Gly Asp Asp Phe Leu Thr Pro Ser Gly Leu Ala Glu Pro
 530 535 540

Arg Val Glu Asp Phe Gly Asn Ala Trp Lys Leu His Gly Asp Cys Gln
 545 550 555 560

Asp Leu Gln Lys Gln His Ser Asp Pro Cys Ala Leu Asn Pro Arg Met
 565 570 575

Thr Arg Phe Ser Glu Glu Ala Cys Ala Val Leu Thr Ser Pro Thr Phe
 580 585 590

Glu Ala Cys His Arg Ala Val Ser Pro Leu Pro Tyr Leu Arg Asn Cys
 595 600 605

Arg Tyr Asp Val Cys Ser Cys Ser Asp Gly Arg Glu Cys Leu Cys Gly
 610 615 620

Ala Leu Ala Ser Tyr Ala Ala Ala Cys Ala Gly Arg Gly Val Arg Val
 625 630 635 640

Ala Trp Arg Glu Pro Gly Arg Cys Glu Leu Asn Cys Pro Lys Gly Gln
645 650 655

Val Tyr Leu Gln Cys Gly Thr Pro Cys Asn Leu Thr Cys Arg Ser Leu
660 665 670

Ser Tyr Pro Asp Glu Glu Cys Asn Glu Ala Cys Leu Glu Gly Cys Phe
675 680 685

Cys Pro Pro Gly Leu Tyr Met Asp Glu Arg Gly Asp Cys Val Pro Lys
690 695 700

Ala Gln Cys Pro Cys Tyr Tyr Asp Gly Glu Ile Phe Gln Pro Glu Asp
705 710 715 720

Ile Phe Ser Asp His His Thr Met Cys Tyr Cys Glu Asp Gly Phe Met
725 730 735

His Cys Thr Met Ser Gly Val Pro Gly Ser Leu Leu Pro Asp Ala Val
740 745 750

Leu Ser Ser Pro Leu Ser His Arg Ser Lys Arg Ser Leu Ser Cys Arg
755 760 765

Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp Asn Leu Arg Ala Glu
770 775 780

Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr Asp Leu Glu Cys Met
785 790 795 800

Ser Met Gly Cys Val Ser Gly Cys Leu Cys Pro Pro Gly Met Val Arg
805 810 815

His Glu Asn Arg Cys Val Ala Leu Glu Arg Cys Pro Cys Phe His Gln
 820 825 830

Gly Lys Glu Tyr Ala Pro Gly Glu Thr Val Lys Ile Gly Cys Asn Thr
 835 840 845

Cys Val Cys Arg Asp Arg Lys Trp Asn Cys Thr Asp His Val Cys Asp
 850 855 860

Ala Thr Cys Ser Thr Ile Gly Met Ala His Tyr Leu Thr Phe Asp Gly
 865 870 875 880

Leu Lys Tyr Leu Phe Pro Gly Glu Cys Gln Tyr Val Leu Val Gln Asp
 885 890 895

Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys
 900 905 910

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

Val Glu Gly Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys
 930 935 940

Arg Pro Met Lys Asp Glu Thr His Phe Glu Val Val Glu Ser Gly Arg
 945 950 955 960

Tyr Ile Ile Leu Leu Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg
 965 970 975

His Leu Ser Ile Ser Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val
 980 985 990

Cys Gly Leu Cys Gly Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr

995					1000					1005				
Ser	Ser	Asn	Leu	Gln	Val	Glu	Glu	Asp	Pro	Val	Asp	Phe	Gly	Asn
	1010					1015					1020			
Ser	Trp	Lys	Val	Ser	Ser	Gln	Cys	Ala	Asp	Thr	Arg	Lys	Val	Pro
	1025					1030					1035			
Leu	Asp	Ser	Ser	Pro	Ala	Thr	Cys	His	Asn	Asn	Ile	Met	Lys	Gln
	1040					1045					1050			
Thr	Met	Val	Asp	Ser	Ser	Cys	Arg	Ile	Leu	Thr	Ser	Asp	Val	Phe
	1055					1060					1065			
Gln	Asp	Cys	Asn	Lys	Leu	Val	Asp	Pro	Glu	Pro	Tyr	Leu	Asp	Val
	1070					1075					1080			
Cys	Ile	Tyr	Asp	Thr	Cys	Ser	Cys	Glu	Ser	Ile	Gly	Asp	Cys	Ala
	1085					1090					1095			
Ala	Phe	Cys	Asp	Thr	Ile	Ala	Ala	Tyr	Ala	His	Val	Cys	Ala	Gln
	1100					1105					1110			
His	Gly	Lys	Val	Val	Thr	Trp	Arg	Thr	Ala	Thr	Leu	Cys	Pro	Gln
	1115					1120					1125			
Ser	Cys	Glu	Glu	Arg	Asn	Leu	Arg	Glu	Asn	Gly	Tyr	Glu	Ala	Glu
	1130					1135					1140			
Trp	Arg	Tyr	Asn	Ser	Cys	Ala	Pro	Ala	Cys	Gln	Val	Thr	Cys	Gln
	1145					1150					1155			
His	Pro	Glu	Pro	Leu	Ala	Cys	Pro	Val	Gln	Cys	Val	Glu	Gly	Cys
	1160					1165					1170			

His Ala His Cys Pro Pro Gly Lys Ile Leu Asp Glu Leu Leu Gln
 1175 1180 1185

Thr Cys Val Asp Pro Glu Asp Cys Pro Val Cys Glu Val Ala Gly
 1190 1195 1200

Arg Arg Phe Ala Ser Gly Lys Lys Val Thr Leu Asn Pro Ser Asp
 1205 1210 1215

Pro Glu His Cys Gln Ile Cys His Cys Asp Val Val Asn Leu Thr
 1220 1225 1230

Cys Glu Ala Cys Gln Glu Pro Gly Thr Ser Glu Ser Ala Thr Pro
 1235 1240 1245

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
 1250 1255 1260

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
 1265 1270 1275

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser
 1280 1285 1290

Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu
 1295 1300 1305

Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu
 1310 1315 1320

Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
 1325 1330 1335

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser
 1340 1345 1350

Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr
 1355 1360 1365

Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu
 1370 1375 1380

Glu Gly Ala Ser Ser Asp Lys Asn Thr Gly Asp Tyr Tyr Glu Asp
 1385 1390 1395

Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala
 1400 1405 1410

Ile Glu Pro Arg Ser Phe Ser Asp Lys Thr His Thr Cys Pro Pro
 1415 1420 1425

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 1430 1435 1440

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 1445 1450 1455

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 1460 1465 1470

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 1475 1480 1485

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
 1490 1495 1500

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
1505 1510 1515

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
1520 1525 1530

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
1535 1540 1545

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
1550 1555 1560

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
1565 1570 1575

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
1580 1585 1590

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
1595 1600 1605

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
1610 1615 1620

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
1625 1630 1635

Lys Ser Leu Ser Leu Ser Pro Gly
1640 1645

<210> 206

<211> 4941

<212> DNA

<213> Artificial Sequence

<220>

<223> Final nucleotide sequence of VWF059A

<400> 206

atgattcctg ccagatttgc cggggtgctg cttgctctgg ccctcatttt gccagggacc
60

ctttgtgcag aaggaactcg cggcagggtca tccacggccc gatgcagcct tttcggaagt
120

gacttcgtca acacctttga tgggagcatg tacagctttg cgggatactg cagttacctc
180

ctggcagggg gctgccagaa acgctccttc tcgattattg gggacttcca gaatggcaag
240

agagtgcgcc tctccgtgta tcttggggaa ttttttgaca tccatttggt tgtcaatggt
300

accgtgacac agggggacca aagagtctcc atgccctatg cctccaaagg gctgtatcta
360

gaaactgagg ctgggtacta caagctgtcc ggtgaggcct atggctttgt ggccaggatc
420

gatggcagcg gcaactttca agtcctgctg tcagacagat acttcaacaa gacctgcggg
480

ctgtgtggca actttaacat ctttgcgtgaa gatgacttta tgaccaaga agggaccttg
540

acctcggacc cttatgactt tgccaactca tgggctctga gcagtggaga acagtgggtg
600

gaacgggcat ctccctcccag cagctcatgc aacatctcct ctggggaaat gcagaagggc
660

ctgtgggagc agtgccagct tctgaagagc acctcgggtg ttgcccgtg ccaccctctg
720

gtggaccccg agccttttgt ggccctgtgt gagaagactt tgtgtgagtg tgctgggggg
780

ctggagtgcg cctgccctgc cctcctggag tacgcccgga cctgtgccca ggagggaatg
840

gtgctgtacg gctggaccga ccacagcgcg tgcagcccag tgtgccctgc tggatatggag
 900
 tataggcagt gtgtgtcccc ttgcgccagg acctgccaga gcctgcacat caatgaaatg
 960
 tgtcaggagc gatgcgtgga tggctgcagc tgccctgagg gacagctcct ggatgaaggc
 1020
 ctctgcgtgg agagcaccga gtgtccctgc gtgcattccg gaaagcgcta ccctcccggc
 1080
 acctccctct ctcgagactg caacacctgc atttgccgaa acagccagtg gatctgcagc
 1140
 aatgaagaat gtccagggga gtgccttgtc actgggtcaat cccacttcaa gagctttgac
 1200
 aacagatact tcaccttcag tgggatctgc cagtacctgc tggcccggga ttgccaggac
 1260
 cactccttct ccattgtcat tgagactgtc cagtgtgctg atgaccgcga cgctgtgtgc
 1320
 acccgctccg tcaccgtccg gctgcctggc ctgcacaaca gccttgtgaa actgaagcat
 1380
 ggggcaggag ttgccatgga tggccaggac atccagctcc ccctcctgaa aggtgacctc
 1440
 cgcattccagc atacagtgac ggcctccgtg cgcctcagct acggggagga cctgcagatg
 1500
 gactgggatg gccgcgggag gctgctggtg aagctgtccc ccgtctatgc cgggaagacc
 1560
 tgcggcctgt gtgggaatta caatggcaac cagggcgacg acttccttac cccctctggg
 1620
 ctggcggagc cccgggtgga ggacttcggg aacgcctgga agctgcacgg ggactgccag
 1680
 gacctgcaga agcagcacag cgatccctgc gccctcaacc cgcgcatgac caggttctcc
 1740

gaggaggcgt 1800	gcgcggtcct	gacgtccccc	acattcgagg	cctgccatcg	tgccgtcagc
ccgctgccct 1860	acctgcggaa	ctgccgctac	gacgtgtgct	cctgctcgga	cggccgcgag
tgctgtgcg 1920	gcgccctggc	cagctatgcc	gcggcctgcg	cggggagagg	cgtgcgcgtc
gcgtggcgcg 1980	agccaggccg	ctgtgagctg	aactgcccga	aaggccaggt	gtacctgcag
tgcgggaccc 2040	cctgcaacct	gacctgccgc	tctctctctt	acccggatga	ggaatgcaat
gaggcctgcc 2100	tggagggtg	cttctgcccc	ccagggtctt	acatggatga	gaggggggac
tgcgtgccca 2160	aggcccagtg	cccctgttac	tatgacggtg	agatcttcca	gccagaagac
atcttctcag 2220	accatcacac	catgtgctac	tgtgaggatg	gcttcatgca	ctgtaccatg
agtggagtcc 2280	ccggaagctt	gctgcctgac	gctgtcctca	gcagtcccct	gtctcatcgc
agcaaaaagga 2340	gcctatcctg	tcggcccccc	atggtcaagc	tggtgtgtcc	cgctgacaac
ctgcgggctg 2400	aagggtcga	gtgtaccaaa	acgtgccaga	actatgacct	ggagtgcattg
agcatgggct 2460	gtgtctctgg	ctgcctctgc	ccccgggca	tggtccggca	tgagaacaga
tgtgtggccc 2520	tggaaggtg	tccctgcttc	catcagggca	aggagtatgc	ccctggagaa
acagtgaaga 2580	ttggctgcaa	cacttgtgtc	tgtcgggacc	ggaagtggaa	ctgcacagac
catgtgtgtg 2640	atgccacgtg	ctccacgata	ggcatggccc	actacctcac	cttcgacggg

ctcaaatacc tggtccccgg ggagtgccag tacgtttctgg tgcaggatta ctgcggcagt
 2700
 aaccctggga ccttttcggat cctagtgggg aataagggat gcagccaccc ctccagtga
 2760
 tgcaagaaac gggtcaccat cctgggtggag ggaggagaga ttgagctgtt tgacggggag
 2820
 gtgaatgtga agaggcccat gaaggatgag actcactttg aggtgggtgga gtctggccgg
 2880
 tacatcattc tgctgctggg caaagccctc tccgtgggtct gggaccgcca cctgagcatc
 2940
 tccgtgggtcc tgaagcagac ataccaggag aaagtgtgtg gcctgtgtgg gaattttgat
 3000
 ggcattccaga acaatgacct caccagcagc aacctccaag tggaggaaga ccctgtggac
 3060
 tttgggaact cctggaaagt gagctcgcag tgtgctgaca ccagaaaagt gcctctggac
 3120
 tcatcccctg ccacctgcca taacaacatc atgaagcaga cgatgggtgga ttctctctgt
 3180
 agaatcctta ccagtgcagt cttccaggac tgcaacaagc tgggtggaccc cgagccatat
 3240
 ctggatgtct gcatttacga cacctgctcc tgtgagtcca ttgggggactg cgccgcattc
 3300
 tgcgacacca ttgctgccta tgcccacgtg tgtgcccagc atggcaaggt ggtgacctgg
 3360
 aggacggcca cattgtgccc ccagagctgc gaggagagga atctccggga gaacgggtat
 3420
 gaggctgagt ggcgctataa cagctgtgca cctgcctgtc aagtcacgtg tcagcaccct
 3480
 gagccactgg cctgccctgt gcagtgtgtg gagggctgcc atgcccactg ccctccaggg
 3540

aaaatcctgg atgagctttt gcagacctgc gttgaccctg aagactgtcc agtgtgtgag
 3600

gtggctggcc ggcgttttgc ctcaggaaag aaagtcacct tgaatcccag tgaccctgag
 3660

cactgccaga tttgccactg tgatgtttgtc aacctcacct gtgaagcctg ccaggagccg
 3720

ggtacatcag agagcgccac ccctgaaagt ggtcccggga gcgagccagc cacatctggg
 3780

tcggaaacgc caggcacatc cgagtctgca actcccagagt ccggacctgg ctccgagcct
 3840

gccactagcg gctccgagac tccgggaact tccgagagcg ctacaccaga aagcggaccc
 3900

ggaaccagta ccgaacctag cgagggctct gctccgggca gcccagccgg ctctcctaca
 3960

tccacggagg agggcacttc cgaatccgcc accccggagt cagggccagg atctgaaccc
 4020

gctacctcag gcagtgagac gccaggaacg agcgagtccg ctacaccgga gagtgggcca
 4080

gggagccctg ctggatctcc tacgtccact gaggaagggt caccagcggg ctgcccacc
 4140

agcactgaag aagggtgcctc gtctgacaag aacactgggtg attattacga ggacagttat
 4200

gaagatatatt cagcatactt gctgagtaaa aacaatgcca ttgaaccaag aagctttctt
 4260

gacaaaactc acacatgccc accgtgccc a gctccagaac tcctgggcgg accgtcagtc
 4320

ttctctttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca
 4380

tgcgtggtgg tggacgtgag ccacgaagac cctgagggtca agttcaactg gtatgtggac
 4440

ggcgtggaag tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac
4500

cgtgtggtca gcgtcctcac cgtcctgcac caagactggc tgaatggcaa ggagtacaag
4560

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa
4620

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag
4680

aaccaagtta gcctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag
4740

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gttggactcc
4800

gacggctcct tcttcctcta ctccaagctc accgtggaca agagcagggtg gcagcagggg
4860

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc
4920

c t c t c c c t g t c t c c g g g t t g a
4941

<210> 207

<211> 1946

<212> PRT

<213> Artificial Sequence

<220>

<223> FVIII(XTEN)-Fc w lead A

<400> 207

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

565

570

575

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

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

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

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

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

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

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

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

Leu Leu Lys Val Ser Ser Cys Asp Lys 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 Gly Thr Ser Glu Ser Ala Thr
 740 745 750

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
 755 760 765

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu
 770 775 780

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr
 785 790 795 800

Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
 805 810 815

Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser
 820 825 830

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 835 840 845

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 850 855 860

Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro
 865 870 875 880

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser
 885 890 895

Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
 900 905 910

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
 915 920 925

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
 930 935 940

Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
 945 950 955 960

Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser
 965 970 975

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser
 980 985 990

Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
 995 1000 1005

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr
 1010 1015 1020

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala Ser Ser Glu Ile
 1025 1030 1035

Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr Asp
 1040 1045 1050

Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr
 1055 1060 1065

Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr
 1070 1075 1080

Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly
 1085 1090 1095

Met	Ser	Ser	Ser	Pro	His	Val	Leu	Arg	Asn	Arg	Ala	Gln	Ser	Gly
1100						1105					1110			
Ser	Val	Pro	Gln	Phe	Lys	Lys	Val	Val	Phe	Gln	Glu	Phe	Thr	Asp
1115						1120					1125			
Gly	Ser	Phe	Thr	Gln	Pro	Leu	Tyr	Arg	Gly	Glu	Leu	Asn	Glu	His
1130						1135					1140			
Leu	Gly	Leu	Leu	Gly	Pro	Tyr	Ile	Arg	Ala	Glu	Val	Glu	Asp	Asn
1145						1150					1155			
Ile	Met	Val	Thr	Phe	Arg	Asn	Gln	Ala	Ser	Arg	Pro	Tyr	Ser	Phe
1160						1165					1170			
Tyr	Ser	Ser	Leu	Ile	Ser	Tyr	Glu	Glu	Asp	Gln	Arg	Gln	Gly	Ala
1175						1180					1185			
Glu	Pro	Arg	Lys	Asn	Phe	Val	Lys	Pro	Asn	Glu	Thr	Lys	Thr	Tyr
1190						1195					1200			
Phe	Trp	Lys	Val	Gln	His	His	Met	Ala	Pro	Thr	Lys	Asp	Glu	Phe
1205						1210					1215			
Asp	Cys	Lys	Ala	Trp	Ala	Tyr	Phe	Ser	Asp	Val	Asp	Leu	Glu	Lys
1220						1225					1230			
Asp	Val	His	Ser	Gly	Leu	Ile	Gly	Pro	Leu	Leu	Val	Cys	His	Thr
1235						1240					1245			
Asn	Thr	Leu	Asn	Pro	Ala	His	Gly	Arg	Gln	Val	Thr	Val	Gln	Glu
1250						1255					1260			
Phe	Ala	Leu	Phe	Phe	Thr	Ile	Phe	Asp	Glu	Thr	Lys	Ser	Trp	Tyr

1265						1270						1275			
Phe	Thr	Glu	Asn	Met	Glu	Arg	Asn	Cys	Arg	Ala	Pro	Cys	Asn	Ile	
1280						1285					1290				
Gln	Met	Glu	Asp	Pro	Thr	Phe	Lys	Glu	Asn	Tyr	Arg	Phe	His	Ala	
1295						1300					1305				
Ile	Asn	Gly	Tyr	Ile	Met	Asp	Thr	Leu	Pro	Gly	Leu	Val	Met	Ala	
1310						1315					1320				
Gln	Asp	Gln	Arg	Ile	Arg	Trp	Tyr	Leu	Leu	Ser	Met	Gly	Ser	Asn	
1325						1330					1335				
Glu	Asn	Ile	His	Ser	Ile	His	Phe	Ser	Gly	His	Val	Phe	Thr	Val	
1340						1345					1350				
Arg	Lys	Lys	Glu	Glu	Tyr	Lys	Met	Ala	Leu	Tyr	Asn	Leu	Tyr	Pro	
1355						1360					1365				
Gly	Val	Phe	Glu	Thr	Val	Glu	Met	Leu	Pro	Ser	Lys	Ala	Gly	Ile	
1370						1375					1380				
Trp	Arg	Val	Glu	Cys	Leu	Ile	Gly	Glu	His	Leu	His	Ala	Gly	Met	
1385						1390					1395				
Ser	Thr	Leu	Phe	Leu	Val	Tyr	Ser	Asn	Lys	Cys	Gln	Thr	Pro	Leu	
1400						1405					1410				
Gly	Met	Ala	Ser	Gly	His	Ile	Arg	Asp	Phe	Gln	Ile	Thr	Ala	Ser	
1415						1420					1425				
Gly	Gln	Tyr	Gly	Gln	Trp	Ala	Pro	Lys	Leu	Ala	Arg	Leu	His	Tyr	
1430						1435					1440				

Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Pro Phe Ser Trp
 1445 1450 1455

Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His Gly Ile Lys
 1460 1465 1470

Thr Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr Ile Ser Gln
 1475 1480 1485

Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp Gln Thr Tyr
 1490 1495 1500

Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe Gly Asn Val
 1505 1510 1515

Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro Pro Ile Ile
 1520 1525 1530

Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg Ser
 1535 1540 1545

Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn Ser Cys Ser
 1550 1555 1560

Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln Ile
 1565 1570 1575

Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser Pro
 1580 1585 1590

Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg
 1595 1600 1605

Pro 1610	Gln	Val	Asn	Asn	Pro	Lys 1615	Glu	Trp	Leu	Gln	Val 1620	Asp	Phe	Gln
Lys 1625	Thr	Met	Lys	Val	Thr	Gly 1630	Val	Thr	Thr	Gln	Gly 1635	Val	Lys	Ser
Leu 1640	Leu	Thr	Ser	Met	Tyr	Val 1645	Lys	Glu	Phe	Leu	Ile 1650	Ser	Ser	Ser
Gln 1655	Asp	Gly	His	Gln	Trp	Thr 1660	Leu	Phe	Phe	Gln	Asn 1665	Gly	Lys	Val
Lys 1670	Val	Phe	Gln	Gly	Asn	Gln 1675	Asp	Ser	Phe	Thr	Pro 1680	Val	Val	Asn
Ser 1685	Leu	Asp	Pro	Pro	Leu	Leu 1690	Thr	Arg	Tyr	Leu	Arg 1695	Ile	His	Pro
Gln 1700	Ser	Trp	Val	His	Gln	Ile 1705	Ala	Leu	Arg	Met	Glu 1710	Val	Leu	Gly
Cys 1715	Glu	Ala	Gln	Asp	Leu	Tyr 1720	Asp	Lys	Thr	His	Thr 1725	Cys	Pro	Pro
Cys 1730	Pro	Ala	Pro	Glu	Leu	Leu 1735	Gly	Gly	Pro	Ser	Val 1740	Phe	Leu	Phe
Pro 1745	Pro	Lys	Pro	Lys	Asp	Thr 1750	Leu	Met	Ile	Ser	Arg 1755	Thr	Pro	Glu
Val 1760	Thr	Cys	Val	Val	Val	Asp 1765	Val	Ser	His	Glu	Asp 1770	Pro	Glu	Val

Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys
1775						1780					1785			
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
1790						1795					1800			
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
1805						1810					1815			
Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu
1820						1825					1830			
Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
1835						1840					1845			
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val
1850						1855					1860			
Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala
1865						1870					1875			
Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr
1880						1885					1890			
Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser
1895						1900					1905			
Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe
1910						1915					1920			
Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln
1925						1930					1935			
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly							

1940

1945

<210> 208
 <211> 22
 <212> PRT
 <213> Homo sapiens

<400> 208

Met Ile Pro Ala Arg Phe Ala Gly Val Leu Leu Ala Leu Ala Leu Ile
 1 5 10 15

Leu Pro Gly Thr Leu Cys
 20

<210> 209
 <211> 741
 <212> PRT
 <213> Homo sapiens

<400> 209

Ala Glu Gly Thr Arg Gly Arg Ser Ser Thr Ala Arg Cys Ser Leu Phe
 1 5 10 15

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

Gly Tyr Cys Ser Tyr Leu Leu Ala Gly Gly Cys Gln Lys Arg Ser Phe
 35 40 45

Ser Ile Ile Gly Asp Phe Gln Asn Gly Lys Arg Val Ser Leu Ser Val
 50 55 60

Tyr Leu Gly Glu Phe Phe Asp Ile His Leu Phe Val Asn Gly Thr Val
 65 70 75 80

Thr Gln Gly Asp Gln Arg Val Ser Met Pro Tyr Ala Ser Lys Gly Leu
 85 90 95

Tyr Leu Glu Thr Glu Ala Gly Tyr Tyr Lys Leu Ser Gly Glu Ala Tyr
 100 105 110

Gly Phe Val Ala Arg Ile Asp Gly Ser Gly Asn Phe Gln Val Leu Leu
 115 120 125

Ser Asp Arg Tyr Phe Asn Lys Thr Cys Gly Leu Cys Gly Asn Phe Asn
 130 135 140

Ile Phe Ala Glu Asp Asp Phe Met Thr Gln Glu Gly Thr Leu Thr Ser
 145 150 155 160

Asp Pro Tyr Asp Phe Ala Asn Ser Trp Ala Leu Ser Ser Gly Glu Gln
 165 170 175

Trp Cys Glu Arg Ala Ser Pro Pro Ser Ser Ser Cys Asn Ile Ser Ser
 180 185 190

Gly Glu Met Gln Lys Gly Leu Trp Glu Gln Cys Gln Leu Leu Lys Ser
 195 200 205

Thr Ser Val Phe Ala Arg Cys His Pro Leu Val Asp Pro Glu Pro Phe
 210 215 220

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

Cys Ala Cys Pro Ala Leu Leu Glu Tyr Ala Arg Thr Cys Ala Gln Glu
 245 250 255

Gly Met Val Leu Tyr Gly Trp Thr Asp His Ser Ala Cys Ser Pro Val

260

265

270

Cys Pro Ala Gly Met Glu Tyr Arg Gln Cys Val Ser Pro Cys Ala Arg
 275 280 285

Thr Cys Gln Ser Leu His Ile Asn Glu Met Cys Gln Glu Arg Cys Val
 290 295 300

Asp Gly Cys Ser Cys Pro Glu Gly Gln Leu Leu Asp Glu Gly Leu Cys
 305 310 315 320

Val Glu Ser Thr Glu Cys Pro Cys Val His Ser Gly Lys Arg Tyr Pro
 325 330 335

Pro Gly Thr Ser Leu Ser Arg Asp Cys Asn Thr Cys Ile Cys Arg Asn
 340 345 350

Ser Gln Trp Ile Cys Ser Asn Glu Glu Cys Pro Gly Glu Cys Leu Val
 355 360 365

Thr Gly Gln Ser His Phe Lys Ser Phe Asp Asn Arg Tyr Phe Thr Phe
 370 375 380

Ser Gly Ile Cys Gln Tyr Leu Leu Ala Arg Asp Cys Gln Asp His Ser
 385 390 395 400

Phe Ser Ile Val Ile Glu Thr Val Gln Cys Ala Asp Asp Arg Asp Ala
 405 410 415

Val Cys Thr Arg Ser Val Thr Val Arg Leu Pro Gly Leu His Asn Ser
 420 425 430

Leu Val Lys Leu Lys His Gly Ala Gly Val Ala Met Asp Gly Gln Asp
 435 440 445

Ile Gln Leu Pro Leu Leu Lys Gly Asp Leu Arg Ile Gln His Thr Val
 450 455 460

Thr Ala Ser Val Arg Leu Ser Tyr Gly Glu Asp Leu Gln Met Asp Trp
 465 470 475 480

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

Lys Thr Cys Gly Leu Cys Gly Asn Tyr Asn Gly Asn Gln Gly Asp Asp
 500 505 510

Phe Leu Thr Pro Ser Gly Leu Ala Glu Pro Arg Val Glu Asp Phe Gly
 515 520 525

Asn Ala Trp Lys Leu His Gly Asp Cys Gln Asp Leu Gln Lys Gln His
 530 535 540

Ser Asp Pro Cys Ala Leu Asn Pro Arg Met Thr Arg Phe Ser Glu Glu
 545 550 555 560

Ala Cys Ala Val Leu Thr Ser Pro Thr Phe Glu Ala Cys His Arg Ala
 565 570 575

Val Ser Pro Leu Pro Tyr Leu Arg Asn Cys Arg Tyr Asp Val Cys Ser
 580 585 590

Cys Ser Asp Gly Arg Glu Cys Leu Cys Gly Ala Leu Ala Ser Tyr Ala
 595 600 605

Ala Ala Cys Ala Gly Arg Gly Val Arg Val Ala Trp Arg Glu Pro Gly
 610 615 620

Arg Cys Glu Leu Asn Cys Pro Lys Gly Gln Val Tyr Leu Gln Cys Gly
 625 630 635 640

Thr Pro Cys Asn Leu Thr Cys Arg Ser Leu Ser Tyr Pro Asp Glu Glu
 645 650 655

Cys Asn Glu Ala Cys Leu Glu Gly Cys Phe Cys Pro Pro Gly Leu Tyr
 660 665 670

Met Asp Glu Arg Gly Asp Cys Val Pro Lys Ala Gln Cys Pro Cys Tyr
 675 680 685

Tyr Asp Gly Glu Ile Phe Gln Pro Glu Asp Ile Phe Ser Asp His His
 690 695 700

Thr Met Cys Tyr Cys Glu Asp Gly Phe Met His Cys Thr Met Ser Gly
 705 710 715 720

Val Pro Gly Ser Leu Leu Pro Asp Ala Val Leu Ser Ser Pro Leu Ser
 725 730 735

His Arg Ser Lys Arg
 740

<210> 210
 <211> 103
 <212> PRT
 <213> Homo sapiens

<400> 210

Ser Leu Ser Cys Arg Pro Pro Met Val Lys Leu Val Cys Pro Ala Asp
 1 5 10 15

Asn Leu Arg Ala Glu Gly Leu Glu Cys Thr Lys Thr Cys Gln Asn Tyr

Ser His Pro Ser Val Lys Cys Lys Lys Arg Val Thr Ile Leu Val Glu
50 55 60

Gly Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys Arg Pro
 65 70 75 80

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

Ile Leu Leu Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg His Leu
 100 105 110

Ser Ile Ser Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val Cys Gly
 115 120 125

Leu Cys Gly Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr Ser Ser
 130 135 140

Asn Leu Gln Val Glu Glu Asp Pro Val Asp Phe Gly Asn Ser Trp Lys
 145 150 155 160

Val Ser Ser Gln Cys Ala Asp Thr Arg Lys Val Pro Leu Asp Ser Ser
 165 170 175

Pro Ala Thr Cys His Asn Asn Ile Met Lys Gln Thr Met Val Asp Ser
 180 185 190

Ser Cys Arg Ile Leu Thr Ser Asp Val Phe Gln Asp Cys Asn Lys Leu
 195 200 205

Val Asp Pro Glu Pro Tyr Leu Asp Val Cys Ile Tyr Asp Thr Cys Ser
 210 215 220

Cys Glu Ser Ile Gly Asp Cys Ala Cys Phe Cys Asp Thr Ile Ala Ala
 225 230 235 240

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

Leu Tyr Val Glu Asp Ile Ser Glu Pro Pro Leu His Asp Phe Tyr Cys
 20 25 30

Ser Arg Leu Leu Asp Leu Val Phe Leu Leu Asp Gly Ser Ser Arg Leu
 35 40 45

Ser Glu Ala Glu Phe Glu Val Leu Lys Ala Phe Val Val Asp Met Met
 50 55 60

Glu Arg Leu Arg Ile Ser Gln Lys Trp Val Arg Val Ala Val Val Glu
 65 70 75 80

Tyr His Asp Gly Ser His Ala Tyr Ile Gly Leu Lys Asp Arg Lys Arg
 85 90 95

Pro Ser Glu Leu Arg Arg Ile Ala Ser Gln Val Lys Tyr Ala Gly Ser
 100 105 110

Gln Val Ala Ser Thr Ser Glu Val Leu Lys Tyr Thr Leu Phe Gln Ile
 115 120 125

Phe Ser Lys Ile Asp Arg Pro Glu Ala Ser Arg Ile Ala Leu Leu Leu
 130 135 140

Met Ala Ser Gln Glu Pro Gln Arg Met Ser Arg Asn Phe Val Arg Tyr
 145 150 155 160

Val Gln Gly Leu Lys Lys Lys Lys Val Ile Val Ile Pro Val Gly Ile
 165 170 175

Gly Pro His Ala Asn Leu Lys Gln Ile Arg Leu Ile Glu Lys Gln Ala
 180 185 190

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

Gln Arg Asp Glu Ile Val Ser Tyr Leu Cys Asp Leu Ala Pro Glu Ala
 210 215 220

Pro Pro Pro Thr Leu Pro Pro Asp Met Ala Gln Val Thr Val Gly
 225 230 235

<210> 213
 <211> 1334
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (537)..(537)
 <223> Xaa can be any naturally occurring amino acid

<400> 213

Pro Gly Leu Leu Gly Val Ser Thr Leu Gly Pro Lys Arg Asn Ser Met
 1 5 10 15

Val Leu Asp Val Ala Phe Val Leu Glu Gly Ser Asp Lys Ile Gly Glu
 20 25 30

Ala Asp Phe Asn Arg Ser Lys Glu Phe Met Glu Glu Val Ile Gln Arg
 35 40 45

Met Asp Val Gly Gln Asp Ser Ile His Val Thr Val Leu Gln Tyr Ser
 50 55 60

Tyr Met Val Thr Val Glu Tyr Pro Phe Ser Glu Ala Gln Ser Lys Gly
 65 70 75 80

Asp Ile Leu Gln Arg Val Arg Glu Ile Arg Tyr Gln Gly Gly Asn Arg
85 90 95

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

Val Ser Gln Gly Asp Arg Glu Gln Ala Pro Asn Leu Val Tyr Met Val
115 120 125

Thr Gly Asn Pro Ala Ser Asp Glu Ile Lys Arg Leu Pro Gly Asp Ile
130 135 140

Gln Val Val Pro Ile Gly Val Gly Pro Asn Ala Asn Val Gln Glu Leu
145 150 155 160

Glu Arg Ile Gly Trp Pro Asn Ala Pro Ile Leu Ile Gln Asp Phe Glu
165 170 175

Thr Leu Pro Arg Glu Ala Pro Asp Leu Val Leu Gln Arg Cys Cys Ser
180 185 190

Gly Glu Gly Leu Gln Ile Pro Thr Leu Ser Pro Ala Pro Asp Cys Ser
195 200 205

Gln Pro Leu Asp Val Ile Leu Leu Leu Asp Gly Ser Ser Ser Phe Pro
210 215 220

Ala Ser Tyr Phe Asp Glu Met Lys Ser Phe Ala Lys Ala Phe Ile Ser
225 230 235 240

Lys Ala Asn Ile Gly Pro Arg Leu Thr Gln Val Ser Val Leu Gln Tyr
245 250 255

Gly Ser Ile Thr Thr Ile Asp Val Pro Trp Asn Val Val Pro Glu Lys
 260 265 270

Ala His Leu Leu Ser Leu Val Asp Val Met Gln Arg Glu Gly Gly Pro
 275 280 285

Ser Gln Ile Gly Asp Ala Leu Gly Phe Ala Val Arg Tyr Leu Thr Ser
 290 295 300

Glu Met His Gly Ala Arg Pro Gly Ala Ser Lys Ala Val Val Ile Leu
 305 310 315 320

Val Thr Asp Val Ser Val Asp Ser Val Asp Ala Ala Ala Asp Ala Ala
 325 330 335

Arg Ser Asn Arg Val Thr Val Phe Pro Ile Gly Ile Gly Asp Arg Tyr
 340 345 350

Asp Ala Ala Gln Leu Arg Ile Leu Ala Gly Pro Ala Gly Asp Ser Asn
 355 360 365

Val Val Lys Leu Gln Arg Ile Glu Asp Leu Pro Thr Met Val Thr Leu
 370 375 380

Gly Asn Ser Phe Leu His Lys Leu Cys Ser Gly Phe Val Arg Ile Cys
 385 390 395 400

Met Asp Glu Asp Gly Asn Glu Lys Arg Pro Gly Asp Val Trp Thr Leu
 405 410 415

Pro Asp Gln Cys His Thr Val Thr Cys Gln Pro Asp Gly Gln Thr Leu
 420 425 430

Leu Lys Ser His Arg Val Asn Cys Asp Arg Gly Leu Arg Pro Ser Cys

435

440

445

Pro Asn Ser Gln Ser Pro Val Lys Val Glu Glu Thr Cys Gly Cys Arg
 450 455 460

Trp Thr Cys Pro Cys Val Cys Thr Gly Ser Ser Thr Arg His Ile Val
 465 470 475 480

Thr Phe Asp Gly Gln Asn Phe Lys Leu Thr Gly Ser Cys Ser Tyr Val
 485 490 495

Leu Phe Gln Asn Lys Glu Gln Asp Leu Glu Val Ile Leu His Asn Gly
 500 505 510

Ala Cys Ser Pro Gly Ala Arg Gln Gly Cys Met Lys Ser Ile Glu Val
 515 520 525

Lys His Ser Ala Leu Ser Val Glu Xaa His Ser Asp Met Glu Val Thr
 530 535 540

Val Asn Gly Arg Leu Val Ser Val Pro Tyr Val Gly Gly Asn Met Glu
 545 550 555 560

Val Asn Val Tyr Gly Ala Ile Met His Glu Val Arg Phe Asn His Leu
 565 570 575

Gly His Ile Phe Thr Phe Thr Pro Gln Asn Asn Glu Phe Gln Leu Gln
 580 585 590

Leu Ser Pro Lys Thr Phe Ala Ser Lys Thr Tyr Gly Leu Cys Gly Ile
 595 600 605

Cys Asp Glu Asn Gly Ala Asn Asp Phe Met Leu Arg Asp Gly Thr Val
 610 615 620

Thr Thr Asp Trp Lys Thr Leu Val Gln Glu Trp Thr Val Gln Arg Pro
 625 630 635 640

Gly Gln Thr Cys Gln Pro Ile Leu Glu Glu Gln Cys Leu Val Pro Asp
 645 650 655

Ser Ser His Cys Gln Val Leu Leu Leu Pro Leu Phe Ala Glu Cys His
 660 665 670

Lys Val Leu Ala Pro Ala Thr Phe Tyr Ala Ile Cys Gln Gln Asp Ser
 675 680 685

Cys His Gln Glu Gln Val Cys Glu Val Ile Ala Ser Tyr Ala His Leu
 690 695 700

Cys Arg Thr Asn Gly Val Cys Val Asp Trp Arg Thr Pro Asp Phe Cys
 705 710 715 720

Ala Met Ser Cys Pro Pro Ser Leu Val Tyr Asn His Cys Glu His Gly
 725 730 735

Cys Pro Arg His Cys Asp Gly Asn Val Ser Ser Cys Gly Asp His Pro
 740 745 750

Ser Glu Gly Cys Phe Cys Pro Pro Asp Lys Val Met Leu Glu Gly Ser
 755 760 765

Cys Val Pro Glu Glu Ala Cys Thr Gln Cys Ile Gly Glu Asp Gly Val
 770 775 780

Gln His Gln Phe Leu Glu Ala Trp Val Pro Asp His Gln Pro Cys Gln
 785 790 795 800

Ile Cys Thr Cys Leu Ser Gly Arg Lys Val Asn Cys Thr Thr Gln Pro
805 810 815

Cys Pro Thr Ala Lys Ala Pro Thr Cys Gly Leu Cys Glu Val Ala Arg
820 825 830

Leu Arg Gln Asn Ala Asp Gln Cys Cys Pro Glu Tyr Glu Cys Val Cys
835 840 845

Asp Pro Val Ser Cys Asp Leu Pro Pro Val Pro His Cys Glu Arg Gly
850 855 860

Leu Gln Pro Thr Leu Thr Asn Pro Gly Glu Cys Arg Pro Asn Phe Thr
865 870 875 880

Cys Ala Cys Arg Lys Glu Glu Cys Lys Arg Val Ser Pro Pro Ser Cys
885 890 895

Pro Pro His Arg Leu Pro Thr Leu Arg Lys Thr Gln Cys Cys Asp Glu
900 905 910

Tyr Glu Cys Ala Cys Asn Cys Val Asn Ser Thr Val Ser Cys Pro Leu
915 920 925

Gly Tyr Leu Ala Ser Thr Ala Thr Asn Asp Cys Gly Cys Thr Thr Thr
930 935 940

Thr Cys Leu Pro Asp Lys Val Cys Val His Arg Ser Thr Ile Tyr Pro
945 950 955 960

Val Gly Gln Phe Trp Glu Glu Gly Cys Asp Val Cys Thr Cys Thr Asp
965 970 975

Met Glu Asp Ala Val Met Gly Leu Arg Val Ala Gln Cys Ser Gln Lys
 980 985 990

Pro Cys Glu Asp Ser Cys Arg Ser Gly Phe Thr Tyr Val Leu His Glu
 995 1000 1005

Gly Glu Cys Cys Gly Arg Cys Leu Pro Ser Ala Cys Glu Val Val
 1010 1015 1020

Thr Gly Ser Pro Arg Gly Asp Ser Gln Ser Ser Trp Lys Ser Val
 1025 1030 1035

Gly Ser Gln Trp Ala Ser Pro Glu Asn Pro Cys Leu Ile Asn Glu
 1040 1045 1050

Cys Val Arg Val Lys Glu Glu Val Phe Ile Gln Gln Arg Asn Val
 1055 1060 1065

Ser Cys Pro Gln Leu Glu Val Pro Val Cys Pro Ser Gly Phe Gln
 1070 1075 1080

Leu Ser Cys Lys Thr Ser Ala Cys Cys Pro Ser Cys Arg Cys Glu
 1085 1090 1095

Arg Met Glu Ala Cys Met Leu Asn Gly Thr Val Ile Gly Pro Gly
 1100 1105 1110

Lys Thr Val Met Ile Asp Val Cys Thr Thr Cys Arg Cys Met Val
 1115 1120 1125

Gln Val Gly Val Ile Ser Gly Phe Lys Leu Glu Cys Arg Lys Thr
 1130 1135 1140

Thr Cys Asn Pro Cys Pro Leu Gly Tyr Lys Glu Glu Asn Asn Thr

1145

1150

1155

Gly Glu Cys Cys Gly Arg Cys Leu Pro Thr Ala Cys Thr Ile Gln
 1160 1165 1170

Leu Arg Gly Gly Gln Ile Met Thr Leu Lys Arg Asp Glu Thr Leu
 1175 1180 1185

Gln Asp Gly Cys Asp Thr His Phe Cys Lys Val Asn Glu Arg Gly
 1190 1195 1200

Glu Tyr Phe Trp Glu Lys Arg Val Thr Gly Cys Pro Pro Phe Asp
 1205 1210 1215

Glu His Lys Cys Leu Ala Glu Gly Gly Lys Ile Met Lys Ile Pro
 1220 1225 1230

Gly Thr Cys Cys Asp Thr Cys Glu Glu Pro Glu Cys Asn Asp Ile
 1235 1240 1245

Thr Ala Arg Leu Gln Tyr Val Lys Val Gly Ser Cys Lys Ser Glu
 1250 1255 1260

Val Glu Val Asp Ile His Tyr Cys Gln Gly Lys Cys Ala Ser Lys
 1265 1270 1275

Ala Met Tyr Ser Ile Asp Ile Asn Asp Val Gln Asp Gln Cys Ser
 1280 1285 1290

Cys Cys Ser Pro Thr Arg Thr Glu Pro Met Gln Val Ala Leu His
 1295 1300 1305

Cys Thr Asn Gly Ser Val Val Tyr His Glu Val Leu Asn Ala Met
 1310 1315 1320

Glu Cys Lys Cys Ser Pro Arg Lys Cys Ser Lys
 1325 1330

<210> 214
 <211> 374
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VWF D3 region EAE

<400> 214

Cys Ser Thr Ile Gly Met Ala His Tyr Leu Thr Phe Asp Gly Leu Lys
 1 5 10 15

Tyr Leu Phe Pro Gly Glu Cys Gln Tyr Val Leu Val Gln Asp Tyr Cys
 20 25 30

Gly Ser Asn Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys Gly Cys
 35 40 45

Ser His Pro Ser Val Lys Cys Lys Lys Arg Val Thr Ile Leu Val Glu
 50 55 60

Gly Gly Glu Ile Glu Leu Phe Asp Gly Glu Val Asn Val Lys Arg Pro
 65 70 75 80

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

Ile Leu Leu Leu Gly Lys Ala Leu Ser Val Val Trp Asp Arg His Leu
 100 105 110

Ser Ile Ser Val Val Leu Lys Gln Thr Tyr Gln Glu Lys Val Cys Gly

115

120

125

Leu Cys Gly Asn Phe Asp Gly Ile Gln Asn Asn Asp Leu Thr Ser Ser
 130 135 140

Asn Leu Gln Val Glu Glu Asp Pro Val Asp Phe Gly Asn Ser Trp Lys
 145 150 155 160

Val Ser Ser Gln Cys Ala Asp Thr Arg Lys Val Pro Leu Asp Ser Ser
 165 170 175

Pro Ala Thr Cys His Asn Asn Ile Met Lys Gln Thr Met Val Asp Ser
 180 185 190

Ser Cys Arg Ile Leu Thr Ser Asp Val Phe Gln Asp Cys Asn Lys Leu
 195 200 205

Val Asp Pro Glu Pro Tyr Leu Asp Val Cys Ile Tyr Asp Thr Cys Ser
 210 215 220

Cys Glu Ser Ile Gly Asp Cys Ala Ala Phe Cys Asp Thr Ile Ala Ala
 225 230 235 240

Tyr Ala His Val Cys Ala Gln His Gly Lys Val Val Thr Trp Arg Thr
 245 250 255

Ala Thr Leu Cys Pro Gln Ser Cys Glu Glu Arg Asn Leu Arg Glu Asn
 260 265 270

Gly Tyr Glu Ala Glu Trp Arg Tyr Asn Ser Cys Ala Pro Ala Cys Gln
 275 280 285

Val Thr Cys Gln His Pro Glu Pro Leu Ala Cys Pro Val Gln Cys Val
 290 295 300

Glu Gly Cys His Ala His Cys Pro Pro Gly Lys Ile Leu Asp Glu Leu
 305 310 315 320

Leu Gln Thr Cys Val Asp Pro Glu Asp Cys Pro Val Cys Glu Val Ala
 325 330 335

Gly Arg Arg Phe Ala Ser Gly Lys Lys Val Thr Leu Asn Pro Ser Asp
 340 345 350

Pro Glu His Cys Gln Ile Cys His Cys Asp Val Val Asn Leu Thr Cys
 355 360 365

Glu Ala Cys Gln Glu Pro
 370

<210> 215

<211> 745

<212> PRT

<213> Artificial Sequence

<220>

<223> 1 to 745 of FVIII

<400> 215

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

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

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

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

50

55

60

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Leu Leu Lys Val Ser Ser Cys Asp Lys 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
 740 745

<210> 216

<211> 684

<212> PRT

<213> Artificial Sequence

<220>

<223> FVIII 1649-2332

<400> 216

Glu	Ile	Thr	Arg	Thr	Thr	Leu	Gln	Ser	Asp	Gln	Glu	Glu	Ile	Asp	Tyr
1				5					10					15	

Asp	Asp	Thr	Ile	Ser	Val	Glu	Met	Lys	Lys	Glu	Asp	Phe	Asp	Ile	Tyr
			20					25					30		

Asp	Glu	Asp	Glu	Asn	Gln	Ser	Pro	Arg	Ser	Phe	Gln	Lys	Lys	Thr	Arg
		35					40					45			

His	Tyr	Phe	Ile	Ala	Ala	Val	Glu	Arg	Leu	Trp	Asp	Tyr	Gly	Met	Ser
	50					55					60				

Ser	Ser	Pro	His	Val	Leu	Arg	Asn	Arg	Ala	Gln	Ser	Gly	Ser	Val	Pro
65					70					75					80

Gln	Phe	Lys	Lys	Val	Val	Phe	Gln	Glu	Phe	Thr	Asp	Gly	Ser	Phe	Thr
				85					90					95	

Gln	Pro	Leu	Tyr	Arg	Gly	Glu	Leu	Asn	Glu	His	Leu	Gly	Leu	Leu	Gly
			100					105					110		

Pro	Tyr	Ile	Arg	Ala	Glu	Val	Glu	Asp	Asn	Ile	Met	Val	Thr	Phe	Arg
		115					120					125			

Asn	Gln	Ala	Ser	Arg	Pro	Tyr	Ser	Phe	Tyr	Ser	Ser	Leu	Ile	Ser	Tyr
	130					135					140				

Glu	Glu	Asp	Gln	Arg	Gln	Gly	Ala	Glu	Pro	Arg	Lys	Asn	Phe	Val	Lys
145					150					155					160

Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His Met Ala
 165 170 175

Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe Ser Asp
 180 185 190

Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly Pro Leu Leu
 195 200 205

Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln Val Thr
 210 215 220

Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr Lys Ser
 225 230 235 240

Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro Cys Asn
 245 250 255

Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg Phe His Ala
 260 265 270

Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu Val Met Ala Gln
 275 280 285

Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met Gly Ser Asn Glu Asn
 290 295 300

Ile His Ser Ile His Phe Ser Gly His Val Phe Thr Val Arg Lys Lys
 305 310 315 320

Glu Glu Tyr Lys Met Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe Glu
 325 330 335

Thr Val Glu Met Leu Pro Ser Lys Ala Gly Ile Trp Arg Val Glu Cys

340

345

350

Leu Ile Gly Glu His Leu His Ala Gly Met Ser Thr Leu Phe Leu Val
 355 360 365

Tyr Ser Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile
 370 375 380

Arg Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro
 385 390 395 400

Lys Leu Ala Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr
 405 410 415

Lys Glu Pro Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile
 420 425 430

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

Tyr Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
 450 455 460

Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe Gly
 465 470 475 480

Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro Pro Ile
 485 490 495

Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg Ser
 500 505 510

Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn Ser Cys Ser Met
 515 520 525

Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala
 530 535 540

Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser Pro Ser Lys Ala
 545 550 555 560

Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln Val Asn
 565 570 575

Asn Pro Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val
 580 585 590

Thr Gly Val Thr Thr Gln Gly Val Lys Ser Leu Leu Thr Ser Met Tyr
 595 600 605

Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr
 610 615 620

Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp
 625 630 635 640

Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg
 645 650 655

Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg
 660 665 670

Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
 675 680

<210> 217

<211> 226

<212> PRT

<213> Artificial Sequence

<220>

<223> Fc region

<400> 217

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

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

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
130 135 140

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

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 165 170 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 210 215 220

Pro Gly
 225

<210> 218

<211> 291

<212> PRT

<213> Artificial Sequence

<220>

<223> XTEN AE288-3

<400> 218

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
 1 5 10 15

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
 20 25 30

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
 35 40 45

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr

50

55

60

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
 65 70 75 80

Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
 85 90 95

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu
 100 105 110

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr
 115 120 125

Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
 130 135 140

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu
 145 150 155 160

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro
 165 170 175

Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
 180 185 190

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro
 195 200 205

Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr
 210 215 220

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
 225 230 235 240

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro
245 250 255

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
260 265 270

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
275 280 285

Ala Ser Ser
290