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(54)名稱

治療A型血友病的方法

(57)摘要

本公開提供一種治療有需要的人類個體的 A 型血友病的方法，該方法包括以給藥間隔向該個體施用嵌合多肽，該嵌合多肽包含(i)因子 VIII(FVIII)蛋白，和(ii)包含 VWF 的 D'域和 VWF 的 D3 域之馮威里氏因子(von Willebrand factor，VWF)片段。

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.

指定代表圖：

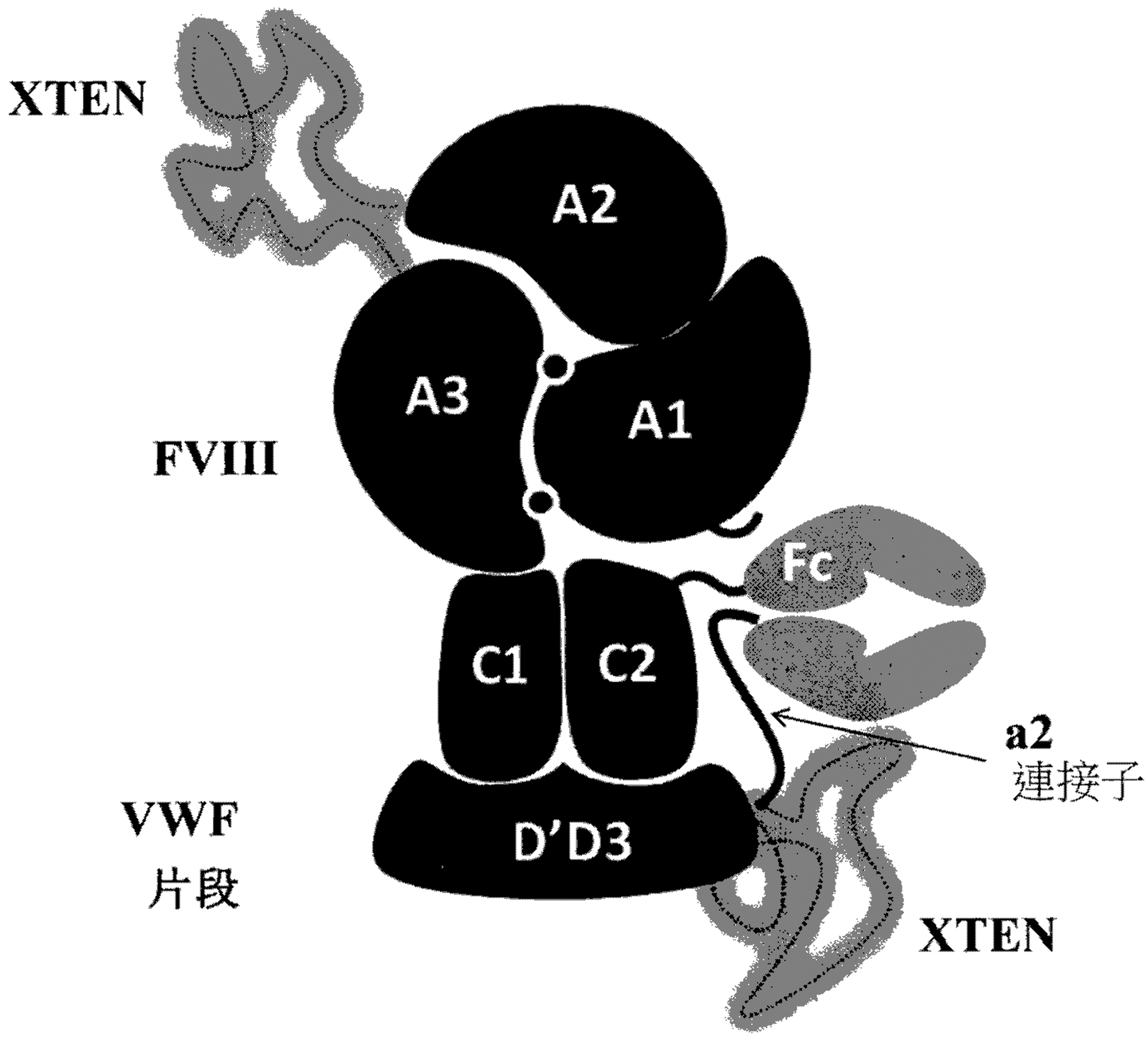

XTEN
A2
A3
A1
FVIII
Fc
C1
C2
a2
連接子
VWF
片段
D'D3
XTEN

圖1

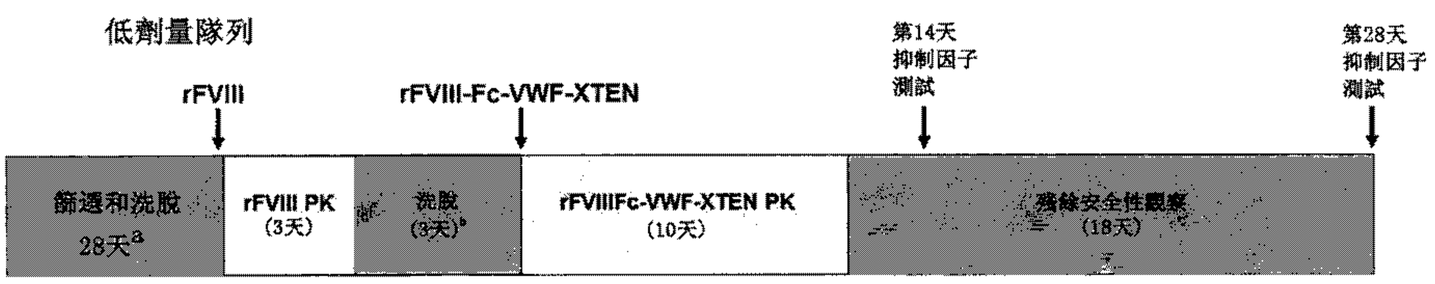

低劑量隊列
rFVIII
rFVIII-Fc-VWF-XTEN
第14天
抑制因子
測試
第28天
抑制因子
測試
篩選和洗脫
28天[a]
rFVIII PK
(3天)
洗脫
(3天)[b]
rFVIIIFc-VWF-XTEN PK
(10天)
殘餘安全性觀察
(18天)

圖2A

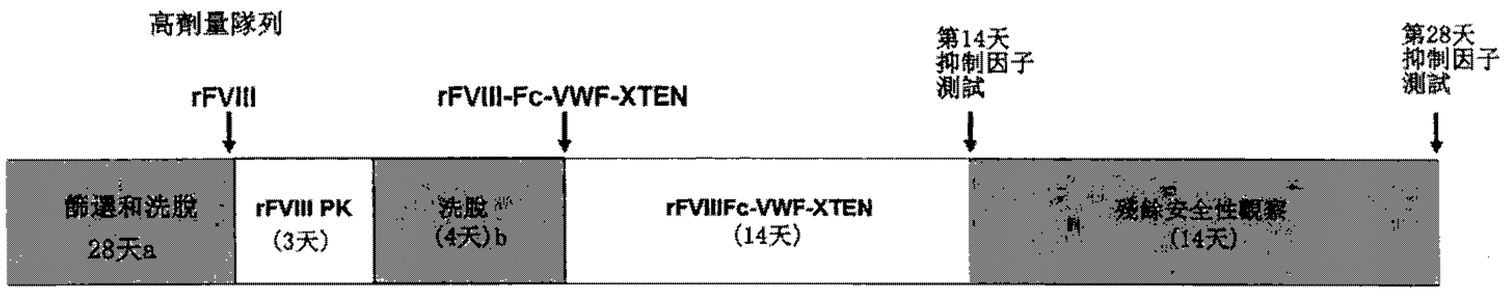

高劑量隊列
rFVIII
rFVIII-Fc-VWF-XTEN
第14天
抑制因子
測試
第28天
抑制因子
測試
篩選和洗脫
28天a
rFVIII PK
(3天)
洗脫
(4天)b
rFVIIIFc-VWF-XTEN
(14天)
殘餘安全性觀察
(14天)

圖2B

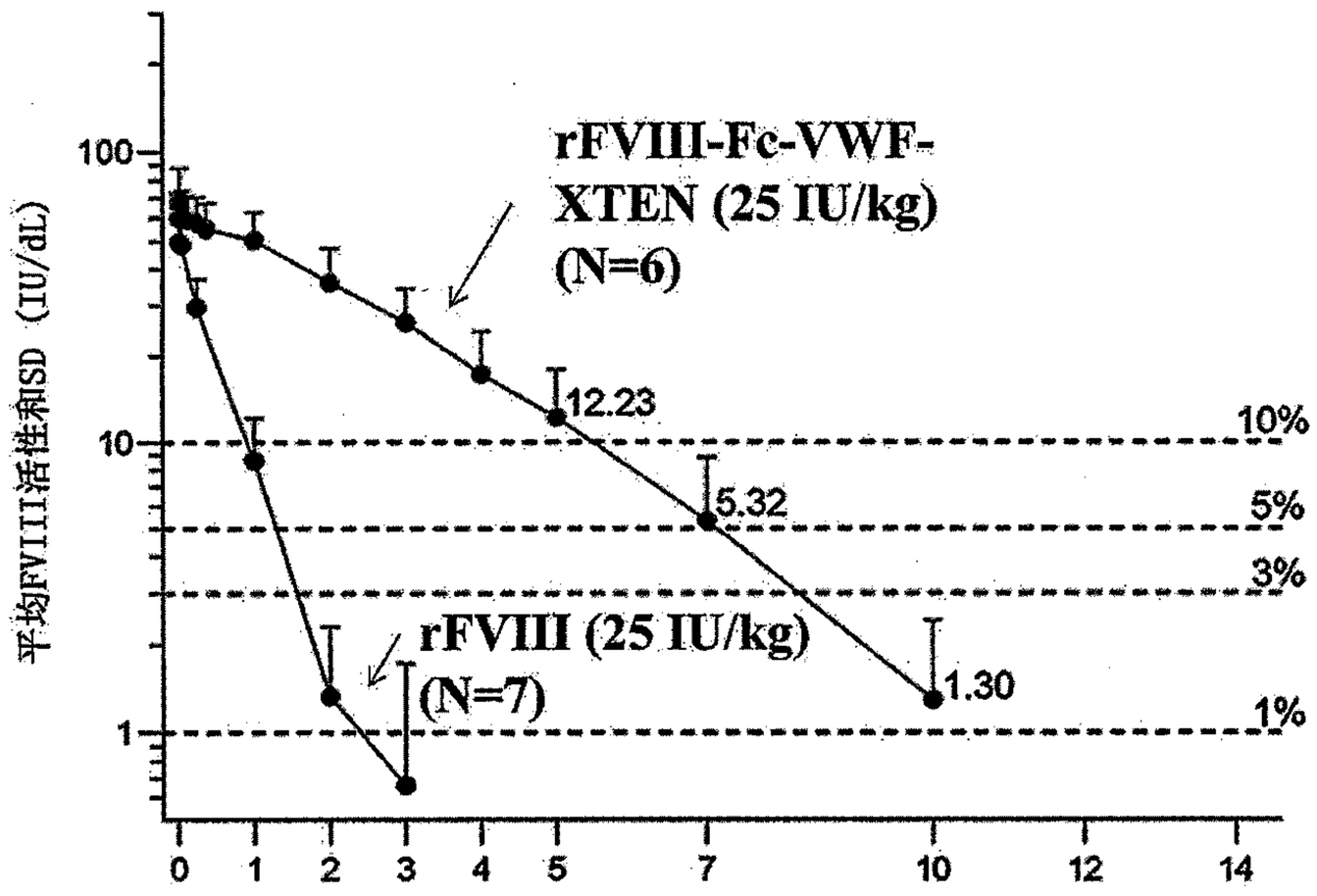

平均FVIII活性和SD（IU/dL）
100
10
1
rFVIII-Fc-VWF-XTEN (25 IU/kg)
(N=6)
12.23
5.32
1.30
rFVIII (25 IU/kg)
(N=7)
10%
5%
3%
1%
0
1
2
3
4
5
7
10
12
14
輸注結束後的天數

圖3A

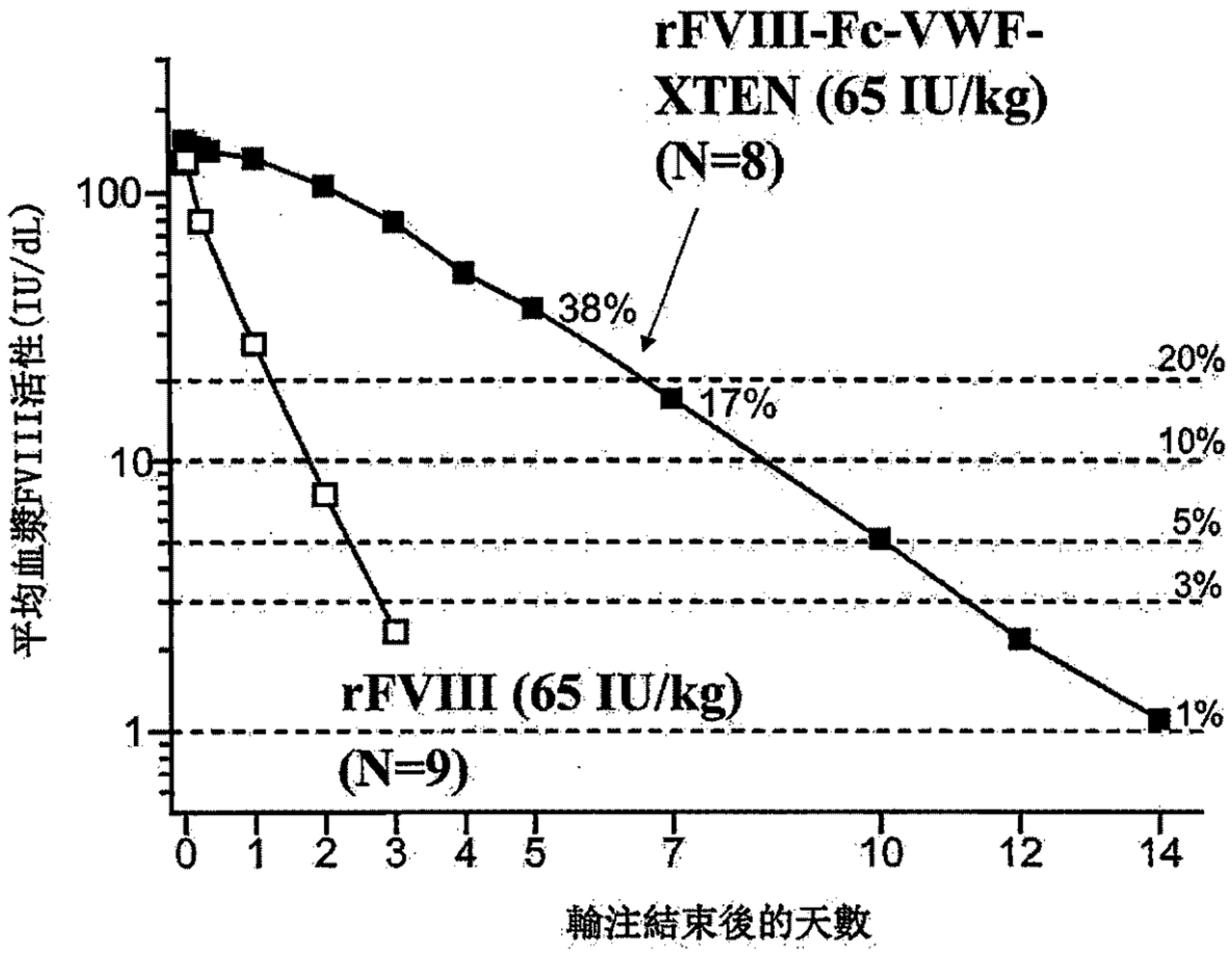

rFVIII-Fc-VWF-XTEN (65 IU/kg)
(N=8)
rFVIII (65 IU/kg)
(N=9)
平均血漿FVIII活性(IU/dL)
100
10
1
38%
20%
17%
10%
5%
3%
1%
0 1 2 3 4 5 7 10 12 14
輸注結束後的天數

圖3B

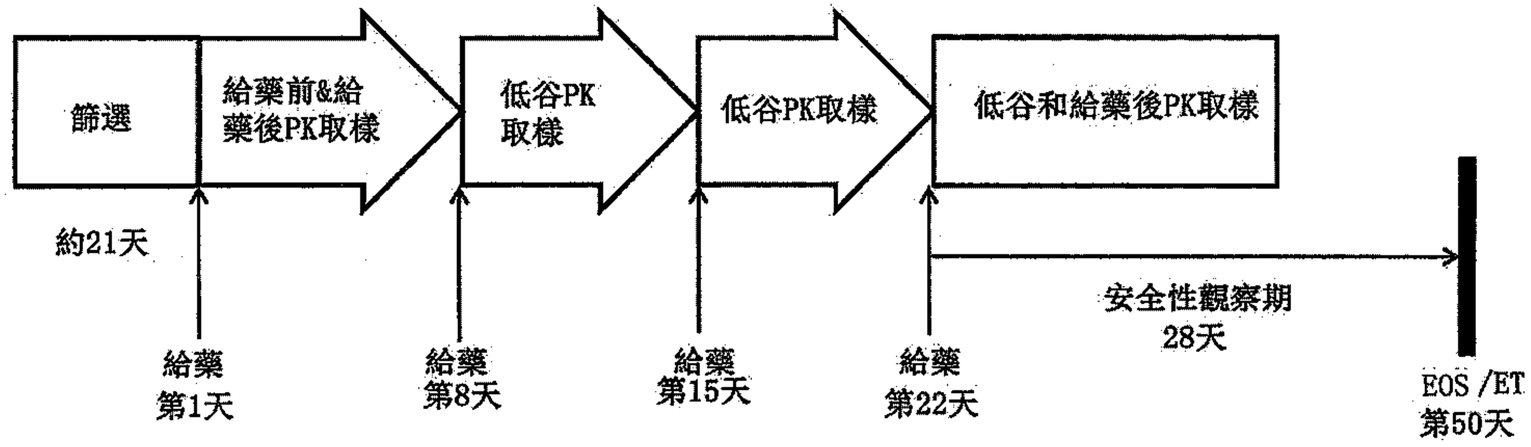

篩選
給藥前&給藥後PK取樣
低谷PK取樣
低谷PK取樣
低谷和給藥後PK取樣
約21天
給藥 第1天
給藥 第8天
給藥 第15天
給藥 第22天
安全性觀察期 28天
EOS /ET 第50天

圖4

202015723

【發明摘要】

【中文發明名稱】治療A型血友病的方法

【英文發明名稱】METHODS OF TREATING HEMOPHILIA A

【中文】

本公開提供一種治療有需要的人類個體的A型血友病的方法，該方法包括以給藥間隔向該個體施用嵌合多肽，該嵌合多肽包含(i) 因子VIII (FVIII)蛋白，和(ii) 包含VWF的D'域和VWF的D3域之馮威里氏因子(von Willebrand factor，VWF)片段。

【英文】

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.

【指定代表圖】

圖1至圖4

【代表圖之符號簡單說明】

無

【特徵化學式】

無

【發明說明書】

【中文發明名稱】治療A型血友病的方法

【英文發明名稱】METHODS OF TREATING HEMOPHILIA A

優先權申請的引用

【0001】　本申請主張於2018年5月18日提交的美國臨時申請號62/673,670，於2018年7月31日提交的美國臨時申請號62/712,880，於2018年11月30日提交的美國臨時申請號62/773,785，和於2019年2月5日提交的美國臨時申請號62/801,576的優先權的權益，其中每個通過提述以其整體併入本文。

電子提交的序列表的引用

以ASCII文本文件電子提交的序列表(名稱：SA9-461PC_SeqListing；大小：922千字節；創建日期：2019年5月14日)的內容通過提述以其整體併入本文。

【技術領域】

【0002】　本申請案提供一種治療有需要的人類個體的A型血友病的方法，該方法包括以給藥間隔向該個體施用嵌合多肽，該嵌合多肽包含(i) 因子VIII (FVIII)蛋白，和(ii) 包含VWF的D'域和VWF的D3域之馮威里氏因子(von Willebrand factor，VWF)片段。

【先前技術】

背景技術

【0003】　A型血友病是由編碼凝血因子VIII (coagulation factor VIII, FVIII)的基因的缺陷引起的出血障礙，且影響10,000個男性出生者中的1-2個。Graw等, *Nat. Rev. Genet.* 6(6): 488-501 (2005)。受A型血友病影響的患者可經輸注純化的或重組產生的FVIII來治療。已知許多可商購的FVIII產品其半衰期為約8-12小時，這需要向患者頻繁靜脈內施用。參見Weiner M.A.和Cairo, M.S., Pediatric Hematology Secrets, Lee, M.T., 12. Disorders of Coagulation, Elsevier Health Sciences, 2001; Lillicrap, D. Thromb. Res. 122 增刊4:S2-8 (2008)。此外，已經嘗試了許多方法以便延長FVIII半衰期。例如，延長凝血因子(clotting factor)的半衰期

的開發中方法，包括聚乙二醇化、糖基聚乙二醇化(glycopegylation)和與白蛋白的綴合。參見Dumont等, *Blood*. 119(13): 3024-3030 (2012)。已經在人類中證明了一致的結果，例如，據報導，相較於ADVATE®，rFVIIIFc在A型血友病患者中改善半衰期多達~1.7倍。參見Powell等, *Blood*. 119(13):3031-3037 (2012)。因此，儘管改善不多，但半衰期增加指示其它半衰期限制性因素的存在。參見Liu, T.等, 2007 ISTH會議，摘要#P-M-035；Henrik, A.等, 2011 ISTH會議，摘要#P=MO-181；Liu, T等, 2011 ISTH會議摘要#P-WE-131。

【0004】 目前推薦的護理標準涉及定期施用FVIII(常規預防)以使出血事件的數目最小化。常規預防與長期成果的改善有關，但其是一種高要求的方案，由於需要頻繁的靜脈內(IV)施用而受限制。參見Manco-Johnson等, *N Engl J Med.357(6)*:535-44 (2007)。延長半衰期的FVIII產品已經降低了用於預防的FVIII施用的頻率；然而，所有這些產品均與馮威里氏因子(von Willebrand factor，VWF)相互作用並具有相當的循環半衰期，與由於內源性VWF的半衰期引起的rFVIII變異體的半衰期上限一致。參見，例如，Pipe等，*Blood*. 128(16): 2007-16 (2016)。這些FVIII產品的預防性給藥是每3至5天。

【0005】 更長時間段預防並控制出血事件(導致更少頻率的施用)的下一代延長半衰期的FVIII產品，將可能會解決堅持高要求預防性方案的挑戰，從而可改善血友病患者的生活質量。

【發明內容】

【0006】 本公開的某些方面涉及一種治療有需要的人類個體的A型血友病的方法，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，該嵌合多肽包含(i) 因子VIII (FVIII)蛋白和(ii)包含VWF的D'域和VWF的D3域的馮威里氏因子(von Willebrand factor，VWF)片段，其中該多劑量中的至少一個為約15 IU/kg至約100 IU/kg，且該給藥間隔為至少約每7天。

【0007】 在一些實施例中，該多劑量包含至少兩個劑量、至少三個劑量、至少四個劑量、至少五個劑量、至少六個劑量、至少七個劑量、至少八個劑量、

至少九個劑量、至少十個劑量、至少十一個劑量、至少十二個劑量、至少十三個劑量、至少十四個劑量、至少十五個劑量、至少十六個劑量、至少十七個劑量、至少十八個劑量、至少十九個劑量、至少二十個劑量、或更多個。

【0008】　在一些實施例中，A型血友病的治療包括控制或降低有需要的個體人類個體的出血事件的發生率或頻率。在一些實施例中，A型血友病的治療包括預防或治療有需要的個體人類個體的出血事件。

【0009】　在一些實施例中，該多劑量的至少一個為約20 IU/kg至約95 IU/kg、約20 IU/kg至約90 IU/kg、約20 IU/kg至約85 IU/kg、約20 IU/kg至約80 IU/kg、約20 IU/kg至約75 IU/kg、約20 IU/kg至約70 IU/kg、約20 IU/kg至約65 IU/kg、約20 IU/kg至約60 IU/kg、約20 IU/kg至約55 IU/kg、約20 IU/kg至約50 IU/kg、約20 IU/kg至約45 IU/kg、約20 IU/kg至約40 IU/kg、約20 IU/kg至約35 IU/kg、約20 IU/kg至約30 IU/kg、或約20 IU/kg至約25 IU/kg。在一些實施例中，該多劑量中的至少一個為約20 IU/kg至約100 IU/kg、約25 IU/kg至約100 IU/kg、約30 IU/kg至約100 IU/kg、約35 IU/kg至約100 IU/kg、約40 IU/kg至約100 IU/kg、約45 IU/kg至約100 IU/kg、約50 IU/kg至約100 IU/kg、約55 IU/kg至約100 IU/kg、約60 IU/kg至約100 IU/kg、約65 IU/kg至約100 IU/kg、約70 IU/kg至約100 IU/kg、約75 IU/kg至約100 IU/kg、約80 IU/kg至約100 IU/kg、約85 IU/kg至約100 IU/kg、或約90 IU/kg至約100 IU/kg。

【0010】　在一些實施例中，該多劑量中的至少一個為約20 IU/kg至約80 IU/kg，約25 IU/kg至約75 IU/kg、約30 IU/kg至約70 IU/kg、約35 IU/kg至約65 IU/kg、約40 IU/kg至約60 IU/kg、或約45 IU/kg至約55 IU/kg。在一些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg。

【0011】　在一些實施例中，該多劑量中的至少一個為約20 IU/kg、約25 IU/kg、約30 IU/kg、約35 IU/kg、約40 IU/kg、約45 IU/kg、約50 IU/kg、約55 IU/kg、約60 IU/kg、約65 IU/kg、約70 IU/kg、約75 IU/kg、約80 IU/kg、約85 IU/kg、約90 IU/kg、約95 IU/kg、或約100 IU/kg。在一些實施例中，該多劑量中的至少一個為約25 IU/kg。在一些實施例中，該多劑量中的至少一個為約50 IU/kg。在一些

實施例中，該多劑量中的至少一個為約65 IU/kg。在一些實施例中，該多劑量中的至少一個為約80 IU/kg。

【0012】　在一些實施例中，該給藥間隔為至少約5天、至少約6天、至少約7天、至少約8天、至少約9天、至少約10天、至少約11天、至少約12天、至少約13天、至少約14天、至少約15天、至少約16天、至少約17天、至少約18天、至少約19天、至少約20天、至少約21天、至少約22天、至少約23天、至少約24天、至少約25天、至少約26天、至少約27天、至少約28天、至少約29天、至少約30天、或至少約31天。

【0013】　在一些實施例中，該給藥頻率為至少每週一次、至少每2週一次、至少每3週一次、或至少每4週一次。在一些實施例中，該給藥間隔為至少每週一次。在一些實施例中，該給藥間隔為至少每兩週一次。

【0014】　在一些實施例中，該嵌合多肽係施用於預防性治療。

【0015】　在一些實施例中，該FVIII蛋白通過共價鍵與該VWF片段締合。在一些實施例中，該共價鍵是肽鍵或雙硫鍵。

【0016】　在一些實施例中，該FVIII蛋白包含FVIII多肽和第一延長半衰期的部分。在一些實施例中，該第一延長半衰期的部分與該FVIII多肽的C端或N端融合。在一些實施例中，該第一延長半衰期的部分被插入在該FVIII多肽內。在一些實施例中，該第一延長半衰期的部分被插入在該FVIII多肽的B域。在一些實施例中，該第一延長半衰期的部分被插入在該FVIII多肽內，緊鄰對應於SEQ ID NO: 65的胺基酸殘基745的下游。在一些實施例中，該第一延長半衰期的部分通過連接子與該FVIII多肽融合。

【0017】　在一些實施例中，該VWF片段包含第二延長半衰期的部分。在一些實施例中，該第二延長半衰期的部分與該VWF片段的C端或N端融合。在一些實施例中，該第二延長半衰期的部分被插入在該VWF片段內。在一些實施例中，該第二延長半衰期的部分與該VWF片段的C端融合。在一些實施例中，該第二延長半衰期的部分通過連接子與該VWF片段融合。

【0018】　在一些實施例中，該第一延長半衰期的部分、該第二延長半衰期的

部分、或二者選自下列群組：白蛋白、免疫球蛋白Fc區、XTEN序列、人絨毛膜促性腺激素的β次單元的C端肽(CTP)、PAS序列、HAP序列、轉鐵蛋白、白蛋白結合部分、或其任何片段、衍生物、變異體、和其任何組合。

【0019】　在一些實施例中，該第一延長半衰期的部分包含第一XTEN。

【0020】　在一些實施例中，該第一XTEN被插入在該FVIII多肽內，緊鄰對應於SEQ ID NO: 65的胺基酸殘基745的胺基酸的下游。

【0021】　在一些實施例中，該第二延長半衰期的部分包含第二XTEN。在一些實施例中，該第二XTEN與該VWF片段的C端融合。

【0022】　在一些實施例中，該FVIII蛋白包含第一免疫球蛋白(Ig)恆定區或其部分。在一些實施例中，該第一Ig恆定區或其部分與該FVIII多肽的C端或N端融合。在一些實施例中，該第一Ig恆定區或其部分被插入在該FVIII多肽內。在一些實施例中，該第一Ig恆定區或其部分與該FVIII多肽的C端融合。在一些實施例中，該第一Ig恆定區或其部分通過連接子與該FVIII多肽融合。在一些實施例中，該第一Ig恆定區或其部分包含第一Fc域或其部分。

【0023】　在一些實施例中，該VWF片段包含第二Ig恆定區或其部分。在一些實施例中，該第二Ig恆定區或其部分與該VWF片段的C端或N端融合。在一些實施例中，該第二Ig恆定區或其部分被插入在該VWF片段內。在一些實施例中，該第二Ig恆定區或其部分與該VWF片段的C端融合。在一些實施例中，該第二Ig恆定區或其部分通過連接子與該VWF片段融合。在一些實施例中，該連接子是可切割的連接子。在一些實施例中，該第二Ig恆定區或其部分包含第二Fc域或其部分。

【0024】　在一些實施例中，該FVIII蛋白和該VWF片段通過該第一Fc域和該第二Fc域之間的共價鍵彼此締合。在一些實施例中，該FVIII蛋白和該VWF片段通過該FVIII蛋白和該VWF片段之間的非共價相互作用進一步彼此締合。

【0025】　在一個方面中，本文公開的是一種治療個體人類個體的A型血友病的方法，該方法包括以給藥間隔向有需要的該個體施用多劑量的嵌合多肽，其中該嵌合多肽包含：(i) FVIII蛋白，其包含包含SEQ ID NO: 215的胺基酸序列的第

一FVIII多肽片段；包含SEQ ID NO: 8 (AE288)的胺基酸序列的第一XTEN序列；包含SEQ ID NO: 216的胺基酸序列的第二FVIII多肽片段；和包含SEQ ID NO: 217的胺基酸序列的第一Fc區；和(ii) VWF蛋白，其包含：VWF的D'域，該D'域包含SEQ ID NO: 210的胺基酸序列；VWF的D3域，該D3域包含SEQ ID NO: 214的胺基酸序列；包含SEQ ID NO: 58 (AE144_5A)的胺基酸序列的第二XTEN序列；包含SEQ ID NO: 88的胺基酸序列的a2連接子；和包含SEQ ID NO: 217的胺基酸序列的第二Fc區，且其中該第一Fc區通過雙硫鍵與該第二Fc區共價連接。

【0026】 在一些實施例中，該嵌合多肽包含FVIII蛋白，該FVIII蛋白包含FVIII多肽、第一XTEN序列、第一Fc區、和VWF蛋白，該VWF蛋白包含VWF的D'域、VWF的D3域、第二XTEN序列、FVIII的a2連接子和第二Fc區，其中該FVIII多肽包含SEQ ID NO: 215的胺基酸序列，該第一XTEN序列包含AE288 (SEQ ID NO：8)的胺基酸序列，且與SEQ ID NO: 215的C端融合，該FVIII多肽進一步包含SEQ ID NO：216的胺基酸序列，該第一Fc區包含SEQ ID NO: 217的胺基酸序列，且與SEQ ID NO: 216的C端融合；VWF的D'域包含SEQ ID NO: 210的胺基酸序列；VWF的D3域包含SEQ ID NO：214的胺基酸序列，該第二XTEN序列包含AE144_5A (SEQ ID NO：58)的胺基酸序列，且與VWF的D3域的C端融合；該a2連接子包含SEQ ID NO：88的胺基酸序列，且與該第二XTEN序列的C端融合；該第二Fc區包含SEQ ID NO：217的胺基酸序列，且與該a2連接子的C端融合；且其中該第一Fc區通過雙硫鍵與該第二Fc區連接。

【0027】 在一些實施例中，該嵌合多肽包含包含FVIII信號肽的FVIII蛋白，該FVIII信號肽包含SEQ ID NO: 64的胺基酸序列。在一些實施例中，該嵌合多肽包含包含VWF信號肽的VWF蛋白，該VWF信號肽包含SEQ ID NO：208的胺基酸序列。在一些實施例中，該嵌合多肽包含包含VWF的D1D2域的VWF蛋白，該D1D2域包含SEQ ID NO: 209的胺基酸序列。

【0028】 在一些實施例中，該嵌合多肽包含FVIII蛋白，該FVIII蛋白包含與SEQ ID NO: 201、SEQ ID NO: 203、或SEQ ID NO: 207至少約80%、90%、95%、或100%相同(identical)的胺基酸序列；且VWF蛋白包含與SEQ ID NO: 202或SEQ

ID NO: 205至少約80%、90%、95%、或100%相同的胺基酸序列。

【0029】 在一個實施例中，該嵌合多肽包含包含SEQ ID NO: 203的胺基酸序列的FVIII蛋白和包含SEQ ID NO: 205的胺基酸序列的VWF蛋白。在另一個實施例中，該嵌合多肽包含包含SEQ ID NO: 201的胺基酸序列的FVIII蛋白和包含SEQ ID NO: 202的胺基酸序列的VWF蛋白。在另一個實施例中，該嵌合多肽包含包含SEQ ID NO: 207的胺基酸序列的FVIII蛋白和包含SEQ ID NO: 202的胺基酸序列的VWF蛋白。

【0030】 在一些實施例中，該嵌合多肽包含FVIII蛋白，該FVIII蛋白包含與選自以下的序列至少約80%、90%、95%、或100%相同的胺基酸序列：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)、FVIII199 (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)、或FVIII-312A (SEQ ID NO: 203)；且VWF蛋白包含與選自以下的序列至少約80%、90%、95%、或100%相同的胺基酸序列：VWF031 (SEQ ID NO: 86)、VWF034 (SEQ ID NO: 87)、VWF059 (SEQ ID NO: 197)、VWF059A (SEQ ID NO: 202)、或VWF036。

【0031】 在一些實施例中，該嵌合多肽通過選自下列群組的途徑施用：靜脈內注射、靜脈內輸注、皮下施用、肌肉內施用、口服施用、鼻腔施用、和肺部施用。

【0032】 在一些實施例中，在施用後，該嵌合多肽導致FVIII血漿活性水平為至少約1%、至少約2%、至少約3%、至少約4%、至少約5%、至少約6%、至少約7%、至少約8%、至少約9%、或至少約10%。在一些實施例中，該FVIII血漿活性水平為至少約3%。在一些實施例中，該FVIII血漿活性水平為至少約5%。

【0033】 在一些實施例中，在施用後，該嵌合多肽導致FVIII血漿活性水平為

至少約1 IU/dL、至少約2 IU/dL、至少約3 IU/dL、至少約4 IU/dL、至少約5 IU/dL、至少約6 IU/dL、至少約7 IU/dL、至少約8 IU/dL、至少約9 IU/dL、或至少約10 IU/dL。在一些實施例中，該FVIII血漿活性水平為至少約3 IU/dL。在一些實施例中，該FVIII血漿活性水平為至少約5 IU/dL。

【0034】 在一些實施例中，在施用該嵌合多肽後至少約5天，該FVIII血漿活性水平為至少約10 IU/dL。在一些實施例中，在施用該嵌合多肽後至少約7天，該FVIII血漿活性水平為至少約5 IU/dL。在一些實施例中，在施用該嵌合多肽後至少約8天，該FVIII血漿活性水平為至少約3 IU/dL。在一些實施例中，在施用該嵌合多肽後至少約10天，該FVIII血漿活性水平為至少約1 IU/dL。

【0035】 在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約80 IU/kg。在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約65 IU/kg。在一些實施例中，該多劑量中的至少一個為約65 IU/kg至約80 IU/kg。在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約80 IU/kg，且該給藥間隔為至少約7天。在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約65 IU/kg，且該給藥間隔為至少約5天。在一些實施例中，該多劑量中的至少一個為約65 IU/kg至約80 IU/kg，且該給藥間隔為至少約5天。

【0036】 在一些實施例中，該多劑量中的至少一個為約50 IU/kg。在一些實施例中，該多劑量為約50 IU/kg，且該給藥間隔為約5天。在一些實施例中，該多劑量為約50 IU/kg，且該給藥間隔為約7天。在一些實施例中，該多劑量為約50 IU/kg，且該給藥間隔為約14天。

【0037】 在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約80 IU/kg。在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約65 IU/kg。在一些實施例中，該多劑量中的至少一個為約65 IU/kg至約80 IU/kg。在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約80 IU/kg，且該給藥間隔為至少約7天。在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約65 IU/kg，且該給藥間隔為至少約7天。在一些實施例中，該多劑量中的至少一個為約65 IU/kg至約80 IU/kg，且該給藥間隔為至少約7天。

【0038】　在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約80 IU/kg，且該給藥間隔為至少約10天。在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約65 IU/kg，且該給藥間隔為至少約10天。在一些實施例中，該多劑量中的至少一個為約65 IU/kg至約80 IU/kg，且該給藥間隔為至少約10天。

【0039】　在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約80 IU/kg，且該給藥間隔為至少約14天。在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約65 IU/kg，且該給藥間隔為至少約14天。在一些實施例中，該多劑量中的至少一個為約65 IU/kg至約80 IU/kg，且該給藥間隔為至少約14天。

【0040】　在一些實施例中，該多劑量中的至少一個为約50 IU/kg至約80 IU/kg，且該給藥間隔為至少約1周。在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約65 IU/kg，且該給藥間隔為至少約1周。在一些實施例中，該多劑量中的至少一個為約65 IU/kg至約80 IU/kg，且該給藥間隔為至少約1周。

【0041】　在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約80 IU/kg，且該給藥間隔為至少約2周。在一些實施例中，該多劑量中的至少一個為約50 IU/kg至約65 IU/kg，且該給藥間隔為至少約2周。在一些實施例中，該多劑量中的至少一個为約65 IU/kg至約80 IU/kg，且該給藥間隔為至少約2周。

【0042】　在一些實施例中，該給藥間隔為至少約5天。在一些實施例中，該給藥間隔為至少約7天。在一些實施例中，該給藥間隔為約5天至約14天。在一些實施例中，該給藥間隔為約7天至約14天。在一些實施例中，該給藥間隔為至少約10天。在一些實施例中，該給藥間隔為約10天至約21天。在一些實施例中，該給藥間隔為約14天至約21天。在一些實施例中，該給藥間隔為約14天。

【0043】　在一些實施例中，該個體人類個體是女性。在一些實施例中，該個體人類個體是兒童。在一些實施例中，該個體人類個體是小於或等於約12歲、小於約11歲、小於約10歲、小於約9歲、小於約8歲、小於約7歲、小於約6歲、小於約5歲、小於約4歲、小於約3歲、小於約2歲、或小於約1歲的兒童。

【0044】　在一些實施例中，該施用在該個體人類個體中誘發對FVIII的免疫耐

受。在一些實施例中，該施用在該個體人類個體中降低對FVIII抑制性免疫反應。在一些實施例中，該對FVIII抑制性免疫反應包含在該個體人類個體中高效價（titer）的抗FVIII抗體。

【0045】 在一些實施例中，該嵌合多肽的施用在該施用的約7天、約10天、約11天、約12天、約13天、約14天、約15天、約20天、約24天、約25天、約28天、約30天、或約35天後不誘發FVIII抑制因子。在一些實施例中，該嵌合多肽的施用在該施用的約28天後不誘發FVIII抑制因子。

【圖式簡單說明】

【0046】 圖1是rFVIIIFc-VWF-XTEN的示意圖。FVIII：因子VIII；VWF：馮威里氏因子；A1、A2、A3、C1、C2：FVIII的域；D'D3：VWF的域；Fc：免疫球蛋白恆定區的Fc區。

【0047】 圖2A和2B顯示在以低劑量隊列施用25 IU/kg rFVIIIFc-VWF-XTEN的人類患者中(圖2A)和在以高劑量隊列施用65 IU/kg rFVIIIFc-VWF-XTEN的人類患者中(圖2B)測試rFVIIIFc-VWF-XTEN的安全性和療效的流程。

【0048】 圖3A-3B是校正基線的FVIII活性水平的圖示，該校正基線的FVIII活性水平係基於患有重度A型血友病的個體人類個體其活化部分凝血活酶時間(aPTT)測試結果，個體係施用了25 IU/kg rFVIII，隨後進行洗脫期，然後施用25 IU/kg rFVIIIFc-VWF-XTEN (圖3A；低劑量隊列)，或者係施用65 IU/kg rFVIII，隨後進行洗脫期，然後施用65 IU/kg rFVIIIFc-VWF-XTEN (圖3B；高劑量隊列)。水平虛線指示3%、5%、10%、和20% FVIII活性。

【0049】 圖4是臨床研究設計的示意圖，其係用於在患有嚴重A型血友病、年齡為18-25歲的成人男性、先前經治療的患者(PTP)中評定rFVIIIFc-VWF-XTEN的安全性和耐受性，rFVIIIFc-VWF-XTEN每週一次劑量為50 IU/kg或65 IU/kg，總共四次給藥。EOS = 研究結束；ET = 提前終止；PK = 藥物代謝動力學。

【實施方式】

【0050】　本公開涉及一種治療有需要的個體人類個體的出血性疾病或病況(例如，A型血友病)的方法，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，該嵌合多肽包含(i)因子VIII (FVIII)多肽和(ii)包含VWF的D'域和VWF的D3域的馮威里氏因子(VWF)片段。在一些實施例中，該多劑量中的至少一個為約15 IU/kg至約100 IU/kg。在一些實施例中，該給藥間隔為至少約每5天。在一些實施例中，該給藥間隔為至少約每7天。

I．定義

【0051】　值得注意的是術語「一個(a或an)」實體是指一個或多個該實體；例如，應理解「一個核苷酸序列」代表一個或多個核苷酸序列。同樣地，術語「一(a)」(或「an」)、「一個或多個」和「至少一個」在本文中可互換地使用。

【0052】　此外，「和/或」當在本文中使用時，其被視為具有或不具有另一個特徵或組成的兩個指定特徵或組成中的每一個的具體公開。因此，在本文中以詞組的形式使用的術語「和/或」，諸如「A和/或B」，旨在包括「A和B」、「A或B」、「A」(單獨的)、和「B」(單獨的)。同樣地，如以詞組形式使用的術語「和/或」，諸如「A、B、和/或C」旨在包含下列方面中的每一個：A、B、和C；A、B、或C；A或C；A或B；B或C；A和C；A和B；B和C；A (單獨的)；B (單獨的)；和C (單獨的)。

【0053】　應理解的是，無論在本文中何處用語言「包含(comprising)」來描述方面，還提供了以術語「由.....構成」和/或「基本上由……構成」描述的其他類似方面。

【0054】　除非另有定義，否則本文使用的所有技術和科學術語具有本公開涉及的領域中的普通技術人員所通常理解的相同含義。例如，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，為本領域技術人員提供本公開中使用的許多術語的通用字典。

【0055】 單位、前綴、和符號以其Système International de Unites (SI)可接受的形式表示。數字範圍包括定義範圍的數字。除非另有指示，否則胺基酸序列以胺基到羧基的方向從左向右書寫。本文提供的標題不是對本公開的各個方面的限制。因此，通過參考整個說明書，可以更全面地定義下面直接定義的術語。

【0056】 術語「約」在本文中用於意指近似、大致、大約或在區域內。當術語「約」與數字範圍結合使用時，它通過延伸所示數值的上下邊界來修改該範圍。通常，術語「約」可通過，例如10%，向上或向下(更高或更低)的差異來修改高於和低於所述值的數值。

【0057】 術語「多核苷酸」或「核苷酸」旨在包含單個的核酸以及複數的核酸，且是指經分離的核酸分子或構築體（construct），例如，信使RNA(mRNA)或質體DNA (pDNA)。在某些實施例中，多核苷酸包含常見的磷酸二酯鍵或非常見的鍵(例如，醯胺鍵，諸如肽核酸(PNA)中發現的)。術語「核酸」是指存在於多核苷酸中的任何一個或多個核酸區段，例如，DNA或RNA片段。「經分離的」核酸或多核苷酸是指以從天然環境中去除的核酸分子、DNA或RNA。例如，出於本公開的目的，認為載體中含有的編碼因子VIII多肽的重組多核苷酸是經分離的。經分離的多核苷酸的其他實例，包括保持在異源宿主細胞中或從溶液中其他多核苷酸中所純化(部分地或基本上純化)的重組多核苷酸。經分離的RNA分子包括本公開的多核苷酸其體內或體外RNA轉錄本。根據本公開之經分開的多核苷酸或核酸，進一步包括合成所產生的此類分子。此外，多核苷酸或核酸可包括調控元件，諸如啟動子、增強子、核糖體結合位點、或轉錄終止信號。

【0058】 由哺乳動物細胞分泌的某些蛋白係與分泌性信號肽締合，一旦開始穿過粗面內質網輸出生長的蛋白質鏈，該分泌信號肽就從成熟蛋白質上切割下來。本領域中普通技術人員知道信號肽通常與多肽的N端融合，且從完整或「全長」多肽中切割，以產生分泌形式或「成熟」形式的多肽。在某些實施例中，天然信號肽或保留有直接分泌多肽能力的序列之功能性衍生物可操作地與多肽締合。另外，可使用異源哺乳動物信號肽，例如，人類組織纖溶酶原激活物(TPA)或小鼠β-葡萄糖醛酸酶信號肽，或其功能性衍生物。

【0059】　如本文所用的，術語「多肽」旨在包含單一條的「多肽」以及複數條的「多肽」，且是指由通過醯胺鍵(也稱為肽鍵)線性連接的單體(胺基酸)構成的分子。術語「多肽」是指任何一條或多條之兩個或多於兩個胺基酸的鏈，且並不是指具體長度的產物。因此，肽、二肽、三肽、寡肽、「蛋白」、「胺基酸鏈」或用於指兩個或多個胺基酸的一條鏈或多條鏈的任何其他術語，係包括在「多肽」的定義內，且術語「多肽」可代替這些術語中的任何術語使用，或與這些術語中的任何術語可互換地使用。術語「多肽」還意指多肽的表現後修飾產物，包括但不限於糖基化、乙醯化作用、磷酸化作用、醯胺化作用，通過已知的保護/阻斷基團的衍生化、溶蛋白性切割、或通過非天然存在的胺基酸的修飾。多肽可衍生自自然生物來源或通過重組技術所產生，但不一定從指定的核酸序列轉譯。其可以任何方式生成，包括通過化學合成的方式。

【0060】　「經分離的」多肽或其片段、變異體、或衍生物是指未在其自然環境中的多肽。不需要特定程度的純化。例如，經分離的多肽係簡單地從其天然(native)或自然(natural)環境中移出。出於本公開的目的，認為在宿主細胞中表現的重組產生的多肽和蛋白是經分離的，如同通過任何適合的技術分開、分級或部分地或基本上純化的天然或重組多肽。

【0061】　本公開還包括多肽的片段或變異體，和其任何組合。術語「片段」或「變異體」當是指本公開的多肽結合域或結合分子時，係包括保留參考多肽的至少一些性質(例如，FcRn結合域或Fc變異體的FcRn結合親和力，FVIII變異體的凝血活性，VWF片段的FVIII結合活性)的任何多肽。除了本文別處討論的具體抗體片段外，多肽的片段包括蛋白水解片段，以及刪除片段，但不包括自然存在地全長多肽(或成熟多肽)。本公開的多肽結合域或結合分子的變異體包括如上所述的片段，且還有具有由於胺基酸替代、缺失或插入而改變的胺基酸序列的多肽。變異體可天然或非天然地存在。非天然存在的變異體可使用本領域已知的誘變技術來產生。變異體多肽可包含保守性或非保守性胺基酸替代、缺失或添加。

【0062】　本文中使用的術語「一個或多個VWF蛋白(VWF protein或VWF

proteins)」意指與FVIII相互作用並保留通常由全長VWF所提供的至少一種或多種性質的任何VWF片段，該性質為例如，防止對FVIIIa的不成熟活化，防止不成熟蛋白水解，防止與磷脂膜締合(其可導致不成熟的清除)，防止結合FVIII清除受體(該受體可結合至裸FVIII但不結合與VWF結合的FVIII)，和/或穩定FVIII重鏈和輕鏈的相互作用。本文中提及的VWF片段是短於全長VWF蛋白的VWF多肽，其中該VWF片段保留與FVIII 相互作用和/或結合的能力。

【0063】 「保守性胺基酸替代」是胺基酸殘基係由具有相似側鏈的胺基酸殘基所取代。具有相似側鏈的胺基酸殘基家族已經在本領域中定義，包括鹼性側鏈(例如，離胺酸、精胺酸、組胺酸)，酸性側鏈(例如，天門冬胺酸、麩胺酸)，無電荷的極性側鏈(例如，甘胺酸、天門冬醯胺酸、麩醯胺酸、絲胺酸、蘇胺酸、酪胺酸、半胱胺酸)，非極性側鏈(例如，丙胺酸、撖胺酸、白胺酸、異白胺酸、脯胺酸、苯丙胺酸、甲硫胺酸、色胺酸)，β-支鏈側鏈(例如，蘇胺酸、撖胺酸、異白胺酸)和芳香族側鏈(例如，酪胺酸、苯丙胺酸、色胺酸、組胺酸)。因此，如果多肽中的胺基酸由來自相同側鏈家族的另一胺基酸所取代，則認為該替代是保守性的。在其它實施例中，一串胺基酸可以用結構相似但在側鏈家族成員的順序和/或組成上不同的胺基酸串來保守性地取代。

【0064】 如本領域中已知的，兩個多肽之間的「序列同一性」係通過比較一個多肽的胺基酸序列和第二多肽的序列來確定。當在本文中討論時，可使用本領域中已知的方法和計算機程式/軟體來確定任何特定多肽是否與另一多肽至少約50%、60%、70%、75%、80%、85%、90%、95%、99%、或100%相同，所述方法和計算機程式/軟體諸如，但不限於，BESTFIT程序(Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711)。BESTFIT使用Smith和Waterman, Advances in Applied Mathematics 2:482-489 (1981)的局部同源性算法，以發現兩個序列之間同源性的最佳區段。當使用BESTFIT或任何其他序列比對程序來確定特定序列與根據本公開的參考序列是否例如有95%相同時，其參數係自然被設定，使得在全長參考多肽序列上計算同一性百分比且允許出現至多為在參考序

列胺基酸總數5%的同源性缺口。

【0065】　如本文所用的，VWF序列或FVIII蛋白質序列中的「對應的胺基酸」或「等同胺基酸」係藉由進行最大化第一VWF或FVIII序列和第二VWF或FVIII序列之間的同一性或相似性之鑑定來找出。用於鑒定第二VWF或FVIII序列中的等同胺基酸的數目係基於用以鑒定該第一VWF或FVIII序列中的相應胺基酸的數目。

【0066】　如本文所用的，術語「插入位點」是指在FVIII多肽，或其片段、變異體、或衍生物中的位置，其是緊鄰可插入延長半衰期的部分或異源部分的位置的下游。「插入位點」被指定為數字，該數字是成熟之天然FVIII (SEQ ID NO:65)中的插入位點(其緊鄰C端)對應於插入位置的胺基酸的號碼。例如，詞組「a3包含在對應於SEQ ID NO: 65的胺基酸1656的插入位點處的XTEN」，係指示該異源部分係位於對應於SEQ ID NO: 65的胺基酸1656和胺基酸1657的兩個胺基酸之間。

【0067】　如本文所用的詞組「緊鄰胺基酸下游」是指緊鄰胺基酸的末端羧基基團的位置。例如，緊鄰對應於成熟野生型FVIII蛋白的胺基酸745的下游的插入位點，意指對應於成熟野生型FVIII蛋白的胺基酸745和胺基酸746之間的插入位點。相似地，詞組「緊鄰胺基酸上游」是指緊鄰胺基酸的末端胺基基團的位置。

【0068】　如本文所用的詞組「插入位點的兩個胺基酸之間」是指在兩個鄰近的胺基酸之間插入有XTEN或任何其他多肽的位置。因此，詞組「緊鄰胺基酸下游插入的」和「在插入位點的兩個胺基酸之間插入的」與「在插入位點處插入的」係同義地使用。

【0069】　如本文所用的術語「插入的(inserted)」、「被插入(is inserted)」、「插入至...中(inserted into)」或語法上相關的術語，是指XTEN在嵌合多肽中相對於天然成熟的人類FVIII中的類似位置。如本文所用的術語是指重組FVIII多肽相對於天然成熟的人類FVIII的特性，且並不指示、暗示或推斷任何製造嵌合多肽的方法或過程。例如，關於本文所提供的嵌合多肽，詞組「XTEN係被插入至緊鄰FVIII多肽的殘基745的下游中」，意指嵌合多肽係包含緊鄰對應於天然成熟

的人類FVIII中的胺基酸745的下游的XTEN，例如，係以對應於天然成熟人FVIII的胺基酸745和746的胺基酸邊界。

【0070】 「融合」或「嵌合」蛋白係包含第一胺基酸序列，其與第二胺基酸序列連接，其在自然界中不是天然連接的。正常情況下在分開的蛋白中所存在的胺基酸序列，可以一起放在融合多肽中，或正常情況下在同一蛋白中存在的胺基酸序列可以在融合多肽中以新的排列方式重新放置，例如本公開的因子VIII域與Ig Fc域之融合。舉例來說，融合蛋白係通過化學合成，或通過創建和轉譯一個多核苷酸來製成，在所述的多核苷酸中其胜肽區域係以期望的關係來編碼。嵌合多肽可進一步包含第二胺基酸序列，其係通過共價鍵、非肽鍵或非共價鍵與該第一胺基酸序列締合。

【0071】 如本文所用的術語「連接的」是指共價地或非共價地與第二胺基酸序列或核苷酸序列對應接合的第一胺基酸序列或核苷酸序列。第一胺基酸或核苷酸序列可與第二胺基酸或核苷酸序列直接接合或並列，或者，可由介於中間的序列將該第一序列與該第二序列共價地接合。術語「連接的」不僅意指第一胺基酸序列與第二胺基酸序列在C端或N端處的融合，還包括將整個第一胺基酸序列(或第二胺基酸序列)插入至第二胺基酸序列(或第一胺基酸序列，各自地)中的任何兩個胺基酸中。在一些實施例中，第一胺基酸序列可通過肽鍵或連接子與第二胺基酸序列連接。第一核苷酸序列可通過磷酸二酯鍵或連接子與第二核苷酸序列連接。該連接子可以是單肽或多肽(對於多肽鏈而言)、或核苷酸或核苷酸鏈(對於核苷酸鏈而言)、或任何化學部分(對多肽和多核苷酸鏈而言)。術語「連接的」也由連接符號(-)所表示。

【0072】 如本文所用的術語「與...締合」是指在第一胺基酸鏈和第二胺基酸鏈之間所形成的共價或非共價鍵。在一些實施例中，術語「與...締合」意指共價鍵、非肽鍵或非共價鍵。此關聯可由冒號指示，例如(:)。在其他實施例中，其意指除肽鍵外的共價鍵。例如，胺基酸半胱胺酸包含巰基基團，該巰基基團可與第二個半胱胺酸殘基上的巰基基團形成雙硫鍵或橋。在大多數天然存在的IgG分子中，CH1和CL區可通過雙硫鍵締合，且其兩個重鏈通過位置239和242

（對應於Kabat編號系統，對應於EU編號系統則為位置226或229）的兩個雙硫鍵締合。共價鍵的實例包括，但不限於，肽鍵、金屬鍵、氫鍵、雙硫鍵、σ鍵、π鍵、δ鍵、糖苷鍵、不可知鍵(agnostic bond)、彎曲鍵、偶極鍵、π反向鍵、雙鍵、三鍵、四重鍵、五重鍵、六重鍵、共軛、超共軛、芳香、哈普托數(hapticity)或反鍵合。非共價鍵的非限制性實例包括離子鍵(例如，陽離子-π鍵或鹽鍵)、金屬鍵、氫鍵(例如，二氫鍵、二氫絡合物、低勢壘氫鍵或對稱氫鍵)、范德華力、倫敦分散力、機械鍵、鹵素鍵、親金相互作用、嵌入、堆積、熵力、或化學極性。

【0073】　如本文所用的，術語「切割位點」或「酶切割位點」是指由酶識別的位點。某些酶切割位點包含細胞內加工位點。在一些實施例中，多肽具有於凝血級聯作用期間活化的酶所切割的酶切割位點，使得此位點的切割發生在凝塊形成處。舉例來說，示例性的此位點包括，由凝血酶、因子XIa或因子Xa識別的位點。示例性FXIa切割位點包括，例如，TQSFNDFTR (SEQ ID NO: 1)和SVSQTSKLTR (SEQ ID NO: 3)。示例性的凝血酶切割位點包括，例如，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)、和IEPRSFS (SEQ ID NO: 194)。其他酶切割位點是本領域中已知的，且在本文的其他處中描述。

【0074】　如本文所用的，術語「加工位點」或「細胞內加工位點」是指多肽中的一種類型的酶切割位點，其是在該多肽轉譯後才作為酶的靶標。在一些實施例中，此類酶在從高基氏體腔到反式高基氏體區室之間的轉運發揮作用。細胞內加工酶在從細胞中分泌蛋白之前切割多肽。此類加工位點的實例包括，例如，由內肽酶的PACE/弗林蛋白酶(其中PACE是成對鹼性胺基酸切割酶(Paired basic Amino acid Cleaving Enzyme)的首字母縮寫)家族靶向的加工位點。這些酶位於高基氏體膜，並在序列基序Arg-[任何殘基]-(Lys或Arg)-Arg的羧基端位點上切割蛋白。如本文所用的，「弗林蛋白酶」家族的酶包括，例如，PCSK1(也稱為PC1/PC3)、PCSK2(也稱為PC2)、PCSK3(也稱為弗林蛋白酶或PACE)、PCSK4(也

稱為PC4)、PCSK5(也稱為PC5或PC6)、PCSK6(也稱為PACE4)、或PCSK7(也稱為PC7/LPC、PC8、或SPC7)。其他加工位點是本領域中已知的。

【0075】　在包括一個以上加工或切割位點的構築體中，應該理解，此類位點可以是相同的或不同的。

【0076】　如本文所用的「可加工的連接子」是指包含至少一種細胞內加工位點的連接子，其係於本文的其他處描述。

【0077】　如本文所用的，術語「半衰期」是指特定多肽在體內的生物半衰期。半衰期可表示為一半的施用至個體體的量，從動物中的循環和/或其他組織中清除所需要的時間。當給定多肽的清除曲線構建為時間的函數時，該曲線通常是雙相的，具有快速的α相和更長的β相。α相一般係表示所施用的Fc多肽在血管內和血管外空間之間的平衡，且係（部分地）取決於多肽的大小。β相一般係表示多肽在血管內空間中的分解代謝。在一些實施例中，FVIII和包含有FVIII的嵌合多肽係為單相，且因此不具有α相，而僅是單一的β相。因此，在某些實施例中，如本文所用的術語半衰期，是指多肽在β相中的半衰期。人類抗體在人中的典型β相半衰期為21天。在某些實施例中，半衰期表示為末期的半衰期。

【0078】　如本文所用的止血障礙意指基因遺傳性或後天性病症，其表徵為因形成纖維蛋白凝塊的能力受損或不能形成纖維蛋白凝塊，而自發地或因創傷而出血的傾向。此類障礙的實例包括血友病。三種主要的形式是A型血友病(因子VIII缺乏)、B型血友病(因子IX缺乏或「克裡斯馬斯病(Christmas disease)」)和C型血友病(因子XI缺乏，輕度出血傾向)。其他止血障礙包括，例如，血管性血友病(Von Willebrand disease)、因子XI缺乏(PTA缺乏)、因子XII缺乏、纖維蛋白原、凝血酶原、因子V、因子VII、因子X或因子XIII的缺乏或結構異常、伯-蘇綜合征(Bernard-Soulier syndrome)，其在GPIb有缺陷或缺乏GPIb。GPIb (VWF的受體)可以是有缺陷的且導致初期凝塊形成(初期止血)的缺少和增加的出血傾向)，和Glanzman和Naegeli的血小板機能不全(Glanzmann血小板機能不全)。在肝衰竭(急性和慢性形式)中，通過肝產生的凝血因子不足；這可增加出血風險。

【0079】　如本文所用的「施用(Administer或administering)」是指向個體施用

本文所述的組合物，例如嵌合多肽。該組合物，例如嵌合多肽，可使用本領域中已知的方法向個體施用。特別地，該組合物，例如嵌合多肽，可由靜脈內、皮下、肌肉內、皮內、或經由任何粘膜表面，例如口服、舌下、經頰、經鼻、經直腸、經陰道或經由肺部途徑來施用。在一些實施例中，該施用是自我施用。在一些實施例中，係由父母向兒童施用該嵌合多肽。在一些實施例中，該嵌合多肽由醫療保健從業者諸如醫師、醫生或護士施用至個體。

【0080】 如本文所用的，術語「劑量(dose)」是指向個體單次施用組合物。單劑量可以一次全部施用（例如作為單次推注劑量），或在一段時間內施用，例如經由靜脈內輸注。術語「多劑量」意指多於一個劑量，例如多於一次施用。

【0081】 當提及共同施用多於一種組合物時，一定劑量的組合物A可與一定劑量的組合物B同時施用。或者，一定劑量的組合物A可在一定劑量的組合物B之前或之後施用。在一些實施例中，將組合物A和組合物B組合成單一配製劑。

【0082】 如本文所用的，術語「間隔」或「給藥間隔」是指施用至個體的第一劑量的組合物A和隨後劑量的相同組合物之間所經過的時間。給藥間隔可指第一劑量和第二劑量之間所經過的時間，或者給藥間隔可指多個劑量之間所經過的時間。

【0083】 如本文所用的術語「給藥頻率」是指每個具體給藥間隔所施用的劑量數目。例如，給藥頻率可寫為一週一次、每兩週一次等。因此，7天的給藥間隔還可寫為7天一次或每週一次或一週一次的給藥間隔。

【0084】 如本文所用的術語「預防性治療」是指施用於治療血友病的療法，其中此類治療旨在預防或降低血友病的一種或多種症狀(例如出血事件，例如一次或多次自發出血事件，和/或關節損傷)的嚴重性。參見Jimenez-Yuste等人，Blood Transfus. 12(3):314-19 (2014)。為了預防或降低此類症狀(例如，出血事件和關節疾病的進展)的嚴重性，A型血友病患者可以接受定期輸注凝血因子作為預防性治療方案的一部分。此類預防性治療的基礎是觀察到，相較於具有重度血友病的患者，具有1%或更多量的凝血因子(例如FVIII)的血友病患者很少經歷自發出血事件，且具有較少與血友病相關的合併症。參見，例如，Coppola A.等，Semin.

Thromb. Hemost.38(1): 79-94 (2012)。治療這些血友病患者的醫療保健從業者推測在定期輸注情況下維持因子的量在大約1%，可潛在性地降低血友病症狀的風險，該症狀包括出血事件和關節損傷。參見同上。隨後的研究已經證實了接受凝血因子預防性治療的小兒血友病患者中有這些益處，這使得預防性治療成為具有重度血友病患者的目標。參見同上。

【0085】 「預防性」治療還可指向個體優先施用本文所述的組合物(例如，嵌合多肽)，以便控制、管理、預防或降低A型血友病其一種或多種症狀的發生或嚴重性，例如出血事件。用凝血因子(例如FVIII)的預防性治療是針對具有重度A型血友病的個體的護理標準。參見，例如，Oldenburg，Blood 125:2038-44 (2015)。在一些實施例中，預防性治療是指向有需要的個體施用本文公開的組合物以降低A型血友病的一種或多種症狀的發生。預防性治療可包括施用多個劑量。用於預防性治療的多劑量一般係以特定給藥間隔施用。在某些實施例中，年化出血率降低至少於10、少於9、少於8、少於7、少於6、少於5、少於4、少於3、少於2、或少於1。

【0086】 術語「按需治療」或「發病期治療(episodic treatment)」是指針對A型血友病的症狀(例如，出血事件)作出反應，或在可引起出血的活動之前，「根據需要」施用嵌合分子。在一個方面中，當出血開始(諸如損傷後)時，或當預期出血(諸如手術前)時，可向個體給予按需治療。在另一方面中，可在使出血風險增加的活動(諸如接觸性運動)之前，給予按需治療。在一些實施例中，按需治療係以單一劑量給予。在其他實施例中，按需治療係作為第一劑量給予，隨後給予一個或多個另外的劑量。當嵌合多肽按需施用時，該一個或多個另外的劑量可在施用該第一劑量後至少約12小時、至少約24小時、至少約36小時、至少約48小時、至少約60小時、至少約72小時、至少約84小時、至少約96小時、至少約108小時、或至少約120小時施用。應該注意的是，然而，與按需治療相關聯的給藥間隔，並不與用於預防性治療的給藥間隔相同。

【0087】 在一些實施例中，需要一般止血劑的個體係正在或即將經受手術。本公開的嵌合多肽可在手術之前或之後施用。本公開的嵌合多肽還可在手術期

間或之後施用以控制急性出血事件。當嵌合多肽在手術之前施用時，該施用可以在手術之前至少約1小時、至少約2小時、至少約4小時、至少約8小時、至少約12小時、至少約24小時、至少約36小時、至少約48小時、或至少約72小時。當嵌合多肽在手術後施用時，該施用可以在手術後至少約1小時、至少約2小時、至少約4小時、至少約8小時、至少約12小時、至少約24小時、至少約36小時、至少約48小時、或至少約72小時。該手術可包括，但不限於，肝移植、肝切除術、牙科手術、或幹細胞移植。

【0088】　如本文所用的術語「急性出血」是指一出血事件，不論其根本原因為何。例如，個體可具有創傷、尿毒癥、遺傳性出血障礙(例如，因子VII缺乏)血小板障礙，或因凝血因子抗體的產生而產生的抗性。

【0089】　如本文所用的「治療(treat)、(treatment)、(treating)」是指，例如，疾病或病況的嚴重性的降低；疾病過程的持續時間的降低；與疾病或病況相關聯的一種或多種症狀的改善；為具有疾病或病況的個體提供有益作用，而不必然治癒該疾病或病況，或預防與疾病或病況相關聯的一種或多種症狀。在一些實施例中，術語「治療(treating或treatment)」意指通過施用本公開的嵌合多肽或VWF片段來維持個體的FVIII波谷濃度（trough level）為至少約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、或20 IU/dL。如本文所用的，血友病患者中的「波谷濃度」是在施用下一劑量之前，以因子療法(例如，FVIII療法)所達到的最低濃度量。在其他實施例中，治療意指在給藥間隔之間維持FVIII波谷濃度為至少約1 IU/dL。在其他實施例中，治療意指在給藥間隔之間維持FVIII波谷濃度為至少約3 IU/dL。在其他實施例中，治療意指在給藥間隔之間維持FVIII波谷濃度為至少約5 IU/dL。在其他實施例中，治療意指在給藥間隔期間維持FVIII波谷濃度在約1和約20 IU/dL之間、約2和約20 IU/dL之間、約3和約20 IU/dL之間、約4和約20 IU/dL之間、約5和約20 IU/dL之間、約6和約20 IU/dL之間、約7和約20 IU/dL之間、約8和約20 IU/dL之間、約9和約20 IU/dL之間、或約10和約20 IU/dL之間。

【0090】　疾病或病況的治療還可包括在給藥間隔之間維持個體中FVIII的活性相當於非血友病個體中的FVIII活性的至少約1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、11%、12%、13%、14%、15%、16%、17%、18%、19%、或20%。在其他實施例中，治療意指在給藥間隔之間維持FVIII活性水平為至少約1%。在其他實施例中，治療意指在給藥間隔之間維持FVIII活性水平為至少約2%。在其他實施例中，治療意指在給藥間隔之間維持FVIII活性水平為至少約3%。在其他實施例中，治療意指在給藥間隔之間維持FVIII活性水平維至少約4%。在其他實施例中，治療意指在給藥間隔之間維持FVIII活性水平為至少約5%。在其他實施例中，治療意指在給藥間隔之間維持FVIII活性水平為至少約6%。在其他實施例中，治療意指在給藥間隔之間維持FVIII活性水平為至少約7%。在其他實施例中，治療意指在給藥間隔之間維持FVIII活性水平為至少約8%。在其他實施例中，治療意指在給藥間隔之間維持FVIII活性水平為至少約9%。在其他實施例中，治療意指在給藥間隔之間維持FVIII活性水平為至少約10%。治療需要的最低波谷濃度可通過一種或多種已知方法量測(例如，本文所述的aPTT測定法或生色測定法)且可針對每個人進行調整(增加或降低)。

II．本公開的方法

【0091】　本公開的某些方面涉及向有需要的個體治療其A型血友病的方法，該方法包括以給藥間隔向該個體施用嵌合多肽，該嵌合多肽包含FVIII蛋白和VWF片段。在一些實施例中，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，例如，rFVIIIFc-VWF-XTEN，該嵌合多肽包含(i) FVIII蛋白和(ii) 包含VWF的D'域和VWF D3域的VWF片段。在其他方面中，本公開涉及向有需要的個體治療出血疾病或病況(例如A型血友病)的方法，該方法包括以給藥間隔向該個體施用多劑量的FVIII蛋白和多劑量的VWF片段。

【0092】　在一些實施例中，該多劑量包含至少兩個劑量、至少三個劑量、至少四個劑量、至少五個劑量、至少六個劑量、至少七個劑量、至少八個劑量、至少九個劑量、至少十個劑量、至少十一個劑量、至少十二個劑量、至少十三

個劑量、至少十四個劑量、至少十五個劑量、至少十六個劑量、至少十七個劑量、至少十八個劑量、至少十九個劑量、至少二十個劑量、或更多個。在一些實施例中，該多劑量施用至少約1個月、至少約2個月、至少約3個月、至少約4個月、至少約5個月、至少約6個月、至少約12個月、至少約18個月、至少約2年、至少約3年、至少約4年、至少約5年、至少約10年、至少約15年、至少約20年、或至少約25年。

【0093】 在某些實施例中，本公開的方法涉及治療A型血友病。在一些實施例中，A型血友病的治療包括對有需要的個體人類個體預防其出血事件。在一些實施例中，A型血友病的治療包括向有需要的個體人類個體治療其出血事件。在一些實施例中，A型血友病的治療包括對有需要的個體人類個體控制其出血事件的發生率或頻率。在一些實施例中，A型血友病的治療包括降低有需要的個體人類個體其出血事件的發生率或頻率。

A．劑量

【0094】 在一些實施例中，該嵌合多肽(例如rFVIIIFc-VWF-XTEN)係以單劑量或以多劑量來施用。在一些實施例中，該多劑量中的每一個的量是相同的。在其他實施例中，該多劑量中的一個或多個與另一多劑量中的一個或多個不同。在一些實施例中，該嵌合多肽的多劑量中的至少一個為約5 IU/kg至約200 IU/kg，或約10 IU/kg至約150 IU/kg。在某些實施例中，該多劑量中的至少一個為約15 IU/kg至約100 IU/kg。在一些實施例中，該多劑量中的至少一個為約20 IU/kg至約95 IU/kg、約20 IU/kg至約90 IU/kg、約20 IU/kg至約85 IU/kg、約20 IU/kg至約80 IU/kg、約20 IU/kg至約75 IU/kg、約20 IU/kg至約70 IU/kg、約20 IU/kg至約65 IU/kg、約20 IU/kg至約60 IU/kg、約20 IU/kg至約55 IU/kg、約20 IU/kg至約50 IU/kg、約20 IU/kg至約45 IU/kg、約20 IU/kg至約40 IU/kg、約20 IU/kg至約35 IU/kg、約20 IU/kg至約30 IU/kg、或約20 IU/kg至約25 IU/kg。

【0095】 在一些實施例中，該多劑量中的至少一個為約20 IU/kg至約100 IU/kg、約25 IU/kg至約100 IU/kg、約30 IU/kg至約100 IU/kg、約35 IU/kg至約100 IU/kg、約40 IU/kg至約100 IU/kg、約45 IU/kg至約100 IU/kg、約50 IU/kg至約100 IU/kg、

約55 IU/kg至約100 IU/kg、約60 IU/kg至約100 IU/kg、約65 IU/kg至約100 IU/kg、約70 IU/kg至約100 IU/kg、約75 IU/kg至約100 IU/kg、約80 IU/kg至約100 IU/kg、約85 IU/kg至約100 IU/kg、或約90 IU/kg至約100 IU/kg。在一些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg。

【0096】　在一些實施例中，該嵌合多肽的多劑量中的至少一個為約50 IU/kg至約150 IU/kg、約50 IU/kg至約140 IU/kg、約50 IU/kg至約130 IU/kg、約50 IU/kg至約120 IU/kg、約50 IU/kg至約110 IU/kg、或約50 IU/kg至約100 IU/kg。在一些實施例中，該嵌合多肽的多劑量中的至少一個為約50 IU/kg至約95 IU/kg、約50 IU/kg至約90 IU/kg、約50 IU/kg至約85 IU/kg、約50 IU/kg至約80 IU/kg、約50 IU/kg至約75 IU/kg、約50 IU/kg至約70 IU/kg、約50 IU/kg至約65 IU/kg、約50 IU/kg至約60 IU/kg、約50 IU/kg至約55 IU/kg。在某些實施例中，該嵌合多肽的多劑量中的至少一個為約50 IU/kg至約80 IU/kg。在某些實施例中，該嵌合多肽的多劑量中的至少一個為約50 IU/kg至約65 IU/kg。

【0097】　在一些實施例中，該嵌合多肽的多劑量中的至少一個為約60 IU/kg至約150 IU/kg、約60 IU/kg至約140 IU/kg、約60 IU/kg至約130 IU/kg、約60 IU/kg至約120 IU/kg、約60 IU/kg至約110 IU/kg、或約60 IU/kg至約100 IU/kg。在一些實施例中，該嵌合多肽的多劑量中的至少一個為約60 IU/kg至約95 IU/kg、約60 IU/kg至約90 IU/kg、約60 IU/kg至約85 IU/kg、約60 IU/kg至約80 IU/kg、約60 IU/kg至約75 IU/kg、約60 IU/kg至約70 IU/kg、或約60 IU/kg至約65 IU/kg。

【0098】　在一些實施例中，該嵌合多肽的多劑量中的至少一個為約65 IU/kg至約150 IU/kg、約65 IU/kg至約140 IU/kg、約65 IU/kg至約130 IU/kg、約65 IU/kg至約120 IU/kg、約65 IU/kg至約110 IU/kg、或約65 IU/kg至約100 IU/kg。在一些實施例中，該嵌合多肽的多劑量中的至少一個為約65 IU/kg至約95 IU/kg、約65 IU/kg至約90 IU/kg、約65 IU/kg至約85 IU/kg、約65 IU/kg至約80 IU/kg、約65 IU/kg至約75 IU/kg、或約65 IU/kg至約70 IU/kg。在某些實施例中，該嵌合多肽的多劑量中的至少一個為約65 IU/kg至約80 IU/kg。

【0099】　在一些實施例中，該多劑量中的至少一個為約5 IU/kg、約10 IU/kg、

約15 IU/kg、約20 IU/kg、約25 IU/kg、約30 IU/kg、約35 IU/kg、約40 IU/kg、約45 IU/kg、約50 IU/kg、約55 IU/kg、約60 IU/kg、約65 IU/kg、約70 IU/kg、約75 IU/kg、約80 IU/kg、約85 IU/kg、約90 IU/kg、約95 IU/kg、約100 IU/kg、約125 IU/kg、約150 IU/kg、約175 IU/kg、或約200 IU/kg。在某些實施例中，該多劑量中的至少一個為約25 IU/kg。在某些實施例中，該多劑量中的至少一個為約30 IU/kg。在某些實施例中，該多劑量中的至少一個為約35 IU/kg。在某些實施例中，該多劑量中的至少一個為約40 IU/kg。在某些實施例中，該多劑量中的至少一個為約45 IU/kg。在某些實施例中，該多劑量中的至少一個為約50 IU/kg。在某些實施例中，該多劑量中的至少一個為約55 IU/kg。在某些實施例中，該多劑量中的至少一個為約60 IU/kg。在某些實施例中，該多劑量中的至少一個為約65 IU/kg。在某些實施例中，該多劑量中的至少一個為約70 IU/kg。在某些實施例中，該多劑量中的至少一個為約75 IU/kg。在某些實施例中，該多劑量中的至少一個為約80 IU/kg。在某些實施例中，該多劑量中的至少一個為約85 IU/kg。在某些實施例中，該多劑量中的至少一個為約90 IU/kg。在某些實施例中，該多劑量中的至少一個為約95 IU/kg。在某些實施例中，該多劑量中的至少一個為約100 IU/kg。

【0100】　在一些實施例中，該多劑量中的每一劑量為約25 IU/kg。在一些實施例中，該多劑量中的每一劑量為約30 IU/kg。在一些實施例中，該多劑量中的每一劑量為約35 IU/kg。在一些實施例中，該多劑量中的每一劑量為約40 IU/kg。在一些實施例中，該多劑量中的每一劑量為約45 IU/kg。在一些實施例中，該多劑量中的每一劑量為約50 IU/kg。在一些實施例中，該多劑量中的每一劑量為約55 IU/kg。在一些實施例中，該多劑量中的每一劑量為約60 IU/kg。在一些實施例中，該多劑量中的每一劑量為約65 IU/kg。在一些實施例中，該多劑量中的每一劑量為約70 IU/kg。在一些實施例中，該多劑量中的每一劑量為約75 IU/kg。在一些實施例中，該多劑量中的每一劑量為約80 IU/kg。在一些實施例中，該多劑量中的每一劑量為約85 IU/kg。在一些實施例中，該多劑量中的每一劑量為約90 IU/kg。在一些實施例中，該多劑量中的每一劑量為約95 IU/kg。在一些實施例中，該多劑量中的每一劑量為約100 IU/kg。

【0101】　在一些實施例中，該嵌合多肽(例如rFVIIIFc-VWF-XTEN)係預防性地施用。當預防性地施用時，該多劑量中的至少一個可以是約15 IU/kg至約100 IU/kg。在某些實施例中，預防性施用的該多劑量中的至少一個為約25 IU/kg、約30 IU/kg、約35 IU/kg、約40 IU/kg、約45 IU/kg、約50 IU/kg、約55 IU/kg、約60 IU/kg、約65 IU/kg、約70 IU/kg、約75 IU/kg、約80 IU/kg、約85 IU/kg、約90 IU/kg、約95 IU/kg、或約100 IU/kg。在一些實施例中，預防性施用的該多劑量中的至少一個為約25 IU/kg。在其他實施例中，預防性施用的該多劑量中的至少一個為約50 IU/kg。在其他實施例中，預防性施用的該多劑量中的至少一個為約65 IU/kg。在其他實施例中，預防性施用的該多劑量中的至少一個為約80 IU/kg。

【0102】　在一些實施例中，該嵌合多肽(例如rFVIIIFc-VWF-XTEN)係按需施用。當按需施用時，該嵌合多肽可以以單劑量或以多劑量施用。在一些實施例中，該嵌合多肽以約15 IU/kg至約100 IU/kg的一個或多個劑量施用。在某些實施例中，該嵌合多肽以約25 IU/kg、約30 IU/kg、約35 IU/kg、約40 IU/kg、約45 IU/kg、約50 IU/kg、約55 IU/kg、約60 IU/kg、約65 IU/kg、約70 IU/kg、約75 IU/kg、約80 IU/kg、約85 IU/kg、約90 IU/kg、約95 IU/kg、或約100 IU/kg的一個或多個劑量按需施用。在一些實施例中，該嵌合多肽以約25 IU/kg的一個或多個劑量按需施用。在其他實施例中，該嵌合多肽以約50 IU/kg的一個或多個劑量按需施用。在其他實施例中，該嵌合多肽以約65 IU/kg的一個或多個劑量按需施用。在其他實施例中，該嵌合多肽以約80 IU/kg的一個或多個劑量按需施用。

【0103】　在一些實施例中，根據本方法的該嵌合多肽的施用係在該施用的約7天、約10天、約11天、約12天、約13天、約14天、約15天、約20天、約24天、約25天、約28天、約30天、或約35天後不誘發FVIII抑制因子。在一些實施例中，該嵌合多肽的施用係在施用的約28天後不誘導FVIII抑制因子。

B．給藥間隔

【0104】　在某些實施例中，尤其是預防性治療，該嵌合多肽(例如rFVIIIFc-VWF-XTEN)係以給藥間隔以多劑量施用。在一些實施例中，該給藥間隔為至少約3天、至少約4天、至少約5天、至少約6天、至少約7天、至少約8天、

至少約9天、至少約10天、至少約11天、至少約12天、至少約13天、至少約14天、至少約15天、至少約16天、至少約17天、至少約18天、至少約19天、至少約20天、至少約21天、至少約22天、至少約23天、至少約24天、至少約25天、至少約26天、至少約27天、至少約28天、至少約29天、至少約30天、或至少約31天。

【0105】 在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約5天。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約6天。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約7天。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約8天。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約9天。在某些實施例中，該給藥間隔為至少約10天。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約11天。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約12天。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約13天。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約14天。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約21天。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約27天。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約30天。

【0106】 在一些實施例中，該給藥頻率(例如用於預防性治療A型血友病)為每週至少兩次、每週至少一次、每2周至少一次、每3周至少一次、每4周至少一次、每5周至少一次、或每6周至少一次。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為每週至少一次。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少2周。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少3周。在某些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少4周。

【0107】 在一些實施例中，該給藥頻率(例如用於預防性治療A型血友病)為每三個月約2次、每月約1次、每月約2次、每月約3次、每個月約4次、每月約5次、每月約6次、每月約7次、或每月約8次。在某些實施例中，該給藥頻率為每月約

1次。在某些實施例中，該給藥頻率為每月約2次。在某些實施例中，該給藥頻率為每月約3次。在某些實施例中，該給藥頻率為每月約4次。在某些實施例中，該給藥頻率為每月約5次。在某些實施例中，該給藥頻率為每月約6次。

【0108】　在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約3至5天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約4至6天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約4至7天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約4至8天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約4至9天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約4至10天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約5至7天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約5至8天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約5至9天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約5至10天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約6至8天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約6至9天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約6至10天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約7至9天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約7至10天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約7至11天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約7至12天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約7至13天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約7至14天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約8至14天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約9至14天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約10至14天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約11至14天。在一些實

施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約10至21天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約12至14天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約12至15天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約13至15天。在一些實施例中，該給藥間隔(例如用於預防性治療A型血友病)為至少約14至21天。

【0109】 在一些實施例中，該多劑量中的至少一個係根據表1中所述的劑量和給藥頻率來施用。

表1A：給藥量和對應的給藥頻率，例如，用於預防性治療血友病。

	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天	5 IU/kg 每 5天	10 IU/kg 每 5天	15 IU/kg 每 5天	20 IU/kg 每 5天	25 IU/kg 每 5天	30 IU/kg 每 5天	35 IU/kg 每 5天	40 IU/kg 每 5天	45 IU/kg 每 5天	50 IU/kg 每 5天
6天	5 IU/kg 每 6天	10 IU/kg 每 6天	15 IU/kg 每 6天	20 IU/kg 每 6天	25 IU/kg 每 6天	30 IU/kg 每 6天	35 IU/kg 每 6天	40 IU/kg 每 6天	45 IU/kg 每 6天	50 IU/kg 每 6天
7天	5 IU/kg 每 7天	10 IU/kg 每 7天	15 IU/kg 每 7天	20 IU/kg 每 7天	25 IU/kg 每 7天	30 IU/kg 每 7天	35 IU/kg 每 7天	40 IU/kg 每 7天	45 IU/kg 每 7天	50 IU/kg 每 7天
8天	5 IU/kg 每 8天	10 IU/kg 每 8天	15 IU/kg 每 8天	20 IU/kg 每 8天	25 IU/kg 每 8天	30 IU/kg 每 8天	35 IU/kg 每 8天	40 IU/kg 每 8天	45 IU/kg 每 8天	50 IU/kg 每 8天
9天	5 IU/kg 每 9天	10 IU/kg 每 9天	15 IU/kg 每 9天	20 IU/kg 每 9天	25 IU/kg 每 9天	30 IU/kg 每 9天	35 IU/kg 每 9天	40 IU/kg 每 9天	45 IU/kg 每 9天	50 IU/kg 每 9天
10天	5 IU/kg 每 10天	10 IU/kg 每 10天	15 IU/kg 每 10天	20 IU/kg 每 10天	25 IU/kg 每 10天	30 IU/kg 每 10天	35 IU/kg 每 10天	40 IU/kg 每 10天	45 IU/kg 每 10天	50 IU/kg 每 10天
11天	5 IU/kg 每 11天	10 IU/kg 每 11天	15 IU/kg 每 11天	20 IU/kg 每 11天	25 IU/kg 每 11天	30 IU/kg 每 11天	35 IU/kg 每 11天	40 IU/kg 每 11天	45 IU/kg 每 11天	50 IU/kg 每 11天
12天	5 IU/kg 每 12天	10 IU/kg 每 12天	15 IU/kg 每 12天	20 IU/kg 每 12天	25 IU/kg 每 12天	30 IU/kg 每 12天	35 IU/kg 每 12天	40 IU/kg 每 12天	45 IU/kg 每 12天	50 IU/kg 每 12天

13 天	5 IU/kg 每 13 天	10 IU/kg 每 13 天	15 IU/kg 每 13 天	20 IU/kg 每 13 天	25 IU/kg 每 13 天	30 IU/kg 每 13 天	35 IU/kg 每 13 天	40 IU/kg 每 13 天	45 IU/kg 每 13 天	50 IU/kg 每 13 天
14 天	5 IU/kg 每 14 天	10 IU/kg 每 14 天	15 IU/kg 每 14 天	20 IU/kg 每 14 天	25 IU/kg 每 14 天	30 IU/kg 每 14 天	35 IU/kg 每 14 天	40 IU/kg 每 14 天	45 IU/kg 每 14 天	50 IU/kg 每 14 天
15 天	5 IU/kg 每 15 天	10 IU/kg 每 15 天	15 IU/kg 每 15 天	20 IU/kg 每 15 天	25 IU/kg 每 15 天	30 IU/kg 每 15 天	35 IU/kg 每 15 天	40 IU/kg 每 15 天	45 IU/kg 每 15 天	50 IU/kg 每 15 天
16 天	5 IU/kg 每 16 天	10 IU/kg 每 16 天	15 IU/kg 每 16 天	20 IU/kg 每 16 天	25 IU/kg 每 16 天	30 IU/kg 每 16 天	35 IU/kg 每 16 天	40 IU/kg 每 16 天	45 IU/kg 每 16 天	50 IU/kg 每 16 天
17 天	5 IU/kg 每 17 天	10 IU/kg 每 17 天	15 IU/kg 每 17 天	20 IU/kg 每 17 天	25 IU/kg 每 17 天	30 IU/kg 每 17 天	35 IU/kg 每 17 天	40 IU/kg 每 17 天	45 IU/kg 每 17 天	50 IU/kg 每 17 天
18 天	5 IU/kg 每 18 天	10 IU/kg 每 18 天	15 IU/kg 每 18 天	20 IU/kg 每 18 天	25 IU/kg 每 18 天	30 IU/kg 每 18 天	35 IU/kg 每 18 天	40 IU/kg 每 18 天	45 IU/kg 每 18 天	50 IU/kg 每 18 天
19 天	5 IU/kg 每 19 天	10 IU/kg 每 19 天	15 IU/kg 每 19 天	20 IU/kg 每 19 天	25 IU/kg 每 19 天	30 IU/kg 每 19 天	35 IU/kg 每 19 天	40 IU/kg 每 19 天	45 IU/kg 每 19 天	50 IU/kg 每 19 天
20 天	5 IU/kg 每 20 天	10 IU/kg 每 20 天	15 IU/kg 每 20 天	20 IU/kg 每 20 天	25 IU/kg 每 20 天	30 IU/kg 每 20 天	35 IU/kg 每 20 天	40 IU/kg 每 20 天	45 IU/kg 每 20 天	50 IU/kg 每 20 天
21 天	5 IU/kg 每 21 天	10 IU/kg 每 21 天	15 IU/kg 每 21 天	20 IU/kg 每 21 天	25 IU/kg 每 21 天	30 IU/kg 每 21 天	35 IU/kg 每 21 天	40 IU/kg 每 21 天	45 IU/kg 每 21 天	50 IU/kg 每 21 天
	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 天	55 IU/kg 每 5 天	60 IU/kg 每 5 天	65 IU/kg 每 5 天	70 IU/kg 每 5 天	75 IU/kg 每 5 天	80 IU/kg 每 5 天	85 IU/kg 每 5 天	90 IU/kg 每 5 天	95 IU/kg 每 5 天	100 IU/kg 每 5 天
6 天	55 IU/kg 每 6 天	60 IU/kg 每 6 天	65 IU/kg 每 6 天	70 IU/kg 每 6 天	75 IU/kg 每 6 天	80 IU/kg 每 6 天	85 IU/kg 每 6 天	90 IU/kg 每 6 天	95 IU/kg 每 6 天	100 IU/kg 每 6 天
7 天	55 IU/kg 每 7 天	60 IU/kg 每 7 天	65 IU/kg 每 7 天	70 IU/kg 每 7 天	75 IU/kg 每 7 天	80 IU/kg 每 7 天	85 IU/kg 每 7 天	90 IU/kg 每 7 天	95 IU/kg 每 7 天	100 IU/kg 每 7 天
8 天	55 IU/kg 每	60 IU/kg 每	65 IU/kg 每	70 IU/kg 每	75 IU/kg 每	80 IU/kg 每	85 IU/kg 每	90 IU/kg 每	95 IU/kg 每	100 IU/kg 每

	8天	8天	8天	8天	8天	8天	8天	8天	8天	8天
9天	55 IU/kg 每 9天	60 IU/kg 每 9天	65 IU/kg 每 9天	70 IU/kg 每 9天	75 IU/kg 每 9天	80 IU/kg 每 9天	85 IU/kg 每 9天	90 IU/kg 每 9天	95 IU/kg 每 9天	100 IU/kg 每 9天
10天	55 IU/kg 每 10天	60 IU/kg 每 10天	65 IU/kg 每 10天	70 IU/kg 每 10天	75 IU/kg 每 10天	80 IU/kg 每 10天	85 IU/kg 每 10天	90 IU/kg 每 10天	95 IU/kg 每 10天	100 IU/kg 每 10天
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16天	55 IU/kg 每 16天	60 IU/kg 每 16天	65 IU/kg 每 16天	70 IU/kg 每 16天	75 IU/kg 每 16天	80 IU/kg 每 16天	85 IU/kg 每 16天	90 IU/kg 每 16天	95 IU/kg 每 16天	100 IU/kg 每 16天
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18天	55 IU/kg 每 18天	60 IU/kg 每 18天	65 IU/kg 每 18天	70 IU/kg 每 18天	75 IU/kg 每 18天	80 IU/kg 每 18天	85 IU/kg 每 18天	90 IU/kg 每 18天	95 IU/kg 每 18天	100 IU/kg 每 18天
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	21天	21天	21天	21天	21天	21天	21天	21天	21天	21天

表1B：給藥量和相應的給藥間隔，例如，用於預防性治療血友病。

	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天	55 IU/kg 每 5天	60 IU/kg 每 5天	65 IU/kg 每 5天	70 IU/kg 每 5天	75 IU/kg 每 5天	80 IU/kg 每 5天	85 IU/kg 每 5天	90 IU/kg 每 5天	95 IU/kg 每 5天	100 IU/kg 每 5天
6天	55 IU/kg 每 6天	60 IU/kg 每 6天	65 IU/kg 每 6天	70 IU/kg 每 6天	75 IU/kg 每 6天	80 IU/kg 每 6天	85 IU/kg 每 6天	90 IU/kg 每 6天	95 IU/kg 每 6天	100 IU/kg 每 6天
7天	55 IU/kg 每 7天	60 IU/kg 每 7天	65 IU/kg 每 7天	70 IU/kg 每 7天	75 IU/kg 每 7天	80 IU/kg 每 7天	85 IU/kg 每 7天	90 IU/kg 每 7天	95 IU/kg 每 7天	100 IU/kg 每 7天
8天	55 IU/kg 每 8天	60 IU/kg 每 8天	65 IU/kg 每 8天	70 IU/kg 每 8天	75 IU/kg 每 8天	80 IU/kg 每 8天	85 IU/kg 每 8天	90 IU/kg 每 8天	95 IU/kg 每 8天	100 IU/kg 每 8天
9天	55 IU/kg 每 9天	60 IU/kg 每 9天	65 IU/kg 每 9天	70 IU/kg 每 9天	75 IU/kg 每 9天	80 IU/kg 每 9天	85 IU/kg 每 9天	90 IU/kg 每 9天	95 IU/kg 每 9天	100 IU/kg 每 9天
10天	55 IU/kg 每 10天	60 IU/kg 每 10天	65 IU/kg 每 10天	70 IU/kg 每 10天	75 IU/kg 每 10天	80 IU/kg 每 10天	85 IU/kg 每 10天	90 IU/kg 每 10天	95 IU/kg 每 10天	100 IU/kg 每 10天
11天	55 IU/kg 每 11天	60 IU/kg 每 11天	65 IU/kg 每 11天	70 IU/kg 每 11天	75 IU/kg 每 11天	80 IU/kg 每 11天	85 IU/kg 每 11天	90 IU/kg 每 11天	95 IU/kg 每 11天	100 IU/kg 每 11天
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16天	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

	每 16天	每 16天	每 16天	每 16天	每 16天	每 16天	每 16天	每 16天	每 16天	每 16天
17天	55 IU/kg 每 17天	60 IU/kg 每 17天	65 IU/kg 每 17天	70 IU/kg 每 17天	75 IU/kg 每 17天	80 IU/kg 每 17天	85 IU/kg 每 17天	90 IU/kg 每 17天	95 IU/kg 每 17天	100 IU/kg 每 17天
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	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天	55 IU/kg 每 5天	60 IU/kg 每 5天	65 IU/kg 每 5天	70 IU/kg 每 5天	75 IU/kg 每 5天	80 IU/kg 每 5天	85 IU/kg 每 5天	90 IU/kg 每 5天	95 IU/kg 每 5天	100 IU/kg 每 5天
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【0110】　在一些實施例中，諸如用於預防性治療A型血友病，該多劑量中的至少一個係以至少約5至14天的給藥間隔以約25 IU/kg至約65 IU/kg的劑量施用。在一些實施例中，該多劑量中的至少一個係以至少約6至14天的給藥間隔以約25 IU/kg至約65 IU/kg的劑量施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約6至10天的給藥間隔施用。在一些實施例中，

該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約6至8天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約6至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約6至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約6至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約6至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約7至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約7至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約7至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約7至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約7至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約7至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約8至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約9至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約10至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約10至21天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約11至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約12至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約12至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg的劑量以至少約13至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg至約65 IU/kg

的劑量以至少約14至21天的給藥間隔施用。

【0111】 在一些實施例中，諸如用於預防性治療A型血友病，該多劑量中的至少一個係以約25 IU/kg的劑量以至少約5至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個係以約25 IU/kg的劑量以至少約6至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約6至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約6至8天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約6至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約6至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約6至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約6至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約7至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約7至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約7至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約7至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約7至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約7至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約8至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約9至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約10至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約10至21天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約11至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約12至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至

少約12至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約13至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約25 IU/kg的劑量以至少約14至21天的給藥間隔施用。

【0112】　在一些實施例中，諸如用於預防性治療A型血友病，該多劑量中的至少一個係以約50 IU/kg的劑量以至少約5至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個係以約50 IU/kg的劑量以至少約6至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約6至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約6至8天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約6至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約6至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約6至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約6至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約7至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約7至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約7至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約7至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約7至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約7至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約8至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約9至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約10至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約10至21天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約11至14天的給藥間隔施用。在一

些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約12至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約12至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約13至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg的劑量以至少約14至21天的給藥間隔施用。

【0113】 在一些實施例中，諸如用於預防性治療的A型血友病，該多劑量中的至少一個係以約65 IU/kg的劑量以至少約5至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個係以約65 IU/kg的劑量以至少約6至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約6至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約6至8天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約6至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約6至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約6至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約6至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約7至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約7至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約7至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約7至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約7至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約7至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約8至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約9至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約10至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個

以約65 IU/kg的劑量以至少約10至21天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約11至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約12至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約12至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約13至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg的劑量以至少約14至21天的給藥間隔施用。

【0114】　在一些實施例中，諸如用於預防性治療A型血友病，該多劑量中的至少一個係以約80 IU/kg的劑量以至少約5至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個係以約80 IU/kg的劑量以至少約6至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約6至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約6至8天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約6至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約6至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約6至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約6至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約7至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約7至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約7至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約7至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約7至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約7至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約8至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約9至14天

的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約10至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約10至21天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約11至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約12至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約12至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約13至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約80 IU/kg的劑量以至少約14至21天的給藥間隔施用。

【0115】　在一些實施例中，諸如用於預防性治療A型血友病，該多劑量中的至少一個係以約50 IU/kg至約80 IU/kg的劑量以至少約5至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個係以約50 IU/kg至約80 IU/kg的劑量以至少約6至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約6至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約6至8天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約6至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約6至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約6至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約6至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約7至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約7至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約7至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約7至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80

IU/kg的劑量以至少約7至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約7至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約8至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約9至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約10至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約10至21天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約11至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約12至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約12至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約13至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約80 IU/kg的劑量以至少約14至21天的給藥間隔施用。

【0116】　在一些實施例中，諸如用於預防性治療A型血友病，該多劑量中的至少一個係以約50 IU/kg至約65 IU/kg的劑量以至少約5至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個係以約50 IU/kg至約65 IU/kg的劑量以至少約6至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約6至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約6至8天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約6至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約6至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約6至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約6至13天的給藥間隔施用。在一些實施例中，該多劑

量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約7至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約7至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約7至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約7至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約7至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約7至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約8至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約9至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約10至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約10至21天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約11至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約12至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約12至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約13至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約50 IU/kg至約65 IU/kg的劑量以至少約14至21天的給藥間隔施用。

【0117】　在一些實施例中，諸如用於預防性治療A型血友病，該多劑量中的至少一個係以約65 IU/kg至約80 IU/kg的劑量以至少約5至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個係以約65 IU/kg至約80 IU/kg的劑量以至少約6至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約6至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約6至8天的給藥

間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約6至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約6至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約6至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約6至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約7至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約7至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約7至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約7至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約7至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約7至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約8至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約9至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約10至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約10至21天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約11至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約12至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約12至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約13至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約14至21天的給藥間隔施用。

【0118】 在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個係以約65 IU/kg至約80 IU/kg的劑量以至少約2至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個係以約65 IU/kg至約80 IU/kg的劑量以至少約2至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約2至8天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約2至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約2至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約2至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約2至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約4至9天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約4至10天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約4至11天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約4至12天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約4至13天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約4至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約5至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約6至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約7至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約8至14天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約10至15天的給藥間隔

施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約10至21天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約13至15天的給藥間隔施用。在一些實施例中，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約14至21天的給藥間隔施用。

【0119】 在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個係以約65 IU/kg至約80 IU/kg的劑量以至少約5天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個係以約65 IU/kg至約80 IU/kg的劑量以至少約7天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約6天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約5天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約4天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約3天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約2天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約8天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約9天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約10天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約11天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑

量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約12天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約13天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約14天的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個以約65 IU/kg至約80 IU/kg的劑量以至少約21天的給藥間隔施用。

【0120】 在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個係以約65 IU/kg至約80 IU/kg的劑量以至少約1周的給藥間隔施用。在一些實施例中，諸如用於預防性治療小兒個體的A型血友病，該多劑量中的至少一個係以約65 IU/kg至約80 IU/kg的劑量以約每1周至少兩次的給藥頻率施用。

【0121】 在某些實施例中，諸如用於預防性治療A型血友病，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，該嵌合多肽包含(i) FVIII蛋白和(ii) 包含VWF的D'域和VWF的D3域的VWF片段，例如rFVIIIFc-VWF-XTEN，其中該多劑量中的至少一個為約15 IU/kg至約100 IU/kg，且該給藥間隔為至少約5天。在某些實施例中，諸如用於預防性治療A型血友病，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，該嵌合多肽包含(i) FVIII蛋白和(ii) 包含VWF的D'域和VWF的D3域的VWF片段，其中該多劑量中的至少一個為約15 IU/kg至約100 IU/kg，且該給藥間隔為至少約7天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約8天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約9天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約10天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約11天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約12天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約13天。在某些實

施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約14天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約15天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約16天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約17天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約18天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約19天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約20天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg至約65 IU/kg，且該給藥間隔為至少約21天。

【0122】　在某些實施例中，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，該嵌合多肽包含(i) FVIII蛋白和(ii) 包含VWF的D'域和VWF的D3域的VWF片段，例如rFVIIIFc-VWF-XTEN，其中該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約5天。在某些實施例中，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，該嵌合多肽包含(i) FVIII蛋白和(ii) 包含VWF的D'域和VWF的D3域的VWF片段，其中該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約6天。在一些實施例中，該方法是用於預防性治療A型血友病的。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約7天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約8天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約9天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約10天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約11天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約12天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約13天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約14天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約15天。在某些實施例

中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約16天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約17天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約18天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約19天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約20天。在某些實施例中，該多劑量中的至少一個為約25 IU/kg，且該給藥間隔為至少約21天。

【0123】　在某些實施例中，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，該嵌合多肽包含(i) FVIII蛋白和(ii) 包含VWF的D'域和VWF的D3域的VWF片段，例如rFVIIIFc-VWF-XTEN，其中該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約5天。在某些實施例中，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，該嵌合多肽包含(i) FVIII蛋白和(ii) 包含VWF的D'域和VWF的D3域的VWF片段，其中該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約6天。在一些實施例中，該方法是用於預防性治療A型血友病的。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約7天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約8天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約9天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約10天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約11天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約12天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約13天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約14天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約15天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約16天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約17天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約

18天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約19天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約20天。在某些實施例中，該多劑量中的至少一個為約50 IU/kg，且該給藥間隔為至少約21天。

【0124】 在某些實施例中，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，該嵌合多肽包含(i) FVIII蛋白和(ii) 包含VWF的D'域和VWF的D3域的VWF片段，例如rFVIIIFc-VWF-XTEN，其中該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約5天。在某些實施例中，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，該嵌合多肽包含(i) FVIII蛋白和(ii) 包含VWF的D'域和VWF的D3域的VWF片段，其中該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約6天。在一些實施例中，該方法是用於預防性治療A型血友病的。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約7天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約8天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約9天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約10天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約11天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約12天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約13天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約14天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約15天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約16天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約17天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約18天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約19天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且該給藥間隔為至少約20天。在某些實施例中，該多劑量中的至少一個為約65 IU/kg，且

該給藥間隔為至少約21天。

【0125】　在某些實施例中，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，該嵌合多肽包含(i) FVIII蛋白和(ii) 包含VWF的D'域和VWF的D3域的VWF片段，例如rFVIIIFc-VWF-XTEN，其中該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約5天。在某些實施例中，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，該嵌合多肽包含(i) FVIII蛋白和(ii) 包含VWF的D'域和VWF的D3域的VWF片段，其中該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約6天。在一些實施例中，該方法是用於預防性治療A型血友病的。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約7天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約8天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約9天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約10天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約11天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約12天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約13天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約14天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約15天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約16天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約17天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約18天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約19天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約20天。在某些實施例中，該多劑量中的至少一個為約80 IU/kg，且該給藥間隔為至少約21天。

【0126】　在一些實施例中，該嵌合多肽係施用於預防性治療A型血友病。A型血友病的預防性治療包括在連續或幾乎連續的基礎上減輕或降低A型血友病的

症狀的嚴重性。在一些實施例中，該預防性治療在A型血友病的症狀出現前(例如，出血事件之前)施用。在其他實施例中，該預防性治療在定期的基礎(例如以本文所述的給藥間隔)上施用，以預防該症狀的發病，或減輕該症狀發病之前的症狀的嚴重性。本文公開的任何給藥間隔可用在A型血友病的預防性治療中。

【0127】　在其他實施例中，該嵌合多肽在可引起A型血友病的一種或多種症狀的活動前施用，例如作為按需治療。舉例來說，本公開的嵌合多肽可在該個體經受手術或參與以其他方式增加物理創傷和/或出血事件風險之活動前，向罹患A型血友病的個體施用。當以按需來施用時，該嵌合多肽可作為單劑量或作為多劑量施用。在一些實施例中，該按需治療包括以至少約12小時、至少約24小時、至少約36小時、至少約48小時、至少約60小時、至少約72小時、至少約84小時、至少約96小時、至少約108小時或至少約120小時的給藥間隔來施用多劑量的該嵌合多肽。在某些實施例中，該按需治療包括施用至少2個劑量，至少3個劑量，至少4個劑量或至少5個劑量的該嵌合多肽。

【0128】　在一些實施例中，該個體先前已經經一種或多種FVIII取代療法的治療。在某些實施例中，該個體未能對先前的FVIII取代療法產生反應。在某些實施例中，該FVIII取代療法是ELOCTATE®或百因止(ADVATE®)。在一些實施例中，該個體是成人。在一些實施例中，該個體是成人男性。在其他實施例中，該個體是成人女性。在其他實施例中，該個體是兒童，例如，小於或等於約12歲、小於或等於或等於約11歲、小於或等於約10歲、小於或等於約9歲、小於或等於約8歲、小於或等於約7歲、小於或等於約6歲、小於或等於約5歲、小於或等於約4歲、小於或等於約3歲、小於或等於約2歲、或小於或等於約1歲)。在一些實施例中，該個體是女性。在一些實施例中，該個體是男性。在一些實施例中，該個體是小於或等於約12歲的女性。在一些實施例中，該個體是小於或等於約11歲的女性。在一些實施例中，該個體是小於或等於約10歲的女性。

【0129】　本文所述的嵌合多肽可通過本領域中已知的任何方式來施用。在一些實施例中，該嵌合多肽係通過選自下列群組的途徑來施用：靜脈內注射、靜脈內輸注、皮下施用、肌肉內施用、口服施用、皮下施用、鼻腔施用和肺部施

用。在一些實施例中，該嵌合多肽係以靜脈內施用。在其他實施例中，該嵌合多肽係以皮下施用。

【0130】　在一些實施例中，該嵌合多肽(例如，rFVIIIFc-VWF-XTEN)在施用後係導致FVIII血漿活性水平為至少約1%、至少約2%、至少約3%、至少約4%、至少約5%、至少約6%、至少約7%、至少約8%、至少約9%、或至少約10%。在某些實施例中，該FVIII血漿活性水平為至少約3%。在一些實施例中，該FVIII血漿活性水平為至少約4%。在一些實施例中，該FVIII血漿活性水平為至少約5%。在一些實施例中，該FVIII血漿活性水平為至少約4%。在一些實施例中，該FVIII血漿活性水平為至少約5%。在一些實施例中，該FVIII血漿活性水平為至少約5.6%。在一些實施例中，該FVIII血漿活性水平為至少約7%。在一些實施例中，該FVIII血漿活性水平為至少約10%。在一些實施例中，該FVIII血漿活性水平為至少約12%。在一些實施例中，該FVIII血漿活性水平為至少約12.95%。如本文所用的，血漿活性水平表示為百分比(%)。或者，血漿活性可以以IU/dL單位表示，其中1%等於1 IU/dL。

【0131】　在一些實施例中，在(例如以25 IU/kg的劑量)施用該嵌合多肽後至少約5天，該FVIII血漿活性水平為至少約10%。在一些實施例中，在(例如以25 IU/kg的劑量)施用該嵌合多肽後至少約5天，該FVIII血漿活性水平為至少約12%。在一些實施例中，在(例如以25 IU/kg的劑量)施用該嵌合多肽後至少約5天，該FVIII血漿活性水平為至少約12.95%。在一些實施例中，在(例如以25 IU/kg的劑量)施用該嵌合多肽後至少約7天，該FVIII血漿活性水平為至少約5%。在一些實施例中，在(例如以25 IU/kg的劑量)施用該嵌合多肽後至少約7天，該FVIII血漿活性水平為至少約5.6%。在一些實施例中，在(例如以25 IU/kg的劑量)施用該嵌合多肽後至少約8天，該FVIII血漿活性水平為至少約3%。在一些實施例中，在(例如以25 IU/kg的劑量)施用該嵌合多肽後至少約10天，該FVIII血漿活性水平為至少約1%。

【0132】　本公開還包括治療A型血友病的方法，該方法包括向個體施用組合物，該組合物包含(i) FVIII蛋白和(ii) VWF片段。在一些實施例中，該FVIII蛋白存在

於第一配製劑中，且該VWF片段存在於第二配製劑中。在其他實施例中，該FVIII蛋白和該VWF片段存在於同一配製劑中。在特定的實施例中，該FVIII蛋白和該VWF片段是單一配製劑中分開的組分。在某些實施例中，該FVIII蛋白(例如，單鏈FVIII、FVIII-Fc、聚乙二醇化的FVIII、全長成熟FVIII、或B域缺失的FVIII)係以本文公開的劑量，例如，25 IU/kg、30 IU/kg、35 IU/kg、40 IU/kg、45 IU/kg、50 IU/kg、55 IU/kg、60 IU/kg、或65 IU/kg，且以至少6天、至少7天、至少8天、至少9天、至少10天、至少11天、至少12天、至少13天、或至少14天的給藥間隔來施用，且該VWF片段係以VWF片段對比施用的FVIII分子為至少約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、或500,000:1的劑量來施用。在其他實施例中，該VWF片段與該FVIII蛋白同時、在該FVIII蛋白後立即、剛好在該FVIII蛋白之前來施用。在某些實施例中，該VWF片段係在該FVIII蛋白之前約0.5小時、約1小時、約1.5小時、約2小時、約2.5小時、約3小時、約3.5小時、約4小時、約4.5小時、約5小時、約5.5小時、或約6小時施用。在其他實施例中，該FVIII蛋白在該VWF片段之前約0.5小時、約1小時、約1.5小時、約2小時、約2.5小時、約3小時、約3.5小時、約4小時、約4.5小時、約5小時、約5.5小時、或約6小時施用。

C．免疫耐受誘發

【0133】　本公開的某些方面涉及向有需要的個體治療其A型血友病的方法，該方法包括以給藥間隔向該個體施用嵌合多肽，該嵌合多肽包含FVIII蛋白和VWF片段，其中該嵌合多肽在該個體中誘發對FVIII的免疫耐受。本公開的某些方面涉及向有需要的個體治療其A型血友病的方法，該方法包括以給藥間隔向該個體施用嵌合多肽，該嵌合多肽包含FVIII蛋白和VWF片段，其中該嵌合多肽在該個體中降低對FVIII的抑制性反應。本公開的某些方面涉及向有需要的個體治療其A型血友病的方法，該方法包括以給藥間隔向該個體施用嵌合多肽，該嵌合多肽包含FVIII蛋白和VWF片段，其中該嵌合多肽在施用後不誘發對該嵌合多肽的免

疫反應。本公開的另一方面涉及在具有血友病的人中誘發免疫耐受的方法，該方法包括(1) 向該人施用有效量的本文所述的嵌合多肽(例如，rFVIIIFc-VWF-XTEN)，其中該有效量的該嵌合多肽在該人中誘發免疫耐受。使用包含FVIII和Fc的嵌合多肽的免疫耐受誘發的多種方法，公開在國際專利號WO 2018/102760 A1中，其透過提述以其整體併入本文。

【0134】 在某些實施例中，該方法進一步包括(2)在誘發免疫耐受後，向該人施用該組合物或該嵌合多肽的逐漸減少的用藥法（tapering regimen）。在某些實施例中，當在人中抑制性抗體的效價（titer）少於約0.6 BU時，出現免疫耐受的誘發。在某些實施例中，當在人中抑制性抗體的效價少於約0.6 BU且若血漿中監測到凝血因子活性的恢復率為60%時，出現免疫耐受的誘發。在本公開的一些實施例中，該方法進一步包括(3)在該逐漸減少的用藥法後，向該人施用預防性劑量的凝血因子，例如本文所述的嵌合多肽，如rFVIIIFc-VWF-XTEN。

【0135】 在某些方面中，該人尚未用針對凝血因子(例如，針對FVIII)的先前免疫耐受療法治療。該嵌合多肽(例如，rFVIIIFc-VWF-XTEN)可在已經確定該人已經產生了抑制因子免疫反應的任何時間(例如在量測該人中的抑制性免疫反應的水平後)施用至該人。在其他實施例中，該嵌合多肽(例如rFVIIIFc-VWF-XTEN)可施用至尚未產生一種或多種抑制因子免疫反應的人，以預防抑制因子免疫反應的發生。在一些實施例中，該嵌合多肽(例如，rFVIIIFc-VWF-XTEN)施用至有高度可能性會發生抑制因子免疫反應(例如，家族史、遺傳易感性或顯示有生物標誌物)的人。在一些實施例中，該方法進一步包括在施用前量測抑制性免疫反應水平或發展抑制因子免疫反應的可能性。

【0136】 在一些實施例中，該嵌合多肽(例如rFVIIIFc-VWF-XTEN)在已經(例如，在量測過該人之抑制性免疫反應的水平或發展出抑制因子免疫反應的可能性後)確定了該人已經產生了抑制因子免疫反應或該人具有發生抑制因子免疫反應的可能性後，少於約1天、少於約2天、少於約3天、少於約4天、少於約5天、少於約6天、少於約7天、少於約2周、少於約3周、少於約4周、少於約2個月、

少於約3個月、少於約4個月、少於約5個月、少於約6個月、少於約1年、少於約2年、少於約3年、少於約4年、或少於約5年被施用至該人。在某些實施例中，該嵌合多肽(例如，rFVIIIFc-VWF-XTEN)在已經(例如，在量測過該人之抑制性免疫反應的水平或發展出抑制因子免疫反應的可能性後)確定了該人已經產生了抑制因子免疫反應或該人具有發生抑制因子免疫反應的可能性後立即被施用至該人。在特定的實施例中，該嵌合多肽(例如rFVIIIFc-VWF-XTEN)在已經(例如，在量測過該人之抑制性免疫反應的水平或發展出抑制因子免疫反應的可能性後)確定了該人已經產生了抑制因子免疫反應或該人具有發生抑制因子免疫反應的可能性後少於約5分鐘、少於約10分鐘、少於約15分鐘、少於約20分鐘、少於約30分鐘、少於約45分鐘、少於約1小時、少於約2小時、少於約3小時、少於約4小時、少於約5小時、少於約6小時、少於約7小時、少於約8小時、少於約9小時、少於約10小時、少於約11小時、少於約12小時、約18小時、或少於約24小時被施用至該人。在特定的實施例中，該嵌合多肽(例如rFVIIIFc-VWF-XTEN)在已經(例如，在量測過人之抑制性免疫反應的水平或發展出抑制因子免疫反應的可能性後)確定了該人已經產生了抑制因子免疫反應或該人具有發生抑制因子免疫反應的可能性後約5分鐘、約10分鐘、約15分鐘、約20分鐘、約30分鐘、約45分鐘、約1小時、約2小時、約3小時、約4小時、約5小時、約6小時、約7小時、約8小時、約9小時、約10小時、約11小時、約12小時、約18小時、或約24小時被施用至該人。在某些實施例中，該嵌合多肽(例如rFVIIIFc-VWF-XTEN)在已經(例如，在量測過該人之抑制性免疫反應的水平或發展出抑制因子免疫反應的可能性後)確定了該人已經產生了抑制因子免疫反應或該人具有發生抑制因子免疫反應的可能性後少於約1天被施用至該人。

【0137】　免疫反應的誘導可持續直至抑制因子的水平低於某些水平或直至抑制因子無法被偵測到。在某些實施例中，誘導期可持續至少約24周、至少約26周、至少約28周、至少約30周、至少約32周、至少約34周、至少約36周、至少約38周、至少約40周、至少約42周、至少約44周、至少約46周、至少約48周、至少約50周、至少約52周、至少約54周、至少約56周、至少約58周、至少約60

周、至少約62周、至少約64周、至少約66周、至少約68周、至少約70周。在特定的實施例中，誘導期少於60周。

【0138】　通過本發明的方法來治療的抑制性免疫反應包括人體內對凝血因子治療的一種或多種作用產生消極影響的任何反應。在一些實施例中，該抑制性免疫反應包含產生針對凝血因子的抑制性抗體，例如抑制性抗FVIII抗體。在某些實施例中，本公開的方法進一步包括在施用有效量的本文所述的嵌合多肽(例如，rFVIIIFc-VWF-XTEN)或編碼該嵌合多肽的多核苷酸之前(例如，在基線處)或之後，係量測人體中一種或多種抑制性抗體的效價。在一些實施例中，在施用之前(例如，在基線處)的抑制性抗體的效價為至少約0.6 Bethesda單位(BU)。在某些實施例中，在施用之前(例如，在基線處)的抑制性抗體的效價為至少約1 BU、至少約2 BU、至少約3 BU、至少約4 BU、至少約5 BU、至少約6 BU、至少約7 BU、至少約10 BU、至少約20 BU、至少約30 BU、至少約40 BU、至少約50 BU、至少約100 BU、至少約150 BU、或至少約200 BU。在一個特定的實施例中，在施用之前(例如，在基線處)的抑制性抗體的效價為至少約5 BU。

【0139】　在一些實施例中，本發明的方法降低個體人類個體中相對於施用之前其抑制性抗體的效價。在某些實施例中，在施用之後的抑制性抗體的效價少於約0.6 BU。在一些實施例中，在施用之後的抑制性抗體的效價為少於約0.5 BU、少於約0.4 BU、少於約0.3 BU、少於約0.2 BU、或少於約0.1 BU。在一個特定的實施例中，在施用之後的抑制性抗體的效價為0 BU。在其他實施例中，在施用之後的抑制性抗體的效價為少於5 BU、少於4 BU、少於3 BU、少於2 BU、少於1 BU、少於0.9 BU、少於0.8 BU、少於0.7 BU、或少於0.6 BU。

【0140】　在一些實施例中，相較於在未經處理的對照組和僅用凝血因子處理的人之巨噬細胞分化情況，施用本文所述的嵌合多肽(例如rFVIIIFc-VWF-XTEN)係增加人體中巨噬細胞向M2樣表型的分化。在一些實施例中，M2樣表型包括上調NRF2路徑、PPARγ路徑、或NRF2路徑和PPARγ路徑二者。在一些實施例中，M2樣表型包括上調CD206 (MRC1)。在一些實施例中，M2樣表型包括上調ARG1。在一些實施例中，M2樣表型包括上調CD206 (MRC1)和ARG1。

【0141】　在一些實施例中，相對於未經治療的個體中或僅用凝血因子處理的個體中一種或多種基因的表現，施用本文所述的嵌合多肽(例如，rFVIIIFc-VWF-XTEN)係導致人中一種或多種基因有更高的表現。在一些實施例中，該施用係導致選自下列群組的一種或多種基因有更高表現：Hmox1、PPARγ、LPL、EGR2、SLCO4A1、血紅素加氧酶1 (HO-1)、氧化應激誘導的生長抑制因子1 (OSGIN1)、超氧化物歧化酶1 (SOD1)、谷胱甘肽-二硫化物還原酶(GSR)、麩胺酸-半胱胺酸連接酶催化亞基(GCLC)、麩胺酸-半胱胺酸連接酶修飾亞基(GCLM)、NAD(P)H醌脫氫酶1 (NQO1)、脂肪酸結合蛋白5 (FABP5)、B7-H3 (CD276)、SLAM家族成員3 (SLAMF3；淋巴細胞抗原9；LY9)、SLAM家族成員7 (SLAMF7)、甘露糖受體C型1 (MRC1)、溶質運載蛋白家族12成員4 (SLC12A)、神經氈蛋白1 (NRP1)、和其任何組合。在一些實施例中，該施用係導致NRF2路徑的一種或多種基因有更高表現。在某些實施例中，NRF2路徑的一種或多種基因係選自下列群組：HO-1、OSGIN1、SOD1、GSR、GCLC、GCLM、NQO1、和其任何組合。在一些實施例中，該施用係導致PPARγ路徑的一種或多種基因有更高表現。在一些實施例中，PPARγ路徑的一種或多種基因係選自下列群組：PPARγ、LPL、FABP5、EGR2、和其任何組合。在一些實施例中，該施用係導致選自下列群組的一種或多種基因有更高表現：B7-H3 (CD276)、SLAMF3、SLAMF7、MRC1、SLC12A、NRP1、和其任何組合。在特定的實施例中，相對於在未經治療的人中或僅施用了凝血因子的人之一種或多種基因的表現，該施用係導致一種或多種基因有更高表現，其中該表現高至少約1.5倍、高至少約2倍、高至少約2.5倍、高至少約3倍、高至少約3.5倍、高至少約4倍、高至少約4.5倍、或高至少約5倍。

【0142】　在一些實施例中，該一種或多種基因的差異表現係在施用本文所述的嵌合多肽(例如，rFVIIIFc-VWF-XTEN)後少於6小時觀察到。在一些實施例中，該差異表現係在施用後少於12小時觀察到。在一些實施例中，該差異表現係在施用後少於18小時觀察到。在一些實施例中，該差異表現在施用後少於24小時觀察到。

【0143】　在一些實施例中，抑制性免疫反應包含細胞介導的免疫反應。在某些實施例中，該細胞介導的免疫反應包含細胞因子的釋放。在一些實施例中，該細胞因子是與增加的免疫反應相關聯的任何細胞因子。在一些實施例中，該細胞因子係選自下列群組：IL-1、IL-6、IL-16、IL-12、IL-4、IL-17、腫瘤壞死因子α (TNF-α)、干擾素α、干擾素γ及其任何組合。在一個實施例中，該細胞介導的免疫反應包含血清量有所增加的IL-12。在另一個實施例中，該細胞介導的免疫反應包含血清量有所增加的IL-4。在另一個實施例中，該細胞介導的免疫反應包含血清量有所增加的IL-17。在另一個實施例中，該細胞介導的免疫反應包含血清量有所增加的TNF-α。

【0144】　多種基因突變係已與發展出抑制性免疫反應的風險增加聯繫起來。例如，Hap2內的TNF-α-308G>A多態性(其與TNF的組成型和誘導型轉錄水平增加有關)係已與發展抑制性免疫反應的風險增加聯繫起來。參見Astermark等, Blood 108: 3739-3745 (2006)，其通過提述以其整體併入本文。因此，在一些實施例中，該人具有與TNF-α增加相關聯的遺傳多態性。在一些實施例中，該多態性是TNF-α -308G>A多態性。在一些實施例中，該人具有IL10基因中的多態性，例如與IL10的分泌增加相關聯的多態性。在一些實施例中，FVIII-Fc係被施用至在IL10基因啟動子區中具有IL10G微衛星的等位基因134的個體。參見Astermark等 Hemostatis, Thrombosis, and Vascular Biology 108: 3739-3745 (2006)，其通過提述以其整體併入。

【0145】　在一些實施例中，該人具有與CTLA-4 (細胞毒性T淋巴細胞抗原4)表現降低相關聯的遺傳多態性。在一些實施例中，該人具有DR15 (HLA-DR15)或DQB0602 MHC (主要組織相容性複合物) II類分子中的突變。與具有血友病的個體中的抑制性免疫反應相關聯的其他MHC II類分子為A3、B7、C7、DQA0102、C2、DQA0103、DQB0603、和DR13 (參見Inhibitors in Patients with Hemophilia, E.C. Rodriguez-Merchan & C.A. Lee, Eds., Blackwell Science, Ltd,, 2002)。

【0146】　在一些實施例中，相較於在經過具有以FVIII蛋白所構成的多肽之在先治療後的個體中的一種或多種細胞因子的量，本公開的方法係降低個體該一

種或多種細胞因子的量個體。在另一個實施例中，相較於施用前的個體體內的一種或多種細胞因子的量，本公開的方法係降低該個體中該一種或多種細胞因子的量個體。在其他實施例中，相對於施用之前一種或多種耐受原分子的表現，在施用本公開的方法後，該一種或多種耐受原分子的表現係增加。在某些實施例中，該一種或多種耐受原分子係選自IL-10、TGF-β、IL-35、IDO-1及其任何組合。

【0147】 在其他實施例中，該免疫反應包含選自下列群組的臨床症狀：出血傾向增加、高凝血因子消耗、缺乏對凝血因子療法的反應、凝血因子療法的功效降低、凝血因子的半衰期縮短，及其任何組合。在某些實施例中，該免疫反應包含選自下列群組的臨床症狀：出血傾向增加、凝血因子消耗增加、缺乏對凝血因子療法的反應、凝血因子療法的功效降低、血漿中監測的凝血因子活性的恢復降低、凝血因子的半衰期縮短，及其任何組合。

【0148】 在某些實施例中，該人先前經診斷具有抑制性免疫反應。此類診斷可使用本領域中已知的任何方法進行。例如，如果該人具有一種或多種下列情況：(a) 凝血因子的抑制性抗體的效價大於或等於0.6 BU；(b) 一種或多種選自於IL-12、IL-4、IL-17、和TNF-α的細胞因子的血清水平增加；(c) 出血傾向增加；(d) 高凝血因子消耗；(e) 缺乏對凝血因子療法的反應；(f) 凝血因子療法的功效降低；(g) 凝血因子的半衰期縮短，及其任何組合，則該人可表徵為對凝血因子(例如FVIII)具有免疫反應。在一個特定的實施例中，如果該人的凝血因子的抑制性抗體的效價大於或等於0.6 BU，則該人表徵為對凝血因子具有免疫反應。

【0149】 在一些實施例中，該人先前經診斷為在施用前至少約1個月、至少約2個月、至少約3個月、至少約4個月、至少約5個月、至少約6個月、至少約7個月、至少約8個月、至少約9個月、至少約10個月、至少約11個月、至少約12個月、至少約13個月、至少約14個月、至少約15個月、至少約16個月、至少約17個月、至少約18個月、至少約19個月、至少約20個月、至少約21個月、至少約22個月、至少約23個月、至少約24個月、至少約27個月、至少約30個月、至少約33個月、至少約36個月、至少約39個月、至少約42個月、至少約45個月、至少約48

年、至少約51個月、至少約54個月、至少約57個月、至少約60個月、至少約6年、至少約7年、至少約8年、至少約10年、至少約15年、或至少約20年已經發展出對凝血因子的抑制性免疫反應。在一個實施例中，該人先前經診斷為在施用前至少5年已經發展出對凝血因子的抑制性免疫反應。

【0150】　在一些實施例中，相較於誘發免疫耐受的標準護理方法，本公開的方法係提供經改善的耐受時間。如本文所用的術語「耐受時間」是指以第一劑量施用包含有凝血因子和Fc區的組合物或嵌合蛋白與在人體中產生免疫耐受之間的時間。減少耐受時間對於人體具有顯著的益處，包括但不限於降低實現耐受所需要的總經濟負擔。在一些實施例中，該耐受時間為約1至約24周、約1至約23周、約1至約22周、約1至約21周、約2至約20周、約2至約19周、約2至約18周、約2至約17周、約3至約16周、約3至約15周、約3至約14周、約3至約13周、約4至約12周、約4至約11周、約4至約10周、約4至約9周、約5至約8周、約5至約7周、約5至約6周、約1至約12周、約1至約11周、約1至約10周、約1至約9周、約1至約8周、約1至約7周、約1至約6周、約1至約5周、或約1至約4周。在一些實施例中，該耐受時間為少於約70周、少於約65周、少於約60周、少於約58周、少於約56周、少於約54周、少於約52周、少於約50周、少於約48周、少於約46周、少於約44周、少於約42周、少於約40周、少於約38周、少於約36周、少於約34周、少於約32周、少於約30周、少於約28周、少於約26周、少於約24周、少於約23周、少於約22周、少於約21周、少於約20周、少於約19周、少於約18周、少於約17周、少於約16周、少於約15周、少於約14周、少於約13周、少於約12周、少於約11周、少於約10周、少於約9周、少於約8周、少於約7周、少於約6周、少於約5周、少於約4周、少於約3周、少於約2周、或少於約1周。在某些實施例中，該耐受時間為約4至約12周。在一個實施例中，該耐受時間為約4周。在另一個實施例中，該耐受時間為約12周。在一些實施例中，該耐受時間為少於約10個月。在一些實施例中，該耐受時間為少於約9個月。在一些實施例中，該耐受時間為少於約8個月。在一些實施例中，該耐受時間為少於約7個月。在一些實施例中，該耐受時間為少於約6個月。在一些實施例中，該耐受時間為

少於約5個月。在一些實施例中，該耐受時間為少於約4個月。在一些實施例中，相較於僅用凝血因子治療後的耐受時間，本公開的方法導致在使用包含有凝血因子和Fc區的組合物和嵌合蛋白的治療後的人體中有更短的耐受時間。

【0151】 在一些實施例中，發生免疫耐受的表徵在於凝血因子的抑制性抗體效價少於約0.6 BU。在一些實施例中，發生免疫耐受的表徵在於凝血因子的抑制性抗體效價少於約0.5 BU。在一些實施例中，發生免疫耐受的表徵在於凝血因子的抑制性抗體效價少於約0.4 BU。在一些實施例中，發生免疫耐受的發展的表徵在於凝血因子的抑制性抗體效價少於約0.3 BU。在一些實施例中，發生免疫耐受的表徵在於凝血因子的抑制性抗體效價少於約0.2 BU。在一些實施例中，發生免疫耐受的表徵在於凝血因子的抑制性抗體效價少於約0.1 BU。在一些實施例中，發生免疫耐受的表徵在於凝血因子的抑制性抗體效價為0.0 BU。在某些實施例中，抑制性免疫抗體的效價在兩個連續量測(例如在四周的週期內的兩個連續周中)中觀察到。

【0152】 在一些實施例中，發生免疫耐受的表徵在於增量恢復>66% (例如，增量的恢復為約67%、約68%、約69%、約70%、約71%、約72%、約73%、約74%、約75%、約76%、約77%、約78%、約79%、約80%、約81%、約82%、約83%、約84%、約85%、約86%、約87%、約88%、約89%、約90%、約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%、約99%、或約100%)。如本文所用的，「增量恢復」是指輸注後15-30分鐘的FVIII峰值量。

【0153】 在誘導期和逐漸減少期結束之後，接著可對個體進行嵌合蛋白的預防性治療。預防性給藥方案可以是本文公開的任何給藥方案。

【0154】 在一些實施例中，使用本公開的方法治療的人係正在接受或最近已經接受了免疫刺激療法。舉例來說，在經受干擾素治療的HCV陽性A型血友病患者中或在具有與抗逆轉錄病毒療法相關聯的免疫重建發炎癥候群的HIV陽性A型血友病患者中已報導有抑制因子。參見Report of Expert Meeting on FVIII Products and Inhibitor Development, European Medicines Agency (2006年2月28日至3月2日)。因此，在一些實施例中，該人正在接受干擾素療法。在一些實施例中，

該人正在接受抗病毒療法。在一些實施例中，該人正在接受抗逆轉錄病毒療法且具有免疫重建發炎癥候群。

【0155】　在某些實施例中，該人對凝血因子(例如FVIII)的暴露天數(ED)少於150。在一個實施例中，該人的ED少於50。在另一個實施例中，該人的ED少於20。

【0156】　本公開的某些方面涉及在有需要的個體中降低對凝血因子的過敏或過敏反應的嚴重性或發生的方法，該方法包括向該個體施用包含凝血因子和Fc區的組合物或嵌合蛋白。在一些實施例中，該組合物或該嵌合蛋白的施用係降低對凝血因子的過敏樣反應的嚴重性。在一些實施例中，該組合物或該嵌合蛋白的施用係降低對凝血因子的過敏反應的嚴重性。

III．嵌合多肽

【0157】　可用於本公開的嵌合多肽包含FVIII蛋白，該FVIII蛋白包含FVIII多肽和包含VWF的D'域和D3域的VWF片段。該VWF片段用於防止或阻斷該FVIII蛋白與內源性VWF相互作用，從而防止FVIII蛋白通過VWF清除路徑而被清除。為了防止該FVIII蛋白與該VWF片段的解離，在一些實施例中，該FVIII蛋白和該VWF片段係藉由比FVIII和VWF間的自然相互作用更強的締合來彼此直接地或間接地締合。

【0158】　在某些實施例中，該FVIII蛋白係通過共價鍵與VWF片段締合。該共價鍵可以是本領域中已知的任何共價鍵。在一些實施例中，該共價鍵是雙硫鍵。在一些實施例中，該共價鍵是肽鍵。在其他實施例中，該FVIII蛋白經修飾以增加該FVIII蛋白和該VWF片段之間的相互作用的強度。在其他實施例中，該VWF片段係經修飾以增加該FVIII蛋白和該VWF片段之間的相互作用強度。在另一些其他的實施例中，該FVIII蛋白和該VWF蛋白二者係經修飾以增加該FVIII蛋白和該VWF片段之間的相互作用強度。

【0159】　在特定的實施例中，該FVIII蛋白包含FVIII多肽和包含VWF的D'域和D3域的VWF片段，其係通過FVIII多肽序列中的至少一個胺基酸與VWF的D'和

D3域中的至少一個胺基酸之間的至少一個共價鍵直接締合。在其他實施例中，該FVIII蛋白和該VWF片段係通過FVIII多肽序列中的至少一個胺基酸與VWF的D'和D3域所直接或間接融合的異源序列中的至少一個胺基酸之間的至少一個共價鍵來間接締合。在其他實施例中，該FVIII蛋白和該VWF片段係通過VWF片段序列中的至少一個胺基酸與FVIII多肽所直接或間接融合的異源序列中的至少一個胺基酸之間的至少一個共價鍵來間接締合。在另一些其他的實施例中，該FVIII蛋白和該VWF片段係通過與VWF的D'和D3域所直接或間接融合的異源序列中的至少一個胺基酸與FVIII多肽所直接或間接融合的異源序列中的至少一個胺基酸之間的至少一個共價鍵來間接締合。

【0160】 本公開的FVIII蛋白可包含FVIII多肽和一個或多個異源部分，例如延長半衰期的部分，該異源部分係與該FVIII多肽直接或間接地融合。本公開的VWF片段還可包含VWF的D'域和D3域和一個或多個異源部分，例如，延長半衰期的部分，該異源部分係與VWF的D'域和D3域直接或間接地融合。在一些實施例中，可用於本公開的FVIII蛋白實質上由FVIII多肽構成或係由FVIII多肽構成，且可用於本公開的VWF片段包含VWF的D'域和D3域和一個或多個異源部分，例如，延長半衰期的部分，該異源部分與VWF的D'域和D3域直接或間接地融合。在一些實施例中，該FVIII蛋白包含FVIII多肽和一個或多個異源部分，例如，延長半衰期的部分，該異源部分與該FVIII多肽係直接或間接地融合，且可用於本公開的VWF片段實質上由VWF的D'域和D3域構成或係由VWF的D'域和D3域構成。在一些實施例中，該嵌合多肽包含FVIII蛋白和VWF片段，該FVIII蛋白實質上由FVIII多肽構成或係由FVIII多肽構成，且該VWF片段實質上由VWF的D'域和D3域構成或係由VWF的D'域和D3域構成。

【0161】 在一些實施例中，本文公開的嵌合多肽或蛋白是FVIII-XTEN-Fc/D'D3-XTEN-Fc異源二聚體。在一個實施例中，該FVIII-XTEN-Fc/D'D3-XTEN-Fc異源二聚體嵌合多肽包含：(i)FVIII蛋白，其包含FVIII多肽、插入在FVIII多肽的B域內的XTEN、和第一Fc區；和(ii)VWF蛋白，

其包含VWF片段、第二XTEN序列、a2連接子、和第二Fc區。示例性的FVIII-XTEN-Fc/D'D3-XTEN-Fc異源二聚體、rFVIIIFc-VWF-XTEN係呈現在圖1中。

【0162】 在一具體的實施例中，該嵌合多肽是rFVIIIFc-VWF-XTEN。在另一具體的實施例中，rFVIIIFc-VWF-XTEN包含(i)含有SEQ ID NO: 203的胺基酸序列的FVIII蛋白和(ii)含有SEQ ID NO: 205胺基酸序列的VWF蛋白。在再另一實施例中，rFVIIIFc-VWF-XTEN包含經由雙硫鍵共價連接的(i)FVIII蛋白和(ii)VWF蛋白。

III.A · 因子 VIII 多肽

【0163】 如本文所用的「因子VIII」，其在本申請中縮寫為「FVIII」，除非另有規定，否則意指在凝血過程中正常作用的有功能的FVIII多肽。因此，術語FVIII包括變異體多肽，其是有功能的（functional）。「FVIII蛋白」用於指單獨的FVIII多肽(或蛋白)、與另外的多肽融合的FVIII多肽、和與一個或多個多肽締合的FVIII多肽，只要該FVIII蛋白表現出FVIII的功能/活性。術語「FVIII多肽」、「FVIII部分」或「FVIII」是指單獨的FVIII多肽序列。FVIII的功能/活性實例包括但不限於，激活凝血的能力、作為因子IX的輔因子的能力、或在Ca^{2+}和磷脂的存在下與因子IX形成十因子(tenase)酶複合物，然後該複合物將因子X轉化為激活形式的Xa。該FVIII多肽可以是人、豬、犬、大鼠、或鼠的FVIII多肽。此外，來自人類和其他物種的FVIII之間的比較已經證實了功能可能所必須的保守殘基(Cameron等, Thromb. Haemost. 79:317-22 (1998)；US 6,251,632)。其全長多肽和多核苷酸序列是已知的，而許多功能性片段、突變體和經修飾的版本者亦同。多種FVIII胺基酸和核苷酸序列例如公開於，美國公開號2015/0158929 A1、2014/0308280 A1、和2014/0370035 A1和國際公開號WO 2015/106052 A1。FVIII多肽例如包括，全長FVIII、減去N端處的Met的全長FVIII、成熟FVIII多肽(減去信號序列)、在N端處具有另外的Met的成熟FVIII多肽，和/或B域全部或部分缺失的

FVIII多肽。FVIII變異體包括B域缺失，不論是部分或全部缺失。

【0164】　本文所用的嵌合多肽的FVIII多肽在血漿中具有FVIII活性。FVIII活性可通過本領域中任何已知的方法量測。許多測試可用於評定凝血系統的功能：活化部分凝血活酶時間(aPTT)測試、生色測定、ROTEM測定、凝血酶原時間(PT)測試(也用於測定INR)、纖維蛋白原測試(通常通過克勞斯(Clauss)方法)、血小板計數、血小板功能測試(通常通過PFA-100)、TCT、出血時間、混合測試(如果患者的血漿與正常血漿混合，是否異常校正)、凝血因子測定、抗磷脂抗體、D-二聚體、基因測試(例如，因子V Leiden、凝血酶原突變G20210A)、稀釋魯塞爾氏毒蛇(Russell's viper)毒液時間(dRVVT)、雜項血小板功能測試、凝血彈性描記法(TEG或Sonoclot)、血栓彈力圖(TEM®，例如，ROTEM®)、或優球蛋白裂解時間(ELT)。

【0165】　aPTT測試是量測「內生性的」(也指接觸激活路徑)和共通的凝血路徑功效的優良指標。此測試常用於量測可商購的重組凝血因子(例如FVIII)的凝血活性。其一般係與凝血酶原時間(PT)結合使用，凝血酶原時間(PT)係測定外生性路徑。(參見，例如，Kamal 等, Mayo Clin Proc., 82(7):864-873 (2007))。在一個實施例中，使用其中使用Dade® Actin® FSL激活的PTT試劑(Siemens Health Care Diagnostics)在BCS® XP分析儀(Siemens Healthcare Diagnostics)上量測FVIII活性的測定法來測試aPTT。在某些實施例中，如通過aPTT測試量測的，該嵌合多肽具有的血漿FVIII活性為至少約1%、至少約2%、至少約3%、至少約4%、至少約5%、至少約6%、至少約7%、至少約8%、至少約9%、至少約10%、至少約11%、至少約12 %、至少約13%、至少約14%、至少約15%、至少約15%、至少約16%、至少約17%、至少約18%、至少約19%、或至少約20%。

【0166】　aPTT測法定還可用於評定在向患者或個體施用之前的嵌合多肽的力價（potency）。(Hubbard AR，等J Thromb Haemost 11: 988–9 (2013))。aPTT測定法可進一步與本文所述的任何測定法結合使用，其在向患者或個體施用之前或施用之後進行。

【0167】 ROTEM分析係提供關於止血的整個動力學信息：凝血時間、凝塊形成、凝塊穩定性和裂解。血栓彈力圖的不同參數取決於血漿凝固系統的活性、血小板功能、血纖蛋白分解、或影響這些相互作用的許多因素。此測定法可提供繼發性止血的全面瞭解。

【0168】 生色測定法機制是基於血液凝固級聯反應的原理，其中激活的FVIII係在激活的因子IX、磷脂和鈣離子的存在下，加速因子X至因子Xa的轉化。因子Xa的活性係藉由對因子Xa具有專一性的對硝基苯胺(pNA)受質之水解來評定的。對硝基苯胺在405nM處所量測到的初始釋放速率係與因子Xa活性成正比，且因此與樣品中的FVIII活性成正比。在一個實施例中，生色測定法是BIOPHEN FVIII:C測定法(Hyphen Biomed，Neurville sur Oise，France)。

【0169】 生色測定法由國際血栓形成與止血學會(ISTH)科學和標準化委員會(SSC)的FVIII和因子IX下屬委員會推薦。自1994年以來，生色測定法也是歐洲藥典中用於指定FVIII濃縮物力價的參考方法。因此，在一些實施例中，包含FVIII多肽的嵌合多肽，係具有與包含成熟FVIII多肽或BDD FVIII多肽(例如，RECOMBINATE®、KOGENATE FS®、HELIXATE FS®、XYNTHA/REFACTO AB®、HEMOFIL-M®、MONARC-M®、MONOCLATE-P®、HUMATE-P®、ALPHANATE®、KOATE-DVI®、AFSTYLA®、AND HYATE:C®)的嵌合多肽所相當的FVIII活性。

【0170】 生色測定法還可用於評定在向患者或個體施用之前的嵌合多肽的力價。(Hubbard AR, 等J Thromb Haemost 11: 988–9 (2013))。生色測定法可進一步與本文所述的任何測定法結合使用，其在向患者或個體施用之前或施用之後進行。

【0171】 在其他實施例中，包含本公開的FVIII多肽的嵌合多肽，係具有與包含成熟FVIII多肽或BDD FVIII多肽(例如，ADVATE®、REFACTO®、或ELOCTATE®)的嵌合多肽相當的因子Xa生成率。

【0172】 為了使因子X活化成為因子Xa，被活化的因子IX (因子IXa)係在Ca^{2+}、膜磷脂、和FVIII輔因子的存在下，水解因子X中的一個精胺酸-異白胺酸鍵，以形成因子Xa。因此，FVIII與因子IX的相互作用在凝血路徑中至關重要。在某些

實施例中，包含FVIII多肽的嵌合多肽可以與含有成熟FVIII多肽序列或BDD FVIII多肽(例如，ADVATE®、REFACTO®、或ELOCTATE®)的嵌合多肽相當的速率與因子IXa相互作用。

【0173】　此外，FVIII係與馮威里氏因子結合，而在循環中無活性。FVIII在未與VWF結合時快速降解，並通過凝血酶的作用從VWF中釋放。在一些實施例中，包含FVIII多肽的嵌合多肽係以與包含成熟FVIII多肽序列或BDD FVIII多肽(例如，ADVATE®、REFACTO®、或ELOCTATE®)的嵌合多肽相當的程度來結合假性血友病因子(例如本文公開的VWF片段)。

【0174】　FVIII可在鈣和磷脂的存在下藉由激活的蛋白C使其失活。激活的蛋白C係在A1域中精胺酸336後切割FVIII重鏈，其係破壞因子X受質的作用位點，且在A2域中的精胺酸562後切割，這增強了A2域的解離並破壞與因子IXa的相互作用位點。此切割還將A2域(43 kDa)對切，並產生A2-N (18 kDa)和A2-C (25 kDa)域。因此，激活的蛋白C可催化重鏈中的多個切割位點。在一些實施例中，激活的蛋白C係以與包含成熟FVIII多肽序列或BDD FVIII多肽(例如，ADVATE®、REFACTO®、或ELOCTATE®)的嵌合多肽相當的程度來使含有FVIII多肽的嵌合多肽失活。

【0175】　在其他實施例中，包含FVIII多肽的嵌合多肽在體內具有與含有成熟FVIII多肽序列或BDD FVIII多肽(例如，ADVATE®、REFACTO®、或ELOCTATE®)的嵌合多肽相當的FVIII活性。在特定的實施例中，包含FVIII多肽的嵌合多肽能夠在HemA小鼠尾靜脈橫斷模型中，以與包含成熟FVIII多肽序列或BDD FVIII多肽(例如，ADVATE®、REFACTO®、或ELOCTATE®)的嵌合多肽相當的程度來保護HemA小鼠。

【0176】　人FVIII序列(全長)的實例如下所示。

表 2：全長人因子 VIII 的胺基酸序列

(全長 FVIII：FVIII 信號肽係標示底線；FVIII 重鏈係標示雙底線；
B 域用斜體表示；且 FVIII 輕鏈以正常文字表示)

信號肽：(SEQ ID NO: 64)
MQIELSTCFFLCLLRFCFS

成熟因子 VIII (SEQ ID NO: 65)*

ATRRYYLGAVELSWDYMQSDLGELPVDARFPPRVPKSFPFNTSVVYKKTLFVEFTDHLFNIAKPRPPWMGLL
GPTIQAEVYDTVVITLKNMASHPVSLHAVGVSYWKASEGAEYDDQTSQREKEDDKVFPGGSHTYVWQVLK
ENGPMASDPLCLTYSYLSHVDLVKDLNSGLIGALLVCREGSLAKEKTQTLHKFILLFAVFDEGKSWHSETKN
SLMQDRDAASARAWPKMHTVNGYVNRSLPGLIGCHRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQA
SLEISPITFLTAQTLLMDLGQFLLFCHISSHQHDGMEAYVKVDSCPEEPQLRMKNNEEAEDYDDDLTDSEMD
VVRFDDDNSPSFIQIRSVAKKHPKTWVHYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQRIGRKYKKVR
FMAYTDETFKTREAIQHESGILGPLLYGEVGDTLLIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDF
PILPGEIFKYKWTVTVEDGPTKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQIMSDKRNVIL
FSVFDENRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAYWYILSIGAQTDF
LSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNRGMTALLKVSSCDKNTGDYY
EDSYEDISAYLLSKNNAIEPR*SFSQNSRHPSTRQKQFNATTIPENDIEKTDPWFAHRTPMPKIQNVSSSDLLMLLRQ*
SPTPHGLSLSDLQEAKYETFSDDPSPGAIDSNNSLSEMTHFRPQLHHSGDMVFTPESGLQLRLNEKLGTTAATELKK
LDFKVSSTSNNLISTIPSDNLAAGTDNTSSLGPPSMPVHYDSQLDTTLFGKKSSPLTESGGPLSLSEENNDSKLLESGL
MNSQESSWGKNVSSTESGRLFKGKRAHGPALLTKDNALFKVSISLLKTNKTSNNSATNRKTHIDGPSLLIENSPSVWQ
NILESDTEFKKVTPLIHDRMLMDKNATALRLNHMSNKTTSSKNMEMVQQKKEGPIPPDAQNPDMSFFKMLFLPES
ARWIQRTHGKNSLNSGQGPSPKQLVSLGPEKSVEGQNFLSEKNKVVVGKGEFTKDVGLKEMVFPSSRNLFLTNLD
NLHENNTHNQEKKIQEEIEKKETLIQENVVLPQIHTVTGTKNFMKNLFLLSTRQNVEGSYDGAYAPVLQDFRSLNDS
TNRTKKHTAHFSKKGEEENLEGLGNQTKQIVEKYACTTRISPNTSQQNFVTQRSKRALKQFRLPLEETELEKRIIVD
DTSTQWSKNMKHLTPSTLTQIDYNEKEKGAITQSPLSDCLTRSHSIPQANRSPLPIAKVSSFPSIRPIYLTRVLFQDNSS
HLPAASYRKKDSGVQESSHFLQGAKKNNLSLAILTLEMTGDQREVGSLGTSATNSVTYKKVENTVLPKPDLPKTSGK
VELLPKVHIYQKDLFPTETSNGSPGHLDLVEGSLLQGTEGAIKWNEANRPGKVPFLRVATESSAKTPSKLLDPLAWD
NHYGTQIPKEEWKSQEKSPEKTAFKKKDTILSLNACESNHAIAAINEGQNKPEIEVTWAKQGRTERLCSQNPPVLKR
*HQR*EITRTTLQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSPRSFQKKTRHYFIAAVERLWDYGMSSSPHVL
RNRAQSGSVPQFKKVVFQEFTDGSFTQPLYRGELNEHLGLLGPYIRAEVEDNIMVTFRNQASRPYSFYSSLIS
YEEDQRQGAEPRKNFVKPNETKTYFWKVQHHMAPTKDEFDCKAWAYFSDVDLEKDVHSGLIGPLLVCHTN
TLNPAHGRQVTVQEFALFFTIFDETKSWYFTENMERNCRAPCNIQMEDPTFKENYRFHAINGYIMDTLPGLV
MAQDQRIRWYLLSMGSNENIHSIHFSGHVFTVRKKEEYKMALYNLYPGVFETVEMLPSKAGIWRVECLIGE
HLHAGMSTLFLVYSNKCQTPLGMASGHIRDFQITASGQYGQWAPKLARLHYSGSINAWSTKEPFSWIKVDL
LAPMIIHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGNVDSSGIKHNIFNPPIIARYIR
LHPTHYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSYFTNMFATWSPSKARLHLQGRSNAWRPQ
VNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTSMYVKEFLISSSQDGHQWTLFFQNGKVKVFQGNQDSFTP
VVNSLDPPLLTRYLRIHPQSWVHQIALRMEVLGCEAQDLY

表 3. 編碼全長 FVIII 的核苷酸序列(SEQ ID NO: 66)*

*劃底線的核酸係編碼信號肽。

661	ATG CAAATAGAGC TCTCCACCTG
721	CTTCTTTCTG TGCCTTTTGC GATTCTGCTT TAGTGCCACC AGAAGATACT ACCTGGGTGC
781	AGTGGAACTG TCATGGGACT ATATGCAAAG TGATCTCGGT GAGCTGCCTG TGGACGCAAG
841	ATTTCCTCCT AGAGTGCCAA AATCTTTTCC ATTCAACACC TCAGTCGTGT ACAAAAAGAC
901	TCTGTTTGTA GAATTCACGG ATCACCTTTT CAACATCGCT AAGCCAAGGC CACCCTGGAT
961	GGGTCTGCTA GGTCCTACCA 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	TAAAATGCAC ACAGTCAATG GTTATGTAAA CAGGTCTCTG CCAGGTCTGA TTGGATGCCA
1501	CAGGAAATCA GTCTATTGGC ATGTGATTGG AATGGGCACC ACTCCTGAAG TGCACTCAAT
1561	ATTCCTCGAA GGTCACACAT TTCTTGTGAG GAACCATCGC CAGGCGTCCT TGGAAATCTC
1621	GCCAATAACT 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 CTTCCTTTAT
1861	CCAAATTCGC TCAGTTGCCA AGAAGCATCC TAAAACTTGG GTACATTACA TTGCTGCTGA

1921	AGAGGAGGAC TGGGACTATG CTCCCTTAGT CCTCGCCCCC 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 CGCTTTCTCC 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 AAACTGTCTT CATGTCGATG GAAAACCCAG GTCTATGGAT
2821	TCTGGGGTGC CACAACTCAG ACTTTCGGAA CAGAGGCATG ACCGCCTTAC TGAAGGTTTC
2881	TAGTTGTGAC AAGAACACTG GTGATTATTA CGAGGACAGT TATGAAGATA TTTCAGCATA
2941	CTTGCTGAGT AAAAACAATG CCATTGAACC AAGAAGCTTC TCCCAGAATT CAAGACACCC
3001	TAGCACTAGG CAAAAGCAAT TTAATGCCAC CACAATTCCA GAAAATGACA TAGAGAAGAC
3061	TGACCCTTGG TTTGCACACA GAACACCTAT GCCTAAAATA CAAAATGTCT CCTCTAGTGA
3121	TTTGTTGATG 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 AAACTTGATT TCAAAGTTTC TAGTACATCA AATAATCTGA TTTCAACAAT
3421	TCCATCAGAC AATTTGGCAG CAGGTACTGA TAATACAAGT TCCTTAGGAC CCCCAAGTAT
3481	GCCAGTTCAT TATGATAGTC AATTAGATAC CACTCTATTT GGCAAAAAGT CATCTCCCCT
3541	TACTGAGTCT GGTGGACCTC TGAGCTTGAG TGAAGAAAAT AATGATTCAA AGTTGTTAGA
3601	ATCAGGTTTA ATGAATAGCC AAGAAAGTTC ATGGGGAAAA AATGTATCGT CAACAGAGAG
3661	TGGTAGGTTA TTTAAAGGGA AAAGAGCTCA TGGACCTGCT TTGTTGACTA AAGATAATGC
3721	CTTATTCAAA GTTAGCATCT CTTTGTTAAA GACAAACAAA ACTTCCAATA ATTCAGCAAC
3781	TAATAGAAAG ACTCACATTG ATGGCCCATC ATTATTAATT GAGAATAGTC CATCAGTCTG
3841	GCAAAATATA TTAGAAAGTG ACACTGAGTT TAAAAAAGTG ACACCTTTGA TTCATGACAG
3901	AATGCTTATG GACAAAAATG CTACAGCTTT GAGGCTAAAT CATATGTCAA ATAAAACTAC
3961	TTCATCAAAA AACATGGAAA TGGTCCAACA GAAAAAAGAG GGCCCCATTC CACCAGATGC
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 AACCTATTTC TTACTAACTT 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 AACAATTCAG ACTCCCACTA GAAGAAACAG AACTTGAAAA
4741	AAGGATAATT GTGGATGACA CCTCAACCCA GTGGTCCAAA AACATGAAAC ATTTGACCCC
4801	GAGCACCCTC 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	CTTGGAGATG ACTGGTGATC AAAGAGAGGT TGGCTCCCTG GGGACAAGTG CCACAAATTC
5161	AGTCACATAC AAGAAAGTTG AGAACACTGT TCTCCCGAAA CCAGACTTGC CCAAAACATC
5221	TGGCAAAGTT GAATTGCTTC CAAAAGTTCA CATTTATCAG AAGGACCTAT TCCCTACGGA
5281	AACTAGCAAT GGGTCTCCTG GCCATCTGGA TCTCGTGGAA 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 GCCCGAAATA 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 CCAAAAGCTG
6421	GTACTTCACT GAAAATATGG AAAGAAACTG CAGGGCTCCC TGCAATATCC AGATGGAAGA
6481	TCCCACTTTT AAAGAGAATT ATCGCTTCCA TGCAATCAAT GGCTACATAA TGGATACACT
6541	ACCTGGCTTA GTAATGGCTC AGGATCAAAG GATTCGATGG TATCTGCTCA GCATGGGCAG
6601	CAATGAAAAC ATCCATTCTA TTCATTTCAG TGGACATGTG TTCACTGTAC GAAAAAAAGA
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 CTTCATTATT 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 ATAGCATTCG 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 GTAACTACTC AGGGAGTAAA
7501	ATCTCTGCTT ACCAGCATGT ATGTGAAGGA GTTCCTCATC TCCAGCAGTC AAGATGGCCA
7561	TCAGTGGACT CTCTTTTTTC AGAATGGCAA AGTAAAGGTT TTTCAGGGAA ATCAAGACTC
7621	CTTCACACCT GTGGTGAACT CTCTAGACCC ACCGTTACTG ACTCGCTACC TTCGAATTCA
7681	CCCCCAGAGT TGGGTGCACC AGATTGCCCT GAGGATGGAG GTTCTGGGCT GCGAGGCACA
7741	GGACCTCTAC

【0177】 FVIII多肽包括全長FVIII、減去N端處的Met的全長FVIII、成熟FVIII(減去信號序列)、在N端處具有另外的Met的成熟FVIII、和/或全部或部分缺失B域的FVIII。在某些實施例中，FVIII變異體包括B域缺失，不論是部分或全部缺失。

【0178】 天然成熟的人類FVIII多肽的序列如SEQ ID NO: 65所示。天然的FVIII多肽具有下式：A1-a1-A2-a2-B-a3-A3-C1-C2，其中A1、A2、和A3是結構上相關的「A域」，B是「B域」，C1和C2是結構上相關的「C域」，且a1、a2和a3是酸性間隔子區域。關於SEQ ID NO:65中的一級胺基酸序列位置，人類FVIII的A1域係從Ala1延伸至約Arg336，a1間隔子區域係從約Met337延伸至約Val374，A2域係從約Ala375延伸至約Tyr719，a2間隔子區域係從約Glu720延伸至約Arg740，B域係從約Ser741延伸至約Arg 1648，a3間隔子區域係從約Glu1649延伸至約Arg1689，A3域係從約Ser1690延伸至約Leu2025，C1域係從約Gly2026延伸至約Asn2072，且C2域係從約Ser2073延伸至Tyr2332。除了特定的蛋白水解切割位點，FVIII的域和區域之間邊界位置的指定可以在不同的參考文獻中有變化。因此，本文中所指稱的邊界係通過使用術語「約」被指定為近似。

【0179】　人類FVIII基因是經分離的且在哺乳動物細胞中表現(Toole, J. J.,等, Nature 312:342-347 (1984)；Gitschier, J., 等, Nature 312:326-330 (1984)；Wood, W. I., 等, Nature 312:330-337 (1984)；Vehar, G. A., 等, Nature 312:337-342 (1984)；WO 87/04187；WO 88/08035；WO 88/03558；和美國專利號4,757,006)。FVIII胺基酸序列從如美國專利號4,965,199中所示的cDNA中推導出來。此外，部分或全部B域缺失的FVIII，係示於美國專利號4,994,371和4,868,112中。在一些實施例中，人FVIII的B域係由如美國專利號5,004,803中所示的人類因子V之B域所取代。編碼有人類因子VIII的cDNA序列和胺基酸序列係分別如美國申請公開號2005/0100990的SEQ ID NO: 1和2所示。

【0180】　豬的FVIII序列係發表於Toole, J. J.,等, Proc. Natl. Acad. Sci. USA 83:5939-5942 (1986)。進一步地，從來自豬脾臟cDNA庫中的FVIII序列之PCR擴增物中所獲得的完整豬cDNA序列，係已經報導於Healey, J. F., 等, Blood 88:4209-4214 (1996)中。具有替代的所有之域、所有次單元、和具體胺基酸序列的雜合性人/豬FVIII，係公開於Lollar和Runge的美國專利號5,364,771、和WO 93/20093中。更近來，WO 94/11503中係報導了豬FVIII的A1和A2域的核苷酸和相應的胺基酸序列，以及具有由相應之人類域所取代的豬A1和/或A2域的嵌合FVIII。美國專利號5,859,204, Lollar, J. S.還公開了豬cDNA和推導出的胺基酸序列。美國專利號6,458,563公開了B域缺失的豬FVIII。

【0181】　Lollar, J. S.的美國專利號5,859,204報導了FVIII的有功能之突變體，該突變體具有較低的抗原性和較低的免疫反應性。Lollar, J. S.的美國專利號6,376,463還報導了FVIII的突變體，該突變體具有較低的免疫反應性。Saenko等的美國申請公開號2005/0100990報導了FVIII的A2域中有功能的突變。

【0182】　在一些實施例中，FVIII多肽(或嵌合多肽的FVIII部分)可以與以下的FVIII胺基酸序列有至少50%、60%、70%、80%、90%、95%、96%、97%、98%、99%、或100%相同：SEQ ID NO: 67的胺基酸1至1438或SEQ ID NO: 65 (不具有信號序列)的胺基酸1至2332，或SEQ ID NO: 64的胺基酸1至19和SEQ ID NO: 67的胺基酸1至1438，或SEQ ID NO: 64的胺基酸1至19和SEQ ID NO: 65 (具有信號

序列)的胺基酸1至2332，其中該FVIII具有凝血活性，例如，激活作為輔因子的因子IX，以將因子X轉化為激活的因子X。該FVIII多肽(或嵌合多肽的FVIII部分)可與SEQ ID NO: 67的胺基酸1至1438或SEQ ID NO: 65 (不具有信號序列)的胺基酸1至2332的FVIII胺基酸序列相同。該FVIII多肽可進一步包含信號序列。

【0183】　如本文所用的FVIII「B域」與由內在胺基酸序列同一性和蛋白水解切割的位點(例如全長人FVIII的殘基Ser741-Arg1648)定義之本領域中已知的B域者相同。其他人類FVIII域係由下列胺基酸殘基所定義：A1，殘基Ala1-Arg372；A2，殘基Ser373-Arg740；A3，殘基Ser1690-Asn2019；C1，殘基Lys2020-Asn2172；C2，殘基Ser2173-Tyr2332。A3-C1-C2序列包括殘基Ser1690-Tyr2332。其餘的序列，殘基Glu1649-Arg1689，通常被稱為a3酸性區域。豬、小鼠和犬FVIII的全數結構域(包括B域)之邊界位置也是本領域已知的。在一些實施例中，FVIII的B域是缺失的(「B域缺失的因子VIII」或「BDD FVIII」)。BDD FVIII的實例是REFACTO® (重組BDD FVIII)，其具有與表4中的序列的因子VIII部分相同的序列。(BDD FVIII重鏈以雙底劃線表示；B域以斜體表示；且BDD FVIII輕鏈以正常文字表示)。在一些實施例中，B域FVIII缺失除5個胺基酸外的全部B域，如表5中所示(SEQ ID NO: 68) (B域以斜體表示)。

表 4. B 域缺失的因子 VIII 的胺基酸序列(B 域缺失，除 14 個胺基酸殘基以外) **(SEQ ID NO: 67)**

ATRRYYLGAVELSWDYMQSDLGELPVDARFPPRVPKSFPFNTSVVYKKTLFVEFTDHLFNIAKPRPPWMGLL
GPTIQAEVYDTVVITLKNMASHPVSLHAVGVSYWKASEGAEYDDQTSQREKEDDKVFPGGSHTYVWQVLK
ENGPMASDPLCLTYSYLSHVDLVKDLNSGLIGALLVCREGSLAKEKTQTLHKFILLFAVFDEGKSWHSETKN
SLMQDRDAASARAWPKMHTVNGYVNRSLPGLIGCHRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQA
SLEISPITFLTAQTLLMDLGQFLLFCHISSHQHDGMEAYVKVDSCPEEPQLRMKNNEEAEDYDDDLTDSEMD
VVRFDDDNSPSFIQIRSVAKKHPKTWVHYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQRIGRKYKKVR
FMAYTDETFKTREAIQHESGILGPLLYGEVGDTLLIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDF
PILPGEIFKYKWTVTVEDGPTKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQIMSDKRNVIL
FSVFDENRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAYWYILSIGAQTDF
LSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNRGMTALLKVSSCDKNTGDYY
EDSYEDISAYLLSKNNAIEPR*SFSQNPPVLKRHQR*EITRTTLQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSP
RSFQKKTRHYFIAAVERLWDYGMSSSPHVLRNRAQSGSVPQFKKVVFQEFTDGSFTQPLYRGELNEHLGLLG
PYIRAEVEDNIMVTFRNQASRPYSFYSSLISYEEDQRQGAEPRKNFVKPNETKTYFWKVQHHMAPTKDEFDC
KAWAYFSDVDLEKDVHSGLIGPLLVCHTNTLNPAHGRQVTVQEFALFFTIFDETKSWYFTENMERNCRAPC
NIQMEDPTFKENYRFHAINGYIMDTLPGLVMAQDQRIRWYLLSMGSNENIHSIHFSGHVFTVRKKEEYKMAL
YNLYPGVFETVEMLPSKAGIWRVECLIGEHLHAGMSTLFLVYSNKCQTPLGMASGHIRDFQITASGQYGQW
APKLARLHYSGSINAWSTKEPFSWIKVDLLAPMIIHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNST
GTLMVFFGNVDSSGIKHNIFNPPIIARYIRLHPTHYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSY
FTNMFATWSPSKARLHLQGRSNAWRPQVNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTSMYVKEFLISSS

QDGHQWTLFFQNGKVKVFQGNQDSFTPVVNSLDPPLLTRYLRIHPQSWVHQIALRMEVLGCEAQDLY

表 5. B 域缺失的因子 VIII 的胺基酸序列(B 域缺失，除 5 個胺基酸殘基以外) (SEQ ID NO: 68)
ATRRYYLGAVELSWDYMQSDLGELPVDARFPPRVPKSFPFNTSVVYKKTLFVEFTDHLFNIAKPRPPWMGLL GPTIQAEVYDTVVITLKNMASHPVSLHAVGVSYWKASEGAEYDDQTSQREKEDDKVFPGGSHTYVWQVLK ENGPMASDPLCLTYSYLSHVDLVKDLNSGLIGALLVCREGSLAKEKTQTLHKFILLFAVFDEGKSWHSETKN SLMQDRDAASARAWPKMHTVNGYVNRSLPGLIGCHRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQA SLEISPITFLTAQTLLMDLGQFLLFCHISSHQHDGMEAYVKVDSCPEEPQLRMKNNEEAEDYDDDLTDSEMD VVRFDDDNSPSFIQIRSVAKKHPKTWVHYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQRIGRKYKKVR FMAYTDETFKTREAIQHESGILGPLLYGEVGDTLLIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDF PILPGEIFKYKWTVTVEDGPTKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQIMSDKRNVIL FSVFDENRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAYWYILSIGAQTDF LSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNRGMTALLKVSSCDKNTGDYY EDSYEDISAYLLSKNNAIEPR*SFSQN*EITRTTLQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSPRSFQKKTRH YFIAAVERLWDYGMSSSPHVLRNRAQSGSVPQFKKVVFQEFTDGSFTQPLYRGELNEHLGLLGPYIRAEVED NIMVTFRNQASRPYSFYSSLISYEEDQRQGAEPRKNFVKPNETKTYFWKVQHHMAPTKDEFDCKAWAYFSD VDLEKDVHSGLIGPLLVCHTNTLNPAHGRQVTVQEFALFFTIFDETKSWYFTENMERNCRAPCNIQMEDPTF KENYRFHAINGYIMDTLPGLVMAQDQRIRWYLLSMGSNENIHSIHFSGHVFTVRKKEEYKMALYNLYPGVF ETVEMLPSKAGIWRVECLIGEHLHAGMSTLFLVYSNKCQTPLGMASGHIRDFQITASGQYGQWAPKLARLH YSGSINAWSTKEPFSWIKVDLLAPMIIHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFF GNVDSSGIKHNIFNPPIIARYIRLHPTHYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSYFTNMFAT WSPSKARLHLQGRSNAWRPQVNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTSMYVKEFLISSSQDGHQW TLFFQNGKVKVFQGNQDSFTPVVNSLDPPLLTRYLRIHPQSWVHQIALRMEVLGCEAQDLY

【0184】 「B域缺失的FVIII」可具有下列專利所公開的全部或部分缺失：美國專利號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、和6,458,563，美國公開號US 2017/0073393 A1和US 2012/308641 A1，和國際公開號WO 2011/041770 A1、WO 2015/106052 A1 (PCT/US2015/010738)、和WO 2016/025764。在一些實施例中，在本公開的方法中使用的B域缺失的FVIII序列包含美國專利號6,316,226的第4欄第4行至第5欄第28行和實例1-5所公開的任何一個缺失(也在US 6,346,513中公開)。在其他實施例中，B域缺失的因子VIII是S743/Q1638 B域缺失的因子VIII (SQ BDD FVIII) (例如具有從胺基酸744至胺基酸1637缺失的因子VIII，例如具有成熟FVIII的胺基酸1-743和胺基酸1638-2332的因子VIII)。在一些實施例中，在本公開的方法中所使用的B域缺失的FVIII具有美國專利號5,789,203的第2欄第26-51行和實例5-8處公開的缺失(也在US 6,060,447、US 5,595,886、和US 6,228,620中公開)。在一些實施例中，B域缺失的因子VIII具有下列者所描述的缺失：美國專利號5,972,885的第1欄第25行至第2

欄第40行；美國專利號6,048,720的第6欄第1-22行和實例1；美國專利號5,543,502的第2欄第17-46行；美國專利號5,171,844的第4欄第22行至第5欄第36行；美國專利號5,112,950的第2頁第2欄第55-68行和實例1；美國專利號4,868,112的第2欄第2行至第19欄第21行和表2；美國專利號7,041,635的第2欄第1行至第3欄第19行、第3欄第40行至第4欄第67行、第7欄第43行至第8欄第26行、和第11欄第5行至第13欄第39行；或美國專利號6,458,563的第4欄第25-53行。在一些實施例中，B域缺失的FVIII多肽具有大部分B域的缺失，但仍含有使初級轉譯產物在體內蛋白水解加工成兩條多肽鏈所必需的B域的胺基末端序列，如WO 91/09122中公開的。在一些實施例中，B域缺失的FVIII多肽係構建成缺失胺基酸747-1638，即B域幾乎完全缺失。Hoeben R.C., 等 J. Biol. Chem. 265 (13): 7318-7323 (1990)。B域缺失的因子VIII多肽還可含有FVIII的胺基酸771–1666或胺基酸868-1562的缺失。Meulien P., 等Protein Eng. 2(4): 301-6 (1988)。作為本公開的一部分的另外B域缺失包括：缺失胺基酸982至1562或760至1639 (Toole等，Proc. Natl. Acad. Sci. U.S.A. (1986) 83, 5939-5942))、797至1562 (Eaton，等Biochemistry (1986) 25:8343-8347))、741至1646 (Kaufman (PCT公開的申請號WO 87/04187))、747-1560 (Sarver，等，DNA (1987) 6:553-564))、741至1648 (Pasek (PCT application No。88/00831))、或816至1598或741至1648 (Lagner (Behring Inst. Mitt. (1988) No 82:16-25, EP 295597))。在特定的實施例中，該B域缺失的FVIII多肽包含成熟FVIII的胺基酸殘基746至1648的缺失(對應於全長FVIII的765至1665的缺失)。在其他實施例中，該B域缺失的FVIII多肽包含成熟FVIII的胺基酸殘基745至1648的缺失(對應於全長FVIII的764至1665的缺失)。

【0185】　在其他實施例中，BDD FVIII係包括含有B域片段的FVIII多肽，該B域片段係保留一個或多個N連接的糖基化位點(例如，殘基757、784、828、900、963，或任選為943)，該B域片段對應於全長FVIII序列的胺基酸序列。B域片段的實例包括Miao, H.Z., 等, Blood 103(a): 3412-3419 (2004), Kasuda, A, 等, J. Thromb. Haemost. 6: 1352-1359 (2008)，和Pipe, S.W., 等, J. Thromb. Haemost. 9: 2235-2242 (2011)中所公開的B域的226個胺基酸或163個胺基酸(即，保留B域前面

的226個胺基酸或163個胺基酸)。在又一些其他的實施例中，BDD FVIII進一步包含殘基309處的點突變(由Phe突變為Ser)以改善BDD FVIII多肽的表現。參見Miao, H.Z., 等, Blood 103(a): 3412-3419 (2004)。在又一些其他的實施例中，該BDD FVIII包括含有部分B域，但不含有一個或多個弗林蛋白酶切割位點(例如，Arg1313和Arg 1648)的FVIII多肽。參見Pipe, S.W., 等, J. Thromb. Haemost. 9: 2235-2242 (2011)。在一些實施例中，該BDD FVIII包含含有對應於成熟全長FVIII的胺基酸765至1652有缺失的單鏈FVIII(也稱為rFVIII-單鏈和AFSTYLA®)。參見美國專利號7,041,635。前述缺失中的每一種可以在任何FVIII序列中進行。

【0186】 在一些實施例中，該FVIII具有部分B域。在一些實施例中，具有部分B域的FVIII多肽為FVIII198。FVIII198是含有單鏈FVIIIFc分子-226N6的部分B域。數字226表示FVIII之B域的N端226號胺基酸，且N6表示B域中的六個N-糖基化位點。

【0187】 在某些實施例中，該FVIII多肽選自公開號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中所公開的FVIII多肽。

【0188】 在一些實施例中，FVIII剛好在胺基酸1648(在全長因子VIII或SEQ ID NO: 65中)、胺基酸754(在S743/Q1638 B域缺失的因子VIII或SEQ ID NO: 67中)處的精胺酸、或對應的精胺酸殘基(在其他變異體中)後被切割，因此產生重鏈和輕鏈。在其他實施例中，FVIII多肽包含重鏈和輕鏈，該重鏈和輕鏈通過金屬離子介導的非共價鍵來連接或締合。

【0189】 在其他實施例中，FVIII是單鏈FVIII，其未剛好在胺基酸1648(在全長因子VIII或SEQ ID NO: 65中)、胺基酸754(在S743/Q1638 B域缺失的VIII或SEQ ID NO: 67中)處的精胺酸、或對應的精胺酸殘基(在其他變異體中)後被切割。單鏈FVIII可包含一個或多個胺基酸替代。在一些實施例中，該胺基酸替代在對應於全長成熟因子VIII多肽(SEQ ID NO: 65)的殘基1648、殘基1645、或二者，或SQ BDD因子VIII (SEQ ID NO: 67)的殘基754、殘基751、或二者的殘基處。該胺基

酸替代可以是除精胺酸外的任何胺基酸，例如，異白胺酸、白胺酸、離胺酸、甲硫胺酸、苯丙胺酸、蘇胺酸、色胺酸、擷胺酸、丙胺酸、天門冬醯胺酸、天門冬胺酸、半胱胺酸、麩胺酸、麩醯胺酸、甘胺酸、脯胺酸、硒代半胱胺酸、絲胺酸、酪胺酸、組胺酸、鳥胺酸、吡咯離胺酸、或牛磺酸。

【0190】　FVIII可進一步由凝血酶切割，然後經活化為FVIIIa，用作激活的因子IX (FIXa)的輔因子。且激活的FIX連同激活的FVIII係形成X酶複合物，並使因子X轉化為激活的因子X (FXa)。為了激活，FVIII在胺基酸372、740、和1689(對應於B域缺失的FVIII序列中的胺基酸372、740、和795)處的三個精胺酸殘基後由凝血酶切割，切割後生成具有50kDa的A1、43kDa的A2、和73kDa的A3-C1-C2鏈的FVIIIa。在一些實施例中，可用於本公開的FVIII多肽是非活化的FVIII。在其他實施例中，該FVIII多肽是激活的FVIII。

【0191】　具有與VWF蛋白連接或締合的FVIII多肽的蛋白，可包含與SEQ ID NO: 65或67至少50%、60%、70%、80%、90%、95%、96%、97%、98%、99%、或100%相同的序列，其中該序列具有FVIII凝血活性，例如，激活因子IX作為輔因子以使因子X轉化為激活的因子X (FXa)。

【0192】　如本文所用的，「雜合」或「嵌合」多肽和蛋白係包括第一多肽和第二多肽的組合。在一些實施例中，該雜合或嵌合多肽係包含單一多肽鏈，例如包含FVIII多肽和XTEN的嵌合多肽。參見，例如，US 2015/0158929 A1，其通過提述以其整體併入本文。在一些實施例中，該雜合或嵌合多肽係包含第一多肽鏈(例如，與XTEN序列和第一Ig恆定區或其部分融合的VWF片段)與第二多肽鏈(例如，與第二Ig恆定區或其部分融合的FVIII多肽)的組合，因此形成異二聚體。參見，例如，US 2015/0266943 A1，US 2016/0251408 A1，US 2017/0073393 A1，其中各文本係通過提述以其整體併入本文。在一些實施例中，在雜合體中的第一多肽和第二多肽係經由蛋白-蛋白相互作用(諸如電荷-電荷或疏水性相互作用)彼此締合。在其他實施例中，第一多肽包含VWF蛋白-XTEN-Fc融合蛋白，且第二多肽包含FVIII-Fc融合蛋白，這使雜合體形成異二聚體，其中該XTEN含有少於288個胺基酸。在其他實施例中，該第一多肽包含VWF蛋白-XTEN-Fc融合蛋

白，且該第二多肽包含FVIII(X)-Fc融合蛋白，這使雜合體形成異二聚體，其中該XTEN含有少於288個胺基酸。該第一多肽和該第二多肽可通過第一Fc區和第二Fc區之間的共價鍵(例如雙硫鍵)來締合。該第一多肽和該第二多肽可進一步通過VWF片段和FVIII多肽之間的結合彼此締合。

【0193】 在某些實施例中，本文公開的嵌合多肽包含FVIII蛋白，該FVIII蛋白包含第一FVIII多肽片段、XTEN序列、第二FVIII多肽片段、和Fc區。在一些實施例中，該FVIII蛋白包含，從N端至C端的方向排列，第一FVIII多肽片，融合至XTEN序列，融合至第二FVIII多肽片段，融合至Fc區。在具體的實施例中，該FVIII蛋白包含含有SEQ ID NO:215之胺基酸序列的第一FVIII多肽片段、含有SEQ ID NO: 8的胺基酸序列的XTEN序列、含有SEQ ID NO: 216的胺基酸序列的第二FVIII多肽，和/或含有SEQ ID NO: 217的胺基酸序列的第一Fc區。

【0194】 在一個具體的實施例中，該嵌合多肽是rFVIIIFc-VWF-XTEN，且包含含有SEQ ID NO: 201之胺基酸序列的FVIII蛋白。在另一個具體的實施例中，rFVIIIFc-VWF-XTEN包含SEQ ID NO: 207的胺基酸序列。

【0195】 在一些實施例中，該FVIII蛋白進一步包含FVIII信號肽序列。在一個具體的實施例中，該FVIII蛋白包含含有SEQ ID NO: 64之胺基酸序列的FVIII信號肽、含有SEQ ID NO: 215之胺基酸序列的第一FVIII多肽片段、含有SEQ ID NO: 8之胺基酸序列的XTEN序列、含有SEQ ID NO: 216之胺基酸序列的第二FVIII多肽，和/或含有SEQ ID NO: 217的胺基酸序列的第一Fc區。

【0196】 在一個具體的實施例中，該嵌合多肽是rFVIIIFc-VWF-XTEN，且包含含有SEQ ID NO: 203之胺基酸序列的FVIII蛋白。在另一個具體的實施例中，rFVIIIFc-VWF-XTEN包含由SEQ ID NO: 204的核酸序列或其片段所編碼的FVIII蛋白。與本文公開之嵌合多肽的FVIII蛋白有關的其他示例性多肽序列係在表18至19中提供。

【0197】 許多有功能的FVIII變異體是已知的，如前後文所討論的。此外，FVIII中的數百個非功能性突變已經在血友病患者中被找出來，且已經確定了，這些突變對FVIII功能的作用更多係是由於它們位於FVIII的3維結構內而非取代的性

質(Cutler等, Hum. Mutat. 19:274-8 (2002))，其通過提述一起整體併入本文。此外，來自人類和其他物種的FVIII之間的比較已經鑒別出了功能可能所必須的保守殘基(Cameron等, Thromb. Haemost. 79:317-22 (1998)；US 6,251,632)，其通過提述以其整體併入本文。

III.B．馮威里氏因子(VWF)片段

【0198】　VWF(也稱為F8VWF)是存在於血漿中的大的多聚體糖蛋白，且在內皮(在懷布爾-帕拉德體（Weibel-Palade bodies）中)、巨核細胞(血小板α-顆粒)、和內皮下結締組織中係組成性地產生。基本的VWF單體是2813個胺基酸的蛋白。每個單體含有多個具有特定功能的特定域，D'/D3域(其結合因子VIII)，A1域(其結合血小板GPIb受體、肝素、和/或可能的膠原)，A3域(其結合膠原)，C1域(當激活時，在該C1域中的RGD域結合血小板整聯蛋白αIIbβ3)，和該蛋白的C末端處的「半胱胺酸結(cysteine knot)」域(其中VWF與血小板衍生的生長因子(PDGF)、轉化生長因子-β (TGFβ)和β-人絨毛膜促性腺激素(βHCG)共有該域)。

【0199】　如本文所用的術語「VWF片段」包括，但不限於，包含D'域和D3域的功能性VWF片段，其能夠抑制內源性VWF與FVIII的結合。在一些實施例中，該VWF片段結合FVIII蛋白。在其他實施例中，該VWF片段阻斷FVIII蛋白上的VWF結合位點，因此抑制FVIII蛋白與內源性VWF的相互作用。在其他實施例中，該VWF片段阻斷FVIII與內源性VWF的結合，因此防止FVIII蛋白通過VWF清除路徑的清除。該VWF片段包括保留VWF的這些活性的衍生物、變異體、突變體、或類似物。

【0200】　人類VWF的2813個單體胺基酸序列在Genbank中報導為登錄號NP000543.2。編碼人類VWF的核苷酸序列在Genbank中報導為登錄號NM000552.3。人類VWF的核苷酸序列命名為SEQ ID NO: 20。SEQ ID NO: 21為全長VWF的胺基酸序列。VWF的每個域在表6中列出。

表6. VWF序列(人)

VWF 域	胺基酸序列
VWF 信號肽 SEQ ID NO: 208 (SEQ ID NO: 21 的胺基酸 1 至 22)	1 MIPARFAGVL LALALILPGT LC22 **[01]**
VWF D1D2 域 SEQ ID NO: 209 (SEQ ID NO: 21 的胺基酸 23 至 763)	23 **AEGTRGRS STARCSLFGS DFVNTFDGSM** 51 **YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG** 101 **TVTQGDQRVS MPYASKGLYL ETEAGYYKLS GEAYGFVARIDGSGNFQVLL** 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 IQLPLLKGDL RIQHTVTASV RLSYGEDLQM** 501 **DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG** 551 **NAWKLHGDCQ DLQKQHSDPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS** 601 **PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCEL** 651 **NCPKGQVYLQ CGTPCNLTCR SLSYPDEECN EACLEGCFCP PGLYMDERGD** 701 **CVPKAQCPCY YDGEIFQPED IFSDHHTMCY CEDGFMHCTM SGVPGSLLPD** **[02]** 751 AVLSSPLSHR SKR 763
VWF D'域 SEQ ID NO: 210 (SEQ ID NO: 21 的胺基酸 764 至 866)	764 SLSCRPP MVKLVCPADN LRAEGLECTKTCQNYDLECM 801 SMGCVSGCLC PPGMVRHENR CVALERCPCF HQGKEYAPGE TVKIGCNTCV **[03]** 851 CRDRKWNCTD HVCDAT 866
VWF D3 域 SEQ ID NO: 211 (SEQ ID NO: 21 的胺基酸 867 至 1240)	867 CSTI GMAHYLTFDG LKYLFPGECQ YVLVQDYCGS 901 NPGTFRILVG NKGCSHPSVK CKKRVTILVE GGEIELFDGE VNVKRPMKDE 951 THFEVVESGR YIILLLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD 1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI 1051 MKQTMVDSSC RILTSDVFQD CNKLVDPEPY LDVCIYDTCS CESIGDCACF 1101 CDTIAAYAHV CAQHGKVVTW RTATLCPQSC EERNLRENGY ECEWRYNSCA 1151 PACQVTCQHP EPLACPVQCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE **[04]** 1201 VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP 1240
VWF A1 域 SEQ ID NO: 212 (SEQ ID NO: 21 的胺基酸 1241 至 1479)	1241 GGLVVPPTDA 1251 PVSPTTLYVE DISEPPLHDF YCSRLLDLVF LLDGSSRLSE AEFEVLKAFV 1301 VDMMERLRIS QKWVRVAVVE YHDGSHAYIG LKDRKRPSEL RRIASQVKYA 1351 GSQVASTSEV LKYTLFQIFS KIDRPEASRI ALLLMASQEP QRMSRNFVRY 1401 VQGLKKKKVI VIPVGIGPHA NLKQIRLIEK QAPENKAFVL SSVDELEQQR 1451 DEIVSYLCDL APEAPPPTLP PDMAQVTVG 1479

VWF A2 域至 C 端 SEQ ID NO: 213 (SEQ ID NO: 21 的胺基酸 1480 至 2813)	1480 1501 1551 1601 1651 1701 1751 1801 1851 1901 1951 2001 2051 2101 2151 2201 2251 2301 2351 2401 2451 2501 2551 2601 2651 2701 2751 **[05]**	PGLLGVSTLGP KRNSMVLDVA FVLEGSDKIG EADFNRSKEF MEEVIQRMDV GQDSIHVTVL QYSYMVTVEY PFSEAQSKGD ILQRVREIRY QGGNRTNTGL ALRYLSDHSF LVSQGDREQA PNLVYMVTGN PASDEIKRLP GDIQVVPIGV GPNANVQELE RIGWPNAPIL IQDFETLPRE APDLVLQRCC SGEGLQIPTL SPAPDCSQPL DVILLLDGSS SFPASYFDEM KSFAKAFISK ANIGPRLTQV SVLQYGSITT IDVPWNVVPE KAHLLSLVDV MQREGGPSQI GDALGFAVRY LTSEMHGARP GASKAVVILV TDVSVDSVDA AADAARSNRV TVFPIGIGDR YDAAQLRILA GPAGDSNVVK LQRIEDLPTM VTLGNSFLHK LCSGFVRICM DEDGNEKRPG DVWTLPDQCH TVTCQPDGQT LLKSHRVNCD RGLRPSCPNS QSPVKVEETC GCRWTCPCVC TGSSTRHIVT FDGQNFKLTG SCSYVLFQNK EQDLEVILHN GACSPGARQG CMKSIEVKHS ALSVEXHSDM EVTVNGRLVS VPYVGGNMEV NVYGAIMHEV RFNHLGHIFT FTPQNNEFQL QLSPKTFASK TYGLCGICDE NGANDFMLRD GTVTTDWKTL VQEWTVQRPG QTCQPILEEQ CLVPDSSHCQ VLLLPLFAEC HKVLAPATFY AICQQDSCHQ EQVCEVIASY AHLCRTNGVC VDWRTPDFCA MSCPPSLVYN HCEHGCPRHC DGNVSSCGDH PSEGCFCPPD KVMLEGSCVP EEACTQCIGE DGVQHQFLEA WVPDHQPCQI CTCLSGRKVN CTTQPCPTAK APTCGLCEVA RLRQNADQCC PEYECVCDPV SCDLPPVPHC ERGLQPTLTN PGECRPNFTC ACRKEECKRV SPPSCPPHRL PTLRKTQCCD EYECACNCVN STVSCPLGYL ASTATNDCGC TTTTCLPDKV CVHRSTIYPV GQFWEEGCDV CTCTDMEDAV MGLRVAQCSQ KPCEDSCRSG FTYVLHEGEC CGRCLPSACE VVTGSPRGDS QSSWKSVGSQ WASPENPCLI NECVRVKEEV FIQQRNVSCP QLEVPVCPSG FQLSCKTSAC CPSCRCERME ACMLNGTVIG PGKTVMIDVC TTCRCMVQVG VISGFKLECR KTTCNPCPLG YKEENNTGEC CGRCLPTACT IQLRGGQIMT LKRDETLQDG CDTHFCKVNE RGEYFWEKRV TGCPPFDEHK CLAEGGKIMK IPGTCCDTCE EPECNDITAR LQYVKVGSCK SEVEVDIHYC QGKCASKAMY SIDINDVQDQ CSCCSPTRTE PMQVALHCTN GSVVYHEVLN 2801 AMECKCSPRK CSK 2813

【0201】 如本文所用的VWF蛋白可以是包含VWF的D'域和D3域的VWF片段，其中該VWF片段結合因子VIII (FVIII)並抑制內源性VWF(全長VWF)與FVIII的結合。包含D'域和D3域的VWF片段可進一步包含VWF域，該VWF域係選自下列群組：A1域、A2域、A3域、D1域、D2域、D4域、B1域、B2域、B3域、C1域、C2域、CK域，其一種或多種片段，和其任何組合。在一些實施例中，VWF片段包含有、實質上由下列片段所構成，或係由下列片段所構成：(1) VWF的D'和D3域或其片段；(2) VWF的D1、D'、和D3域或其片段；(3) VWF的D2、D'、和D3域或其片段；(4) VWF的D1、D2、D'、和D3域或其片段；或(5) VWF的D1、D2、D'、D3、和A1域或其片段。本文所述的VWF片段不含有與VWF清除受體結合的位點。在其他實施例中，本文所述的VWF片段不是SEQ ID NO: 21的胺基酸764至1274。本公開的VWF片段可包含與該VWF片段連接或融合的任何其他序列。例如，本文所述的VWF片段可進一步包含信號肽。

【0202】 在一些實施例中，包含D'域和D3域的VWF片段係與FVIII蛋白結合或

締合。參見，例如，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，其中各文本係通過提述以其整體併入本文。通過與FVIII蛋白的結合或締合，本公開的VWF片段保護FVIII免於蛋白酶切割和FVIII激活，穩定FVIII的重鏈和輕鏈，且防止FVIII通過清道夫受體的清除。在其他實施例中，該VWF片段係與FVIII蛋白結合或締合，並阻斷或防止FVIII蛋白與磷脂或激活的蛋白C的結合。通過防止或抑制FVIII蛋白與內源性、全長VWF的結合，本公開的VWF片段降低FVIII通過VWF清除受體的清除，且因此延長該嵌合多肽的半衰期。因此，該嵌合多肽的半衰期延長是由於與缺乏針對FVIII蛋白的VWF清除受體結合位點的VWF片段的結合或締合，且通過來自含有VWF清除受體結合位點的內源性VWF的VWF片段來屏蔽或保護FVIII蛋白。結合VWF片段的或受VWF片段保護的FVIII蛋白，還可讓FVIII蛋白再循環。通過消除全長VWF分子中所包含的VWF清除路徑受體結合位點，本公開的FVIII/VWF異二聚體從VWF清除路徑中被屏蔽掉，進一步延長了FVIII半衰期。

【0203】　在一些實施例中，可用於本公開的VWF蛋白包含VWF的D'域和D3域，其中該D'域與SEQ ID NO: 21的胺基酸764至866為至少60%、70%、80%、85%、90%、95%、96%、97%、98%、99%、或100%相同，其中該VWF蛋白防止或抑制內源性VWF與FVIII的結合。在其他實施例中，VWF蛋白包含VWF的D'域和D3域，其中該D3域與SEQ ID NO: 21的胺基酸867至1240至少為60%、70%、80%、85%、90%、95%、96%、97%、98%、99%、或100%相同，其中該VWF蛋白防止或抑制內源性VWF與FVIII的結合。在一些實施例中，本文所述的VWF蛋白包含VWF的D'域和D3域，基本上由VWF的D'域和D3域構成，或由VWF的D'域和D3域構成，該VWF的D'域和D3域與SEQ ID NO: 21的胺基酸764至1240至少為60%、70%、80%、85%、90%、95%、96%、97%、98%、99%、或100%相同，其中該

VWF蛋白防止或抑制內源性VWF與FVIII的結合。在其他實施例中，VWF蛋白包含D1、D2、D'、和D3域、實質上由D1、D2、D'、和D3域構成，或係由D1、D2、D'、和D3域構成，該D1、D2、D'、和D3域與SEQ ID NO: 21的胺基酸23至1240至少為60%、70%、80%、85%、90%、95%、96%、97%、98%、99%、或100%相同，其中該VWF蛋白防止或抑制內源性VWF與FVIII的結合。在又一些其他的實施例中，該VWF蛋白進一步包含與其可操作性連接的信號肽。

【0204】　在一些實施例中，可用於本公開的VWF蛋白實質上由以下或係由以下所構成：(1) D'D3域、D1D'D3域、D2D'D3域、或D1D2D'D3域，和(2)另外的VWF序列，其多達約10個胺基酸(例如，從SEQ ID NO: 21的胺基酸764至1240到SEQ ID NO: 21的胺基酸764至1250的任何序列)，多達約15個胺基酸(例如，從SEQ ID NO: 21的胺基酸764至1240到SEQ ID NO: 21的胺基酸764至1255的任何序列)，多達約20個胺基酸(例如，從SEQ ID NO: 21的胺基酸764至1240到SEQ ID NO: 21的胺基酸764至1260的任何序列)，多達約25個胺基酸(例如，從SEQ ID NO: 21的胺基酸764至1240到SEQ ID NO: 21的胺基酸764至1265的任何序列)，或多達約30個胺基酸(例如，從SEQ ID NO: 21的胺基酸764至1240到SEQ ID NO: 21的胺基酸764至1260的任何序列)。在一些實施例中，包含D'域和D3域或基本上由D'域和D3域構成的VWF蛋白既不是SEQ ID NO: 21的胺基酸764至1274，也不是全長成熟VWF。在一些實施例中，該D1D2域係對D'D3域反式表現。在一些實施例中，該D1D2域係對D'D3域順式表現。

【0205】　在其他實施例中，包含與D1D2域連接的D'D3域的VWF蛋白進一步包含細胞內切割位點，例如，(PACE(弗林蛋白酶)或PC5的切割位點)，其允許在表現時從D'D3域中切割D1D2域。細胞內切割位點的非限制性實例在本文的其他地方公開。

【0206】　在又一些其他實施例中，VWF蛋白包含D'域和D3域，但不包含選自下列群組的胺基酸序列：(1) 對應於SEQ ID NO: 21的胺基酸1241至2813，(2) 對應於SEQ ID NO: 21的胺基酸1270至胺基酸2813，(3) 對應於SEQ ID NO: 21的胺基酸1271至胺基酸2813，(4) 對應於SEQ ID NO: 21的胺基酸1272至胺基酸2813，

(5) 對應於SEQ ID NO: 21的胺基酸1273至胺基酸2813，(6) 對應於 SEQ ID NO: 21的胺基酸1274至胺基酸2813，和其任何組合。

【0207】　在又一些其他實施例中，本公開的VWF蛋白包含有對應於D'域、D3域、和A1域的胺基酸序列、實質上由對應於D'域、D3域、和A1域的胺基酸序列構成，或係由對應於D'域、D3域、和A1域的胺基酸序列構成，其中該胺基酸序列與SEQ ID NO: 21的胺基酸764至1479至少為60%、70%、75%、80%、85%、90%、95%、96%、97%、98%、99%、或100%相同，其中該VWF蛋白防止內源性VWF與FVIII的結合。在特定的實施例中，該VWF蛋白不是SEQ ID NO: 21的胺基酸764至1274。

【0208】　在一些實施例中，本公開的VWF蛋白包含D'域和D3域，但不包含至少一種選自下列群組的VWF域(1) A1域，(2) A2域，(3) A3域，(4) D4域，(5) B1域，(6) B2域，(7) B3域，(8) C1域，(9) C2域，(10) CK域，(11) CK域和C2域，(12) CK域、C2域、和C1域，(13) CK域、C2域、C1域、B3域，(14) CK域、C2域、C1域、B3域、B2域，(15) CK域、C2域、C1域、B3域、B2域、和B1域，(16) CK域、C2域、C1域、B3域、B2域、B1域、和D4域，(17) CK域、C2域、C1域、B3域、B2域、B1域、D4域、和A3域，(18) CK域、C2域、C1域、B3域、B2域、B1域、D4域、A3域、和A2域，(19) CK域、C2域、C1域、B3域、B2域、B1域、D4域、A3域、A2域、和A1域，和(20)其任何組合。

【0209】　在又一些其他實施例中，該VWF蛋白包含D'D3域和一種或多種域或模組。此類域或模組的實例包括，但不限於，Zhour等, Blood published online April 6, 2012: DOI 10.1182/blood-2012-01-405134中公開的域和模組，其通過提述以其整體併入本文。例如，該VWF蛋白可包含D'D3域和一種或多種域或模組，其選自下列群組：A1域、A2域、A3域、D4N模組、VWD4模組、C8-4模組、TIL-4模組、C1模組、C2模組、C3模組、C4模組、C5模組、C5模組、C6模組、和其任何組合。

【0210】　在又一些其他實施例中，該VWF蛋白係與異源部分連接，其中該異源部分係與VWF蛋白的N端或C端連接，或插入緊鄰該VWF蛋白中的一個或多個

胺基酸的下游(例如，一個或多個XTEN插入位點)。例如，異源部分在該VWF蛋白中的插入位點可以在D'域、D3域、或二者之中。該異源部分可以是半衰期延長物。

【0211】　在某些實施例中，可用於本公開的VWF蛋白係形成多聚體，例如，二聚體、三聚體、四聚體、五聚體、六聚體、七聚體、或更高級的聚體。在其他實施例中，該VWF蛋白是僅具有一個VWF蛋白的單體。在一些實施例中，本公開的VWF蛋白可具有一個或多個胺基酸替代、缺失、添加、或修飾。在一些實施例中，該VWF蛋白可包括胺基酸替代、缺失、添加、或修飾，使得該VWF蛋白不能形成雙硫鍵或形成二聚體或多聚體。在其他實施例中，該胺基酸替代係在D'域和D3域內。在特定的實施例中，可用於本公開的VWF蛋白含有在對應於 SEQ ID NO: 21殘基1099、殘基1142，或兩個殘基1099和1142處的殘基有至少一個胺基酸替代。該至少一個胺基酸替代可以是非天然存在於野生型VWF中的任何胺基酸。例如，該胺基酸替代可以是除了半胱胺酸外的任何胺基酸，例如，異白胺酸、丙胺酸、白胺酸、天門冬醯胺酸、離胺酸、天門冬胺酸、甲硫胺酸、苯丙胺酸、麩胺酸、蘇胺酸、麩醯胺酸、色胺酸、甘胺酸、擷胺酸、脯胺酸、絲胺酸、酪胺酸、精胺酸、或組胺酸。在另一實例中，該胺基酸替代具有一種或多種防止或抑制VWF蛋白形成多聚體的胺基酸。

【0212】　在某些實施例中，可用於本文的VWF蛋白可進一步經修飾以改善其與FVIII的相互作用，例如，以改善對FVIII的結合親和力。作為非限制性實例，該VWF蛋白包含對應於SEQ ID NO: 21的胺基酸764的殘基處的絲胺酸殘基和對應於SEQ ID NO: 21的胺基酸773的殘基處的離胺酸殘基。殘基764和/或773可有助於該VWF蛋白與FVIII的結合親和力。在其他實施例中，可用於本公開的VWF蛋白可具有其他修飾，例如，該蛋白可以經聚乙二醇化、糖基化、羥乙基澱粉化(hesylated)、或聚唾液酸化。

【0213】　在某些實施例中，本文公開的嵌合多肽包含VWF蛋白，該VWF蛋白包含VWF片段、XTEN序列、FVIII的a2連接子、和Fc區。在一些實施例中，該VWF蛋白包含，以從N端到C端的方向排列，VWF片段，融合至XTEN序列，融合至a2

連接子，融合至Fc區。在某些實施例中，該VWF蛋白包含VWF的D'域(該D'域包含SEQ ID NO: 210的胺基酸序列)，VWF的D3域(該D3域包含SEQ ID NO: 214的胺基酸序列)，包含SEQ ID NO: 58 (AE144_5A)的胺基酸序列的XTEN序列，包含SEQ ID NO: 88的胺基酸序列的a2連接子，和/或包含SEQ ID NO: 217的胺基酸序列的Fc區。

【0214】 在一個具體的實施例中，該嵌合多肽是rFVIIIFc-VWF-XTEN，並包含包含SEQ ID NO: 202的胺基酸序列的VWF蛋白。

【0215】 在一些實施例中，該VWF蛋白包含VWF片段，該VWF片段包含VWF的D1、D2、D'、和/或D3域。在一個實施例中，該VWF片段包含VWF的D1D2域，該D1D2域包含SEQ ID NO: 209的胺基酸序列。在一些實施例中，該VWF蛋白進一步包含VWF信號肽序列。在一個實施例中，該VWF信號肽包含SEQ ID NO: 208的胺基酸序列。在一個具體的實施例中，該VWF蛋白包含：包含SEQ ID NO: 208的胺基酸序列的VWF信號肽，包含SEQ ID NO: 209的胺基酸序列的D1D2區域，VWF的D'域(該D'域包含SEQ ID NO: 210的胺基酸序列)，VWF的D3域(該D3域包含SEQ ID NO: 214的胺基酸序列)，包含SEQ ID NO: 58 (AE144_5A)的胺基酸序列的XTEN序列，包含SEQ ID NO: 88的胺基酸序列的a2連接子，和/或包含SEQ ID NO: 217的胺基酸序列的Fc區。

【0216】 在一個具體的實施例中，該嵌合多肽是rFVIIIFc-VWF-XTEN，並包含含有SEQ ID NO: 205的胺基酸序列之VWF蛋白。在另一具體的實施例中，rFVIIIFc-VWF-XTEN包含由SEQ ID NO: 206的核酸序列所編碼的VWF蛋白或其片段。涉及本文公開的嵌合多肽的VWF蛋白的其他示例性多肽序列係在表18至19中提供。

III.C．延長半衰期的部分（Half-Life Extending Moieties）

【0217】 在一些實施例中，本公開的嵌合多肽包含一個或多個延長半衰期的部分。在一些實施例中，該嵌合多肽的FVIII多肽(即，FVIII蛋白)係與一個或多個延長半衰期的部分融合或締合。在其他實施例中，該嵌合多肽包含至少兩個

延長半衰期的部分，與FVIII多肽融合的第一延長半衰期的部分和與VWF的D'D3域融合的第二延長半衰期的部分。在一些實施例中，該第一延長半衰期的部分與該FVIII多肽的C端或N端融合。在一些實施例中，該第一延長半衰期的部分被插入在該FVIII多肽中。在一些實施例中，該第一延長半衰期的部分被插入在該FVIII多肽的B域中。在一些實施例中，該第一延長半衰期的部分被插入在緊鄰對應於SEQ ID NO: 65的胺基酸殘基745的胺基酸的下游的FVIII多肽中。在一些實施例中，該第一異源部分通過連接子與該FVIII多肽融合。

【0218】　在某些實施例中，該VWF片段中的VWF的D'D3域可與第二延長半衰期的部分融合或締合。在一些實施例中，該第二延長半衰期的部分可與該VWF片段的C端或N端融合。在一些實施例中，該第二延長半衰期的部分被插入在該VWF片段中。在一些實施例中，該第二延長半衰期的部分與該VWF片段的C端融合。在某些實施例中，其中該第二延長半衰期的部分通過連接子與該VWF片段融合。

【0219】　在其他實施例中，該嵌合多肽包含FVIII多肽和包含VWF的D'域和D3域的VWF片段，其中VWF的D'D3域與一個或多個延長半衰期的部分融合，且其中VWF的D'D3域和FVIII多肽係與比FVIII和VWF之間天然存在的鍵更強的鍵來締合。

【0220】　在一些實施例中，該嵌合多肽包含FVIII多肽和包含VWF的D'域和D3域的VWF片段，其中VWF的D'D3域通過連接子與FVIII多肽融合。在一些實施例中，該連接子是可切割的連接子。在一些實施例中，VWF的D'域和D3域通過至少一個非共價鍵與FVIII多肽締合。在某些實施例中，VWF的D'域和D3域進一步與Fc融合。在一些實施例中，VWF的D'域和D3域通過連接子與Fc融合。在一些實施例中，該Fc通過另外的連接子與第二Fc融合。在某些實施例中，該Fc和該第二Fc通過共價鍵(例如雙硫鍵)彼此締合。在特定的實施例中，該嵌合多肽包含FVIII多肽和包含VWF的D'域和D3域的VWF片段，如國際公開號WO 2017/222337 A1中公開的，其通過提述以其整體併入本文。

【0221】　該第一延長半衰期的部分、該第二延長半衰期的部分，或二者可選

自下列群組：FcRn結合配偶體(例如，白蛋白或免疫球蛋白Fc區)、XTEN序列、人絨毛膜促性腺激素的β次單元的C端肽(CTP)、PAS序列、HAP序列、轉鐵蛋白、白蛋白結合部分，或其任何片段、衍生物、變異體，及其任何組合。

III.C.1. Ig恆定區或其部分

【0222】 在一些實施例中，本公開的嵌合多肽還包括通過任何的連接子與FVIII多肽融合的第一Ig恆定區或其部分。該第一Ig恆定區或其部分可被插入在該FVIII多肽中或與該FVIII多肽的C端或N端融合。在一些實施例中，該嵌合多肽進一步包括與VWF蛋白融合的第二Ig恆定區或其部分。該第一Ig恆定區或其部分可被插入在該VWF片段中，或與該VWF片段的C端或N端融合。在特定的實施例中，該第一Ig恆定區係通過共價鍵(例如雙硫鍵)與該第二Ig恒定連接或締合。

【0223】 Ig恆定區或其部分可與另外的異源部分(例如XTEN序列)和VWF蛋白來共同改善嵌合多肽的藥物代謝動力學或藥效動力學。在某些實施例中，Ig恆定區或其部分係延長與恆定區或其部分所融合的分子的半衰期。

【0224】 Ig恆定區由表示CH(恆定重)域(CH1、CH2等)的域構成。取決於其同型的類別(即IgG、IgM、IgA、IgD、或IgE)，恆定區可由三個或四個CH域構成。一些同型(例如IgG)恆定區還含有鉸鏈區。參見Janeway等2001, Immunobiology, Garland Publishing, N.Y., N.Y.。

【0225】 用於產生本公開的嵌合多肽的Ig恆定區或其部分可以獲自許多不同的來源。在一些實施例中，Ig恆定區或其部分係衍生自人類Ig。應理解的是，然而，該Ig恆定區或其部分可衍生自另一哺乳動物物種的Ig，包括例如，齧齒動物(例如小鼠、大鼠、兔、或豚鼠)或非人靈長類動物(例如黑猩猩、獼猴)物種。而且，該Ig恆定區或其部分可衍生自任何Ig類別，其包括IgM、IgG、IgD、IgA、和IgE，和任何Ig同型，其包括IgG1、IgG2、IgG3、和IgG4。在一些實施例中，使用人類同型IgG1。

【0226】 多種Ig恆定區基因序列(例如，人恆定區基因序列)可以以可公開獲得的保藏物的形式來獲得。恆定區域序列可經選擇以具有特定的效用功能(或缺乏特定的效用功能)或經特定修飾以降低免疫原性。許多編碼有一個或多個抗體的

基因序列已經被公開，且適合的Ig恆定區序列(例如，鉸鏈、CH2、和/或CH3序列，或其部分)可以使用本領域公認的技術從這些序列來衍生。然後，可以改變或合成由任何前述方法所獲得的遺傳物質以獲得本公開的多肽。還應理解，本公開的範圍包含恆定區DNA序列的等位基因、變異體和突變。

【0227】 Ig恆定區或其部分的序列可被選殖（cloned），例如，使用聚合酶鏈式反應和選擇用於擴增感興趣的域的引子。為了選殖來自抗體的Ig恆定區或其部分的序列，mRNA可從雜交瘤細胞、脾細胞或淋巴細胞中分離，反轉錄成DNA，且通過PCR擴增抗體基因。PCR擴增方法具體描述於美國專利號4,683,195；4,683,202；4,800,159；4,965,188；以及，例如，「PCR Protocols:A Guide to Methods and Applications」 Innis等eds., Academic Press, San Diego, CA (1990); Ho等1989. Gene 77:51；Horton等1993.Methods Enzymol.217:270)中。PCR可通過共有恆定區引子或通過多個基於公開的重和輕鏈DNA和胺基酸序列的具體引子來開始。如上述所討論的，PCR還可用於分離編碼抗體輕和重鏈的DNA選殖。在此情況中，可通過共有引子或較大的同源探針(諸如小鼠恆定區探針)來篩選文庫。適於擴增抗體基因的許多引子對是本領域中已知的(例如，基於純化的抗體的N端序列的5'基因(Benhar和Pastan.1994.Protein Engineering 7:1509)；快速擴增cDNA末端(Ruberti, F. 等 1994. J. Immunol. Methods 173:33)；抗體先導序列(Larrick 等1989 Biochem. Biophys. Res. Commun. 160:1250))。選殖抗體序列進一步描述於Newman等, 1995年1月25日提交的美國專利號5,658,570中，其通過提述併入本文。

【0228】 本文中使用的Ig恆定區可包括其所有域和鉸鏈區或其部分。在一些實施例中，該Ig恆定區或其部分係包含CH2域、CH3域、和鉸鏈區，即Fc區或FcRn結合配偶體。

【0229】 如本文所用的，術語「Fc區」定義為多肽的一部分，其對應於天然Ig的Fc區，即，如通過其兩條重鏈的各自Fc域的二聚締合形成的。天然Fc區與另一Fc區形成同源二聚體。與此相反，如本文所用的，術語「基因融合的Fc區」或「單鏈Fc區」(scFc區)是指由在單個多肽鏈內(即，在單個連續基因序列中編

碼的)基因連接的Fc域所構成的合成二聚Fc區。

【0230】 在一些實施例中，「Fc區」是指開始於木瓜蛋白酶切割位點(即IgG中的殘基216，將重鏈恆定區的第一殘基定為114)正上游的鉸鏈區且結束於抗體C端的單個Ig重鏈的部分。因此，完整的Fc域包含至少鉸鏈域、CH2域、和CH3域。

【0231】 Ig恆定區的Fc區(其取決於Ig同型)可包括CH2、CH3、和CH4域，以及鉸鏈區。包含Ig的Fc區之嵌合多肽係賦予嵌合多肽數個期望的性質，包括穩定性的增加、血清半衰期的增加(參見Capon等, 1989, Nature 337:525)以及結合Fc受體諸如新生Fc受體(FcRn) (美國專利號6,086,875、6,485,726、6,030,613；WO 03/077834；US2003-0235536A1)，其通過提述以其整體併入本文。

【0232】 Ig恆定區或其部分可以是FcRn結合配偶體。FcRn在成人上皮組織中有活性，並在腸、肺氣道、鼻表面、陰道表面、結腸和直腸表面的管腔中表現(美國專利號6,485,726)。FcRn結合配偶體是Ig的一部分，其結合FcRn。FcRn結合配偶體的另一實例是白蛋白，以下進一步描述。

【0233】 FcRn受體已經從若干哺乳動物物種(包括人)中分離。人類FcRn、猴FcRn、大鼠FcRn、和小鼠FcRn的序列是已知的(Story等 1994, J. Exp. Med. 180:2377)。FcRn受體在相對低的pH下結合IgG (但不結合其他Ig類別，諸如IgA、IgM、IgD、和IgE)，主動地將腔內的IgG跨細胞地向漿膜方向(serosal)轉運，然後在相對較高的pH處（存在於間質液中）釋放IgG。其表現在成人上皮組織中(美國專利號6,485,726、6,030,613、6,086,875；WO 03/077834；US2003-0235536A1)，包括肺和腸上皮(Israel等 1997, Immunology 92:69)、腎近端小管上皮(Kobayashi等 2002, Am. J. Physiol. Renal Physiol. 282:F358)以及鼻上皮、陰道表面、和膽道系統表面。

【0234】 可用於本公開的FcRn結合配偶體包含可由FcRn受體特異性結合的分子，該分子包括整個IgG、IgG的Fc片段，和包括FcRn受體的完整結合區的其他片段。IgG結合至FcRn受體的Fc部分的區域已經根據X射線晶體術被描述(Burmeister等1994, Nature 372:379)。Fc與FcRn的主要接觸面係接近CH2和CH3

域的連接部分。Fc-FcRn接觸全部在單個Ig重鏈內。FcRn結合配偶體包括整個IgG、IgG的Fc片段、和IgG的其他片段，包括FcRn的完整結合區。主要接觸位點包括CH2域的胺基酸殘基248、250-257、272、285、288、290-291、308-311、和314，以及CH3域的胺基酸殘基385-387、428、和433-436。對Ig或Ig片段或區的胺基酸編號的參考均基於Kabat等1991, Sequences of Proteins of Immunological Interest, U.S. Department of Public Health, Bethesda, Md。

【0235】 結合至FcRn的Fc區或FcRn結合配偶體可以通過FcRn有效地穿梭於上皮障壁，從而提供非侵入性手段以全身性地施用所期望的治療分子。此外，包含Fc區或FcRn結合配偶體的融合蛋白通過表現FcRn的細胞被內吞。但是這些融合蛋白不是經標記用於降解，而是再次回收到循環中，從而增加了這些蛋白質的體內半衰期。在某些實施例中，Ig恆定區的部分是Fc區域或FcRn結合配偶體，其一般係經由雙硫鍵和其他非特異性相互作用與另一Fc區或另一FcRn結合配偶體來締合，以形成二聚體和更高階的多聚體。

【0236】 兩個FcRn受體可結合單個Fc分子。結晶學資料表明每個FcRn分子係結合至Fc同源二聚體的單個多肽。在一些實施例中，將FcRn結合配偶體(例如IgG的Fc片段)連接至生物活性分子，提供了以口服、經頰、舌下、經直腸、經陰道，經鼻或經由肺途徑施用的氣霧劑，或經由眼睛途徑來遞送該生物活性分子的手段。在其他實施例中，該嵌合多肽可侵入性地施用，例如以皮下、靜脈內方式。

【0237】 FcRn結合配偶體區域是可由FcRn受體特異性結合的分子或其部分，隨後通過Fc區的FcRn受體進行主動轉運。特異性結合是指形成複合物的兩個分子，該複合物在生理條件下相對穩定。特異性結合的表徵在於高親和力及低至中等載量（capacity），這通常與具有低親和力及中等至高載量的非特異性結合有所區別。典型地，當親和力常數KA高於10^6 M^{-1}，或高於10^8 M^{-1}時，認為結合是特異性的。如果必要的話，可在實質上不影響特異性結合的情況下通過改變結合條件來減少非特異性結合。適當的結合條件諸如分子的濃度、溶液的離子強度、可結合的時間、溫度、阻斷劑的濃度(例如血清白蛋白、乳酪蛋白)等，可由本領域技術人員使用常規技術來最佳化。

【0238】　在某些實施例中，本公開的嵌合多肽包含一個或多個經截切的Fc區，但該經截切的Fc區足以賦予Fc區對Fc受體(FcR)結合特性。例如，Fc區結合至FcRn的部分(即，FcRn結合部分)係包含IgG1的約胺基酸282-438，EU編號(一級接觸位點為CH2域的胺基酸248、250-257、272、285、288、290-291、308-311、和314，和CH3域的胺基酸殘基385-387、428、和433-436)。因此，本公開的Fc區可包含FcRn結合部分或係由FcRn結合部分構成。FcRn結合部分可衍生自任何同型類別(包括IgG1、IgG2、IgG3和IgG4)的重鏈。在一些實施例中，使用來自人類同型IgG1的抗體其FcRn結合部分。在其他實施例中，使用來自人類同型IgG4的抗體其FcRn結合部分。

【0239】　在其他實施例中，「Fc區」包括Fc域的或衍生自Fc域的胺基酸序列。在某些實施例中，Fc區包含下列者的至少一種：鉸鏈(例如，上、中、和/或下鉸鏈區)域(根據EU編號，抗體Fc區的約胺基酸216-230)、CH2域(根據EU編號，抗體Fc區的約胺基酸231-340)、CH3域(根據EU編號，抗體Fc區的約胺基酸341-438)、CH4域，或其變異體、部分，或其片段。在其他實施例中，Fc區包含完整Fc域(即，鉸鏈域、CH2域、和CH3域)。在一些實施例中，Fc區包含下列者，實質上由下列者所構成，或係由下列者所構成：與CH3域(或其部分)融合的鉸鏈域(或其部分)，與CH2域(或其部分)融合的鉸鏈域(或其部分)，與CH3域(或其部分)融合的CH2域(或其部分)，與鉸鏈域(或其部分)和CH3域(或其部分)二者融合的CH2域(或其部分)。在又一些其他的實施例中，Fc區缺乏至少部分的CH2域(例如，全部或部分的CH2域)。在特定的實施例中，Fc區包含對應於EU編號221至447的胺基酸，或由對應於EU編號221至447的胺基酸構成。

【0240】　本文中表示為F、F1、或F2的Fc區可從許多不同的來源獲得。在一些實施例中，該多肽的Fc區衍生自人類Ig。應理解，然而，Fc區可衍生自另一哺乳動物物種的Ig，包括例如，齧齒動物(例如例如小鼠、大鼠、兔、或豚鼠)或非人靈長類動物(例如黑猩猩、獼猴)物種。而且，該Fc域或其部分的多肽可衍生自任何Ig類別(包括IgM、IgG、IgD、IgA和IgE)和任何Ig同型(包括IgG1、IgG2、IgG3和IgG4)。在其他實施例中，使用人類同型IgG1。

【0241】　在某些實施例中，該Fc變異體賦予至少一種由Fc區(包含所述野生型Fc域)給予的效用功能的變化(例如，Fc區結合Fc受體(例如FcγRI、FcγRII、或FcγRIII)或補體蛋白(例如C1q)，或引發抗體依賴性細胞毒性(ADCC)，吞噬作用，或補體依賴性細胞毒性(CDCC)的能力的改善或降低)。在其他實施例中，該Fc變異體提供工程化的半胱胺酸殘基。

【0242】　本公開的Fc區可採用本領域公認的Fc變異體，已知該Fc變異體給予效用功能和/或FcR或FcRn結合的變化(例如，增強或降低)。具體地，本公開的結合分子可包括，例如，以下中公開的一處或多處胺基酸位置的變化(例如，替代)：國際PCT公開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、WO06/047350A2、和WO06/085967A2；美國專利公開號US2007/0231329、US2007/0231329、US2007/0237765、US2007/0237766、US2007/0237767、US2007/0243188、US20070248603、US20070286859、US20080057056；或美國專利號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、和7,317,091，其中每個通過提述併入本文。在一些實施例中，具體的變化(例如，一種或多種本領域中公開的胺基酸的特定替代)可在一處或多處公開的胺基酸位置進行。在其他實施例中，可在一處或多處公開的胺基酸位置進行不同變化(例如，本領域中公開的一處或多處胺基酸位置的不同替代)。

【0243】　IgG的Fc區或FcRn結合配偶體可根據公認的方法(諸如定點誘變等)來修飾，以產生由FcRn所結合的經修飾的IgG或Fc片段或其部分。此類修飾包括遠離FcRn接觸位點的修飾以及接觸位點內的修飾，所述修飾保留或甚至增強與

FcRn的結合。例如，人IgG1 Fc(Fc γ1)中的下列單個胺基酸殘基可被取代而沒有顯著丟失FcRn的Fc結合親和力：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、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、和K447A，其中例如P238A表示位置編號238處的野生型脯胺酸由丙胺酸替代。作為一個實例，一些實施例併入N297A突變，去除高度保守的N-糖基化位點。除了丙胺酸，其他胺基酸可在上面指定的位置處取代野生型胺基酸。突變可被單獨引入至Fc中，導致多於100種與天然Fc不同的Fc區域。此外，可以將這些個別突變中的兩個、三個或更多個的組合一起引入，產生數百種Fc區。而且，本公開的構築體的Fc區之一可以突變，且構築體的其他Fc區完全不突變，或者它們都可以突變但具有不同的突變。

【0244】　某些上述突變可賦予Fc區或FcRn結合配偶體新的功能。例如，一些實施例併入N297A，去除高度保守的N-糖基化位點。此突變的作用在於降低免疫原性，從而增強Fc區的循環半衰期，以及使得Fc區無法結合至FcγRI、FcγRIIA、FcγRIIB、和FcγRIIIA，而不損害對FcRn的親和力(Routledge等 1995, Transplantation 60:847；Friend等 1999, Transplantation 68:1632；Shields等1995, J. Biol. Chem. 276:6591)。作為由上述突變引起的新功能的又一實例，在某些情況中，對FcRn的親和力可以增加到超過野生型的親和力。此增加的親和力可以反映增加的「開啟」速率，減少的「關閉」速率或者增加的「開啟」速率和減少

的「關閉」速率二者。被認為給予對FcRn的親和力所增加的突變其實例包括但不限於，T256A、T307A、E380A、和N434A (Shields等 2001, J. Biol. Chem. 276:6591)。

【0245】 此外，至少三種人Fcγ受體似乎識別下鉸鏈區內IgG上的結合位點，通常是胺基酸234-237。因此，新功能和潛在降低的免疫原性的另一個實例可以由此區的突變引起，例如通過將人IgG1「ELLG」的胺基酸233-236替換為來自IgG2「PVA」的相應序列(具有一個胺基酸缺失)。已經顯示了當已經引入此類突變時，介導多種效用功能的Fcγ72RI、Fcγ72RII、和FcγRIII將不結合IgG1。Ward和Ghetie 1995, Therapeutic Immunology 2:77和Armour 等1999, Eur. J. Immunol. 29:2613。

【0246】 在一些實施例中，Ig恆定區或其部分(例如Fc區)是多肽，其包括序列PKNSSMISNTP(美國專利號5,739,277的SEQ ID NO: 89或SEQ ID NO: 3)，且任選地進一步包括選自以下的序列：HQSLGTQ (SEQ ID NO: 90)、HQNLSDGK (SEQ ID NO: 91)、HQNISDGK (SEQ ID NO: 92)、或VISSHLGQ (SEQ ID NO: 93) (或分別為美國專利號5,739,277的SEQ ID NO: 11、1、2、和31)。

【0247】 在其他實施例中，免疫球蛋白恆定區或其部分係包含鉸鏈區或其部分中的胺基酸序列，該鉸鏈區或其部分係與另一免疫球蛋白恆定區或其部分形成一個或多個雙硫鍵。免疫球蛋白恆定區或其部分的雙硫鍵使包含FVIII多肽的第一多肽和包含VWF片段的第二多肽置於一起，使得內源性VWF不會代替VWF片段且不結合至FVIII多肽。因此，第一免疫球蛋白恆定區或其部分與第二免疫球蛋白恆定區或其部分之間的雙硫鍵係防止內源性VWF和FVIII多肽之間的相互作用。此種VWF和FVIII多肽之間的相互作用的抑制係使嵌合多肽的半衰期超過了兩倍的限度。鉸鏈區或其部分可進一步與CH1、CH2、CH3中的一個或多個域、其片段，和其任何組合連接。在特定的實施例中，該免疫球蛋白恆定區或其部分是鉸鏈區和CH2。

【0248】 在某些實施例中，該Ig恆定區或其部分是半糖基化的。例如，包含兩個Fc區或FcRn結合配偶體的嵌合多肽，可含有第一糖基化的Fc區(例如，糖基

化的CH2區)或FcRn結合配偶體，和第二非糖基化的Fc區域(例如，非糖基化的CH2區)或FcRn結合配偶體。在一些實施例中，連接子可插入在糖基化和非糖基化的Fc區域之間。在其他實施例中，該Fc區語或FcRn結合配偶體經充分糖基化，即所有Fc區域皆經糖基化。在其他實施例中，該Fc區與可以是非糖基化的，即Fc部分均未經糖基化。

【0249】　在某些實施例中，本公開的嵌合多肽包含Ig恆定區或其部分的胺基酸替代(例如，Fc變異體)，其改變Ig恆定區的抗原依賴性效用功能，特別是蛋白的循環半衰期。

【0250】　當相較於缺乏這些替代物的蛋白時，此類蛋白係表現出與FcRn結合的增加或降低，因此，分別具有增加或降低的血清中半衰期。具有對FcRn有改善親和力的Fc變異體被預期係具有較長的血清半衰期，且此類分子在治療哺乳動物的方法中具有有益的應用，其中所施用的多肽係希望會有長半衰期，例如用於治療慢性疾病或病症(參見，例如，美國專利7,348,004、7,404,956、和7,862,820)。與此相反，具有降低的FcRn結合親和力的Fc變異體被預期會具有較短的半衰期，且此類分子也是有益的，例如有益於施用至哺乳動物，在該哺乳動物中，縮短的循環時間可能是有利的，例如有利於體內診斷成像，或當起始多肽在循環中長時間存在時具有毒性副作用的情況下。具有降低的FcRn結合親和力的Fc變異體也不太可能穿過胎盤，因此也可用於治療孕婦的疾病或病症。此外，預期會有降低的FcRn結合親和力的其他應用，係包括希望定位腦、腎、和/或肝的那些應用。一個示例性實施例中，本公開的嵌合多肽表現出從脈管系統穿過腎絲球上皮細胞有降低的轉運情況。在其他實施例中，本公開的嵌合多肽表現出從腦穿過血腦障壁(BBB)至血管空間有降低的轉運情況。在一些實施例中，具有經改變的FcRn結合情況的蛋白係包含至少一個Fc區或FcRn結合配偶體(例如，一個或多個Fc區或FcRn結合配偶體)，該Fc區或FcRn結合配偶體在Ig恆定區的「FcRn結合環」內具有一處或多處胺基酸替代。該FcRn結合環由野生型全長Fc區的胺基酸殘基280-299(根據EU編號)構成。在其他實施例中，本公開的嵌合多肽中具有被改變的FcRn結合親和力的Ig恆定區或其部分，係包含至少一個

Fc區或FcRn結合配偶體，該Fc區或FcRn結合配偶體在15Å FcRn「接觸區」內具有一處或多處胺基酸替代。如本文所用的，術語15Å FcRn「接觸區」包括野生型全長Fc部分下列位置處的殘基：243-261、275-280、282-293、302-319、336-348、367、369、372-389、391、393、408、424、425-440 (EU編號)。在其他實施例中，本公開的具有經改變的FcRn結合親和力的Ig恆定區或其部分，係包含至少一個Fc區或FcRn結合配偶體，該Fc區或FcRn結合配偶體具有一處或多處在對應於下列EU位置中任一個的胺基酸位置處的胺基酸替代：256、277-281、283-288、303-309、313、338、342、376、381、384、385、387、434 (例如，N434A或N434K)、和438。改變FcRn結合活性的示例性胺基酸替代係公開在國際PCT公開號WO05/047327中，其通過提述併入本文。

【0251】　在本公開中使用的Fc區或FcRn結合配偶體還可包含本領域公認的改變嵌合多肽其糖基化的胺基酸替代。例如，連接至VWF的D'D3域或FVIII多肽的嵌合多肽之Fc區或FcRn結合配偶體，可包含具有導致糖基化(例如，N或O連接的糖基化)減少突變的Fc區，或可包含野生型Fc部分的經改變糖型(例如，低海藻糖或無海藻糖聚糖)。

【0252】　在一些實施例中，本公開的未經加工的嵌合多肽可包含基因融合的Fc區(即，scFc區)，其具有兩個或多個獨立選自本文所述的Ig恆定區或其部分的其構成性Ig恆定區或其部分。在一些實施例中，二聚Fc區的Fc區是相同的。在其他實施例中，至少兩個Fc區是不同的。例如，本公開的蛋白其Fc區或FcRn結合配偶體，係包含相同數目的胺基酸殘基，或它們可在長度上相差一個或多個胺基酸殘基(例如，相差約5個胺基酸殘基(例如，1、2、3、4、或5個胺基酸殘基)、約10個殘基、約15個殘基、約20個殘基、約30個殘基、約40個殘基、或約50個殘基)。在又一些其他實施例中，本公開的蛋白其Fc區或FcRn結合配偶體的序列，可在一個或多個胺基酸位置處不同。例如，至少兩個Fc區或FcRn結合配偶體可在約5個胺基酸位置(例如，1、2、3、4、或5個胺基酸位置)、約10個位置、約15個位置、約20個位置、約30個位置、約40個位置、或約50個位置處不同。

III.C.2. XTEN 序列

【0253】 如本文所用的「XTEN序列」是指以非天然存在且基本上非重複性序列所延長長度的多肽，其主要由小型親水性胺基酸構成，其中該序列在生理條件下具有低度的二級或三級結構，或無二級或三級結構。作為嵌合多肽配偶體，XTEN可用作載體，該載體當與本公開的VWF蛋白或FVIII序列連接以產生嵌合多肽時，係賦予某些期望的藥物代謝動力學、物理化學和藥學性質。此類期望的性質包括但不限於增強的藥物代謝動力學參數和溶解度特性。如本文所用的，「XTEN」係明確排除抗體或抗體片段，諸如單鏈抗體，或輕鏈或重鏈的Fc片段。

【0254】 在一些實施例中，當XTEN序列與VWF蛋白和/或第二Ig恆定區或其部分融合時，相較於較長的XTEN序列，較短的XTEN序列係提供經改善的半衰期延長性質。因此，在一些實施例中，與VWF蛋白和/或第二Ig恆定區或其部分融合的XTEN序列，在長度上含有少於288個胺基酸，即比288個胺基酸短。在一些實施例中，與VWF蛋白和/或第二Ig恆定區或其部分融合的XTEN序列，係由其長度介於12個胺基酸至287胺基酸之間的胺基酸序列所構成。在其他實施例中，與VWF蛋白和/或第二Ig恆定區或其部分融合的XTEN序列，包含至少約36個胺基酸、至少約42個胺基酸、至少約72個胺基酸、或至少約144個胺基酸，但少於288個胺基酸。在其他實施例中，與VWF蛋白和/或第二Ig恆定區或其部分融合的XTEN序列，係選自AE36、AG36、AE42、AG42、AE72、AG72、AE144、或AG144。在一些實施例中，與VWF蛋白和/或第二Ig恆定區或其部分融合的XTEN序列，是與SEQ ID NO: 9、SEQ ID NO: 10、SEQ ID NO: 11、或SEQ ID NO: 14為至少80%、85%、90%、95%、96%、97%、98%、99%、或100%相同的胺基酸序列，其中相較於不具有XTEN序列的嵌合多肽，該嵌合多肽表現出經改善的半衰期。

【0255】 本公開的嵌合多肽可進一步包含另外的(第二、第三、或更多)XTEN序列。該另外的XTEN序列可進一步與FVIII多肽或第一Ig恆定區或其部分融合。該另外的XTEN序列可以是任何長度的。例如，與FVIII多肽或第一Ig恆定區或其

部分融合的另外的XTEN序列，是具有大於約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、或2000個胺基酸殘基的肽或多肽。在某些實施例中，該另外的XTEN序列是具有大於約20至約3000個胺基酸殘基、大於約30至約2500個殘基、大於約40至約2000個殘基、大於約50至約1500個殘基、大於約60至約1000個殘基、大於約70至約900個殘基、大於約80至約800個殘基、大於約90至約700殘基、大於約100至約600個殘基、大於約110至約500個殘基、或大於約120至約400個殘基的肽或多肽。在某些實施例中，與FVIII多肽融合的另外的XTEN包含至少約288個胺基酸。在特定的實施例中，與FVIII多肽融合的另外的XTEN包含約288個胺基酸。在特定的實施例中，與FVIII多肽融合的另外的XTEN包含與AE288 (SEQ ID NO: 8)的胺基酸序列為至少約70%、至少約75%、至少約80%、至少約85%、至少約90%、至少約95%、至少約96%、至少約97%、至少約98%、至少約99%、或約100%相同的胺基酸序列。

【0256】 XTEN序列(即與VWF蛋白和/或第二Ig恆定區或其部分融合的XTEN序列，或與FVIII多肽和/或第一Ig恆定區或其部分融合的XTEN序列，或在FVIII多肽內的一個或多個插入位點處插入的XTEN序列)可包含一個或多個為9至14個胺基酸殘基的序列基序，或與該序列基序為至少80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、或99%相同的胺基酸序列，其中該基序包含選自下列群組中的4至6種類型的胺基酸、實質上由選自下列群組中的4至6種類型的胺基酸所構成，或係由選自下列群組中的4至6種類型的胺基酸所構成：甘胺酸(G)、丙胺酸(A)、絲胺酸(S)、蘇胺酸(T)、麩胺酸(E)和脯胺酸(P)。參見US 2010-0239554 A1。

【0257】 在一些實施例中，XTEN序列包含非重疊性序列基序，在XTEN序列中至少約80%、或至少約85%、或至少約90%、或至少約91%、或至少約92%、或至少約93%、或至少約94%、或至少約95%、或至少約96%、或至少約97%、或至少約98%、或至少約99%，或約100%的該序列，係由選自於表7的單個基序家族的非重疊性序列的多個單元構成，以產生家族序列。如本文所用的，「家

族」意指XTEN具有僅自表7的單個基序分類中所選出的基序；即，AD、AE、AF、AG、AM、AQ、BC、或BD XTEN，且XTEN中任何其他不是來自家族基序的胺基酸，係經選擇以獲得所需的性質，諸如為了要藉由編碼讓核苷酸併入限制性位點，併入切割序列，或為了達成FVIII或VWF有更好的連接。在XTEN家族的一些實施例中，XTEN序列包含AD基序家族的，或AE基序家族的，或AF基序家族的，或AG基序家族的，或AM基序家族的，或AQ基序家族的，或BC家族的，或BD家族的多個單元之非重疊性序列基序，所得的XTEN係表現出上述同源性的範圍。在其他實施例中，XTEN包含來自表7的兩個或更多個基序家族的多個單元的基序序列。這些序列可經選擇以實現期望的物理/化學特性，包括諸如由基序的胺基酸組成所賦予的淨電荷、親水性、缺乏二級結構，或缺乏重複性的性質，下文將更充分地描述。在此段上述的實施例中，併入XTEN中的基序可使用本文所述的方法經選擇和裝配以取得約36至約3000個胺基酸殘基的XTEN。

表 7. 12 個胺基酸的 XTEN 序列基序和基序家族

基序家族*	基序序列
AD	GESPGGSSGSES (SEQ ID NO: 24)
AD	GSEGSSGPGESS (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	GTGEPSSTPASE (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)

基序家族*	基序序列
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)

*表示個別基序序列，當其以不同的排列方式併同使用時，係產生「家族序列」

【0258】 在一些實施例中，在本公開中使用的XTEN序列與選自下列群組的序列為至少60%、70%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、或100%相同：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、和AG2004。參見US 2010-0239554 A1。

【0259】 在一些實施例中，該XTEN序列係與選自下列群組的胺基酸序列為至少60%、70%、80%、90%、95%、96%、97%、98%、99%或100%相同：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 IDNO: 58)、AE144_6B (SEQ IDNO: 59)、AG144_A (SEQ ID NO: 60)、AG144_B (SEQ IDNO: 61)、AG144_C (SEQ ID NO: 62)、AG144_F (SEQ IDNO: 63)、AE864 (SEQ ID NO: 15)、AE576 (SEQ ID NO: 16)、AE288 (SEQ IDNO: 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)、及其任何組合。在其他實施

例中，該XTEN序列選自下列群組：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 IDNO: 58)、AE144_6B (SEQ IDNO: 59)、AG144_A (SEQ ID NO: 60)、AG144_B (SEQ IDNO: 61)、AG144_C (SEQ ID NO: 62)、AG144_F (SEQ IDNO: 63)、AE864 (SEQ ID NO: 15)、AE576 (SEQ ID NO: 16)、AE288 (SEQ IDNO: 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)、及其任何組合。在一些實施例中，該XTEN序列是AE288。本公開的某些XTEN序列的胺基酸序列係示於8中。

表 8. XTEN 序列

XTEN	**[06]** 胺基酸序列
AE42 SEQ ID NO:9	GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS **[07]**
AE72 (SEQ ID NO: 10)	GAP TSESATPESG PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG TSTEPSEGSA PGASS
AE144 (SEQ ID NO:11)	GSEPATSGSETPGTSESATPESGPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEG SAPGSEPATSGSETPGSEPATSGSETPGSEPATSGSETPGTSTEPSEGSAPGTSESA PESGPGSEPATSGSETPGTSTEPSEGSAP
AE144_2A (SEQ ID NO: 55)	TSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGTSESATPESGPGTSTEPS EGSAPGTSESATPESGPGSEPATSGSETPGTSTEPSEGSAPGTSTEPSEGSAPGTSESATPESGP GTSESATPESGPG
AE144_3B (SEQ ID NO: 56)	SPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEPS EGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEE 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)	TSTEPSEGSAPGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATS GSETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPG TSTEPSEGSAPG
AG144 SEQ ID NO:14	GTPGSGTASSSPGSSTPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGASPGTSST GSPGASPGTSSTGSPGSSTPSGATGSPGSSPSASTGTGPGASPGTSSTGSPGSSPSA STGTGPGTPGSGTASSSPGSSTPSGATGSP
AG144_A (SEQ ID NO: 60)	GASPGTSSTGSPGSSPSASTGTGPGSSPSASTGTGPGTPGSGTASSSPGSSTPSGATGSPGSSPS ASTGTGPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGTPGSGTASSSPGASPGTSSTG SPGASPGTSSTGSP
AG144_B	GTPGSGTASSSPGSSTPSGATGSPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGSSPS ASTGTGPGSSPSASTGTGPGSSTPSGATGSPGSSTPSGATGSPGASPGTSSTGSPGASPGTSSTG

(SEQ ID NO: 61)	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 (SEQ ID NO: 54)	GSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEP SEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEE GTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESA TPESGPGTSTEPSEGSAPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGSPAGSPTSTEE GTSESATPESGPGTSTEPSEGSAP
AG288 SEQ ID NO:19	PGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGTPGSGTASS SPGSSTPSGATGSPGTPGSGTASSSPGSSTPSGATGSPGSSTPSGATGSPGSSPSASTG TGPGSSPSASTGTGPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGSSPSAST GTGPGSSPSASTGTGPGASPGTSSTGSPGASPGTSSTGSPGSSTPSGATGSPGSSPSAS TGTGPGASPGTSSTGSPGSSPSASTGTGPGTPGSGTASSSPGSSTPSGATGS **[08]**
AE576 SEQ ID NO:16	GSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSA PGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTST EEGTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEG SAPGTSTEPSEGSAPGTSESATPESGPGTSTEPSEGSAPGTSESATPESGPGSEPATSG SETPGTSTEPSEGSAPGTSTEPSEGSAPGTSESATPESGPGTSESATPESGPGSPAGSP TSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEP SEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAG SPTSTEEGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEP ATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSESATPESGPGSPAGSPTSTEEGSP AGSPTSTEEGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAP
AG576 SEQ ID NO:18	PGTPGSGTASSSPGSSTPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGSSTPSGATG SPGSSTPSGATGSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGTPGSGTAS SSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGSSPSASTGTGPGTPGSGTA SSSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGSSTPSGATGSPGSSTPSG ATGSPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGSSTPSGATGSPGSSTPS GATGSPGSSPSASTGTGPGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASSSPGASPG TSSTGSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASSSPGSST PSGATGSPGTPGSGTASSSPGSSTPSGATGSPGTPGSGTASSSPGSSTPSGATGSPGSS TPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGASPGTSSTGSPGTPGSGTASSSPGS STPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGASPGTSSTGS
AE864 SEQ ID NO:15	GSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSA PGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTST EEGTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEG SAPGTSTEPSEGSAPGTSESATPESGPGTSTEPSEGSAPGTSESATPESGPGSEPATSG SETPGTSTEPSEGSAPGTSTEPSEGSAPGTSESATPESGPGTSESATPESGPGSPAGSP TSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEP SEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAG SPTSTEEGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEP ATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSESATPESGPGSPAGSPTSTEEGSP AGSPTSTEEGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGTSESATPESGPGS EPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPG SPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEE GSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSESATPESGPGTSESATPESG PGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGS APGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAP

AG864 SEQ ID NO:17	GASPGTSSTGSPGSSPSASTGTGPGSSPSASTGTGPGTPGSGTASSSPGSSTPSGATGS PGSSPSASTGTGPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGTPGSGTASS SPGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGASPGTSST GSPGTPGSGTASSSPGSSTPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGSSTPSGA TGSPGSSTPSGATGSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGTPGSGT ASSSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGSSPSASTGTGPGTPGSG TASSSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGSSTPSGATGSPGSSTP SGATGSPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGSSTPSGATGSPGSST PSGATGSPGSSPSASTGTGPGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASSSPGAS PGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASSSPGS STPSGATGSPGTPGSGTASSSPGSSTPSGATGSPGTPGSGTASSSPGSSTPSGATGSPG SSTPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGASPGTSSTGSPGTPGSGTASSSP GSSTPSGATGSPGSSPSASTGTGPGSSPSASTGTGPGASPGTSSTGSPGASPGTSSTGS PGSSTPSGATGSPGSSPSASTGTGPGASPGTSSTGSPGSSPSASTGTGPGTPGSGTASS SPGSSTPSGATGSPGSSTPSGATGSPGASPGTSSTGSP

【0260】　在這些實施例中，其中一個或多個XTEN組分由其胺基酸中有少於100%係為4、5、或6種類型的選自於下列胺基酸所構成：甘胺酸(G)、丙胺酸(A)、絲胺酸(S)、蘇胺酸(T)、麩胺酸(E)和脯胺酸(P)，或具有由少於100%的來自表7的序列基序或表8的XTEN序列所構成的序列，XTEN的其他胺基酸殘基係選自其他14種天然L-胺基酸中的任一種，但較佳係選自於親水性胺基酸，使得該XTEN序列含有至少約90%、91%、92%、93%、94%、95%、96%、97%、98%、或至少約99%親水性胺基酸。非甘胺酸(G)、丙胺酸(A)、絲胺酸(S)、蘇胺酸(T)、麩胺酸(E)和脯胺酸(P)的XTEN胺基酸係散佈在整個XTEN序列，位於序列基序內或序列基序之間，或集中在XTEN序列的一個或多個短的序列段(stretch)中，例如，以產生在XTEN和FVIII或VWF組分之間的連接子。在XTEN組分包含除了甘胺酸(G)、丙胺酸(A)、絲胺酸(S)、蘇胺酸(T)、麩胺酸(E)和脯胺酸(P)以外的胺基酸之情況下，較佳是少於約2%或少於約1%的胺基酸是疏水性殘基，使得所得序列通常缺乏二級結構，例如不具有多於2% α螺旋或2% β折疊，如通過本文公開的方法測定的。不太會用來構建XTEN的疏水性殘基，包括色胺酸、苯丙胺酸、酪胺酸、白胺酸、異白胺酸、撷胺酸、和甲硫胺酸。此外，可設計XTEN序列以含有少於5%、或少於4%、或少於3%、或少於2%、或少於1%，或無下列的胺基酸：半胱胺酸(以避免雙硫鍵形成和氧化)、甲硫胺酸(以避免氧化)、天門冬醯胺酸和麩醯胺酸(以避免脫醯胺作用)。因此，在一些實施例中，包含除甘胺酸(G)、丙胺酸(A)、絲胺酸(S)、蘇胺酸(T)、麩胺酸(E)和脯胺酸(P)外等其他胺基酸的XTEN組分，其序列含有少於5%會導致α螺旋和β折疊（藉由Chou-Fasman算法所衡量

者）的殘基，且具有至少90%、或至少約95%、或更高的無規則捲曲形成（藉由GOR算法所衡量者）。

【0261】　在又一些實施例中，在本公開的中使用的XTEN序列係影響本公開的嵌合多肽的物理或化學性質，例如藥物代謝動力學。在本公開的中使用的XTEN序列可表現出一種或多種下列有利的性質：構形彈性、增強的水溶解度、高蛋白酶抗性、低免疫原性、與哺乳動物受體的低度結合、或增加的流體動力學(或斯托克斯(Stokes))半徑。在一些實施例中，與本公開中的FVIII蛋白連接的XTEN序列係增加藥物代謝動力學性質，諸如較長的終末半衰期，或增加的曲線下面積(AUC)，使得相較於野生型FVIII，本文所述的嵌合多肽在體內的保持時間增加。在又一些實施例中，在本公開中使用的XTEN序列係增加藥物代謝動力學性質，諸如較長的終末半衰期，或增加的曲線下面積(AUC)，使得相較於野生型FVIII，FVIII蛋白在體內的保持時間增加。

【0262】　多種方法和測定法可用來測定包含XTEN序列的蛋白其物理/化學性質。此類方法包括但不限於，分析離心分離、EPR、離子交換HPLC、尺寸排阻HPLC、反相HPLC、光散射、毛細管電泳、圓二色譜、差示掃描量熱法、熒光、離子交換HPLC、尺寸排阻HPLC、IR、NMR、拉曼光譜、折光測定法、和UV/可見光譜。另外的方法公開於Amau等, Prot Expr and Purif48, 1-13 (2006)中。

【0263】　其他可根據本公開所使用的XTEN序列實例係公開於美國專利公開號2010/0239554 A1、2010/0323956 A1、2011/0046060 A1、2011/0046061 A1、2011/0077199 A1、或2011/0172146 A1，或國際專利公開號WO 2010091122 A1、WO 2010144502 A2、WO 2010144508 A1、WO 2011028228 A1、WO 2011028229 A1、WO 2011028344 A2、或WO 20130122617 A1中。

III.C.2.　白蛋白

【0264】　白蛋白或其部分可以是FcRn結合配偶體。在某些方面中，在本公開的方法中使用的嵌合多肽包含至少一個白蛋白多肽或其片段、變異體、或衍生物。人類血清白蛋白(HSA或HA)，全長形式為609個胺基酸的蛋白，負責血清的顯著比例的滲透壓，且還作為內源性和外源性配體的載體。如本文所用的術語

「白蛋白」包括全長白蛋白或其功能性片段、變異體、衍生物或類似物。白蛋白或其片段或變異體的實例係公開於美國專利公開號2008/0194481A1、2008/0004206 A1、2008/0161243 A1、2008/0261877 A1、或2008/0153751 A1或PCT申請公開號2008/033413 A2、2009/058322 A1、或2007/021494 A2，其通過提述以其整體併入本文。

【0265】 白蛋白結合多肽(ABP)可包含但不限於，可結合至白蛋白的細菌性白蛋白結合域、白蛋白結合肽、或白蛋白結合抗體片段。來自鏈狀球菌的蛋白G其域3，如Kraulis等, FEBS Lett. 378:190-194 (1996)和Linhult等, Protein Sci. 11:206-213 (2002)所公開的，是細菌性白蛋白結合域的實例。白蛋白結合肽的實例公開於Dennis等, J. Biol. Chem. 2002, 277: 35035-35043 (2002)。白蛋白結合抗體片段的實例係公開於Muller和Kontermann, Curr. Opin. Mol. Ther. 9:319-326 (2007)；Roovers等, Cancer Immunol. Immunother. 56:303-317 (2007)，和Holt等, Prot. Eng. Design Sci., 21:283-288 (2008)中，其通過提述以其整體併入本文。

【0266】 在某些方面中，在本公開的方法中所使用的嵌合多肽，係包含至少一個供非多肽小分子、其變異體、或衍生物可結合至白蛋白的附著位點。例如，該嵌合多肽可包括一個或多個有機白蛋白結合部分。此類白蛋白結合部分的實例為，如Trussel等, Bioconjugate Chem. 20:2286-2292 (2009)中公開的2-(3-馬來亞醯胺丙醯胺基)-6-(4-(4-碘苯基)丁醯胺基)己酸酯(「Albu」標簽)。

【0267】 在某些實施例中，本文所述的VWF片段係與白蛋白融合。在一些實施例中，VWF片段-白蛋白構築體係形成二聚體。在一些實施例中，VWF的與白蛋白融合的D'D3域與FVIII多肽締合。在某些實施例中，融合至白蛋白的VWF之D'D3域係通過比野生型FVIII和VWF之間的天然非共價相互作用更強的相互作用來與FVIII多肽締合。在特定的實施例中，VWF的D'D3域和/或FVIII多肽係包含一個或多個增加VWF的D'D3域和FVIII多肽之間的親和力的突變。在某些實施例中，VWF的D'D3域和/或FVIII多肽係包含一個或多個允許在VWF的D'D3域和/或FVIII多肽之間形成雙硫鍵的突變。

III.C.3. CTP

【0268】 在某些方面中，在本公開的方法中使用的嵌合多肽係包含至少一個人類絨毛膜促性腺激素的β次單元的C端肽(C-terminal peptide，CTP)或其片段、變異體、或衍生物。已知CTP肽用於增加此蛋白的半衰期。參見，例如，美國專利號5,712,122，其通過提述以其整體併入本文。非限制性的示例性CTP肽公開在美國專利申請公開號US 2009/0087411 A1中，其通過提述併入。

III.C.4. PAS

【0269】 在某些方面中，在本公開的方法中使用的嵌合多肽包含至少一個PAS肽或其片段、變異體、或衍生物。如本文所用的，PAS肽或PAS序列意指主要包含丙胺酸和絲胺酸殘基，或主要包含丙胺酸、絲胺酸、和脯胺酸殘基的胺基酸序列，該胺基酸序列在生理條件下係形成無規則捲曲構形。因此，該PAS序列是構成模組、胺基酸聚合物，或為含有丙胺酸、絲胺酸和脯胺酸的序列盒、實質上由丙胺酸、絲胺酸、和脯胺酸構成的序列盒，或係由丙胺酸、絲胺酸、和脯胺酸構成的序列盒，其在嵌合多肽中可作為一部分之異源部分。當PAS序列中添加有除了丙胺酸、絲胺酸、和脯胺酸以外的殘基作為少量成分時，胺基酸聚合物還是可形成無規則捲曲構形。「少量成分」意指除了丙胺酸、絲胺酸、和脯胺酸以外的胺基酸，可在PAS序列中添加到一定程度，例如，多達約12%(即，PAS序列的100個胺基酸中的12個)、多達約10%、多達約9%、多達約8%、約6%、約5%、約4%、約3%、即約2%、或約1%的該胺基酸。不同於丙胺酸、絲胺酸和脯胺酸的胺基酸可選自下列群組：Arg、Asn、Asp、Cys、Gln、Glu、Gly、His、Ile、Leu、Lys、Met、Phe、Thr、Trp、Tyr、和Val。在生理條件下，PAS肽係形成無規則捲曲構形，從而可介導本公開的重組蛋白在體內和/或體外的穩定性增加，且具有促凝血活性。

【0270】 PAS肽的非限制性實例公開在，例如，美國專利公開號2010/0292130 A1；PCT申請公開號WO 2008/155134 A1；和歐洲授權的專利EP2173890。

III.C.5. HAP

【0271】 在某些方面中，在本公開的方法中使用的嵌合多肽包含至少一個均胺基酸聚合物(HAP)肽或其片段、變異體、或衍生物。HAP肽可包含甘胺酸的重複序列，其長度為至少50個胺基酸、至少100個胺基酸、120個胺基酸、140個胺基酸、160個胺基酸、180個胺基酸、200個胺基酸、250個胺基酸、300個胺基酸、350個胺基酸、400個胺基酸、450個胺基酸、或500個胺基酸。HAP序列能夠延長與HAP序列融合或連接的部分的半衰期。HAP序列的非限制性實例包括，但不限於(Gly)n、(Gly4Ser)n或S(Gly4Ser)n，其中n為1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、或20。在一些實施例中，n為20、21、22、23、24、25、26、26、28、29、30、31、32、33、34、35、36、37、38、39、或40。在其他實施例中，n為50、60、70、80、90、100、110、120、130、140、150、160、170、180、190、或200。參見，例如，Schlapschy M等, Protein Eng. Design Selection, 20: 273-284 (2007)。

III.C.6. 轉鐵蛋白

【0272】 在某些方面中，在本公開的方法中使用的嵌合多肽包含至少一個轉鐵蛋白肽或其片段、變異體、或衍生物。任何轉鐵蛋白可與在本公開的方法中使用的嵌合多肽融合。例如，野生型人類Tf (Tf)是679個胺基酸的蛋白，約75 kDa (不考慮糖基化)，具有兩個主要域，N (約330個胺基酸)和C(約340個胺基酸)，其似乎起源於基因重複。參見GenBank登錄號NM001063、XM002793、M12530、XM039845、XM 039847和S95936 (www.ncbi.nlm.nih.gov)，其中全部通過提述以其整體併入本文。

【0273】 轉鐵蛋白通過轉鐵蛋白受體(TfR)介導的內吞作用來運輸鐵。在鐵被釋放到內體區室中，且Tf-TfR複合體被循環到細胞表面後，Tf係被釋放回細胞外空間，以用於下一輪的鐵運輸。Tf擁有超過14至17天的長半衰期(Li等, Trends Pharmacol. Sci. 23:206-209 (2002))。已經研究了轉鐵蛋白融合蛋白的半衰期延長、靶向遞送用於癌症治療、口服遞送和持續激活胰島素原(Brandsma等, Biotechnol.

Adv., 29: 230-238 (2011)；Bai等, Proc. Natl. Acad. Sci. USA 102:7292–7296 (2005)；Kim等, J. Pharmacol. Exp. Ther., 334:682-692 (2010)；Wang等, J. Controlled Release 155:386-392 (2011))。

III.C.7. PEG

【0274】 在某些方面中，在本公開的方法中使用的嵌合多肽包含非多肽異源部分或其片段、變異體、或衍生物的至少一個附著位點。例如，在本公開的方法中使用的嵌合多肽可包括與凝血因子和/或Fc區中的一個或多個胺基酸殘基附著的一個或多個聚乙二醇(PEG)部分。

【0275】 蛋白的聚乙二醇化可是指該蛋白和至少一個聚乙二醇(PEG)分子之間形成的綴合物。多種分子量和平均分子量範圍的PEG係可商購獲得。PEG平均分子量範圍的一般實例包括，但不限於，約200、約300、約400、約600、約1000、約1300-1600、約1450、約2000、約3000、約3000-3750、約3350、約3000-7000、約3500-4500、約5000-7000、約7000-9000、約8000、約10000、約8500-11500、約16000-24000、約35000、約40000、約60000、和約80000道爾頓（Dalton）。這些平均分子量僅作為實例提供，並不意味著以任何方式進行限制。

【0276】 在本公開的方法中所使用的嵌合多肽可經聚乙二醇化以包括單一或聚(例如，2至4個)PEG部分。聚乙二醇化可通過本領域中已知的任何聚乙二醇化反應來進行。用於製備聚乙二醇化蛋白產物的方法將通常包括 (i)在本公開的肽與一個或多個PEG基團附著的條件下，使多肽與聚乙二醇(諸如PEG的反應性酯或醛衍生物)反應；和(ii)獲得一個或多個反應產物。通常，反應的最佳反應條件將根據已知參數和期望的結果以個案確定。

【0277】 本領域技術人員可使用許多PEG附著方法，例如Malik F等, Exp. Hematol. 20:1028-35 (1992)；Francis, Focus on Growth Factors 3(2):4-10 (1992)；歐洲專利公開號EP0401384、EP0154316、和EP0401384；和國際專利申請公開號WO92/16221和WO95/34326。作為非限制性實例，FVIII變異體可含有半胱胺酸替代，且半胱胺酸可進一步與PEG聚合物綴合。參見Mei等，Blood 116:270-279 (2010)和美國專利號7,632,921，其通過提述以其整體併入本文。

【0278】 在某些實施例中，該嵌合多肽係包含與VWF片段共價連接的單鏈FVIII多肽，該VWF片段包含VWF的D'域和D3域，其中該FVIII多肽包含全部或部分B域的缺失，其中該FVIII多肽是聚乙二醇化的，且其中該VWF片段與FVIII多肽(例如，PEG-scFVIII-D'D3、「MG1121」或LAFATE)的N端直接或間接融合。在其他實施例中，該嵌合多肽係包含與VWF片段共價連接的單鏈FVIII多肽，該VWF片段包含VWF的D'域和D3域，其中該FVIII多肽包含全部或部分B域的缺失，其中該VWF片段是聚乙二醇化的，且其中該VWF片段與FVIII多肽(例如，scFVIII-D'D3-PEG)的N端直接或間接融合。在其他實施例中，該嵌合多肽係包含與VWF片段共價連接的單鏈FVIII多肽，該VWF片段包含VWF的D'域和D3域，其中該FVIII多肽包含全部或部分B域的缺失，其中FVIII多肽和該VWF片段是聚乙二醇化的，且其中該VWF片段與FVIII多肽(例如，scFVIII-D'D3-PEG)的N端直接或間接融合。

III.C.8. HES

【0279】 在某些方面中，在本公開的方法中使用的嵌合多肽係包含至少一個羥乙基澱粉(HES)聚合物。HES是天然存在的支鏈澱粉的衍生物，且通過體內的α澱粉酶降解。HES表現出有益的生物學性質，且用作血容積代替劑，且在臨床上用於血液稀釋療法。參見，例如，Sommermeyer等, Krankenhauspharmazie 8:271-278 (1987)； 和Weidler等, Arzneim.-Forschung/Drug Res. 41: 494-498 (1991)。

【0280】 HES主要係以分子量分佈和替代程度所表徵。HES的平均分子量(重均分子量)為1至300 kD、2至200kD、3至100 kD、4至70kD。羥乙基澱粉可進一步表現出0.1至3、0.1至2、0.1至0.9、或0.1至0.8的莫耳替代率（molar degree of substutution），以及相對於羥乙基基團C2:C6替代的比例在2至20的範圍中。平均分子量為約130 kD的HES為來自Fresenius的VOLUVEN®。VOLUVEN®是人工膠體，其例如係用於在低血容量症中之治療和預防的治療性指示所使用的容量代替物。本領域技術人員可使用許多HES附著方法，例如，上述相同的PEG附著方法。

III.C.9. PSA

【0281】 在某些方面中，在本公開的方法中使用的嵌合多肽包含至少一個聚唾液酸(PSA)聚合物。PSA是天然存在且無支鏈的唾液酸聚合物，其係通過某些細菌菌株和哺乳動物中的某些細胞中所產生。參見，例如，Roth J.等(1993) in Polysialic Acid: From Microbes to Man, eds. Roth J., Rutishauser U., Troy F. A. (BirkhäuserVerlag, Basel, Switzerland), pp. 335–348。PSA可生成為多種的聚合程度，從n=約80或以上的唾液酸殘基直至n=2，其係對天然的、細菌性衍生的聚合物形式進行有限的酸水解，或進行神經胺酸酶消化、或進行分餾來產生。本領域技術人員可使用許多PSA附著方法，例如，上述相同的PEG附著方法。在某些方面中，激活的PSA還可與凝血因子內的半胱胺酸胺基酸殘基附著，例如，在FVIII上，或Fc區內的半胱胺酸胺基酸殘基。參見，例如，美國專利號5846951。

III.C.10. 清除受體

【0282】 在某些方面中，若該嵌合多肽的凝血因子包含FVIII多肽和FVIII清除受體或其FVIII結合片段、變異體、或衍生物的至少一個片段，在本公開的方法中所使用的嵌合多肽其半衰期可以被延長。插入可溶形式的清除受體，諸如低密度脂蛋白相關的蛋白受體LRP1或其片段，可阻斷FVIII與清除受體的結合，且從而延長其半衰期，例如是體內半衰期。LRP1是600 kDa的整合膜蛋白，其涉及多種蛋白質(包括FVIII)的受體介導清除。參見，例如，Lenting等, Haemophilia 16:6-16 (2010)。其它適合的FVIII清除受體例如是，LDLR (低密度脂蛋白受體)、VLDLR(極低密度脂蛋白受體)、和巨蛋白(LRP-2)、或其片段。參見，例如，Bovenschen等, Blood 106:906-912 (2005)；Bovenschen, Blood 116:5439-5440 (2010)；Martinelli等, Blood 116:5688-5697 (2010)。

III.D.插入位點

【0283】 在某些方面中，FVIII多肽中的插入位點係位於FVIII多肽的一個或多個域中，該域是N端、A1域、A2域、A3域、B域、C1域、C2域、C端、或其兩個或多於兩個的組合，或位於FVIII多肽的兩個域之間，該兩個域是A1域和a1

酸性區、和a1酸性區和A2域、A2域和a2酸性區、a2酸性區和B域、B域和A3域、和A3域和C1域、C1域和C2域、或其任何組合。例如，可插入XTEN序列的插入位點選自下列群組：N端和A1域、N端和A2域、N端和A3域、N端和B域、N端和C1域、N端和C2域、N端和C端、A1和A2域、A1和A3域、A1和B域、A1和C1域、A1和C2域、A1域和C端、A2和A3域、A2和B域、A2和C1域、A2和C2域、A2域和C端、A3和B域、A3和C1域、A3和C2域、A3域和C端、B和C1域、B和C2域、B域和C端、C1和C2域、C1和C端、C2域和C端，及其兩種或多種組合。

【0284】 在連接XTEN序列或插入XTEN序列後，FVIII多肽(其中XTEN序列在係插入於緊鄰FVIII多肽中的一個或多個胺基酸(例如，一個或多個XTEN插入位點)的下游或在C端或N端處連接)係保留有FVIII活性。XTEN序列可以在FVIII多肽中插入一次或多於一次、兩次、三次、四次、五次、或六次，使得插入不影響FVIII活性(即，FVIII蛋白仍保留凝血性質)。

【0285】 可用於本公開的FVIII多肽可通過任選的連接子在FVIII多肽的N端或C端處，與一個或多個XTEN多肽連接，或通過一個或多個任選的連接子插入在緊鄰FVIII多肽中的一個或多個胺基酸(例如，一個或多個XTEN插入位點)的下游。

【0286】 在又一些其他的實施例中，一個或多個XTEN係被插入在FVIII的B域中。在一個實例中，XTEN被插入在對應於SEQ ID NO: 65的胺基酸740和1640之間，其中在胺基酸740和1640之間的FVIII序列可視情況不存在。在另一實例中，XTEN被插入在對應於SEQ ID NO: 65的胺基酸741和1690之間，其中在胺基酸740和1690之間的FVIII序列可視情況不存在。在其他實例中，XTEN被插入在對應於SEQ ID NO: 65的胺基酸741和1648之間，其中在胺基酸741和1648之間的FVIII序列可視情況不存在。在又一些其他的實例中，XTEN被插入在對應於SEQ ID NO: 65的胺基酸743和1638之間，其中胺基酸743和1638之間的FVIII序列可視情況不存在。在又一些其他的實施例中，XTEN被插入在對應於SEQ ID NO: 65的胺基酸745和1656之間，其中在胺基酸745和1656之間的FVIII序列可視情況不存在。在一些實例中，XTEN被插入在對應於SEQ ID NO: 65的胺基酸745和1657

之間，其中在胺基酸745和1657之間的FVIII序列可視情況不存在。在某些實例中，XTEN被插入在對應於SEQ ID NO: 65的胺基酸745和1667之間，其中在胺基酸745和1667之間FVIII序列可視情況不存在。在又一些其他的實例中，XTEN被插入在對應於SEQ ID NO: 65的胺基酸745和1686之間，其中在胺基酸745和1686之間的FVIII序列可視情況不存在。在一些其他實例中，XTEN被插入在對應於SEQ ID NO: 65的胺基酸747和1642之間，其中在胺基酸747和1642之間的FVIII序列可視情況不存在。在又一些其他實例中，XTEN被插入在對應於SEQ ID NO: 65的胺基酸751和1667之間，其中在胺基酸751和1667之間的FVIII序列可視情況不存在。在一些實施例中，XTEN序列被插入在成熟FVIII多肽的胺基酸745和746之間，或B域缺失的FVIII多肽的對應插入位點。在特定的實施例中，包含具有與AE288 (SEQ ID NO: 8)的胺基酸序列至少約70%、至少約75%、至少約80%、至少約85%、至少約90%、至少約95%、至少約96%、至少約97%、至少約98%、至少約99%、或約100%序列同一性的胺基酸序列的XTEN序列被插入在成熟FVIII的胺基酸745和746之間，其中該成熟FVIII具有胺基酸殘基746至1648的缺失。在特定的實施例中，XTEN被插入在緊鄰表5的B域缺失的FVIII(SEQ ID NO: 68)的胺基酸745的下游。

III.E. 連接子

【0287】 在某些實施例中，本公開的嵌合多肽在FVIII蛋白係中和/或在VWF片段中進一步包含一個或多個連接子。一種類型的連接子是可切割的連接子，當其在體內施用至個體(例如在凝血位點處)時，可由蛋白酶來切割。在一些實施例中，該可切割的連接子允許從XTEN序列切割例如VWF蛋白的基團，從而自嵌合多肽在凝血級聯位點處切割出來，因此讓激活的FVIII(FVIIIa)具有其FVIIIa活性。另一種類型的連接子是可加工的連接子，其含有細胞內切割位點，且因此可在宿主細胞中由細胞內加工酶進行切割，以方便地表現多肽和形成嵌合多肽。

【0288】 一個或多個連接子可存在於嵌合多肽中的任何兩個蛋白之間。在一

些實施例中，嵌合多肽包含第一多肽和第二多肽，該第一多肽包含(i)FVIII多肽和(ii)第一Ig恆定區或其部分，該第二多肽包含(iii)VWF蛋白，(iv)連接子(例如，可切割的連接子)，(v)XTEN序列，和(vi)第二Ig恆定區或其部分。在其他實施例中，嵌合多肽包含第一多肽和第二多肽，該第一多肽包含(i)FVIII多肽和(ii) 第一Ig恆定區或其部分，該第二多肽包含(iii)VWF蛋白，(iv)XTEN序列，(v)連接子(例如可切割的連接子)，和(vi)第二Ig恆定區或其部分。在其他實施例中，嵌合多肽包含第一多肽和第二多肽，該第一多肽包含(i)FVIII多肽和(ii)第一Ig恆定區或其部分，該第二多肽包含(iii)VWF蛋白，(iv)第一連接子(例如可切割的連接子)，(v)XTEN序列，(vi)第二連接子(例如可切割的連接子)，和(vii)第二Ig恆定區或其部分。在一些實施例中，該第一多肽在FVIII多肽和第一Ig恆定區之間進一步包含連接子(例如可切割的連接子)。

【0289】　在某些實施例中，嵌合多肽包含單鏈，該單鏈包含(i) FVIII多肽，(ii)第一Ig恆定區或其部分，(iii)連接子 (例如可加工的連接子)，(iv) VWF蛋白，(v) XTEN序列，和(vi) 第二Ig恆定區或其部分。在其他實施例中，嵌合多肽包含單鏈，該單鏈包含(i)FVIII多肽，(ii)第一Ig恆定區或其部分，(iii)第一連接子(例如可加工的連接子)，(iv)VWF蛋白，(v)第二連接子(例如可切割的連接子)，(vi)XTEN序列，和(vii)第二Ig恆定區或其部分。在該嵌合多肽在宿主細胞中表現後，該可加工的連接子可經加工；因此在宿主細胞中所產生的嵌合多肽可以是包含兩條或三條多肽鏈的最終形式。

【0290】　可用於本公開的連接子可包含任何有機分子。可在本公開的嵌合多肽中使用的連接子的實例公開於，例如，US 2011/0183907 A1、US 2016/0229903 A1、和US 2016/0251408 A1中，其中各文本係通過提述以其整體併入本文。在一些實施例中，該連接子包含聚合物，例如，聚乙二醇(PEG)或羥乙基澱粉(HES)。在其他實施例中，該連接子包含胺基酸序列。該連接子可包含至少約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、或2000個胺基酸。該連接子可包含1-5個胺基酸、1-10個胺基酸、1-20個胺基酸、10-50

個胺基酸、50-100個胺基酸、100-200個胺基酸、200-300個胺基酸、300-400個胺基酸、400-500個胺基酸、500-600個胺基酸、600-700個胺基酸、700-800個胺基酸、800-900個胺基酸、或900-1000個胺基酸。在一些實施例中，該連接子包含XTEN序列。XTEN的另外的實例可根據本公開來使用，且公開於美國專利公開號2010/0239554 A1、2010/0323956 A1、2011/0046060 A1、2011/0046061 A1、2011/0077199 A1、或2011/0172146 A1，或國際專利公開號WO 2010091122 A1、WO 2010144502 A2、WO 2010144508 A1、WO 2011028228 A1、WO 2011028229 A1、或WO 2011028344 A2中。在其他實施例中，該連接子是PAS序列。

【0291】　在某些實施例中，該連接子是聚合物，例如，聚乙二醇(PEG)或羥乙基澱粉(HES)。在其他實施例中，該連接子是胺基酸序列。該連接子可包含至少約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、或2000個胺基酸。該連接子可包含1-5個胺基酸、1-10個胺基酸、1-20個胺基酸、10-50個胺基酸、50-100個胺基酸、100-200個胺基酸、200-300個胺基酸、300-400個胺基酸、400-500個胺基酸、500-600個胺基酸、600-700個胺基酸、700-800個胺基酸、800-900個胺基酸、或900-1000個胺基酸。

【0292】　連接子的實例是本領域中熟知的。在某些實施例中，該連接子包含序列G_n。該連接子可包含序列$(GA)_n$。該連接子可包含序列$(GGS)_n$。在其他實施例中，該連接子包含$(GGGS)_n$ (SEQ ID NO: 101)。在又一些其他的實施例中，該連接子包含序列$(GGS)_n(GGGGS)_n$ (SEQ ID NO: 95)。在這些情況中，n可以是從1-100的整數。在其他情況中，n可以是從1-20的整數，即，1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、或20。連接子的實例包括但不限於，GGG、SGGSGGS (SEQ ID NO: 96)、GGSGGSGGSGGSGGG (SEQ ID NO: 97)、GGSGGSGGGGSGGGGS (SEQ ID NO: 98)、GGSGGSGGSGGSGGSGGS (SEQ ID NO: 99)、或GGGGSGGGGSGGGGS (SEQ ID NO: 100)。該連接子不消除或減少VWF蛋白活性或因子VIII的凝血活性。任選地，該連接子係增強VWF蛋白活性或因子VIII蛋白的凝血活性，例如藉由進

一步減少立體障礙作用，並使VWF蛋白或因子VIII部分更易接近其靶結合位點。

【0293】　在某些實施例中，可用於嵌合多肽的連接子為15-25個胺基酸長。在其他實施例中，可用於嵌合多肽的連接子為15-20個胺基酸長。在一些實施例中，可用於嵌合多肽的連接子為10-25個胺基酸長。在其他實施例中，可用於嵌合多肽的連接子為15個胺基酸長。在又一些其他的實施例中，可用於嵌合多肽的連接子為$(GGGGS)_n$ (SEQ ID NO: 94)，其中G表示甘胺酸，S表示絲胺酸，且n為從1-20的整數。

III.F. 切割位點

【0294】　可切割連接子可以併入能夠通過化學方法(例如，酯鍵的水解)、酶促(即，併入蛋白酶切割序列)、或光解(例如，生色團諸如3-胺基-3-(2-硝基苯基)丙酸(ANP))來切割的部分，以便從另一分子釋放一個分子。適於本公開的嵌合多肽的可切割連接子其實例可見於，例如，US 2016/0229903 A1和US 2016/0251408 A1中，其中個文本通過提述以其整體併入本文。

【0295】　在某些實施例中，可切割連接子在N端或C端或二者處包含一個或多個切割位點。在其他實施例中，該可切割連接子實質上由或係由一個或多個可切割位點所構成。在其他實施例中，該可切割連接子包含本文所述的異源胺基酸連接子序列或聚合物和一個或多個可切割位點。

【0296】　在某些實施例中，可切割連接子包含一個或多個可在宿主細胞中切割的切割位點(即，細胞內加工位點)。切割位點的非限制性實例包括RRRR (SEQ ID NO: 102)、RKRRKR (SEQ ID NO: 103)、和RRRRS (SEQ ID NO: 104)。

【0297】　在一些實施例中，可切割連接子包含來自FVIII的a1區、來自FVIII的a2區、來自FVIII的a3區、凝血酶可切割位點，該凝血酶可切割位點包含X-V-P-R (SEQ ID NO: 105)和PAR1外位點(exosite)相互作用基序，其中X是脂肪族胺基酸，或其任何組合。在其他實施例中，可用於本公開

的可切割連接子包含a2區，該a2區包含與對應於全長FVIII的Glu720至Arg740至少 為 約80%、 約85%、 約90%、 約95%或100%相同的胺基酸序列，其中a2區能够由凝血酶切割。在特定的實施方案中，可用於本公開的可切割連接子包含a2區，該a2區包含ISDKNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 106)或DKNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 88)。在其他實施方案中，可用於本公開的可切割連接子包含a1區，該a1區包含與對應於全長FVIII的Met337至Arg372至少為約80%、約85%、約90%、約95%、或100%相同的胺基酸序列，其中a1區能够由凝血酶切割。在特定的實施方案中，該a1區包含ISMKNNEEAEDYDDDLTDSEMDVVRFDDDNSPSFIQIRSV (SEQ ID NO: 107)。在一些實施例中，本公开的可切割連接子包含a3區，該a3區包含與對應於全長FVIII的Glu1649至Arg1689至少為約80%、約85%、約90%、約95%、或100%相同的胺基酸序列，其中該a3區能够由凝血酶切割。在某些實施方案中，用於本公開的可切割連接子包含a3區，該a3區包含ISEITRTTLQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSPRSFQ (SEQ ID NO: 108)。

【0298】 在其他實施方案中，可切割連接子包含凝血酶切割位點，該凝血酶切割位點包含X-V-P-R (SEQ ID NO: 105)和PAR1外位點相互作用基序，且其中PAR1外位點相互作用基序包含S-F-L-L-R-N (SEQ ID NO: 109)。PAR1外位點相互作用基序可進一步包含選自以下的胺基酸序列：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)，或其任何组合。在一些實施例中，脂肪族胺基酸選自甘胺酸、丙胺酸、纈胺酸、白胺酸、或異白胺酸。

【0299】　在其他實施方案中，可切割連接子包含一個或多個切割位點，在包含該可切割連接子的嵌合多肽施用至個體後，該切割位點可由蛋白酶切割。在一些實施例中，該切割位點可由選自下列群組的蛋白酶切割：因子XIa、因子XIIa、激肽釋放素（kallikrein）、因子VIIa、因子IXa、因子Xa、因子IIa(凝血酶)、彈性蛋白酶-2、MMP-12、MMP-13、MMP-17、和MMP-20。在其他實施方案中，該切割位點選自下列群組：FXIa切割位點(例如，KLTR↓AET (SEQ ID NO: 121))、FXIa切割位點(例如，DFTR↓VVG (SEQ ID NO: 122))、FXIIa切割 位點(例如，TMTR↓IVGG (SEQ ID NO: 123))、激肽釋放素切割 位點(例如，SPFR↓STGG (SEQ ID NO: 124))、FVIIa切割位點(例如，LQVR↓IVGG (SEQ ID NO: 125))、FIXa切割位點(例如，PLGR↓IVGG (SEQ ID NO: 126))、FXa切割位點(例如，IEGR↓TVGG (SEQ ID NO: 127))、FIIa(凝血酶)切割位點(例如，LTPR↓SLLV (SEQ ID NO: 128))、彈性蛋白酶-2切割位點(例如，LGPV↓SGVP (SEQ ID NO: 129))、顆粒酶-B切割位點(例如，VAGD↓SLEE (SEQ ID NO: 130))、MMP-12切割位點(例如，GPAG↓LGGA (SEQ ID NO: 131))、MMP-13切割位點(例如，GPAG↓LRGA (SEQ ID NO: 132))、MMP-17切割位點(例如，APLG↓LRLR (SEQ ID NO: 133))、MMP-20切割位點(例如，PALP↓LVAQ (SEQ ID NO: 134))、TEV切割位點(例如，ENLYFQ↓G (SEQ ID NO: 135))、腸激酶（Enterokinase）切割位點(例如，DDDK↓IVGG (SEQ ID NO: 136))、蛋白酶3C (PRESCISSION™)切割位點(例如，LEVLFQ↓GP (SEQ ID NO: 137))、和分選酶A（Sortase A）切割位點(例如，LPKT↓GSES) (SEQ ID NO: 138)。在某些實施方案中，FXIa切割位點包括，但不限於，例如，TQSFNDFTR (SEQ ID NO: 1)和SVSQTSKLTR (SEQ ID NO: 3)。非限制性示例性凝血酶切割位點包括，例如，DFLAEGGGVR (SEQ ID NO: 4)、TTKIKPR (SEQ ID NO: 5)、LVPRG (SEQ ID NO:

6)、DKNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 88)、或IEPRSFS (SEQ ID NO: 194)，和包含ALRPR (SEQ ID NO: 7) (例如，ALRPRVVGGA (SEQ ID NO: 145)) 的序列，實質上由由ALRPR (SEQ ID NO: 7) (例如，ALRPRVVGGA (SEQ ID NO: 145))構成的序列，或係由ALRPR (SEQ ID NO: 7) (例如，ALRPRVVGGA (SEQ ID NO: 145))構成的序列。

【0300】 在一些實施例中，該切割位點為TLDPRSFLLRNPNDKYEPFWEDEEK (SEQ ID NO: 146)。在其他實施例中，該切割位點包含DKNTGDYYEDSYEDISAYLLSKNNAIEPRSFS (SEQ ID NO: 88)或其片段。在特定的實施例中，該切割位點包含IEPRSFS (SEQ ID NO: 194)。在其他實施例中，該切割位點包含EPRSFS (SEQ ID NO: 195)，其中該切割位點不是FVIII的全長a2區。在又一些其他的實施例中，該切割位點包含IEPR (SEQ ID NO: 200)。在又一些其他的實施例中，該切割位點包含IEPR(SEQ ID NO: 200)，其中該切割位點不是FVIII的全長a2區，或者不包含FVIII的全長a2區。在其他實施例中，該切割位點包含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)、KNNAIEPRSFS (SEQ ID NO: 190)、NNAIEPRSFS (SEQ ID NO: 191)、NAIEPRSFS (SEQ ID NO: 192)、AIEPRSFS (SEQ ID NO: 193)、或IEPRSFS (SEQ ID NO: 194)。在其他實施例中，該切割位點包含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)、KNNAIEPRSFS (SEQ ID NO: 190)、NNAIEPRSFS (SEQ ID NO: 191)、NAIEPRSFS (SEQ ID NO: 192)、AIEPRSFS (SEQ ID NO: 193)、或IEPRSFS (SEQ ID NO:194)，其中該切割位點不是全長FVIII a2區。在某些實施例中，該可切割連接子在凝血酶切割測定中是可切割的，如本文所提供的或如本領域已知的。

【0301】　在特定的實施例中，本公開的嵌合多肽包含：(i) FVIII蛋白，其包含FVIII多肽、第一XTEN序列、和第一Fc區；和(ii) VWF片段，其包含VWF的 D'

域和VWF的D3域、第二XTEN序列、FVIII的a2連接子、和第二Fc區；其中：

(a) 該FVIII蛋白具有對應於成熟FVIII的胺基酸746至1648的缺失；

(b) 該第一XTEN序列被插入在的FVIII多肽內，其緊鄰對應於成熟FVIII的胺基酸745的下游；

(c) 該第一XTEN序列包含與AE288 (SEQ ID NO: 8)的胺基酸序列具有至少約70%、至少約75%、至少約80%、至少約85%、至少約90%、至少約95%、至少約96%、至少約97%、至少約98%、至少約99%、或約100%序列同一性的胺基酸序列；

(d) 該第一Fc區融合至該FVIII多肽的C端；

(e) 該第二XTEN序列融合至該VWF片段的C端；

(f) 該第二XTEN序列包含與AE144_5A (SEQ ID NO: 58)的胺基酸序列具有至少約70%、至少約75%、至少約80%、至少約85%、至少約90%、至少約95%、至少約96%、至少約97%、至少約98%、至少約99%、或約100%序列同一性的胺基酸序列；

(g) 該a2連接子融合至與該XTEN的C端；

(h) 該a2連接子包含與SEQ ID NO: 88的胺基酸序列具有至少約70%、至少約75%、至少約80%、至少約85%、至少約90%、至少約95%、至少約96%、至少約97%、至少約98%、至少約99%、或約100%序列同一性的胺基酸序列；

(i) 該第二Fc區融合至該a2連接子的C端；且

(j) 該第一Fc區通過雙硫鍵與該第二Fc區共價連接。

【0302】 在特定的實施例中，本公開的嵌合多肽包含兩條多肽序列，第一多肽序列和第二多肽序列，該第一多肽序列包含與選自下列群組的序列至少約80%、90%、95%、或100%相同的胺基酸序列：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)、FVIII199 (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)或FVIII-272 (SEQ ID NO: 85)，該第二多肽序列包含與選自下列群組的序列至少約80%、90%、95%、或100%相同的胺基酸序列VWF031 (SEQ ID NO: 86)、VWF034 (SEQ ID NO: 87)、或VWF-036。

【0303】 在一些實施例中，本公開的嵌合多肽包含兩條多肽序列，第一多肽序列和第二多肽序列，該第一多肽序列包含與SEQ ID NO: 201所示的胺基酸序列至少為約80%、90%、95%、或100%相同的胺基酸序列；該第二多肽序列包含VWF片段以及Fc區，該VWF片段包含VWF的D'域和VWF的D3域。在一些實施例中，本公開的嵌合多肽包含兩條多肽序列，第一多肽序列和第二多肽序列，該第一多肽序列包含FVIII多肽和Fc區；該第二多肽序列包含與SEQ ID NO: 202所示的胺基酸序列至少為約80%、90%、95%、或100%相同的胺基酸序列。在某些實施例中，本公開的嵌合多肽包含兩條多肽序列，第一多肽序列和第二多肽序列，該第一多肽序列包含與SEQ ID NO: 201所示的胺基酸序列至少為約80%、90%、95%、或100%相同的胺基酸序列，該第二多肽序列包含與SEQ ID NO: 202所示的胺基酸序列至少為約80%、90%、95%、或100%相同的胺基酸序列。在特定的實施例中，本公開的嵌合多肽包含兩條多肽序列，第一多肽序列和第二多肽序列，該第一多肽序列包含SEQ ID NO: 201所示的胺基酸序列，該第二多肽序列包含SEQ ID NO: 202所示的胺基酸序列。在其他特定的實施例中，本公開的嵌合多肽包含兩條多肽序列，第一多肽和第二多肽序列，該第一多肽序列包含SEQ ID NO: 201所示的胺基酸序列，該第二多肽序列包含SEQ ID NO: 202所示的胺基酸序列，其中該第一多肽序列和該第二多肽序列通過雙硫鍵彼此連接。

IV. 醫藥組合物

【0304】 含有本公開的嵌合多肽的組合物可含有適合的醫藥上可接受的載劑。例如，它們可含有賦形劑和/或輔料，其有助於有助於將活性化合物加工成經設計用於遞送至作用部位的製劑。

【0305】 該醫藥組合物可經配製用於通過推注注射的非經胃腸型之施用(即靜脈內、皮下、或肌肉內)。用於注射的配製劑，例如在含有添加的防腐劑的安

瓿或多劑量容器中，可以單位劑量形式呈現。該組合物可以採取諸如懸浮液、溶液、或油性或水性媒劑中的乳液的形式，並含有配方劑諸如懸浮劑、穩定劑和/或分散劑。或者，活性成分可以是粉末形式，用於與適合的媒劑(例如無熱原的水)組成。

【0306】　用於非經胃腸型式施用的適當配製劑，還包括水溶性形式的活性化合物水溶液，例如水溶性鹽。此外，可以施用活性化合物的懸浮液作為適合的油性注射懸浮液。適合的親脂性溶劑或媒劑包括脂肪油(例如，芝麻油)、或合成性脂肪酸酯(例如油酸乙酯或甘油三酯)。水性注射懸浮液可含有增加懸浮液粘度的物質，其例如包括羧甲基纖維素鈉、山梨醇和葡聚糖。視情況地，懸浮液還可含有穩定劑。脂質體也可用於包封本發明的分子以遞送到細胞或間質空間中。示例性的醫藥上可接受載劑是生理上相容的溶劑、分散介質、包衣、抗細菌劑和抗真菌劑、等滲透和延遲吸收劑、水、鹽水、磷酸鹽緩衝鹽水、右旋糖、甘油、乙醇等。在一些實施例中，該組合物包含等滲劑，例如，糖、多元醇諸如甘露醇、山梨醇或氯化鈉。在其他實施例中，該組合物包含醫藥上可接受的物質諸如潤濕劑或微量輔助物質諸如潤濕劑或乳化劑、防腐劑或緩衝液，其可增強活性成分的貯存期限或有效性。

【0307】　本公開的組合物可以是多種形式的，例如包括液體(例如，可注射和可輸注的溶液)、分散體、懸浮液、半固體和固體劑型。優選的形式係取決於施用的模式和治療應用。

【0308】　該組合物可配製為溶液、微乳液、分散體、脂質體或其他適用於高藥物濃度的有序結構。無菌可注射溶液可通過將所需量的活性成分併入具有一種以上所列舉的成分或以上列舉成分的組合之適當溶劑中來製備，根據需要，隨後係進行無菌過濾。通常，分散體可通過將活性成分併入無菌媒劑中來製備，該無菌媒劑含有基礎分散介質和來自以上列舉成分中的其他所需成分。至於用來製備無菌可注射溶液的無菌粉末，較佳的製備方法是真空乾燥和冷凍乾燥，其係從先前已經無菌過濾的溶液中產生活性成分的粉末和任何另外所期望的成分。維持溶液的適當流動性可例如藉由使用諸如卵磷脂等包衣形式(coating)、藉

由保持所需的粒子大小(在分散的情況下)，和藉由使用表面活性劑。可注射組合物的延長吸收可通過在組合物中納入延遲吸收的試劑(例如單硬脂酸鹽和明膠)來實現。

【0309】　活性成分可用控釋型的配製劑或裝置來配製。此類配製劑和裝置的實例包括植入物、經皮貼劑、和微囊化遞送系統。可使用可生物降解的生物相容性聚合物，例如，乙烯乙酸乙烯酯、聚酸酐、聚乙醇酸、膠原、聚原酸酯(polyorthoesters)和聚乳酸。用於製備此類配製劑和裝置的方法是本領域中已知的。參見例如，Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978。

【0310】　可注射貯庫配製劑(injectable depot formulations)可通過在生物可降解的聚合物(諸如聚丙交酯-聚乙交酯)中形成藥物的微膠囊化基質來製造。根據藥物與聚合物的比率，以及所採用的聚合物性質，可控制藥物釋放的速率。其他示例性的可生物降解的聚合物為聚原酸酯和聚酸酐。貯庫可注射的配製劑還可通過在脂質體或微乳液中捕獲藥物來製備。

【0311】　補充性活性化合物可被併至組合物中。在一些實施例中，本公開的嵌合多肽係與另一凝血因子或其變異體、片段、類似物或衍生物一起配製。例如，凝血因子包括，但不限於，因子V、因子VII、因子VIII、因子IX、因子X、因子XI、因子XII、因子XIII、凝血酶原、纖維蛋白原、馮威里氏因子或重組可溶性組織因子(rsTF)或任何前述因子的激活形式。止血劑的凝血因子也可包括抗纖維蛋白溶解藥物，例如，ε-胺基-己酸、胺甲環酸。

【0312】　劑量方案可經調節以提供最佳的期望反應。例如，可施用單次推注，可隨時間施用若干分劑量，或可按比例減少或增加劑量，如通過治療情況的緊急狀態所指示的。以劑量單位形式所配製的非經胃腸組合物，係對於易施用性和劑量均勻性而言是有利的。參見，例如，Remington's Pharmaceutical Sciences (Mack Pub. Co., Easton, Pa. 1980)。

【0313】　除了活性化合物外，液體劑型可含有惰性成分，諸如水、乙醇、碳酸乙酯、乙酸乙酯、苯甲醇、苯甲酸苄酯、丙二醇、1,3-丁二醇、二甲基甲醯胺、

油類、甘油、四氫糠醇、聚乙二醇和山梨聚糖的脂肪酸酯。

【0314】　適合的藥物載劑的非限制性實例還描述於E. W. Martin的Remington's Pharmaceutical Sciences中。賦形劑的一些實例包括澱粉、葡萄糖、乳糖、蔗糖、明膠、麥芽、稻米、麵粉、白堊、矽膠、硬脂酸鈉、單硬脂酸甘油酯、滑石、氯化鈉、脫脂乳粉、甘油、丙烯、二醇、水、乙醇等。組合物還可含有pH緩衝劑和潤濕劑或乳化劑。

【0315】　在一些實施例中，醫藥組合物係包含嵌合多肽和醫藥上可接受的載劑。相較於野生型FVIII蛋白或對應的無VWF片段的FVIII蛋白，嵌合多肽中的FVIII蛋白係具有延長的半衰期。在一些實施例中，其中嵌合多肽的半衰期比野生型FVIII延長至少約1.5倍、至少約2倍、至少約2.5倍、至少約3倍、至少約4倍、至少約5倍、至少約6倍、至少約7倍、至少約8倍、至少約9倍、至少約10倍、至少約11倍、或至少約12倍。在其他實施例中，因子VIII的半衰期為至少約17小時、至少約18小時、至少約19小時、至少約20小時、至少約21小時、至少約22小時、至少約23小時、至少約24小時、至少約25小時、至少約26小時、至少約27小時、至少約28小時、至少約29小時、至少約30小時、至少約31小時、至少約32小時、至少約33小時、至少約34小時、至少約35小時、至少約36小時、至少約48小時、至少約60小時、至少約72小時、至少約84小時、至少約96小時、或至少約108小時。在一些實施例中，相較於野生型FVIII，嵌合多肽的半衰期係延長約3倍。

【0316】　在一些實施例中，該組合物通過非經胃腸的施用來施用，非經胃腸的施用可以是靜脈內或皮下施用。

【0317】　在其他實施例中，該組合物可用於治療有需要的個體其出血疾病或病況。該出血疾病或病況係選自下列群組：出血凝固障礙、關節出血、肌肉出血、口腔出血、溢血(hemorrhage)、溢血至肌肉中、口腔溢血、創傷、頭部創傷(trauma capitis)、胃腸出血、顱內溢血、腹腔內溢血、胸腔內溢血、骨折、中樞神經系統出血、咽後間隙中出血、腹膜後間隙中出血、髂腰肌鞘中出血及其任何組合。在又一些其他的實施例中，個體被安排進行手術。在又一些其他的實施例中，治療是預防性的或按需的。

【0318】　現已詳細描述了本公開，通過參考下列實例將會更清楚地理解本發明，包括在此的這些實例僅出於說明的目的，而不旨在限制本公開。本文提及的所有專利、出版物和文章係明確且具體地通過提述併入本文。

實例

實例 1： FVIII-XTEN-Fc/D'D3-XTEN-Fc 異二聚體的第一個人體研究

【0319】　基於因子的替代性療法是血友病護理的基石。傳統的重組FVIII(rFVIII)產品具有短的半衰期，需要頻繁施用。藉由rFVIIIFc (Eloctate®)已帶給患者護理的顯著進步，包括針對A型血友病的最長給藥間隔；在急性、手術期間(perioperative)和緊急情況中充分的出血控制(包括預防性控制)；防止出血無法控制，包括關節保護和改善生活質量；和長期一致和良好表徵的安全性概況。然而，每週或更長的因子VIII預防性給藥仍然未滿足大多數具有A型血友病的人們的需求。

【0320】　本研究探究了rFVIIIFc-VWF-XTEN的安全性和藥物代謝動力學(PK)，該rFVIIIFc-VWF-XTEN是一種嵌合多肽，其包含(i)FVIII多肽，在FVIII多肽的B域內所插入的XTEN，和第一Fc區；和(ii)VWF片段、第二XTEN序列、a2連接子、和第二Fc區(圖1)。

【0321】　**研究設計**

【0322】　本研究的目標是評定單劑量的rFVIIIFc-VWF-XTEN相較於rFVIII的安全性、耐受性和FVIII活性(PK)。患者群包括具有重度A型血友病(<1 IU/dL [<1%]內源性FVIII活性水平)且先前經治療的成人男性，其至少150天暴露於FVIII產品，且沒有陽性抑制因子測試史，或對FVIII施用的反應降低的臨床徵兆。主要終點是實驗室測試中的不良事件和臨床異常，包括抑制因子的發展。關鍵的次要終點包括藥物代謝動力學參數，包括但不限於消除半衰期(t1/2)、清除(CL)、從0至無窮大的曲線下面積($AUC_{0-\infty}$)、平均停留時間(MRT)、和增量恢復(IR)。

【0323】　患者分為低劑量隊列(7名患者；圖2A)或高劑量隊列(9名患者；圖2B)。

每名患者給藥rFVIII (ADVATE®)，隨後為PK取樣期。簡短的洗脫期(對於低劑量隊列(圖2A)為≥ 3天，對於高劑量隊列為≥ 4天(圖2B))後，每位個體接著被施用rFVIIIFc-VWF-XTEN，隨後為PK取樣期。個體在注射rFVIIIFc-VWF-XTEN後，係進行28天的安全性觀察，包括在注射rFVIIIFc-VWF-XTEN後14天和28天時，收集用於抑制因子評定的樣品。在低劑量隊列中的患者，係接受25 IU/kg的rFVIII和25 IU/kg的rFVIIIFc-VWF-XTEN。在高劑量隊列中的患者係接受65 IU/kg的rFVIII和65 IU/kg的rFVIIIFc-VWF-XTEN。

【0324】 **方法**

【0325】 藥物代謝動力學參數係藉由經修改的活化部分凝血活酶時間(aPTT)凝血測定(「一站」測定)來量測。簡單來說，FVIII活性在經修改的aPTT測定中，使用Dade® Actin® FSL激活的PTT試劑(Siemens Health Care Diagnostics)，在BCS® XP分析儀(Siemens Healthcare Diagnostics)上來量測。使用rFVIIIFc-VWF-XTEN特異性校準物來製備7點校準曲線(高：1.500-0.050 IU/mL；低：0.150-0.0025IU/mL)。對於高校準曲線，係將rFVIIIFc-VWF-XTEN校準物[1.000 IU/mL]稀釋到 Tris/BSA緩衝液(50 mM，150 mM氯化鈉，pH 7.4 +/- 0.2，含有1% BSA)中。此稀釋係通過BCS® XP分析儀進行，以生成預先選擇的校準FVIII活性水平。然後以1:2、在Tris/BSA緩衝液中製備的工作稀釋液測試這些樣品。對於低校準曲線，rFVIIIFc-VWF-XTEN校準物[1.000 IU/mL]在免疫缺失的FVIII缺陷血漿(Siemens Healthcare Diagnostics)中通過BCS® XP分析儀來進行稀釋，並進行純淨背景測試(在缺少工作稀釋液的情況下)。校準係進行二重複。通過以IU/mL表示的FVIII活性(x軸)和以秒表示的凝血時間(y軸)來繪製曲線。高和低校準曲線二者均使用線性對數-線性(log-lin)回歸曲線來擬合。

【0326】 使用高校準曲線metatest(在Tris/BSA中1:2、1:4、和1:8的工作稀釋液)或低校準曲線metatest(在免疫缺失的FVIII缺陷血漿中零稀釋、1:2、和1:4的工作稀釋液)以二重複來測試樣品。在適當的工作稀釋後，所有校準物、患者樣品和質量控制樣品係與免疫缺失的FVIII缺陷血漿1:1混合，該血漿含有少於或等於0.010 IU/mL FVIII活性和至少0.400 IU/mL的其他凝血因子。在樣品與此血漿混

合後，添加APTT試劑，且孵育混合物。孵育後，添加氯化鈣，並以光學方式來量測凝塊形成的時間。然後，以一演算法來檢查單個工作稀釋結果是否落在平均值的+/- 15.0%之內，以決定所報告的FVIII活性。除接近定量下限(LLOQ)外，兩個metatest的工作稀釋結果的最小值對於決定所報告的FVIII活性來說是必需的。

【0327】 結果：低劑量隊列

【0328】 個體低劑量隊列係收集7名個體；1名個體在接受rFVIIIFc-VWF-XTEN之前，因與研究不相關的原因退出。6名個體接受單次、低劑量的rFVIIIFc-VWF-XTEN (25 IU/kg)。在低劑量隊列中經治療的前4名個體的特徵包括：具有重度A型血友病 (<1 IU/dL [<1%]的內源性FVIII活性水平)且先前經治療的成人男性個體；所有個體均是高加索人種；個體的年齡範圍為19-60歲，平均年齡為33；且平均體重為85 kg (其範圍為67.2-100.6 kg)。

【0329】 在所有患者中，rFVIIIFc-VWF-XTEN普遍是耐受良好，且在給藥後第14天或第28天未觀察到抑制因子。

【0330】 接受單次低劑量的rFVIIIFc-VWF-XTEN (25 IU/kg)的前6名個體，在5天時其輸注後平均FVIII活性為約12.0%，且在7天時為約5.3%(圖3A)。平均FVIII活性在10天內係保持在1%以上(圖3A)。藉由活化部分凝血活酶時間(aPTT)量測法所量測的，rFVIIIFc-VWF-XTEN (25 IU/kg)和rFVIII (25 IU/kg)的藥物代謝動力學參數係示於**表9**中。觀察到rFVIIIFc-VWF-XTEN在個體人類個體中係具有約37.6小時的平均半衰期，其相較於在相同劑量下所施用的rFVIII平均半衰期(約9.12小時)係高4倍以上。

表9：低劑量隊列的藥物代謝動力學(PK)參數

PK 參數	**rFVIIIFc-VWF-XTEN 幾何平均值 [範圍] (N=6)**	**rFVIII 幾何平均值 [範圍] (N=7)**	**平均比率 [95% CI]**
半衰期，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	51.80	1.35 [1.04，1.77]

	[49.7–98.9]	[43.3–61.9]	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 每 IU/kg	2.72 [1.95–3.80]	2.00 [1.60–2.50]	1.36 [0.98，1.89] P = 0.063

【0331】　**結果：高劑量隊列**

【0332】　個體高劑量隊列係收集9名個體。該等個體被施用單次、高劑量的rFVIIIFc-VWF-XTEN (65 IU/kg)。1名個體因與研究不相關的原因不能測試PK參數。在高劑量隊列中經治療的個體的特徵包括：具有重度A型血友病 (<1 IU/dL [<1%]的內源性FVIII活性水平)且先前經治療的成人男性個體；9名個體中的7名為高加索人種；個體的年齡範圍為32-63歲，平均年齡為44；且平均體重為81.1 kg (其範圍為61.5-100.7 kg)。

【0333】　8名經評估之接受單次高劑量的rFVIIIFc-VWF-XTEN (65 IU/kg)的個體，在5天時的輸注後平均FVIII活性為約38.0%，且在7天時為約17% (圖3B)。平均FVIII活性在14天內保持在1%以上(圖3B)。藉由活化部分凝血活酶時間(aPTT)量測法所量測的，rFVIIIFc-VWF-XTEN (65 IU/kg)和rFVIII (65 IU/kg)的藥物代謝動力學參數係示於**表10**中。觀察到rFVIIIFc-VWF-XTEN在個體人類個體中具有約42.5小時的平均半衰期，其相較於以相同劑量來施用的rFVIII其平均半衰期(約13小時)係高3倍以上。

表10：高劑量隊列的藥物代謝動力學(PK)參數

PK 參數	**rFVIIIFc-VWF-XTEN 幾何平均值 [範圍] (N=8)**	**rFVIII 幾何平均值 [範圍] (N=9)**	**平均比率 [95% CI]**
半衰期(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 每 IU/kg)	2.48 [2.18–2.82]	2.11 [1.79–2.49]	1.18 [1.10-1.26] P < 0.001

【0334】 **結論：**

【0335】 rFVIIIFc-VWF-XTEN在所有患有重度A型血友病且經單次低劑量(25 IU/kg)或單次高劑量(65 IU/kg)治療的患者中耐受良好。無患者發展出針對FVIII的抑制因子。rFVIIIFc-VWF-XTEN顯示了其半衰期比rFVIII高3倍至4倍，這表明VWF施加的半衰期上限係有所突破。持續的高FVIII活性具有針對所有出血類型提供延長保護的潛力。

實例 2：FVIII-XTEN-Fc/D'D3-XTEN-Fc 異二聚體的重複劑量研究

【0336】 在接受單次劑量的rFVIIIFc-VWF-XTEN的個體中，rFVIIIFc-VWF-XTEN的耐受良好，並提供持續的FVIII水平。(實例 1)。本研究將評估重複劑量的rFVIIIFc-VWF-XTEN其安全性和耐受性，並表徵重複劑量的rFVIIIFc-VWF-XTEN其藥物代謝動力學(圖1)。

【0337】 **研究設計**

【0338】 將總共4劑每週一次劑量的rFVIIIFc-VWF-XTEN施用至具有重度A型血友病的成人男性患者，該患者先前已經用FVIII治療進行治療，並接受至少150個暴露天數的此類FVIII治療。將其分為兩個隊列，每個隊列由約10名、年齡為18至65歲的成人男性所構成。隊列1中的每名個體將在第1天、第8天、第15天和第22天，接受總共4次、每週一次、劑量為50 IU/kg 的rFVIIIFc-VWF-XTEN。

【0339】 臨床研究的設計示意圖如圖4所示。在第1天將取得給藥前的藥物代

謝動力學樣品。此外，在第1天和第22天給藥後，取得多個PK樣品，而在第8、15和22天給藥之前係出現低谷(168h)樣品。在最後一劑的rFVIIIFc-VWF-XTEN後，個體將經歷28天的安全性觀察期，包括在最後一劑rFVIIIFc-VWF-XTEN之後14和28天時評定其抑制因子。對於完成施打總共四個每週一劑的rFVIIIFc-VWF-XTEN之個體，安全性觀察期係結束於第50天(+3天)的研究結束(end-of-study，EOS)訪視。對於提早停止治療的個體，安全性觀察期將結束在最後一劑的rFVIIIFc-VWF-XTEN後28天的提前終止(early termination，ET)訪視。

【0340】 該研究的首要目標是評定總共4劑每週一劑的靜脈內(IV)方式施加的rFVIIIFc-VWF-XTEN其安全性和耐受性。主要終點是實驗室測試中發生不良事件(AE)和臨床上的顯著異常，包括經由Nijmegen-modified Bethesda測試法所測定的抑制因子(針對FVIII的中和抗體)的產生。(Verbruggen等, Thrombosis and Haemostasis, 73: 247–251 (1995))。

【0341】 該研究的次要目標是在總共4劑每週一劑IV方式施加後，表徵rFVIIIFc-VWF-XTEN的藥物代謝動力學，其中FVIII活性係藉由一站式(one-stage)活化部分凝血活酶時間(aPTT)凝血測定來測定，如實例1所述的。次要終點是經由參數估計來評定的藥物代謝動力學，包括但不限於最大活性(Cmax)、半衰期(t½)、穩態時的總清除(CLss)、累積指數(AI)、從0至給藥間隔之活性時間曲線下面積(AUC0-tau)、穩態時的分佈容積(Vss)、平均停留時間(MRT)、IR、藥物在下一次施用前達到的最低(低谷)濃度($C_{低谷}$)、和FVIII活性高於基線1%的時間。

【0342】 此研究的探究性目標是在總共4劑每週一劑IV方式施加後，表徵rFVIIIFc-VWF-XTEN的藥物代謝動力學，其中FVIII活性係藉由兩站式(two-stage)生色凝血測定法來測定。探究性終點為經由參數估計評定的PK，該參數包括但不限於Cmax、t½、CLss、AI、AUC0-tau、Vss、MRT、IR、$C_{低谷}$、和FVIII活性高於基線1%的時間。

【0343】 **方法**

【0344】 FVIII活性係經修改的活化部分凝血活酶時間(aPTT)凝血測定法(「一

站式」測定法)來測定，如上文實例1中詳述的。

【0345】　兩站式生色凝血測定法係使用BIOPHEN FVIII:C測定法(Hyphen Biomed 221402-RUO)，在BCS® XP分析儀(Siemens Healthcare Diagnostics)上量測FVIII活性。簡單來說，在恆定數量的因子IXa的存在下，磷脂、鈣和凝血酶激活的FVIII:C係形成酶複合物。此酶複合物反過來激活因子X (FX)，其係以恆定濃度來供應，且超過因子Xa (FXa)。將FX活化為FXa係直接與FVIII:C的數量相關，FVIII:C在恆定且過量的因子IXa的存在下，係為測定中的限制因素。然後，使用特異性的生色性FXa受質(SXa-11 (Hyphen Biomed))來量測所生成的FXa的活性。因子Xa係切割SXa-11，並釋放對硝基苯胺(pNA)。釋放出的pNA的數量係與生成的FXa量成正比。樣品中FVIII:C的量、所生成的FXa的量，和釋放出的pNA的量之間係存在直接關係。pNA的釋放係藉由在405nm波長處的顯色來測定。

【0346】　使用rFVIIIFc-VWF-XTEN特異性校準物來做出8點校準曲線(高：1.500 – 0.150 IU/mL；低：0.200 – 0.008 IU/mL)。對於高校準曲線，1IU/mL的rFVIIIFc-VWF-XTEN係稀釋於Tris/BSA緩衝液中，以生成預先選擇的FVIII活性校準水平。此稀釋係通過BCS® XP分析儀來實施。預先選擇的FVIII活性校準水平係以在Tris/BSA緩衝液中為1:4的工作稀釋液來進行測試。對於低校準曲線，1 IU/mL的rFVIIIFc-VWF-XTEN係在先天性FVIII缺陷的血漿(Helena Laboratories)中以1:4預先稀釋，然後通過BCS® XP分析儀在Tris/BSA緩衝液中進一步稀釋，以生成預先選擇的FVIII活性校準水平，其在反應裝置中係在沒有進一步稀釋的情況下進行測試。

【0347】　校準係進行二重複。以FVIII活性(以IU/mL為單位，x軸)和以吸收度/分鐘(y軸)所表示的變化來繪製曲線。對於高校準曲線，係使用線性對數-對數(log-log)回歸曲線來擬合。對於低校準曲線，使用線性的線性-線性(lin-lin)回歸曲線來擬合。樣品之測試均係進行二重複，不論係於1:4工作稀釋下的高校準曲線中，抑或是在使用先天性FVIII缺陷血漿以1:4稀釋或零稀釋中(不具有工作稀釋)。

【0348】　**結果**

【0349】 *人口統計和基線特徵*

【0350】 10名年齡為18至65歲的成人男性個體係分入隊列1 (50 IU/kg)，而5名年齡為18-65歲(俱連本數)的成人男性個體係分入隊列2 (65 IU/kg)。在50 IU/kg給藥的隊列中，10名個體全數係接受4次劑量的rFVIIIFc-VWF-XTEN。分入65 IU/kg給藥的隊列中之5名個體中，有3名係接受至少1個劑量的rFVIIIFc-VWF-XTEN。入選的所有15名個體均來自保加利亞索非亞(Sofia，Bulgaria)的單一地點。入選的15名個體中，有13名個體係接受至少1個劑量的BIVV001，且包括在人口統計和基線特徵的綜述(summary)中。所有個體均為男性。平均年齡為35歲(範圍：25至55歲)，且所有個體均為白種人。平均體重為86.7 kg(範圍：51.0至130.9 kg)，且平均身體質量指數為25.9 kg/m^2(範圍：16.4至40.9 kg/m^2)。

【0351】 *安全性分析*

【0352】 對於中期分析，總共有13名個體係被包括在安全性分析集(50 IU/kg組中n=10，而65 IU/kg組中n=3)中。所有安全性分析均係基於安全性分析集(Safety Analysis Set)來進行，並包括所有接受至少一個劑量的rFVIIIFc-VWF-XTEN的個體。

【0353】 治療後出現的緊急不良反應事件(treatment-emergent AE，TEAE)係定義為在第一次rFVIIIFc-VWF-XTEN施用開始或之後以及在最後rFVIIIFc-VWF-XTEN施用後28天內的任何不良事件。缺少開始日期的AE被假定為治療後出現的緊急事件，除非停止日期在給藥日期之前。一般性的，係藉由隊列和整體的個體發病率來綜整AE，以及藉由隊列和個體在資料列表中來呈現AE。還可針對每名個體評估治療後出現的緊急重大不良反應事件(Treatment-emergent serious adverse events，TESAE)，但在經治療的個體中未觀察到任何TESAE (**表11**)。

【0354】 入選的15名個體中，13名個體係接受至少1個劑量的rFVIIIFc-VWF-XTEN，且被納入在安全性分析中。該13名個體中的8名被報導有19個TEAE (61.5%) (**表11**)。無重大或相關TEAE被報導，且無個體由於TEAE而停止試驗。最常見的TEAE為關節痛、上呼吸道感染、頭痛和鼻炎(每個TEAE為

2/13名個體；15.4%)。未偵測到產生有針對FVIII的抑制因子，且無嚴重超敏反應(serious hypersensitivity)或過敏反應(anaphylaxis)的報導。在個體總結的每個水平，如果個體被報導有一個或多個事件，則對該個體計數一次。表11中所報導的百分比係基於在每個隊列和總體中接受至少1個劑量的rFVIIIFc-VWF-XTEN的個體人數。

表11. 安全性分析集的治療後出現之緊急不良反應事件(TEAE)的綜述

	rFVIIIFc-VWF-XTEN 50 IU/kg	rFVIIIFc-VWF-XTEN 65 IU/kg	主要手術期 (N=0)	rFVIIIFc-VWF-XTEN 全部經治療的
用 rFVIIIFc-VWF-XTEN 治療的個體的人數	10	3	0	13
TEAE 的總數目	17	2	0	19
具有至少一個 TEAE 的個體	7 (70.0%)	1 (33.3%)	0	8 (61.5%)
具有至少一個相關 TEAE 的個體	0	0	0	0
由於 TEAE 停止研究的個體	0	0	0	0
TESAE 的總數	0	0	0	0
具有至少一個 TESAE 的個體	0	0	0	0
具有至少一個相關 TESAE 的個體	0	0	0	0

【0355】 *免疫原性分析*

【0356】 在篩選時、第1天、第8天、第15天、第22天、第36天、和第50天(EOS或ET訪問)來評定所有個體其抑制因子的發生和抗rFVIIIFc-VWF-XTEN抗體。抑制因子的測試係使用Nijmegen改進的Bethesda測定法，藉由中央實驗室來進行。如果返回的Nijmegen修改Bethesda測定法其結果為≥0.6 BU/mL，則在2至4周內收集並測試另一獨立樣品，以確認抑制因子的發生。對於潛在性抗體形成的測試，

係在中央實驗室使用經驗證的rFVIIIFc-VWF-XTEN特異性抗藥物抗體(ADA)測定法來進行。經確認的陽性樣品係進一步表徵為對FVIII、D'D3或XTEN具有特異性的抗體。經測試為抑制因子發生陽性的個體其數目和百分比，以及經測試為抗rFVIIIFc-VWF-XTEN抗體陽性的個體其數目和百分比，係藉由使用安全性分析集的隊列來加以綜述。

【0357】　無個體在rFVIIIFc-VWF-XTEN施用之後發生抗藥物抗體的陽性測定結果。

【0358】　*藥物代謝動力學分析和結果*

【0359】　一般來說，安全性和PK資料係使用對連續和分類資料的標準綜述統計法(standard summary statistics)來加以綜述。資料係通過隊列來加以綜述。連續變量係使用描述性統計來綜述，描述性統計包括非缺失值(n)、平均值、標准偏差(SD)、中位數、最小值和最大值的數字。藥物代謝動力學參數還使用幾何平均值和百分比變異係數(%CV)來加以綜述。分類變量係藉由計數和百分比來加以綜述。

【0360】　所有PK分析係基於PK分析集(PK analysis set，PKAS)來進行，且包括9名來自50 IU/kg給藥隊列的個體，該個體在rFVIIIFc-VWF-XTEN施用後，收集有足夠的血液樣品。

【0361】　**FVIII活性**

【0362】　為了表徵在總共4劑每週一劑以IV方式施加後的rFVIIIFc-VWF-XTEN其藥物代謝動力學，係在預定的時間點於每個個體中來測定FVIII活性。FVIII活性係藉由隊列、所排定的PK訪視和一站式(活化部分凝血活酶時間[aPTT])凝血測定和生色凝血測定的時間點來加以綜述。以兩種FVIII活性測試之FVIII活性對時間的圖，係以原始和對數尺度來繪製。以隊列、所排定的PK訪視和兩個FVIII活性測定的時間點，來列出每名個體個別之FVIII活性。根據一站式[aPTT]測定法的FVIII活性結果係描述於表12中。根據生色測定法的FVIII活性結果係描述於表13中。

【0363】　簡言之，在第1天給藥後，在72小時處基於一站式和生色測定法的平

均FVIII活性，係分別為45.53%和29.37%，在120小時處分別為21.56%和13.49%，在168小時處分別為7.91%和5.97%。在第22天給藥後，在72小時處基於一站式和生色測定法的平均FVIII活性，係分別為46.28%和30.46%，在120小時處分別為22.30%和14.48%，在168小時處分別為9.83%和6.74%。通常對於所有患者、所有時間點和兩種測定法，在此中期分析中，50 IU/kg QW的rFVIIIFc-VWF-XTEN的$C_{低谷}$其範圍係介於7-10%之間。

【0364】 **PK參數**

【0365】 每個個體的個別PK參數估計值係被列出，並藉由隊列、所排定的PK訪視和兩種FVIII活性測定的時間點來進行描述性地綜述。

【0366】 所有接受50 IU/kg QW的rFVIIIFc-VWF-XTEN的個體，在此中期分析中的幾何平均消除半衰期($t_{1/2}$)，根據一站式測定法係為41.24小時(**表16B**)，而根據生色測定法係為43.87小時(**表17B**)。

【0367】 在第1天給藥後，幾何平均最大FVIII活性(C_{max})在一站式測定法中為113 IU/dL(**表14**)，且在生色測定法中為108 IU/dL(**表15**)。在第22天給藥後，穩態時的幾何平均FVIII活性(C_{maxss})，根據一站式測定法為127 IU/dL(**表16A**)，且根據生色測定法為115 IU/dL (**表17A**)。

【0368】 在第1天給藥後，幾何平均累積FVIII活性(AUC_{0-tau})，根據一站式測定法為7650 hr*IU/dL(**表14**)，且根據生色測定法為5630 hr*IU/dL(**表15**)。在第22天給藥後，幾何平均$AUC0_{-tau}$，根據一站式測定法為8270 hr*IU/dL(**表 16A**)，且根據生色測定法為5880 hr*IU/dL (**表17A**)。

【0369】 在第1天和第22天給藥的C_{max}和AUC_{0-tau}資料，係指出由累積指數(accumulation index，AI)所支持的最小累積為1.07(一站式測定法，**表16B**)和1.08(生色測定法，**表17B**)。對於表12至17中所呈現的所有PK參數資料，出於分析的目的，低於定量下限(BLQ)的值被處理為0。當需要計算PK參數時，由於未捕獲輸注結束時間，根據研究的操作和管理指南文件中的施用指導，將每名個體的輸注持續時間估算為8分鐘。

表12. 基於一站式aPTT凝血測定法的基線校準之FVIII活性水平(IU/dL)綜述：PK分析集(劑量水平：50 IU/kg)

給藥日	時間點	n	平均值(SD)	中位數	Geo.平均值	%CV	Min, Max
第 1 天	注射前	9	0.00 (0.000)	0.00	0.00	--------	0.0, 0.0
	距 SOI 30 分鐘	9	113.17 (20.214)	118.10	111.51	17.862	82.0, 140.2
	距 SOI3 小時	9	109.07 (19.243)	109.90	107.49	17.643	77.4, 135.5
	距 SOI24 小時	9	91.04 (15.231)	92.80	89.88	16.730	68.9, 115.8
	距 SOI48 小時	9	66.38 (12.231)	65.90	65.30	18.426	46.7, 80.3
	距距 SOI72 小時	9	45.53 (6.742)	45.60	45.08	14.807	36.7, 53.9
	距 SOI120 小時	9	21.56 (4.473)	22.20	21.11	20.750	14.2, 27.1
第 8 天	注射前	9	7.91 (2.869)	7.40	7.48	36.265	4.0, 13.1
第 15 天	注射前	9	8.94 (3.322)	7.80	8.34	37.140	3.9, 13.5
第 22 天	注射前	9	9.91 (2.838)	11.61	9.49	28.633	5.0, 12.9
	距 SOI 30 分鐘	9	132.77 (31.741)	131.80	129.56	23.907	96.0, 190.7
	距 SOI 3 小時	9	120.94 (22.168)	126.60	119.03	18.329	85.2, 152.0
	距 SOI 24 小時	9	103.79 (18.513)	110.20	102.21	17.838	74.0, 126.3
	距 SOI 48 小時	9	69.89 (12.812)	68.10	68.84	18.332	49.8, 91.7
	距 SOI 72 小時	9	46.28 (7.720)	47.90	45.68	16.682	33.4, 58.3
	距 SOI 120 小時	9	22.30 (4.979)	21.70	21.77	22.329	13.7, 29.8
	距 SOI 168 小時	9	9.83 (3.847)	9.60	9.16	39.120	4.9, 15.5
	距 SOI 240 小時	9	2.84 (0.999)	2.80	2.68	35.117	1.4, 4.4
	距 SOI 336 小時	9	1.28 (2.651)	0.00	0.00	207.494	0.0, 8.2

縮寫：SD =標准偏差，Geo.平均值=幾何平均值，%CV = 百分比變異係數，Min =最小值，Max =最大值，SOI =注射開始

表13. 基於生色測定法的基線校正之FVIII活性水平(IU/dL)綜述：PK分析集(劑量水平：50 IU/kg)

給藥日	時間點	n	平均值(SD)	中位數	Geo.平均值	%CV	Min, Max
第 1 天	注射前	9	0.00 (0.000)	0.00	0.00	----------	0.0, 0.0
	距 SOI 30 分鐘	9	108.94 (15.126)	113.00	107.99	13.884	87.4, 129.9
	距 SOI3 小時	9	101.86 (13.782)	102.50	100.99	13.531	79.1, 118.3
	距 SOI24 小時	9	71.68 (14.654)	73.50	70.24	20.445	47.8, 93.5
	距 SOI48 小時	9	43.84 (7.086)	43.40	43.32	16.163	32.5, 54.0
	距 SOI72 小時	9	29.37 (5.319)	30.10	28.93	18.112	22.3, 37.2
	距 SOI120 小時	9	13.49 (2.680)	13.80	13.24	19.870	9.4, 17.2
第 8 天	注射前	9	5.97 (1.764)	6.20	5.74	29.568	3.6, 9.4
第 15 天	注射前	9	6.93 (1.736)	6.70	6.74	25.044	4.8, 10.0
第 22 天	注射前	9	7.13 (1.817)	7.50	6.93	25.466	5.0, 10.4
	距 SOI30 分鐘	9	113.58 (14.920)	113.25	112.72	13.137	91.3, 137.6
	距 SOI3 小時	9	109.08 (16.394)	112.50	107.96	15.029	85.4, 132.6
	距 SOI24 小時	9	72.13 (14.985)	71.40	70.78	20.774	56.6, 95.8
	距 SOI48 小時	9	45.23 (4.907)	46.10	44.99	10.847	37.4, 52.3

	距 SOI72 小時	9	30.46 (5.247)	31.20	30.04	17.230	21.4, 39.6
	距 SOI120 小時	9	14.48 (2.862)	13.70	14.23	19.769	10.5, 18.7
	距 SOI168 小時	9	6.74 (1.911)	6.20	6.51	28.328	4.4, 9.7
	距 SOI240 小時	9	2.20 (1.025)	2.20	0.00	46.577	0.0, 3.7
	距 SOI336 小時	9	0.46 (1.021)	0.00	0.00	224.158	0.0, 3.0

縮寫：SD =標准偏差，Geo.平均值=幾何平均值，%CV = 百分比變異係數，Min =最小值，Max =最大值，SOI =注射開始

表14. 第1天給藥，基於一站式aPTT凝血測定法的基線校正之FVIII活性其藥物代謝動力學參數的綜述：PK分析集

個體編號	實際劑量 (IU/kg)	CMAX (IU/dL)	TMAX (hr)	AUC0-tau (hr*IU/dL)	以劑量標準化的 AUC0-tau (hr*kg*IU/dL/IU)	IVR (%)	IR (IU/dL 每 IU/kg)
隊列 1 (50 IU/kg)：BIVV001 第 1 天給藥							
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
平均值	50.00	115	1.33	7740	155	74.4	2.29
中位數	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. 平均值	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)
最小值	49.8	82.0	0.50	5750	115	52.5	1.63
最大值	50.2	140	3.13	9300	186	97.4	2.81

縮寫：Std Dev = 標准偏差，Geo.平均值 = 幾何平均值，%CV = 百分比變異係數，CMAX = 穩態時的最大濃度，TMAX =達到最大濃度的時間，CMAXSS = 穩態時的最大濃度，IVR = 體內恢復，AUC0-inf = 從時間0至無限大的活性-時間曲線下面積，AUC0-tau = 從0至給藥間隔的活性-時間曲線下面積，MRTINF =外推至無窮大的平均停留時間，AI = 累計指數，IR = 增量恢復，$C_{低谷}$ = 在施用下一劑量之前藥物達到的最低濃度，Cavg =達到穩態後的平均濃度，t1/2 = 消除半衰期，CLss =穩態時的清除，Vss = 穩態時的分佈容積

表15：第1天，基於生色測定法的基線校正之FVIII活性其藥物代謝動力學參數的綜述：PK分析集

個體編號	實際劑量 (IU/kg)	CMAX (IU/dL)	TMAX (hr)	AUC0-tau (hr*IU/dL)	以劑量標準化的 AUC0-tau (hr*kg*IU/dL/IU)	IVR (%)	IR (IU/dL 每 IU/kg)
隊列 1 (50 IU/kg)：BIVV001 第 1 天給藥							
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
平均值	50	109	0.51	5700	114	70.8	2.18
中位數	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. 平均值	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)
最小值	49.8	87.4	0.5	4290	85.4	52	1.74
最大值	50.2	130	0.63	7030	140	90.5	2.6

縮寫：Std Dev = 標准偏差，Geo.平均值 = 幾何平均值，%CV = 百分比變異係數，CMAX = 穩態時的最大濃度，TMAX =達到最大濃度的時間，CMAXSS = 穩態時的最大濃度，IVR = 體內恢復，AUC0-inf = 從時間0至無限大的活性-時間曲線下面積，AUC0-tau = 從0至給藥間隔的活性-時間曲線下面積，MRTINF =外推至無限大的平均停留時間，AI = 累積指數，IR = 增量恢復，$C_{低谷}$ = 在施用下一劑量之前藥物達到的最低濃度，Cavg =達到穩態後的平均濃度，t1/2 = 消除半衰期，CLss =穩態時的清除，Vss = 穩態時的分佈容積

表16A. 第22天-基於一站式aPTT凝血測定法的基線校正之FVIII活性其藥物代謝動力學參數的綜述：PK分析集(第1部分)

個體編號	實際劑量 (IU/kg)	CMAX SS (IU/dL)	AUC0-inf (hr*IU/dL)	以劑量標準化的 AUC0-inf (hr*kg*IU/dL/IU)	AUC0-tau (hr*IU/dL)	以劑量標準化的 AUC0-tau (hr*kg*IU/dL/IU)
隊列 1 (50 IU/kg)：BIVV001 第 22 天給藥						
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	9

平均值	49.93	129	8940	179	8370	168
中位數	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. 平均值	49.93	127	8830	177	8270	166
(95% CI)	(49.86, 50.01)	(110, 147)	(7740, 10100)	(155, 202)	(7260, 9410)	(145, 188)
最小值	49.8	96	6130	123	5810	117
最大值	50.1	165	11000	219	10100	201

縮寫：Std Dev = 標准偏差，Geo.平均值 = 幾何平均值，%CV = 百分比變異係數，CMAX = 穩態時的最大濃度，TMAX =達到最大濃度的時間，CMAXSS = 穩態時的最大濃度，IVR = 體內恢復，AUC0-inf = 從時間0至無限大的活性-時間曲線下面積，AUC0-tau = 從0至給藥間隔的活性-時間曲線下面積，MRTINF =外推至無限大的平均停留時間，AI = 累積指數，IR = 增量恢復，$C_{低谷}$ = 在施用下一劑量之前藥物達到的最低濃度，Cavg =濃達到穩態後的平均濃度，t1/2 = 消除半衰期，CLss =穩態時的清除，Vss = 穩態時的分佈容積

表16B. 第22天-基於一站式aPTT凝血測定法的基線校正之FVIII活性其藥物代謝動力學參數的綜述：PK分析集(第2部分)

個體編號	t1/2 (hr)	MRTINF (hr)	CLss (mL/hr/kg	Vss (mL/kg)	AI	$C_{低谷}$ (IU/dL)	Cavg (IU/dL)
隊列 1 (50 IU/kg): BIVV001 第 22 天給藥							
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
平均值	41.62	62.97	0.61	38.5	1.07	9.83	49.8
中位數	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. 平均值	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)
最小值	34.21	49.79	0.5	27	1.03	4.9	34.6
最大值	50.05	78.56	0.86	50.3	1.11	15.5	60

縮寫：Std Dev = 標准偏差，Geo.平均值 = 幾何平均值，%CV = 百分比變異係數，CMAX = 穩態時的最大濃度，TMAX =達到最大濃度的時間，CMAXSS = 穩態時的最大濃度，IVR = 體內恢復，AUC0-inf = 從時間0至無限大的活性-時間曲線下面積，AUC0-tau = 從0至給藥間隔的活性-時間曲線下面積，MRTINF =外推至無限大的平均停留時間，AI = 累積指數，IR = 增量恢復，$C_{低谷}$ = 在施用下一劑量之前藥物達到的最低濃度，Cavg =達到穩態後的平均濃度，t1/2 = 消除半衰期，CLss =穩態時的清除，Vss = 穩態時的分佈容積

表17A. 第22天-基於生色測定法的基線校正之FVIII活性其藥物代謝動力學參數的綜述：PK分析集(第1部分)

個體編號	實際劑量 (IU/kg)	CMAX SS (IU/dL)	AUC0-inf (hr*IU/dL)	以劑量標準化的 AUC0-inf (hr*kg*IU/dL/IU)	AUC0-tau (hr*IU/dL)	以劑量標準化的 AUC0-tau (hr*kg*IU/dL/IU)
隊列 1 (50 IU/kg)：BIVV001 第 22 天給藥						
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
平均值	49.93	115	6360	127	5920	119
中位數	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. 平均值	49.93	115	6320	127	5880	118
(95% CI)	(49.86, 50.01)	(104, 126)	(5760, 6940)	(115, 139)	(5360, 6460)	(107, 129)
最小值	49.8	91.3	5080	102	4780	95.5

縮寫：Std Dev = 標准偏差，Geo.平均值 = 幾何平均值，%CV = 百分比變異係數，CMAX = 穩態時的最大濃度，TMAX =達到最大濃度的時間，CMAXSS = 穩態時的最大濃度，IVR = 體內恢復，AUC0-inf = 從時間0至無限大的活性-時間曲線下面積，AUC0-tau = 從0至給藥間隔的活性-時間曲線下面積，MRTINF =外推至無限大的平均停留時間，AI = 累積指數，IR = 增量恢復，$C_{低谷}$ = 在施用下一劑量之前藥物達到的最低濃度，Cavg =達到穩態後的平均濃度，t1/2 = 消除半衰期，CLss =穩態時的清除，Vss = 穩態時的分佈容積

表17B. 第22天-基於生色測定法的基線校正之FVIII活性其藥物代謝動力學參數的綜述：PK分析集(第2部分)

個體編號	t1/2 (hr)	MRTINF (hr)	CLss (mL/hr/kg	Vss (mL/kg)	AI	$C_{低谷}$ (IU/dL)	Cavg (IU/dL)
隊列 1 (50 IU/kg)：BIVV001 第 22 天給藥							
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
平均值	44.13	61.15	0.85	52.4	1.08	6.74	35.2
中位數	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. 平均值	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)
最小值	35.59	47.89	0.77	38	1.04	4.4	28.4
最大值	53.31	76.94	1.05	67.4	1.13	9.7	38.4

縮寫：Std Dev = 標准偏差，Geo.平均值 = 幾何平均值，%CV = 百分比變異係數，CMAX = 穩態時的最大濃度，TMAX =達到最大濃度的時間，CMAXSS = 穩態時的最大濃度，IVR = 體內恢復，AUC0-inf = 從時間0至無限大的活性-時間曲線下面積，AUC0-tau = 從0至給藥間隔的活性-時間曲線下面積，MRTINF =外推至無限大的平均停留時間，AI = 累積指數，IR = 增量恢復，$C_{低谷}$ = 在施用下一劑量之前藥物達到的最低濃度，Cavg =達到穩態後的平均濃度，t1/2 = 消除半衰期，CLss =穩態時的清除，Vss = 穩態時的分佈容積

【0370】 **結論**

【0371】 與在單劑量研究(實例1)中所觀察到的結果一致，每週給藥rFVIIIFc-VWF-XTEN一般來說是耐受良好的，且在最後一次施用rFVIIIFc-VWF-XTEN後的28天內，未偵測到抑制因子。劑量為50 IU/kg的rFVIIIFc-VWF-XTEN在一站式和生色測定法的情況下，分別表現出平均消除半衰期($t_{1/2}$)為41.24和43.87小時。這些中期結果表明，在單劑量給藥rFVIIIFc-VWF-XTEN中所觀察到的增強的半衰期，在重複給藥QW的情況中得以維持，這強烈表明rFVIIIFc-VWF-XTEN的優點可以藉由讓A型血友病患者根據預防性FVIII給藥時間表接受治療來實現。

實例3：在具有重度A型血友病且先前經治療之患者中的rFVIIIFc-VWF-XTEN第3期試驗

【0372】 本研究將評估50 IU/kg rFVIIIFc-VWF-XTEN (圖1)的安全性和耐受性，並表徵每週一次施用的50 IU/kg rFVIIIFc-VWF-XTEN (圖1)其藥物代謝動力學。該研究的首要目標是，相較於rFVIIIFc-VWF-XTEN按需治療，評估rFVIIIFc-VWF-XTEN的預防性治療功效。該研究的次要目標是評估

rFVIIIFc-VWF-XTEN作為預防性治療，其對出血事件與rFVIIIFc-VWF-XTEN的消耗、關節健康、及以由患者報導結果(Patient-Reported Outcomes PRO)所量測的生活品質的作用，且評估按需治療的rFVIIIFc-VWF-XTEN。

【0373】　此外，藥物代謝動力學(PK)目標是基於aPTT FVIII活性測定法來表徵所有個體其rFVIIIFc-VWF-XTEN預防情況在基線處的PK，並在三個月時對預定義的個體子集進行重複。另外的目標是評估rFVIIIFc-VWF-XTEN在接受手術的個體中的功效，並評估rFVIIIFc-VWF-XTEN的安全性和耐受性。進一步地，關節健康結構性結果將經由超音波法來評定，並評定治療對其它生活質量度量和對醫療保健資源利用的影響。

【0374】　**試驗設計**

【0375】　此試驗是樞紐型(pivotal)、第3期、非盲性(open-label)的多中心試驗，係針對年齡≥12歲且具有重度A型血友病(定義為<1 IU/dL [<1%]的內源性FVIII)的患者中研究靜脈內方式施加之rFVIIIFc-VWF-XTEN其安全性、功效和PK。目前接受按需用藥法的大約25名個體，將根據按需基礎以50 IU/kgIV的劑量接受rFVIIIFc-VWF-XTEN，持續26周，然後根據預防性治療用藥法，以50 IU/kg IV的劑量每週一次地接受rFVIIIFc-VWF-XTEN，持續26周。目前採用預防性治療用藥法的個體，將根據預防性治療用藥法以50 IU/kg IV的劑量接受rFVIIIFc-VWF-XTEN，持續26周。

【0376】　大約140名年齡≥12歲的個體將會入選；在12周時，將對大約16名個體的子集重複PK的評定。

【0377】　將篩選個體，並且在滿足入選標準後，以50 IU/kg IV劑量的rFVIIIFc-VWF-XTEN進行兩種治療用藥法之一(即按需或預防)。所有個體將在洗脫期後(至少4至5天，取決於現在的療法)係經歷基線PK評定。個體將在整個研究期間經歷療效和安全性評定。這些安全性評定將包括測試潛在的抑制因子形成。除非個體入選非盲性延伸研究，否則將在最後一個劑量的rFVIIIFc-VWF-XTEN後的28天，進行後續(follow-up)安全性訪視或電話呼叫。

【0378】　試驗結束(EOS)可能發生在滿足兩個標準時：(i)至少104名個體已經

達到50個暴露天數(ED)，且已經在第50個ED後完成確效的抑制因子測試；且(ii)至少25名個體完成了按需組(on-demand arm)試驗，包括26周的預防性治療期，或提早退出研究。此外，在試驗期間有接受手術之來自任何組(arm)的個體，將包括在手術子集中。至少5名個體中有最少十個主要手術係被針對以在手術環境中評定出血的控制和預防。

【0379】 個體將在大約28天的篩選期內去到診所以確定適格性。除篩選訪視之外，個體將返回診所進行基線、第4周、第12周、第26周、第36周、第52周和EOS/ET的訪視。給藥期間將超過52周。進入預防性治療組的個體將接受52個每週一次劑量的rFVIIIFc-VWF-XTEN和治療出血事件所需的另外劑量。進入按需治療組的個體，將在26周之按需治療期間按需接受rFVIIIFc-VWF-XTEN，且在隨後的26周之預防性治療期間接受26個每週一次劑量的rFVIIIFc-VWF-XTEN和治療出血事件所需的另外劑量。整個試驗將評定安全性。除非個體入選非盲性延伸研究，否則將在最後一次給予rFVIIIFc-VWF-XTEN後的28天進行後續安全性訪視或電話呼叫。

【0380】 該試驗的主要終點是個體進行rFVIIIFc-VWF-XTEN按需治療(26周)對比每週一次的預防性治療(26周)，個體內的年出血率(ABR)比較。

【0381】 該研究的次要終點將包括(i)rFVIIIFc-VWF-XTEN所預防的ABR與歷史ABR(對於參與先前觀察研究的預防組個體)的個體內比較；(ii)出血事件的出現和消耗(總體ABR、按類型和位置計算的ABR，以及每個個體的年度rFVIIIFc-VWF-XTEN總消耗)；(iii)對治療的反應；(iv)療效指數(在第7天維持L3%低谷水平的個體百分比；(v)關節健康；和(vi)生活質量度量的變化(至少18歲的個體其haem-A-QoL和PROMIS-SF的生理功能；和小於18歲的個體其HAEMO-QoL和PROMISPediatric-SF的生理活動)。

【0382】 對治療的反應將包括(i)解決出血事件所需的rFVIIIFc-VWF-XTEN的輸注數目和劑量；(ii)需要單次輸注才能解決的出血事件的百分比；(iii)基於4點反應量表所評定之個體對rFVIIIFc-VWF-XTEN治療個體出血事件的反應；(iv)研究者基於4點反應量表所全面評定個體對rFVIIIFc-VWF-XTEN治療的反應。

【0383】　關節健康評估將包括(i)關節出血事件的ABR；(ii) 根據國際血栓形成與止血學會(ISTH)標準，在52周時的目標關節變形(target joint resolution)；(iii)根據基於經由經修改的血友病關節健康評分(mHJHS)或HJHS)所評定的從基線到52周的絕對變化之功能性結果；(iv)由mHJHS或HJHS所評定的在52周時無關節惡化的個體的百分比。

【0384】　另外的終點包括(i)最大(峰值)血漿藥物濃度(Cmax)、消除半衰期(t½)、累積指數(AI)、血漿濃度-時間曲線下面積(AUC)、穩態時的表觀分佈容積(Vss)、平均停留時間(MRT)、增量恢復(incremental recovery，IR)、低谷血漿濃度($C_{低谷}$)、和高於預定義的FVIII活性水平的時間；(ii) 研究人員或外科醫生基於4點反應量表對個體對rFVIIIFc-VWF-XTEN治療的止血反應的評定，在手術期間維持止血所需的輸注數目和劑量，手術期間的總rFVIIIFc-VWF-XTEN消耗，手術期間的估計失血量，手術期間所需的血液成分的輸注數目和類型，以及手術期間的手術後出血事件；(iii)不良反應事件(AE)和重大不良事件(SAE)的出現，身體檢查、生命體徵和實驗室測試中的臨床顯著異常，以及抑制因子的發生(經由Nijmegen-經修改的Bethesda偵測法所測定之針對FVIII的中和抗體)；和(iv)藉由分組人群中的超音波成像的結構關節健康解剖學結果，其他QoL量測(EQ-5D-5L、PGIC)的變化(僅第52周)，PROMIS疼痛強度，PROMIS-SF疼痛干擾(個體≥ 18歲)，PROMIS小兒-SF疼痛干擾(個體<18歲))，和HRU。

【0385】　**納入/排除標準**

【0386】　符合條件的候選人必須滿足下列合格標準：(1) 知情同意時，年齡≥12歲；(2)重度A型血友病，定義為<1 IU/dL (<1%)內源性的FVIII，如藉由經過認證的臨床實驗室所記載者；(3) 先前經任何重組和/或血漿衍生的FVIII治療(預防性或按需)，或至少150個ED的冷沉澱物之A型血友病；(4)目前採用市售FVIII產品的預防性治療用藥法，且在試驗入組前的12個月內有至少4次出血事件，或目前採用市售FVIII產品的按需治療用藥法，且在入組前12個月內有至少12次出血事件；和(5)篩選時血小板計數≥100,000個細胞/μL(由中央實驗室進行測試，並在第1天給藥之前進行複查)。個體將出於以下原因被排除在外：(1)除A型血友病外的

其它任何凝血障礙；(2)與任何FVIII產品相關的超敏反應或過敏反應的病史；(3)陽性抑制因子測試史或對FVIII施用反應降低的臨床徵兆(抑制因子的家族史不會排除個體)；(4)篩選時所獲取的陽性抑制因子結果，定義為≥0.6 BU/mL；(5)腎功能異常，定義為篩選時所獲取的血清肌酸酐>2.0 mg/dL；(6)篩選時所獲取的血清丙胺酸轉胺酶(ALT)或天門冬胺酸轉胺酶(AST) >5 ×正常值上限(ULN)；(7)篩選時所獲取的血清總膽紅素>3 × ULN；(8)在篩選前12周內使用Fitusiran或艾美賽珠單抗(emicizumab)；(9)在篩選前12周內用單株抗體治療劑、除rFVIIIFc以外的Fc融合蛋白或IV免疫球蛋白進行治療；(10)在篩選前2周內用乙醯水楊酸(ASA)治療或用非固醇類消炎藥(NSAID)治療，其劑量等於或高於每種產品的區域處方信息中所規定的最大劑量；(11)在篩選前12周內用化療和/或其他免疫抑制藥物進行全身治療(除了C型肝炎病毒[HCV]或HIV的治療；允許使用皮質類固醇，但以20 mg/天的潑尼松或其等效物每天或隔日給予全身性皮質類固醇治療持續> 14天除外；允許使用局部、外用和/或吸入類固醇)；和(12)在篩選前8周內進行大手術(大手術定義為任何外科手術(選擇性或緊急手術)，其通常但不總是涉及全身麻醉和/或呼吸輔助，在大手術中主要體腔被穿透和暴露出來，或產生嚴重的身體或生理功能損害(例如，剖腹手術、胸廓切開術、開顱手術、關節置換術、或肢體截肢術))。

序列

VWF031核苷酸序列(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
101 GATGC AGCCT TTTCG 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 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
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 CCCCG 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
901 TATAG GCAGT GTGTG TCCCC TTGCG CCAGG ACCTG CCAGA GCCTG CACAT
951 CAATG AAATG TGTCA GGAGC GATGC GTGGA TGGCT GCAGC TGCCC TGAGG
1001 GACAG CTCCT GGATG AAGGC CTCTG CGTGG AGAGC ACCGA GTGTC CTGC
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
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 GGACT TCGGG
1651 AACGC CTGGA AGCTG CACGG GGACT GCCAG GACCT GCAGA AGCAG CACAG
1701 CGATC CCTGC GCCCT CAACC CGCGC ATGAC CAGGT TCTCC GAGGA GGCGT
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 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
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
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
2451 TGAGA ACAGA TGTGT GGCCC TGGAA AGGTG TCCCT GCTTC CATCA GGGCA
2501 AGGAG TATGC CCCTG GAGAA ACAGT GAAGA TTGGC TGCAA CACTT GTGTC
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2601 CTCCA CGATC GGCAT GGCCC ACTAC CTCAC CTTCG ACGGG CTCAA ATACC
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 CATTC 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
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 CATTC
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
3501 GCAGT GTGTG GAGGG CTGCC ATGCC CACTG CCCTC CAGGG AAAAT CCTGG
3551 ATGAG CTTTT GCAGA CCTGC GTTGA CCCTG AAGAC TGTCC AGTGT GTGAG
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3651 TGACC CTGAG CACTG CCAGA TTTGC CACTG TGATG TTGTC AACCT CACCT
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3901 GAACT CCTGG GCGGA CCGTC AGTCT TCCTC TTCCC CCCAA 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 AAGAC AAAGC CGCGG GAGGA GCAGT ACAAC AGCAC
4101 GTACC GTGTG GTCAG CGTCC TCACC GTCCT GCACC AGGAC TGGCT GAATG
4151 GCAAG GAGTA CAAGT GCAAG GTCTC CAACA AAGCC CTCCC AGCCC CCATC
4201 GAGAA AACCA TCTCC AAAGC CAAAG GGCAG CCCCG 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
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蛋白質序列(SEQ ID NO: 86)

1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFVNTFDGSM
51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
101 TVTQGDQRVS 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 IQLPLLKGDL RIQHTVTASV RLSYGEDLQM
501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
551 NAWKLHGDCQ DLQKQHSDPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCEL
651 NCPKGQVYLQ CGTPCNLTCR 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 CKKRVTILVE GGEIELFDGE VNVKRPMKDE
951 THFEVVESGR YIILLLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
1051 MKQTMVDSSC RILTSDVFQD CNKLVDPEPY LDVCIYDTCS CESIGDCAAF
1101 CDTIAAYAHV CAQHGKVVTW RTATLCPQSC EERNLRENGY EAEWRYNSCA
1151 PACQVTCQHP EPLACPVQCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE
1201 VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP ISGGGGSGGG
1251 GSGGGGSGGG GSGGGGSGGG GSLVPRGSGG GGSGGGGSDK THTCPPCPAP
1301 ELLGGPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV
1351 EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI
1401 EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE
1451 SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL
1501 HNHYTQKSLS LSPGK*

VWF034 核苷酸序列(SEQ ID NO: 148)

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 TTTCG 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 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
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 CCCCG 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
901	TATAG GCAGT GTGTG TCCCC TTGCG CCAGG ACCTG CCAGA GCCTG CACAT
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
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
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 GGACT TCGGG
1651	AACGC CTGGA AGCTG CACGG GGACT GCCAG GACCT GCAGA AGCAG CACAG
1701	CGATC CCTGC GCCCT CAACC CGCGC ATGAC CAGGT TCTCC GAGGA GGCGT
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 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
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
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
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
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 CATTC 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
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 CATTC
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
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 GGCGT TTTGC CTCAG GAAAG AAAGT CACCT TGAAT CCCAG
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
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
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
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 CTGG TCCCC CGGGG CAGCG GAGGC GACAA
4701 AACTC ACACA TGCCC ACCGT GCCCA GCTCC AGAAC TCCTG GGCGG ACCGT
4751 CAGTC TTCCT CTTCC CCCCA AAACC CAAGG ACACC CTCAT GATCT CCCGG
4801 ACCCC TGAGG TCACA TGCGT GGTGG TGGAC GTGAG CCACG AAGAC CCTGA
4851 GGTCA AGTTC AACTG GTACG TGGAC GGCGT 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
5101 GATGA GCTGA CCAAG AACCA GGTCA GCCTG 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
5351 AGAGC CTCTC CCTGT CTCCG GGTAA ATGA

VWF034 蛋白質序列(SEQ ID NO: 87)

1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFVNTFDGSM
51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
101 TVTQGDQRVS 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 IQLPLLKGDL RIQHTVTASV RLSYGEDLQM
501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
551 NAWKLHGDCQ DLQKQHSDPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCEL
651 NCPKGQVYLQ CGTPCNLTCR 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 CKKRVTILVE GGEIELFDGE VNVKRPMKDE
951 THFEVVESGR YIILLLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI

1051 MKQTMVDSSC RILTSDVFQD CNKLVDPEPY LDVCIYDTCS CESIGDCAAF
1101 CDTIAAYAHV CAQHGKVVTW RTATLCPQSC EERNLRENGY EAEWRYNSCA
1151 PACQVTCQHP EPLACPVQCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE
1201 VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP ISGTSESATP
1251 ESGPGSEPAT SGSETPGTSE SATPESGPGS EPATSGSETP GTSESATPES
1301 GPGTSTEPSE GSAPGSPAGS PTSTEEGTSE SATPESGPGS EPATSGSETP
1351 GTSESATPES GPGSPAGSPT STEEGSPAGS PTSTEEGTST EPSEGSAPGT
1401 SESATPESGP GTSESATPES GPGTSESATP ESGPGSEPAT SGSETPGSEP
1451 ATSGSETPGS PAGSPTSTEE GTSTEPSEGS APGTSTEPSE GSAPGSEPAT
1501 SGSETPGTSE SATPESGPGT STEPSEGSAP DIGGGGGSGG GGSLVPRGSG
1551 GDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
1601 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
1651 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV
1701 KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
1751 GNVFSCSVMH EALHNHYTQK SLSLSPGK*

VWF050 核苷酸序列(IHH 三突變體) (SEQ ID NO: 149)

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 TTTCG 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 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
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 CCCCG 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
901 TATAG GCAGT GTGTG TCCCC TTGCG CCAGG ACCTG CCAGA GCCTG CACAT
951 CAATG AAATG TGTCA GGAGC GATGC GTGGA TGGCT GCAGC TGCCC TGAGG
1001 GACAG CTCCT GGATG AAGGC CTCTG CGTGG AGAGC ACCGA GTGTC CTGC
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
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 GGACT TCGGG
1651 AACGC CTGGA AGCTG CACGG GGACT GCCAG GACCT GCAGA AGCAG CACAG
1701 CGATC CCTGC GCCCT CAACC CGCGC ATGAC CAGGT TCTCC GAGGA GGCGT
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 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
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
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
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
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 CATTC 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
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 CATTC
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

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 GGCGT 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 GGTTC CGGTG GCGGG
3751 GGATC CGGCG GTGGA GGTTC CGGCG GTGGA GGTTC CGGTG GCGGG GGATC
3801 CGGTG GCGGG GGATC CCTGG TCCCC CGGGG CAGCG GCGGT GGAGG TTCCG
3851 GTGGC GGGGG ATCCG ACAAA ACTCA CACAT GCCCA CCGTG CCCAG CTCCA
3901 GAACT CCTGG GCGGA CCGTC AGTCT TCCTC TTCCC CCCAA AACCC AAGGA
3951 CACCC TCATG GCCTC CCGGA CCCCT GAGGT CACAT GCGTG GTGGT GGACG
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 CCCCG 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
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 蛋白質序列(IHH 三突變體) (SEQ ID NO: 150)

1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFVNTFDGSM
51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
101 TVTQGDQRVS 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 IQLPLLKGDL RIQHTVTASV RLSYGEDLQM
501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
551 NAWKLHGDCQ DLQKQHSDPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCEL
651 NCPKGQVYLQ CGTPCNLTCR 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 CKKRVTILVE GGEIELFDGE VNVKRPMKDE

951 THFEVVESGR YIILLLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
1051 MKQTMVDSSC RILTSDVFQD CNKLVDPEPY LDVCIYDTCS CESIGDCAAF
1101 CDTIAAYAHV CAQHGKVVTW RTATLCPQSC EERNLRENGY EAEWRYNSCA
1151 PACQVTCQHP EPLACPVQCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE
1201 VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP ISGGGGSGGG
1251 GSGGGGSGGG GSGGGGSGGG GSLVPRGSGG GGSGGGGSDK THTCPPCPAP
1301 ELLGGPSVFL FPPKPKDTLM ASRTPEVTCV VVDVSHEDPE VKFNWYVDGV
1351 EVHNAKTKPR EEQYNSTYRV VSVLTVLAQD WLNGKEYKCK VSNKALPAPI
1401 EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE
1451 SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL
1501 HNAYTQKSLS LSPGK*

VWF057 核苷酸序列(SEQ ID NO: 151)

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 TTCG 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 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
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 CCCCG AGCCT TTGT 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
901 TATAG GCAGT GTGTG TCCCC TTGCG CCAGG ACCTG CCAGA GCCTG CACAT
951 CAATG AAATG TGTCA GGAGC GATGC GTGGA TGGCT GCAGC TGCCC TGAGG
1001 GACAG CTCCT GGATG AAGGC CTCTG CGTGG AGAGC ACCGA GTGTC CTGC
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
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 GGACT TCGGG
1651 AACGC CTGGA AGCTG CACGG GGACT GCCAG GACCT GCAGA AGCAG CACAG
1701 CGATC CCTGC GCCCT CAACC CGCGC ATGAC CAGGT TCTCC GAGGA GGCGT
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 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
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
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
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
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 CATTC 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
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 CATTC
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
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 GGCGT 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
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
4101 TGCTG GATCT CCTAC GTCCA CTGAG GAAGG GTCAC CAGCG GGCTC GCCCA
4151 CCAGC ACTGA AGAAG GTGCC TCGAG CGGCG GTGGA GGTTC CGGTG GCGGG
4201 GGATC CGGTG GCGGG GGATC CGGTG GCGGG GGATC CGGTG GCGGG GGATC
4251 CCTGG TCCCC CGGGG CAGCG GAGGC GACAA AACTC ACACA TGCCC ACCGT
4301 GCCCA GCTCC AGAAC TCCTG GGCGG ACCGT CAGTC TTCCT CTTCC CCCCA
4351 AAACC CAAGG ACACC CTCAT GATCT CCCGG ACCCC TGAGG TCACA TGCGT
4401 GGTGG TGGAC GTGAG CCACG AAGAC CCTGA GGTCA AGTTC AACTG GTACG
4451 TGGAC GGCGT 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
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
4851 GGACA AGAGC AGGTG GCAGC AGGGG AACGT CTTCT CATGC TCCGT GATGC
4901 ATGAG GCTCT GCACA ACCAC TACAC GCAGA AGAGC CTCTC CCTGT CTCCG
4951 GGTAA ATGA

VWF057 蛋白質序列(SEQ ID NO: 152)

1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFVNTFDGSM
51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
101 TVTQGDQRVS 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 IQLPLLKGDL RIQHTVTASV RLSYGEDLQM
501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
551 NAWKLHGDCQ DLQKQHSDPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCEL
651 NCPKGQVYLQ CGTPCNLTCR 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 CKKRVTILVE GGEIELFDGE VNVKRPMKDE
951 THFEVVESGR YIILLLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
1051 MKQTMVDSSC RILTSDVFQD CNKLVDPEPY LDVCIYDTCS CESIGDCAAF
1101 CDTIAAYAHV CAQHGKVVTW 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
1351 TPGTSESATP ESGPGSPAGS PTSTEEGSPA GSPTSTEEGA SSGGGGSGGG
1401 GSGGGGSGGG GSGGGGSLVP RGSGGDKTHT CPPCPAPELL GGPSVFLFPP
1451 KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ
1501 YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE
1551 PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP
1601 PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP
1651 GK*

VWF058 核苷酸序列(具有 IHH 突變的 VWF034) (SEQ ID NO: 153)

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 TTTCG 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 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
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 CCCCG 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
901 TATAG GCAGT GTGTG TCCCC TTGCG CCAGG ACCTG CCAGA GCCTG CACAT
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
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
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 GGACT TCGGG
1651 AACGC CTGGA AGCTG CACGG GGACT GCCAG GACCT GCAGA AGCAG CACAG
1701 CGATC CCTGC GCCCT CAACC CGCGC ATGAC CAGGT TCTCC GAGGA GGCGT
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 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
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
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
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
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 CATTC 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
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 CATTC
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
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 GGCGT TTTGC CTCAG GAAAG AAAGT CACCT TGAAT CCCAG
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
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
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
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 CTGG TCCCC CGGGG CAGCG GAGGC GACAA
4701 AACTC ACACA TGCCC ACCGT GCCCA GCTCC AGAAC TCCTG GGCGG ACCGT
4751 CAGTC TTCCT CTTCC CCCCA AAACC CAAGG ACACC CTCAT GGCCT CCCGG
4801 ACCCC TGAGG TCACA TGCGT GGTGG TGGAC GTGAG CCACG AAGAC CCTGA
4851 GGTCA AGTTC AACTG GTACG TGGAC GGCGT 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
5051 CCAAA GGGCA GCCCC GAGAA CCACA GGTGT ACACC CTGCC CCCAT CCCGC
5101 GATGA GCTGA CCAAG AACCA GGTCA GCCTG 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 ACGCC TACAC GCAGA
5351 AGAGC CTCTC CCTGT CTCCG GGTAA ATGA

VWF058 蛋白質序列(具有 IHH 突變的 VWF034) (SEQ ID NO: 154)

1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFVNTFDGSM
51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
101 TVTQGDQRVS 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 IQLPLLKGDL RIQHTVTASV RLSYGEDLQM
501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
551 NAWKLHGDCQ DLQKQHSDPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCEL
651 NCPKGQVYLQ CGTPCNLTCR 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 CKKRVTILVE GGEIELFDGE VNVKRPMKDE
951 THFEVVESGR YIILLLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
1051 MKQTMVDSSC RILTSDVFQD CNKLVDPEPY LDVCIYDTCS CESIGDCAAF
1101 CDTIAAYAHV CAQHGKVVTW RTATLCPQSC EERNLRENGY EAEWRYNSCA
1151 PACQVTCQHP EPLACPVQCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE
1201 VAGRRFASGK KVTLNPSDPE HCQICHCDVV NLTCEACQEP ISGTSESATP
1251 ESGPGSEPAT SGSETPGTSE SATPESGPGS EPATSGSETP GTSESATPES
1301 GPGTSTEPSE GSAPGSPAGS PTSTEEGTSE SATPESGPGS EPATSGSETP
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 RGSGGDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMASR
1601 TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV
1651 LTVLAQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR
1701 DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF
1751 LYSKLTVDKS RWQQGNVFSC SVMHEALHNA YTQKSLSLSP GK*

FVIII 169 核苷酸序列(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
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 ACACT 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
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 ACAAA 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
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
1101 TGATC TTACT GATTC TGAAA TGGAT GTGGT CAGGT TTGAT GATGA CAACT
1151 CTCCT TCCTT TATCC AAATT CGCTC AGTTG CCAAG AAGCA TCCTA AAACT
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 CATAC
1351 ACAGA TGAAA CCTTT AAGAC TCGTG AAGCT ATTCA GCATG AATCA GGAAT
1401 CTTGG GACCT TTACT 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 TGTAG ATCAA AGAGG AAACC
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 CATAC TGGTA CATTC TAAGC ATTGG AGCAC AGACT GACTT
2001 CCTTT CTGTC TTCTT CTCTG GATAT ACCTT CAAAC ACAAA ATGGT CTATG
2051 AAGAC ACACT 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
2301 AGGTA CCTCA GAGTC TGCTA CCCCC GAGTC AGGGC CAGGA TCAGA GCCAG

2351 CCACC TCCGG GTCTG AGACA CCCGG 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
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
2751 ATCCG AGGGA TCAGC TCCCG 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
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 CATTT 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
3501 CCGTG GAGAA CTAAA 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 TGGAA AGTGC AACAT CATAT GGCAC CCACT AAAGA TGAGT TTGAC
3751 TGCAA AGCCT GGGCT TATTT CTCTG ATGTT GACCT GGAAA AAGAT GTGCA
3801 CTCAG GCCTG ATTGG ACCCC TTCTG GTCTG CCACA CTAAC ACACT 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 TTTAA 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 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 ACACT TTTTC
4301 TGGTG TACAG CAATA AGTGT CAGAC TCCCC TGGGA ATGGC TTCTG GACAC
4351 ATTAG AGATT TTCAG ATTAC AGCTT CAGGA CAATA TGGAC AGTGG GCCCC
4401 AAAGC TGGCC AGACT TCATT ATTCC GGATC AATCA ATGCC TGGAG CACCA
4451 AGGAG CCCTT TTCTT GGATC AAGGT GGATC TGTTG 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
4651 TCATC TGGGA TAAAA CACAA TATTT TTAAC CCTCC AATTA TTGCT 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 TTACT GCTTC ATCCT ACTTT ACCAA
4851 TATGT TTGCC ACCTG GTCTC CTTCA AAAGC TCGAC TTCAC CTCCA AGGGA
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
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
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 GGACT GGCTG AATGG CAAGG AGTAC
5551 AAGTG CAAGG TCTCC AACAA AGCCC TCCCA GCCCC CATCG AGAAA ACCAT
5601 CTCCA AAGCC AAAGG GCAGC CCCGA GAACC ACAGG TGTAC ACCCT GCCCC
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 CACTA
5901 CACGC AGAAG AGCCT CTCCC TGTCT CCGGG TAAAT GA

FVIII 169 蛋白質序列(SEQ ID NO:70)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQSDL GELPVDARFP
51 PRVPKSFPFN TSVVYKKTLF 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
401 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
451 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
601 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL

651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS
701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED 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
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 KVVFQEFTDG SFTQPLYRGE LNEHLGLLGP YIRAEVEDNI MVTFRNQASR
1201 PYSFYSSLIS YEEDQRQGAE PRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
1251 CKAWAYFSDV DLEKDVHSGL IGPLLVCHTN TLNPAHGRQV TVQEFALFFT
1301 IFDETKSWYF TENMERNCRA PCNIQMEDPT FKENYRFHAI NGYIMDTLPG
1351 LVMAQDQRIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
1401 VFETVEMLPS KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPLGMASGH
1451 IRDFQITASG QYGQWAPKLA RLHYSGSINA WSTKEPFSWI KVDLLAPMII
1501 HGIKTQGARQ KFSSLYISQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
1551 SSGIKHNIFN PPIIARYIRL HPTHYSIRST LRMELMGCDL NSCSMPLGME
1601 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ
1651 VDFQKTMKVT GVTTQGVKSL LTSMYVKEFL ISSSQDGHQW TLFFQNGKVK
1701 VFQGNQDSFT PVVNSLDPPL LTRYLRIHPQ SWVHQIALRM EVLGCEAQDL
1751 YDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
1801 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
1851 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV
1901 KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
1951 GNVFSCSVMH EALHNHYTQK SLSLSPGK*

FVIII 263 核苷酸序列(IHH 三突變體) (SEQ ID NO: 156)

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 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 CGGCT
251 CCGAG ACTCC GGGAA CTTCC GAGAG CGCTA CACCA GAAAG CGGAC CCGGA
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
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 ACACT TAAGA ACATG GCTTC CCATC CTGTC AGTCT
801 TCATG CTGTT GGTGT ATCCT ACTGG AAAGC TTCTG AGGGA GCTGA ATATG
851 ATGAT CAGAC CAGTC AAAGG GAGAA AGAAG ATGAT AAAGT CTTCC 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
1051 GGGAG TCTGG CCAAG GAAAA GACAC AGACC TTGCA CAAAT TTATA CTACT
1101 TTTTG CTGTA TTTGA TGAAG GGAAA AGTTG GCACT CAGAA ACAAA 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
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 GATTC TGAAA TGGAT GTGGT CAGGT TTGAT GATGA CAACT
1601 CTCCT TCCTT TATCC AAATT CGCTC AGTTG CCAAG AAGCA TCCTA AAACT
1651 TGGGT ACATT ACATT GCTGC TGAAG AGGAG GACTG GGACT ATGCT CCCTT
1701 AGTCC TCGCC CCCGA TGACA GAAGT TATAA AAGTC AATAT TTGAA CAATG
1751 GCCCT CAGCG GATTG GTAGG AAGTA CAAAA AAGTC CGATT TATGG CATAC
1801 ACAGA TGAAA 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
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 ACAAA GAATC TGTAG ATCAA AGAGG AAACC
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 CATAC TGGTA CATTC TAAGC ATTGG AGCAC AGACT GACTT
2451 CCTTT CTGTC TTCTT CTCTG GATAT ACCTT CAAAC ACAAA ATGGT CTATG
2501 AAGAC ACACT CACCC TATTC CCATT CTCAG GAGAA ACTGT CTTCA TGTCG
2551 ATGGA AAACC CAGGT CTATG GATTC 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
2701 AGTAA AAACA ATGCC ATTGA ACCAA GAAGC TTCTC TCAAA ACGGC GCGCC
2751 AGGTA CCTCA GAGTC TGCTA CCCCC GAGTC AGGGC CAGGA TCAGA GCCAG
2801 CCACC TCCGG GTCTG AGACA CCCGG GACTT CCGAG AGTGC CACCC CTGAG
2851 TCCGG ACCCG GGTCC GAGCC CGCCA CTTCC GGCTC CGAAA CTCCC GGCAC

2901 AAGCG AGAGC GCTAC CCCAG AGTCA GGACC AGGAA CATCT ACAGA GCCCT
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 CTCCC GCTGG GAGCC CCACC TCCAC TGAGG AGGGA
3151 TCTCC TGCTG GCTCT CCAAC ATCTA CTGAG GAAGG TACCT CAACC GAGCC
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
3451 CCAAG CGAGG GCTCC GCACC CGGAA CAAGC ACTGA ACCCA GTGAG GGTTC
3501 AGCAC CCGGC TCTGA GCCGG CCACA AGTGG CAGTG AGACA CCCGG CACTT
3551 CAGAG AGTGC CACCC CCGAG AGTGG CCCAG GCACT AGTAC CGAGC CCTCT
3601 GAAGG CAGTG CGCCA GCCTC GAGCC CACCA GTCTT GAAAC GCCAT CAAGC
3651 TGAAA TAACT CGTAC TACTC TTCAG TCAGA TCAAG AGGAA ATCGA TTATG
3701 ATGAT ACCAT ATCAG TTGAA ATGAA GAAGG AAGAT TTTGA CATTT ATGAT
3751 GAGGA TGAAA 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 CTAAA TGAAC ATTTG GGACT 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
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 GGAAA AAGAT GTGCA
4251 CTCAG GCCTG ATTGG ACCCC TTCTG GTCTG CCACA CTAAC ACACT GAACC
4301 CTGCT CATGG GAGAC AAGTG ACAGT ACAGG AATTT GCTCT GTTTT TCACC
4351 ATCTT TGATG AGACC AAAAG CTGGT ACTTC ACTGA AAATA TGGAA AGAAA
4401 CTGCA GGGCT CCCTG CAATA TCCAG ATGGA AGATC CCACT TTTAA 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 CATTT CAGTG GACAT GTGTT CACTG
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 ACACT TTTTC
4751 TGGTG TACAG CAATA AGTGT CAGAC TCCCC TGGGA ATGGC TTCTG GACAC
4801 ATTAG AGATT TTCAG ATTAC AGCTT CAGGA CAATA TGGAC AGTGG GCCCC
4851 AAAGC TGGCC AGACT TCATT ATTCC GGATC AATCA ATGCC TGGAG CACCA
4901 AGGAG CCCTT TTCTT GGATC AAGGT GGATC TGTTG 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 GGAAA TTCCA CTGGA ACCTT AATGG TCTTC TTTGG CAATG TGGAT

5101 TCATC TGGGA TAAAA CACAA TATTT TTAAC CCTCC AATTA TTGCT CGATA
5151 CATCC GTTTG CACCC AACTC ATTAT AGCAT TCGCA GCACT CTTCG CATGG
5201 AGTTG ATGGG CTGTG ATTTA AATAG TTGCA GCATG CCATT GGGAA TGGAG
5251 AGTAA AGCAA TATCA GATGC ACAGA TTACT GCTTC ATCCT ACTTT ACCAA
5301 TATGT TTGCC ACCTG GTCTC CTTCA AAAGC TCGAC TTCAC CTCCA AGGGA
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
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 CCAAA ACCCA AGGAC ACCCT CATGG
5801 CCTCC CGGAC CCCTG AGGTC ACATG CGTGG TGGTG GACGT GAGCC ACGAA
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 GGACT GGCTG AATGG CAAGG AGTAC
6001 AAGTG CAAGG TCTCC AACAA AGCCC TCCCA GCCCC CATCG AGAAA ACCAT
6051 CTCCA AAGCC AAAGG GCAGC CCCGA GAACC ACAGG TGTAC ACCCT GCCCC
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
6351 CACGC AGAAG AGCCT CTCCC TGTCT CCGGG TAAAT GA

FVIII 263 蛋白質序列(IHH 三突變體) (SEQ ID NO: 157)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQGAP TSESATPESG
51 PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
101 TSTEPSEGSA PGSPAGSPTS TEEGTSESAT PESGPGSEPA TSGSETPGTS
151 ESATPESGPG SPAGSPTSTE EGSPAGSPTS TEEGASSSDL GELPVDARFP
201 PRVPKSFPFN TSVVYKKTLF 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
451 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
501 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
551 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
601 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
701 YYSSFVNMER 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 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
1201 EGSAPASSPP VLKRHQAEIT RTTLQSDQEE IDYDDTISVE MKKEDFDIYD
1251 EDENQSPRSF QKKTRHYFIA AVERLWDYGM SSSPHVLRNR AQSGSVPQFK
1301 KVVFQEFTDG SFTQPLYRGE LNEHLGLLGP YIRAEVEDNI MVTFRNQASR
1351 PYSFYSSLIS YEEDQRQGAE PRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
1401 CKAWAYFSDV DLEKDVHSGL IGPLLVCHTN TLNPAHGRQV TVQEFALFFT
1451 IFDETKSWYF TENMERNCRA PCNIQMEDPT FKENYRFHAI NGYIMDTLPG
1501 LVMAQDQRIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
1551 VFETVEMLPS KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPLGMASGH
1601 IRDFQITASG QYGQWAPKLA RLHYSGSINA WSTKEPFSWI KVDLLAPMII
1651 HGIKTQGARQ KFSSLYISQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
1701 SSGIKHNIFN PPIIARYIRL HPTHYSIRST LRMELMGCDL NSCSMPLGME
1751 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ
1801 VDFQKTMKVT GVTTQGVKSL LTSMYVKEFL ISSSQDGHQW TLFFQNGKVK
1851 VFQGNQDSFT PVVNSLDPPL LTRYLRIHPQ SWVHQIALRM EVLGCEAQDL
1901 YDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMASRTPEV TCVVVDVSHE
1951 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL AQDWLNGKEY
2001 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV
2051 KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
2101 GNVFSCSVMH EALHNAYTQK SLSLSPGK*

FVIII 282 核苷酸序列(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
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 ACACT 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
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 ACAAA 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
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
1101 TGATC TTACT GATTC TGAAA TGGAT GTGGT CAGGT TTGAT GATGA CAACT
1151 CTCCT TCCTT TATCC AAATT CGCTC AGTTG CCAAG AAGCA TCCTA AAACT
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 CATAC
1351 ACAGA TGAAA CCTTT AAGAC TCGTG AAGCT ATTCA GCATG AATCA GGAAT
1401 CTTGG GACCT TTACT 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 TGTAG ATCAA AGAGG AAACC
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 CATAC TGGTA CATTC TAAGC ATTGG AGCAC AGACT GACTT
2001 CCTTT CTGTC TTCTT CTCTG GATAT ACCTT CAAAC ACAAA ATGGT CTATG
2051 AAGAC ACACT 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
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
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 GGTCA
2701 CCAGC GGGCT CGCCC ACCAG CACTG AAGAA GGTGC CTCGA GCCCA CCAGT
2751 CTTGA AACGC CATCA AGCTG AAATA ACTCG TACTA CTCTT CAGTC AGATC
2801 AAGAG GAAAT CGATT ATGAT GATAC CATAT CAGTT GAAAT GAAGA AGGAA

2851 GATTT TGACA TTTAT GATGA GGATG AAAAT CAGAG CCCCC GCAGC TTTCA
2901 AAAGA AAACA CGACA CTATT TTATT GCTGC AGTGG AGAGG CTCTG GGATT
2951 ATGGG ATGAG TAGCT CCCCA 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 GGTAA CTTTC
3151 AGAAA TCAGG CCTCT CGTCC CTATT CCTTC TATTC TAGCC TTATT TCTTA
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
3451 TTTGC TCTGT TTTTC ACCAT CTTTG ATGAG ACCAA AAGCT GGTAC TTCAC
3501 TGAAA ATATG GAAAG AAACT GCAGG 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
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
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 CTTAA TGGTC
4201 TTCTT TGGCA ATGTG GATTC ATCTG GGATA AAACA CAATA TTTTT AACCC
4251 TCCAA TTATT GCTCG ATACA TCCGT TTGCA CCCAA CTCAT TATAG CATTC
4301 GCAGC ACTCT TCGCA TGGAG TTGAT GGGCT GTGAT TTAAA TAGTT GCAGC
4351 ATGCC ATTGG GAATG GAGAG TAAAG CAATA TCAGA TGCAC AGATT ACTGC
4401 TTCAT CCTAC TTTAC CAATA TGTTT GCCAC CTGGT CTCCT TCAAA AGCTC
4451 GACTT CACCT CCAAG GGAGG AGTAA TGCCT GGAGA CCTCA GGTGA ATAAT
4501 CCAAA AGAGT GGCTG CAAGT GGACT 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 CCTTC ACACC
4701 TGTGG TGAAC TCTCT AGACC CACCG TTACT GACTC GCTAC CTTCG AATTC
4751 ACCCC CAGAG TTGGG TGCAC CAGAT TGCCC TGAGG ATGGA GGTTC TGGGC
4801 TGCGA GGCAC AGGAC CTCTA CGACA AAACT CACAC 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
4951 GTGGA CGTGA GCCAC GAAGA CCCTG AGGTC AAGTT CAACT GGTAC GTGGA
5001 CGGCG TGGAG GTGCA TAATG CCAAG ACAAA 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 CCCCA TCGAG AAAAC CATCT CCAAA GCCAA AGGGC AGCCC CGAGA ACCAC
5201 AGGTG TACAC CCTGC CCCCA TCCCG GGATG AGCTG ACCAA GAACC AGGTC
5251 AGCCT GACCT GCCTG GTCAA AGGCT TCTAT CCCAG CGACA TCGCC GTGGA
5301 GTGGG AGAGC AATGG GCAGC CGGAG AACAA 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
5451 GGCTC TGCAC AACCA CTACA CGCAG AAGAG CCTCT CCCTG TCTCC GGGTA
5501 AATGA

FVIII 282 蛋白質序列(SEQ ID NO: 159)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQSDL GELPVDARFP
51 PRVPKSFPFN TSVVYKKTLF 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
401 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
451 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
601 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF 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
901 PAGSPTSTEE GASSPPVLKR HQAEITRTTL QSDQEEIDYD DTISVEMKKE
951 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP HVLRNRAQSG
1001 SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
1051 RNQASRPYSF YSSLISYEED QRQGAEPRKN FVKPNETKTY FWKVQHHMAP
1101 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE
1151 FALFFTIFDE TKSWYFTENM ERNCRAPCNI QMEDPTFKEN YRFHAINGYI
1201 MDTLPGLVMA QDQRIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
1251 YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
1301 GMASGHIRDF QITASGQYGQ WAPKLARLHY SGSINAWSTK EPFSWIKVDL
1351 LAPMIIHGIK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
1401 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS
1451 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
1501 PKEWLQVDFQ KTMKVTGVTT QGVKSLLTSM YVKEFLISSS QDGHQWTLFF

1551 QNGKVKVFQG NQDSFTPVVN SLDPPLLTRY LRIHPQSWVH QIALRMEVLG
1601 CEAQDLYDKT HTCPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
1651 VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW
1701 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV
1751 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD
1801 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

FVIII 283 核苷酸序列(具有 IHH 三突變體的 FVIII 169) (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
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 ACACT 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
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 ACAAA 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
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
1101 TGATC TTACT GATTC TGAAA TGGAT GTGGT CAGGT TTGAT GATGA CAACT
1151 CTCCT TCCTT TATCC AAATT CGCTC AGTTG CCAAG AAGCA TCCTA AAACT
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 CATAC
1351 ACAGA TGAAA CCTTT AAGAC TCGTG AAGCT ATTCA GCATG AATCA GGAAT
1401 CTTGG GACCT TTACT 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 TGTAG ATCAA AGAGG AAACC

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 CATAC TGGTA CATTC TAAGC ATTGG AGCAC AGACT GACTT
2001 CCTTT CTGTC TTCTT CTCTG GATAT ACCTT CAAAC ACAAA ATGGT CTATG
2051 AAGAC ACACT 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
2301 AGGTA CCTCA GAGTC TGCTA CCCCC GAGTC AGGGC CAGGA TCAGA GCCAG
2351 CCACC TCCGG GTCTG AGACA CCCGG 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
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
2751 ATCCG AGGGA TCAGC TCCCG 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
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 CATTT 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
3501 CCGTG GAGAA CTAAA 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 TGGAA AGTGC AACAT CATAT GGCAC CCACT AAAGA TGAGT TTGAC
3751 TGCAA AGCCT GGGCT TATTT CTCTG ATGTT GACCT GGAAA AAGAT GTGCA
3801 CTCAG GCCTG ATTGG ACCCC TTCTG GTCTG CCACA CTAAC ACACT 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 TTTAA 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 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 ACACT TTTTC
4301 TGGTG TACAG CAATA AGTGT CAGAC TCCCC TGGGA ATGGC TTCTG GACAC
4351 ATTAG AGATT TTCAG ATTAC AGCTT CAGGA CAATA TGGAC AGTGG GCCCC
4401 AAAGC TGGCC AGACT TCATT ATTCC GGATC AATCA ATGCC TGGAG CACCA
4451 AGGAG CCCTT TTCTT GGATC AAGGT GGATC TGTTG 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
4651 TCATC TGGGA TAAAA CACAA TATTT TTAAC CCTCC AATTA TTGCT 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 TTACT GCTTC ATCCT ACTTT ACCAA
4851 TATGT TTGCC ACCTG GTCTC CTTCA AAAGC TCGAC TTCAC CTCCA AGGGA
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
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
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 GGACT GGCTG AATGG CAAGG AGTAC
5551 AAGTG CAAGG TCTCC AACAA AGCCC TCCCA GCCCC CATCG AGAAA ACCAT
5601 CTCCA AAGCC AAAGG GCAGC CCCGA GAACC ACAGG TGTAC ACCCT GCCCC
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

FVIII 283 蛋白質序列(具有 IHH 三突變的 FVIII 169) (SEQ ID NO: 161)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQSDL GELPVDARFP

51 PRVPKSFPFN TSVVYKKTLF 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
401 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
451 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
601 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS
701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED 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
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 KVVFQEFTDG SFTQPLYRGE LNEHLGLLGP YIRAEVEDNI MVTFRNQASR
1201 PYSFYSSLIS YEEDQRQGAE PRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
1251 CKAWAYFSDV DLEKDVHSGL IGPLLVCHTN TLNPAHGRQV TVQEFALFFT
1301 IFDETKSWYF TENMERNCRA PCNIQMEDPT FKENYRFHAI NGYIMDTLPG
1351 LVMAQDQRIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
1401 VFETVEMLPS KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPLGMASGH
1451 IRDFQITASG QYGQWAPKLA RLHYSGSINA WSTKEPFSWI KVDLLAPMII
1501 HGIKTQGARQ KFSSLYISQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
1551 SSGIKHNIFN PPIIARYIRL HPTHYSIRST LRMELMGCDL NSCSMPLGME
1601 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ
1651 VDFQKTMKVT GVTTQGVKSL LTSMYVKEFL ISSSQDGHQW TLFFQNGKVK
1701 VFQGNQDSFT PVVNSLDPPL LTRYLRIHPQ SWVHQIALRM EVLGCEAQDL
1751 YDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMASRTPEV TCVVVDVSHE
1801 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL AQDWLNGKEY
1851 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV
1901 KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
1951 GNVFSCSVMH EALHNAYTQK SLSLSPGK*

pSYNFVIII 010 核苷酸序列-(雙鏈 FVIIIFc) (SEQ ID NO: 162)

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

101 ACTATATGCA AAGTGATCTC GGTGAGCTGC CTGTGGACGC AAGATTTCCT
151 CCTAGAGTGC CAAAATCTTT TCCATTCAAC ACCTCAGTCG TGTACAAAAA
201 GACTCTGTTT GTAGAATTCA CGGATCACCT TTTCAACATC GCTAAGCCAA
251 GGCCACCCTG GATGGGTCTG CTAGGTCCTA CCATCCAGGC TGAGGTTTAT
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
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
801 CCACAGGAAA TCAGTCTATT GGCATGTGAT TGGAATGGGC ACCACTCCTG
851 AAGTGCACTC AATATTCCTC GAAGGTCACA CATTTCTTGT GAGGAACCAT
901 CGCCAGGCGT CCTTGGAAAT 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
1151 CTCCTTCCTT TATCCAAATT CGCTCAGTTG CCAAGAAGCA TCCTAAAACT
1201 TGGGTACATT ACATTGCTGC TGAAGAGGAG GACTGGGACT ATGCTCCCTT
1251 AGTCCTCGCC CCCGATGACA GAAGTTATAA AAGTCAATAT TTGAACAATG
1301 GCCCTCAGCG GATTGGTAGG AAGTACAAAA AAGTCCGATT TATGGCATAC
1351 ACAGATGAAA CCTTTAAGAC TCGTGAAGCT ATTCAGCATG AATCAGGAAT
1401 CTTGGGACCT TTACTTTATG GGGAAGTTGG 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
1651 TATTACTCTA GTTTCGTTAA 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
1901 ACAGCATCAA TGGCTATGTT TTTGATAGTT TGCAGTTGTC AGTTTGTTTG
1951 CATGAGGTGG CATACTGGTA CATTCTAAGC ATTGGAGCAC AGACTGACTT
2001 CCTTTCTGTC TTCTTCTCTG GATATACCTT CAAACACAAA ATGGTCTATG
2051 AAGACACACT CACCCTATTC CCATTCTCAG GAGAAACTGT CTTCATGTCG
2101 ATGGAAAACC CAGGTCTATG GATTCTGGGG TGCCACAACT CAGACTTTCG
2151 GAACAGAGGC ATGACCGCCT TACTGAAGGT TTCTAGTTGT GACAAGAACA
2201 CTGGTGATTA TTACGAGGAC AGTTATGAAG ATATTTCAGC ATACTTGCTG
2251 AGTAAAAACA ATGCCATTGA ACCAAGAAGC TTCTCTCAAA ACCCACCAGT

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
2551 AGTGTCCCTC AGTTCAAGAA AGTTGTTTTC CAGGAATTTA CTGATGGCTC
2601 CTTTACTCAG CCCTTATACC GTGGAGAACT AAATGAACAT TTGGGACTCC
2651 TGGGGCCATA TATAAGAGCA GAAGTTGAAG ATAATATCAT GGTAACTTTC
2701 AGAAATCAGG CCTCTCGTCC CTATTCCTTC TATTCTAGCC TTATTTCTTA
2751 TGAGGAAGAT CAGAGGCAAG GAGCAGAACC TAGAAAAAAC TTTGTCAAGC
2801 CTAATGAAAC CAAAACTTAC TTTTGGAAAG TGCAACATCA TATGGCACCC
2851 ACTAAAGATG AGTTTGACTG CAAAGCCTGG GCTTATTTCT CTGATGTTGA
2901 CCTGGAAAAA GATGTGCACT CAGGCCTGAT TGGACCCCTT CTGGTCTGCC
2951 ACACTAACAC ACTGAACCCT GCTCATGGGA GACAAGTGAC AGTACAGGAA
3001 TTTGCTCTGT TTTTCACCAT CTTTGATGAG ACCAAAAGCT GGTACTTCAC
3051 TGAAAATATG GAAAGAAACT GCAGGGCTCC CTGCAATATC CAGATGGAAG
3101 ATCCCACTTT TAAAGAGAAT TATCGCTTCC ATGCAATCAA TGGCTACATA
3151 ATGGATACAC TACCTGGCTT AGTAATGGCT CAGGATCAAA GGATTCGATG
3201 GTATCTGCTC AGCATGGGCA GCAATGAAAA CATCCATTCT ATTCATTTCA
3251 GTGGACATGT GTTCACTGTA CGAAAAAAAG AGGAGTATAA AATGGCACTG
3301 TACAATCTCT ATCCAGGTGT TTTTGAGACA GTGGAAATGT TACCATCCAA
3351 AGCTGGAATT TGGCGGGTGG AATGCCTTAT TGGCGAGCAT CTACATGCTG
3401 GGATGAGCAC ACTTTTTCTG GTGTACAGCA ATAAGTGTCA GACTCCCCTG
3451 GGAATGGCTT CTGGACACAT TAGAGATTTT CAGATTACAG CTTCAGGACA
3501 ATATGGACAG TGGGCCCCAA AGCTGGCCAG ACTTCATTAT TCCGGATCAA
3551 TCAATGCCTG GAGCACCAAG GAGCCCTTTT CTTGGATCAA GGTGGATCTG
3601 TTGGCACCAA TGATTATTCA CGGCATCAAG ACCCAGGGTG CCCGTCAGAA
3651 GTTCTCCAGC CTCTACATCT CTCAGTTTAT CATCATGTAT AGTCTTGATG
3701 GGAAGAAGTG GCAGACTTAT CGAGGAAATT CCACTGGAAC CTTAATGGTC
3751 TTCTTTGGCA ATGTGGATTC ATCTGGGATA AAACACAATA TTTTTAACCC
3801 TCCAATTATT GCTCGATACA TCCGTTTGCA CCCAACTCAT TATAGCATTC
3851 GCAGCACTCT TCGCATGGAG TTGATGGGCT GTGATTTAAA TAGTTGCAGC
3901 ATGCCATTGG GAATGGAGAG TAAAGCAATA TCAGATGCAC AGATTACTGC
3951 TTCATCCTAC TTTACCAATA TGTTTGCCAC CTGGTCTCCT TCAAAAGCTC
4001 GACTTCACCT CCAAGGGAGG AGTAATGCCT GGAGACCTCA GGTGAATAAT
4051 CCAAAAGAGT GGCTGCAAGT GGACTTCCAG AAGACAATGA AAGTCACAGG
4101 AGTAACTACT CAGGGAGTAA AATCTCTGCT TACCAGCATG TATGTGAAGG
4151 AGTTCCTCAT CTCCAGCAGT CAAGATGGCC ATCAGTGGAC TCTCTTTTTT
4201 CAGAATGGCA AAGTAAAGGT TTTTCAGGGA AATCAAGACT CCTTCACACC
4251 TGTGGTGAAC TCTCTAGACC CACCGTTACT GACTCGCTAC CTTCGAATTC
4301 ACCCCCAGAG TTGGGTGCAC CAGATTGCCC TGAGGATGGA GGTTCTGGGC
4351 TGCGAGGCAC AGGACCTCTA CGACAAAACT CACACATGCC CACCGTGCCC
4401 AGCTCCAGAA CTCCTGGGCG GACCGTCAGT CTTCCTCTTC CCCCCAAAAC
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
4701 CCCCATCGAG AAAACCATCT CCAAAGCCAA AGGGCAGCCC CGAGAACCAC
4751 AGGTGTACAC CCTGCCCCCA TCCCGGGATG AGCTGACCAA GAACCAGGTC
4801 AGCCTGACCT GCCTGGTCAA AGGCTTCTAT CCCAGCGACA TCGCCGTGGA
4851 GTGGGAGAGC AATGGGCAGC CGGAGAACAA CTACAAGACC ACGCCTCCCG
4901 TGTTGGACTC CGACGGCTCC TTCTTCCTCT ACAGCAAGCT CACCGTGGAC
4951 AAGAGCAGGT GGCAGCAGGG GAACGTCTTC TCATGCTCCG TGATGCATGA
5001 GGCTCTGCAC AACCACTACA CGCAGAAGAG CCTCTCCCTG TCTCCGGGTA
5051 AATGA

pSYNFVIII 010 蛋白質序列-(雙鏈 FVIIIFc)(SEQ ID NO: 163)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQSDL GELPVDARFP
51 PRVPKSFPFN TSVVYKKTLF 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
401 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
451 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
601 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS
701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL
751 SKNNAIEPRS FSQNPPVLKR HQREITRTTL QSDQEEIDYD DTISVEMKKE
801 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP HVLRNRAQSG
851 SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
901 RNQASRPYSF YSSLISYEED QRQGAEPRKN FVKPNETKTY FWKVQHHMAP
951 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE
1001 FALFFTIFDE TKSWYFTENM ERNCRAPCNI QMEDPTFKEN YRFHAINGYI
1051 MDTLPGLVMA QDQRIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
1101 YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
1151 GMASGHIRDF QITASGQYGQ WAPKLARLHY SGSINAWSTK EPFSWIKVDL
1201 LAPMIIHGIK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
1251 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS
1301 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
1351 PKEWLQVDFQ KTMKVTGVTT QGVKSLLTSM YVKEFLISSS QDGHQWTLFF
1401 QNGKVKVFQG NQDSFTPVVN SLDPPLLTRY LRIHPQSWVH QIALRMEVLG

1451 CEAQDLYDKT HTCPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
1501 VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW
1551 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV
1601 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD
1651 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

FVIII 195 蛋白質序列(在胺基酸 1656 和 1900 處具有兩個 144 AE XTEN 的雙鏈 FVIIIFc) (SEQ ID NO: 73)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQSDL GELPVDARFP
51 PRVPKSFPFN TSVVYKKTLF 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
401 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
451 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
601 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS
701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL
751 SKNNAIEPRS FSQNPPVLKR HQREITRTTL QSDPGTPGSG 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 SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
1051 RNQASRPYSF YSSLISYEED QRQGAEPRKN FVKPNETKTY FWKVQHHMAP
1101 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE
1151 FALFFTIFDE TKSWYFTENM ERNCRGAPTS ESATPESGPG SEPATSGSET
1201 PGTSESATPE SGPGSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG
1251 TSESATPESG PGSPAGSPTS TEEGSPAGSP TSTEEGSPAG SPTSTEEGTS
1301 ESATPESGPG TSTEPSEGSA PGASSAPCNI QMEDPTFKEN YRFHAINGYI
1351 MDTLPGLVMA QDQRIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
1401 YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
1451 GMASGHIRDF QITASGQYGQ WAPKLARLHY SGSINAWSTK EPFSWIKVDL
1501 LAPMIIHGIK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
1551 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS
1601 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
1651 PKEWLQVDFQ KTMKVTGVTT QGVKSLLTSM YVKEFLISSS QDGHQWTLFF
1701 QNGKVKVFQG NQDSFTPVVN SLDPPLLTRY LRIHPQSWVH QIALRMEVLG

1751 CEAQDLYDKT HTCPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
1801 VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW
1851 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV
1901 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD
1951 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

pSYN-FVIII-173 成熟蛋白質序列(SEQ ID NO: 72):

1 ATRRYYLGAV ELSWDYMQSD LGELPVDARF PPRVPKSFPF NTSVVYKKTL
51 FVEFTDHLFN IAKPRPPWMG LLGPTIQAEV YDTVVITLKN MASHPVSLHA
101 VGVSYWKASE GAEYDDQTSQ REKEDDKVFP GGSHTYVWQV LKENGPMASD
151 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
401 APDDRSYKSQ YLNNGPQRIG RKYKKVRFMA YTDETFKTRE AIQHESGILG
451 PLLYGEVGDT LLIIFKNQAS RPYNIYPHGI TDVRPLYSRR LPKGVKHLKD
501 FPILPGEIFK YKWTVTVEDG PTKSDPRCLT RYYSSFVNME RDLASGLIGP
551 LLICYKESVD QRGNQIMSDK RNVILFSVFD ENRSWYLTEN IQRFLPNPAG
601 VQLEDPEFQA SNIMHSINGY VFDSLQLSVC LHEVAYWYIL SIGAQTDFLS
651 VFFSGYTFKH KMVYEDTLTL FPFSGETVFM SMENPGLWIL GCHNSDFRNR
701 GMTALLKVSS CDKNTGDYYE 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
951 TPGSEPATSG SETPGSPAGS PTSTEEGTST EPSEGSAPGT STEPSEGSAP
1001 GSEPATSGSE TPGTSESATP ESGPGTSTEP SEGSAPASSP PVLKRHQREI
1051 TRTTLQSDQE EIDYDDTISV EMKKEDFDIY DEDENQSPRS FQKKTRHYFI
1101 AAVERLWDYG MSSSPHVLRN RAQSGSVPQF KKVVFQEFTD GSFTQPLYRG
1151 ELNEHLGLLG PYIRAEVEDN IMVTFRNQAS RPYSFYSSLI SYEEDQRQGA
1201 EPRKNFVKPN ETKTYFWKVQ HHMAPTKDEF DCKAWAYFSD VDLEKDVHSG
1251 LIGPLLVCHT NTLNPAHGRQ VTVQEFALFF TIFDETKSWY FTENMERNCR
1301 APCNIQMEDP TFKENYRFHA INGYIMDTLP GLVMAQDQRI RWYLLSMGSN
1351 ENIHSIHFSG HVFTVRKKEE YKMALYNLYP GVFETVEMLP SKAGIWRVEC
1401 LIGEHLHAGM STLFLVYSNK CQTPLGMASG HIRDFQITAS GQYGQWAPKL
1451 ARLHYSGSIN AWSTKEPFSW IKVDLLAPMI IHGIKTQGAR QKFSSLYISQ
1501 FIIMYSLDGK KWQTYRGNST GTLMVFFGNV DSSGIKHNIF NPPIIARYIR
1551 LHPTHYSIRS TLRMELMGCD LNSCSMPLGM ESKAISDAQI TASSYFTNMF
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
1851 AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE
1901 NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ
1951 KSLSLSPGK

FVIII 196蛋白質序列(在胺基酸26、1656和1900處具有三個144 AE XTEN的雙鏈FVIIIFc) (SEQ ID NO: 74)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQSDL GELPVGAPGS
51 SPSASTGTGP GSSPSASTGT GPGASPGTSS TGSPGASPGT SSTGSPGSST
101 PSGATGSPGS SPSASTGTGP GASPGTSSTG SPGSSPSAST GTGPGTPGSG
151 TASSSPGSST PSGATGSPGS STPSGATGSP GASPGTSSTG SPASSDARFP
201 PRVPKSFPFN TSVVYKKTLF 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
451 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
501 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
551 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
601 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
701 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
751 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
801 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS
851 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL
901 SKNNAIEPRS FSQNPPVLKR HQREITRTTL QGAPGTPGSG TASSSPGASP
951 GTSSTGSPGA SPGTSSTGSP GASPGTSSTG SPGSSPSAST GTGPGTPGSG
1001 TASSSPGASP GTSSTGSPGA SPGTSSTGSP GASPGTSSTG SPGSSTPSGA
1051 TGSPGSSTPS GATGSPGASP GTSSTGSPAS SSDQEEIDYD DTISVEMKKE
1101 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP HVLRNRAQSG
1151 SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
1201 RNQASRPYSF YSSLISYEED QRQGAEPRKN FVKPNETKTY FWKVQHHMAP
1251 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE
1301 FALFFTIFDE TKSWYFTENM ERNCRGAPTS ESATPESGPG SEPATSGSET
1351 PGTSESATPE SGPGSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG
1401 TSESATPESG PGSPAGSPTS TEEGSPAGSP TSTEEGSPAG SPTSTEEGTS
1451 ESATPESGPG TSTEPSEGSA PGASSAPCNI QMEDPTFKEN YRFHAINGYI
1501 MDTLPGLVMA QDQRIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
1551 YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
1601 GMASGHIRDF QITASGQYGQ WAPKLARLHY SGSINAWSTK EPFSWIKVDL
1651 LAPMIIHGIK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
1701 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS
1751 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
1801 PKEWLQVDFQ KTMKVTGVTT QGVKSLLTSM YVKEFLISSS QDGHQWTLFF

1851 QNGKVKVFQG NQDSFTPVVN SLDPPLLTRY LRIHPQSWVH QIALRMEVLG
1901 CEAQDLYDKT HTCPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
1951 VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW
2001 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV
2051 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD
2101 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

FVIII 199 蛋白質序列(在胺基酸 1656 和 1900 處具有三個 144 AE XTEN 的單鏈 FVIIIFc) (SEQ ID NO: 75)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQSDL GELPVDARFP
51 PRVPKSFPFN TSVVYKKTLF 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
401 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
451 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
601 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS
701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL
751 SKNNAIEPRS FSQNPPVLKR HQAEITRTTL 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 SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
1051 RNQASRPYSF YSSLISYEED QRQGAEPRKN FVKPNETKTY FWKVQHHMAP
1101 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE
1151 FALFFTIFDE TKSWYFTENM ERNCRGAPTS ESATPESGPG SEPATSGSET
1201 PGTSESATPE SGPGSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG
1251 TSESATPESG PGSPAGSPTS TEEGSPAGSP TSTEEGSPAG SPTSTEEGTS
1301 ESATPESGPG TSTEPSEGSA PGASSAPCNI QMEDPTFKEN YRFHAINGYI
1351 MDTLPGLVMA QDQRIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
1401 YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
1451 GMASGHIRDF QITASGQYGQ WAPKLARLHY SGSINAWSTK EPFSWIKVDL
1501 LAPMIIHGIK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
1551 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS
1601 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
1651 PKEWLQVDFQ KTMKVTGVTT QGVKSLLTSM YVKEFLISSS QDGHQWTLFF
1701 QNGKVKVFQG NQDSFTPVVN SLDPPLLTRY LRIHPQSWVH QIALRMEVLG

1751 CEAQDLYDKT HTCPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
1801 VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW
1851 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV
1901 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD
1951 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

FVIII 201蛋白質序列(在胺基酸26、1656和1900處具有三個144 AE XTEN的單鏈FVIIIFc) (SEQ ID NO: 76)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQSDL GELPVGAPGS
51 SPSASTGTGP GSSPSASTGT GPGASPGTSS TGSPGASPGT SSTGSPGSST
101 PSGATGSPGS SPSASTGTGP GASPGTSSTG SPGSSPSAST GTGPGTPGSG
151 TASSSPGSST PSGATGSPGS STPSGATGSP GASPGTSSTG SPASSDARFP
201 PRVPKSFPFN TSVVYKKTLF 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
451 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
501 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
551 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
601 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
701 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
751 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
801 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS
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
1101 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP HVLRNRAQSG
1151 SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
1201 RNQASRPYSF YSSLISYEED QRQGAEPRKN FVKPNETKTY FWKVQHHMAP
1251 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE
1301 FALFFTIFDE TKSWYFTENM ERNCRGAPTS ESATPESGPG SEPATSGSET
1351 PGTSESATPE SGPGSEPATS GSETPGTSES ATPESGPGTS TEPSEGSAPG
1401 TSESATPESG PGSPAGSPTS TEEGSPAGSP TSTEEGSPAG SPTSTEEGTS
1451 ESATPESGPG TSTEPSEGSA PGASSAPCNI QMEDPTFKEN YRFHAINGYI
1501 MDTLPGLVMA QDQRIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
1551 YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
1601 GMASGHIRDF QITASGQYGQ WAPKLARLHY SGSINAWSTK EPFSWIKVDL
1651 LAPMIIHGIK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
1701 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS

1751 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
1801 PKEWLQVDFQ KTMKVTGVTT QGVKSLLTSM YVKEFLISSS QDGHQWTLFF
1851 QNGKVKVFQG NQDSFTPVVN SLDPPLLTRY LRIHPQSWVH QIALRMEVLG
1901 CEAQDLYDKT HTCPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
1951 VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW
2001 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV
2051 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD
2101 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

FVIII 203 蛋白質序列(具有兩個 AE XTEN 的單鏈 FVIIIFc；一個為 B 域中的 288AE XTEN，一個為在胺基酸 1900 處的 144 AE XTEN) (SEQ ID NO: 77)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQSDL GELPVDARFP
51 PRVPKSFPFN TSVVYKKTLF 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
401 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
451 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
601 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS
701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED 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
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 KVVFQEFTDG SFTQPLYRGE LNEHLGLLGP YIRAEVEDNI MVTFRNQASR
1201 PYSFYSSLIS YEEDQRQGAE PRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
1251 CKAWAYFSDV DLEKDVHSGL IGPLLVCHTN TLNPAHGRQV TVQEFALFFT
1301 IFDETKSWYF TENMERNCRG APTSESATPE SGPGSEPATS GSETPGTSES
1351 ATPESGPGSE PATSGSETPG TSESATPESG PGTSTEPSEG SAPGTSESAT
1401 PESGPGSPAG SPTSTEEGSP AGSPTSTEEG SPAGSPTSTE EGTSESATPE
1451 SGPGTSTEPS EGSAPGASSA PCNIQMEDPT FKENYRFHAI NGYIMDTLPG
1501 LVMAQDQRIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
1551 VFETVEMLPS KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPLGMASGH
1601 IRDFQITASG QYGQWAPKLA RLHYSGSINA WSTKEPFSWI KVDLLAPMII

1651 HGIKTQGARQ KFSSLYISQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
1701 SSGIKHNIFN PPIIARYIRL HPTHYSIRST LRMELMGCDL NSCSMPLGME
1751 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ
1801 VDFQKTMKVT GVTTQGVKSL LTSMYVKEFL ISSSQDGHQW TLFFQNGKVK
1851 VFQGNQDSFT PVVNSLDPPL LTRYLRIHPQ SWVHQIALRM EVLGCEAQDL
1901 YDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
1951 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
2001 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV
2051 KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
2101 GNVFSCSVMH EALHNHYTQK SLSLSPGK*

FVIII 204 蛋白質序列(具有兩個 AE XTEN 的單鏈 FVIIIFc；一個為 B 域中的 288AE XTEN，且一個為在胺基酸 403 處的 144 AE XTEN) (SEQ ID NO: 78)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQSDL GELPVDARFP
51 PRVPKSFPFN TSVVYKKTLF 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
401 WVHYIAAEEE DWDYAPLVLA PDGAPTSTEP SEGSAPGSPA GSPTSTEEGT
451 STEPSEGSAP GTSTEPSEGS APGTSESATP ESGPGTSTEP SEGSAPGTSE
501 SATPESGPGS EPATSGSETP GTSTEPSEGS APGTSTEPSE GSAPGTSESA
551 TPESGPGTSE SATPESGPGA SSDRSYKSQY LNNGPQRIGR KYKKVRFMAY
601 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
701 YYSSFVNMER 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 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
1201 EGSAPASSPP VLKRHQAEIT RTTLQSDQEE IDYDDTISVE MKKEDFDIYD
1251 EDENQSPRSF QKKTRHYFIA AVERLWDYGM SSSPHVLRNR AQSGSVPQFK
1301 KVVFQEFTDG SFTQPLYRGE LNEHLGLLGP YIRAEVEDNI MVTFRNQASR
1351 PYSFYSSLIS YEEDQRQGAE PRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
1401 CKAWAYFSDV DLEKDVHSGL IGPLLVCHTN TLNPAHGRQV TVQEFALFFT
1451 IFDETKSWYF TENMERNCRA PCNIQMEDPT FKENYRFHAI NGYIMDTLPG

1501 LVMAQDQRIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
1551 VFETVEMLPS KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPLGMASGH
1601 IRDFQITASG QYGQWAPKLA RLHYSGSINA WSTKEPFSWI KVDLLAPMII
1651 HGIKTQGARQ KFSSLYISQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
1701 SSGIKHNIFN PPIIARYIRL HPTHYSIRST LRMELMGCDL NSCSMPLGME
1751 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ
1801 VDFQKTMKVT GVTTQGVKSL LTSMYVKEFL ISSSQDGHQW TLFFQNGKVK
1851 VFQGNQDSFT PVVNSLDPPL LTRYLRIHPQ SWVHQIALRM EVLGCEAQDL
1901 YDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
1951 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
2001 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV
2051 KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
2101 GNVFSCSVMH EALHNHYTQK SLSLSPGK*

FVIII 205 蛋白質序列(具有兩個 AE XTEN 的單鏈 FVIIIFc；一個為 B 域中的 288AE XTEN，且一個為在胺基酸 18 處的 144 AE XTEN) (SEQ ID NO: 79)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQGAP TSESATPESG
51 PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
101 TSTEPSEGSA PGSPAGSPTS TEEGTSESAT PESGPGSEPA TSGSETPGTS
151 ESATPESGPG SPAGSPTSTE EGSPAGSPTS TEEGASSSDL GELPVDARFP
201 PRVPKSFPFN TSVVYKKTLF 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
451 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
501 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
551 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
601 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
701 YYSSFVNMER 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 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
1201 EGSAPASSPP VLKRHQAEIT RTTLQSDQEE IDYDDTISVE MKKEDFDIYD
1251 EDENQSPRSF QKKTRHYFIA AVERLWDYGM SSSPHVLRNR AQSGSVPQFK
1301 KVVFQEFTDG SFTQPLYRGE LNEHLGLLGP YIRAEVEDNI MVTFRNQASR

1351 PYSFYSSLIS YEEDQRQGAE PRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
1401 CKAWAYFSDV DLEKDVHSGL IGPLLVCHTN TLNPAHGRQV TVQEFALFFT
1451 IFDETKSWYF TENMERNCRA PCNIQMEDPT FKENYRFHAI NGYIMDTLPG
1501 LVMAQDQRIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
1551 VFETVEMLPS KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPLGMASGH
1601 IRDFQITASG QYGQWAPKLA RLHYSGSINA WSTKEPFSWI KVDLLAPMII
1651 HGIKTQGARQ KFSSLYISQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
1701 SSGIKHNIFN PPIIARYIRL HPTHYSIRST LRMELMGCDL NSCSMPLGME
1751 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ
1801 VDFQKTMKVT GVTTQGVKSL LTSMYVKEFL ISSSQDGHQW TLFFQNGKVK
1851 VFQGNQDSFT PVVNSLDPPL LTRYLRIHPQ SWVHQIALRM EVLGCEAQDL
1901 YDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE
1951 DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY
2001 KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV
2051 KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
2101 GNVFSCSVMH EALHNHYTQK SLSLSPGK*

pSYN FVIII 266 蛋白質序列(在胺基酸 18 處具有 42 AE-XTEN 且在 B 域中具有 288 AE XTEN 的 FVIII Fc) SEQ ID NO: 80)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQGAP GSPAGSPTST
51 EEGTSESATP ESGPGSEPAT SGSETPASSS DLGELPVDAR FPPRVPKSFP
101 FNTSVVYKKT LFVEFTDHLF NIAKPRPPWM GLLGPTIQAE VYDTVVITLK
151 NMASHPVSLH AVGVSYWKAS EGAEYDDQTS QREKEDDKVF PGGSHTYVWQ
201 VLKENGPMAS DPLCLTYSYL SHVDLVKDLN SGLIGALLVC REGSLAKEKT
251 QTLHKFILLF AVFDEGKSWH SETKNSLMQD RDAASARAWP KMHTVNGYVN
301 RSLPGLIGCH RKSVYWHVIG MGTTPEVHSI FLEGHTFLVR NHRQASLEIS
351 PITFLTAQTL LMDLGQFLLF CHISSHQHDG MEAYVKVDSC PEEPQLRMKN
401 NEEAEDYDDD LTDSEMDVVR FDDDNSPSFI QIRSVAKKHP KTWVHYIAAE
451 EEDWDYAPLV LAPDDRSYKS QYLNNGPQRI GRKYKKVRFM AYTDETFKTR
501 EAIQHESGIL GPLLYGEVGD TLLIIFKNQA SRPYNIYPHG ITDVRPLYSR
551 RLPKGVKHLK DFPILPGEIF KYKWTVTVED GPTKSDPRCL TRYYSSFVNM
601 ERDLASGLIG PLLICYKESV DQRGNQIMSD KRNVILFSVF DENRSWYLTE
651 NIQRFLPNPA GVQLEDPEFQ ASNIMHSING YVFDSLQLSV CLHEVAYWYI
701 LSIGAQTDFL SVFFSGYTFK HKMVYEDTLT LFPFSGETVF MSMENPGLWI
751 LGCHNSDFRN RGMTALLKVS SCDKNTGDYY EDSYEDISAY LLSKNNAIEP
801 RSFSQNGAPG TSESATPESG PGSEPATSGS ETPGTSESAT PESGPGSEPA
851 TSGSETPGTS ESATPESGPG TSTEPSEGSA PGSPAGSPTS TEEGTSESAT
901 PESGPGSEPA TSGSETPGTS ESATPESGPG SPAGSPTSTE EGSPAGSPTS
951 TEEGTSTEPS EGSAPGTSES ATPESGPGTS ESATPESGPG TSESATPESG
1001 PGSEPATSGS ETPGSEPATS GSETPGSPAG SPTSTEEGTS TEPSEGSAPG
1051 TSTEPSEGSA PGSEPATSGS ETPGTSESAT PESGPGTSTE PSEGSAPASS
1101 PPVLKRHQAE ITRTTLQSDQ EEIDYDDTIS VEMKKEDFDI YDEDENQSPR
1151 SFQKKTRHYF IAAVERLWDY GMSSSPHVLR NRAQSGSVPQ FKKVVFQEFT

1201 DGSFTQPLYR GELNEHLGLL GPYIRAEVED NIMVTFRNQA SRPYSFYSSL
1251 ISYEEDQRQG AEPRKNFVKP NETKTYFWKV QHHMAPTKDE FDCKAWAYFS
1301 DVDLEKDVHS GLIGPLLVCH TNTLNPAHGR QVTVQEFALF FTIFDETKSW
1351 YFTENMERNC RAPCNIQMED PTFKENYRFH AINGYIMDTL PGLVMAQDQR
1401 IRWYLLSMGS NENIHSIHFS GHVFTVRKKE EYKMALYNLY PGVFETVEML
1451 PSKAGIWRVE CLIGEHLHAG MSTLFLVYSN KCQTPLGMAS GHIRDFQITA
1501 SGQYGQWAPK LARLHYSGSI NAWSTKEPFS WIKVDLLAPM IIHGIKTQGA
1551 RQKFSSLYIS QFIIMYSLDG KKWQTYRGNS TGTLMVFFGN VDSSGIKHNI
1601 FNPPIIARYI RLHPTHYSIR STLRMELMGC DLNSCSMPLG MESKAISDAQ
1651 ITASSYFTNM FATWSPSKAR LHLQGRSNAW RPQVNNPKEW LQVDFQKTMK
1701 VTGVTTQGVK SLLTSMYVKE FLISSSQDGH QWTLFFQNGK VKVFQGNQDS
1751 FTPVVNSLDP PLLTRYLRIH PQSWVHQIAL RMEVLGCEAQ DLYDKTHTCP
1801 PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW
1851 YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA
1901 LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI
1951 AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV
2001 MHEALHNHYT QKSLSLSPGK *

pSYN FVIII 267蛋白質序列(在胺基酸18處具有72 AE-XTEN且在B域中具有288AE XTEN的FVIII Fc) SEQ ID NO: 81)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQGAP TSESATPESG
51 PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
101 TSTEPSEGSA PGASSSDLGE LPVDARFPPR VPKSFPFNTS VVYKKTLFVE
151 FTDHLFNIAK PRPPWMGLLG PTIQAEVYDT VVITLKNMAS HPVSLHAVGV
201 SYWKASEGAE YDDQTSQREK EDDKVFPGGS HTYVWQVLKE NGPMASDPLC
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 EMDVVRFDDD NSPSFIQIRS VAKKHPKTWV HYIAAEEEDW DYAPLVLAPD
501 DRSYKSQYLN NGPQRIGRKY KKVRFMAYTD ETFKTREAIQ HESGILGPLL
551 YGEVGDTLLI IFKNQASRPY NIYPHGITDV RPLYSRRLPK GVKHLKDFPI
601 LPGEIFKYKW TVTVEDGPTK SDPRCLTRYY SSFVNMERDL ASGLIGPLLI
651 CYKESVDQRG NQIMSDKRNV ILFSVFDENR SWYLTENIQR FLPNPAGVQL
701 EDPEFQASNI MHSINGYVFD SLQLSVCLHE VAYWYILSIG AQTDFLSVFF
751 SGYTFKHKMV YEDTLTLFPF SGETVFMSME NPGLWILGCH NSDFRNRGMT
801 ALLKVSSCDK NTGDYYEDSY EDISAYLLSK NNAIEPRSFS QNGAPGTSES
851 ATPESGPGSE PATSGSETPG TSESATPESG PGSEPATSGS ETPGTSESAT
901 PESGPGTSTE PSEGSAPGSP AGSPTSTEEG TSESATPESG PGSEPATSGS
951 ETPGTSESAT PESGPGSPAG SPTSTEEGSP AGSPTSTEEG TSTEPSEGSA
1001 PGTSESATPE SGPGTSESAT PESGPGTSES ATPESGPGSE PATSGSETPG
1051 SEPATSGSET PGSPAGSPTS TEEGTSTEPS EGSAPGTSTE PSEGSAPGSE
1101 PATSGSETPG TSESATPESG PGTSTEPSEG SAPASSPPVL KRHQAEITRT

1151 TLQSDQEEID YDDTISVEMK KEDFDIYDED ENQSPRSFQK KTRHYFIAAV
1201 ERLWDYGMSS SPHVLRNRAQ SGSVPQFKKV VFQEFTDGSF TQPLYRGELN
1251 EHLGLLGPYI RAEVEDNIMV TFRNQASRPY SFYSSLISYE EDQRQGAEPR
1301 KNFVKPNETK TYFWKVQHHM APTKDEFDCK AWAYFSDVDL EKDVHSGLIG
1351 PLLVCHTNTL NPAHGRQVTV QEFALFFTIF DETKSWYFTE NMERNCRAPC
1401 NIQMEDPTFK ENYRFHAING YIMDTLPGLV MAQDQRIRWY LLSMGSNENI
1451 HSIHFSGHVF TVRKKEEYKM ALYNLYPGVF ETVEMLPSKA GIWRVECLIG
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
1751 SMYVKEFLIS SSQDGHQWTL FFQNGKVKVF QGNQDSFTPV VNSLDPPLLT
1801 RYLRIHPQSW VHQIALRMEV LGCEAQDLYD KTHTCPPCPA PELLGGPSVF
1851 LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP
1901 REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG
1951 QPREPQVYTL PPSRDELTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY
2001 KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL
2051 SLSPGK*

pSYN FVIII 268 蛋白質序列(在胺基酸 18 處具有 144 AE-XTEN 的 FVIII Fc) SEQ ID NO: 82)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQGAP TSESATPESG
51 PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
101 TSTEPSEGSA PGSPAGSPTS TEEGTSESAT PESGPGSEPA TSGSETPGTS
151 ESATPESGPG SPAGSPTSTE EGSPAGSPTS TEEGASSSDL GELPVDARFP
201 PRVPKSFPFN TSVVYKKTLF 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
451 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
501 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
551 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
601 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
701 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
751 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
801 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS
851 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL
901 SKNNAIEPRS FSQNPPVLKR HQAEITRTTL QSDQEEIDYD DTISVEMKKE
951 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP HVLRNRAQSG
1001 SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF
1051 RNQASRPYSF YSSLISYEED QRQGAEPRKN FVKPNETKTY FWKVQHHMAP

1101 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE
1151 FALFFTIFDE TKSWYFTENM ERNCRAPCNI QMEDPTFKEN YRFHAINGYI
1201 MDTLPGLVMA QDQRIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL
1251 YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL
1301 GMASGHIRDF QITASGQYGQ WAPKLARLHY SGSINAWSTK EPFSWIKVDL
1351 LAPMIIHGIK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV
1401 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS
1451 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN
1501 PKEWLQVDFQ KTMKVTGVTT QGVKSLLTSM YVKEFLISSS QDGHQWTLFF
1551 QNGKVKVFQG NQDSFTPVVN SLDPPLLTRY LRIHPQSWVH QIALRMEVLG
1601 CEAQDLYDKT HTCPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV
1651 VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW
1701 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV
1751 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD
1801 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

pSYN FVIII 269 蛋白質序列(在胺基酸 18 處具有 72 AE-XTEN 的 FVIII Fc) SEQ ID NO: 83)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQGAP TSESATPESG
51 PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
101 TSTEPSEGSA PGASSSDLGE LPVDARFPPR VPKSFPFNTS VVYKKTLFVE
151 FTDHLFNIAK PRPPWMGLLG PTIQAEVYDT VVITLKNMAS HPVSLHAVGV
201 SYWKASEGAE YDDQTSQREK EDDKVFPGGS HTYVWQVLKE NGPMASDPLC
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 EMDVVRFDDD NSPSFIQIRS VAKKHPKTWV HYIAAEEEDW DYAPLVLAPD
501 DRSYKSQYLN NGPQRIGRKY KKVRFMAYTD ETFKTREAIQ HESGILGPLL
551 YGEVGDTLLI IFKNQASRPY NIYPHGITDV RPLYSRRLPK GVKHLKDFPI
601 LPGEIFKYKW TVTVEDGPTK SDPRCLTRYY SSFVNMERDL ASGLIGPLLI
651 CYKESVDQRG NQIMSDKRNV ILFSVFDENR SWYLTENIQR FLPNPAGVQL
701 EDPEFQASNI MHSINGYVFD SLQLSVCLHE VAYWYILSIG AQTDFLSVFF
751 SGYTFKHKMV YEDTLTLFPF SGETVFMSME NPGLWILGCH NSDFRNRGMT
801 ALLKVSSCDK NTGDYYEDSY EDISAYLLSK NNAIEPRSFS QNPPVLKRHQ
851 AEITRTTLQS DQEEIDYDDT ISVEMKKEDF DIYDEDENQS PRSFQKKTRH
901 YFIAAVERLW DYGMSSSPHV LRNRAQSGSV PQFKKVVFQE FTDGSFTQPL
951 YRGELNEHLG LLGPYIRAEV EDNIMVTFRN QASRPYSFYS SLISYEEDQR
1001 QGAEPRKNFV KPNETKTYFW KVQHHMAPTK DEFDCKAWAY FSDVDLEKDV
1051 HSGLIGPLLV CHTNTLNPAH GRQVTVQEFA LFFTIFDETK SWYFTENMER
1101 NCRAPCNIQM EDPTFKENYR FHAINGYIMD TLPGLVMAQD QRIRWYLLSM
1151 GSNENIHSIH FSGHVFTVRK KEEYKMALYN LYPGVFETVE MLPSKAGIWR
1201 VECLIGEHLH AGMSTLFLVY SNKCQTPLGM ASGHIRDFQI TASGQYGQWA
1251 PKLARLHYSG SINAWSTKEP FSWIKVDLLA PMIIHGIKTQ GARQKFSSLY

1301 ISQFIIMYSL DGKKWQTYRG NSTGTLMVFF GNVDSSGIKH NIFNPPIIAR
1351 YIRLHPTHYS IRSTLRMELM GCDLNSCSMP LGMESKAISD AQITASSYFT
1401 NMFATWSPSK ARLHLQGRSN AWRPQVNNPK EWLQVDFQKT MKVTGVTTQG
1451 VKSLLTSMYV KEFLISSSQD GHQWTLFFQN GKVKVFQGNQ DSFTPVVNSL
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 PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH
1751 YTQKSLSLSP GK*

pSYNFVIII271 蛋白質序列(在胺基酸 18 處具有 42 AE-XTEN 的 FVIII Fc)SEQ ID NO: 84)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQGAP GSPAGSPTST
51 EEGTSESATP ESGPGSEPAT SGSETPASSS DLGELPVDAR FPPRVPKSFP
101 FNTSVVYKKT LFVEFTDHLF NIAKPRPPWM GLLGPTIQAE VYDTVVITLK
151 NMASHPVSLH AVGVSYWKAS EGAEYDDQTS QREKEDDKVF PGGSHTYVWQ
201 VLKENGPMAS DPLCLTYSYL SHVDLVKDLN SGLIGALLVC REGSLAKEKT
251 QTLHKFILLF AVFDEGKSWH SETKNSLMQD RDAASARAWP KMHTVNGYVN
301 RSLPGLIGCH RKSVYWHVIG MGTTPEVHSI FLEGHTFLVR NHRQASLEIS
351 PITFLTAQTL LMDLGQFLLF CHISSHQHDG MEAYVKVDSC PEEPQLRMKN
401 NEEAEDYDDD LTDSEMDVVR FDDDNSPSFI QIRSVAKKHP KTWVHYIAAE
451 EEDWDYAPLV LAPDDRSYKS QYLNNGPQRI GRKYKKVRFM AYTDETFKTR
501 EAIQHESGIL GPLLYGEVGD TLLIIFKNQA SRPYNIYPHG ITDVRPLYSR
551 RLPKGVKHLK DFPILPGEIF KYKWTVTVED GPTKSDPRCL TRYYSSFVNM
601 ERDLASGLIG PLLICYKESV DQRGNQIMSD KRNVILFSVF DENRSWYLTE
651 NIQRFLPNPA GVQLEDPEFQ ASNIMHSING YVFDSLQLSV CLHEVAYWYI
701 LSIGAQTDFL SVFFSGYTFK HKMVYEDTLT LFPFSGETVF MSMENPGLWI
751 LGCHNSDFRN RGMTALLKVS SCDKNTGDYY EDSYEDISAY LLSKNNAIEP
801 RSFSQNPPVL KRHQAEITRT TLQSDQEEID YDDTISVEMK KEDFDIYDED
851 ENQSPRSFQK KTRHYFIAAV ERLWDYGMSS SPHVLRNRAQ SGSVPQFKKV
901 VFQEFTDGSF TQPLYRGELN EHLGLLGPYI RAEVEDNIMV TFRNQASRPY
951 SFYSSLISYE EDQRQGAEPR KNFVKPNETK TYFWKVQHHM APTKDEFDCK
1001 AWAYFSDVDL EKDVHSGLIG PLLVCHTNTL NPAHGRQVTV QEFALFFTIF
1051 DETKSWYFTE NMERNCRAPC NIQMEDPTFK ENYRFHAING YIMDTLPGLV
1101 MAQDQRIRWY LLSMGSNENI HSIHFSGHVF TVRKKEEYKM ALYNLYPGVF
1151 ETVEMLPSKA GIWRVECLIG EHLHAGMSTL FLVYSNKCQT PLGMASGHIR
1201 DFQITASGQY GQWAPKLARL HYSGSINAWS TKEPFSWIKV DLLAPMIIHG
1251 IKTQGARQKF SSLYISQFII MYSLDGKKWQ TYRGNSTGTL MVFFGNVDSS
1301 GIKHNIFNPP IIARYIRLHP THYSIRSTLR MELMGCDLNS CSMPLGMESK
1351 AISDAQITAS SYFTNMFATW SPSKARLHLQ GRSNAWRPQV NNPKEWLQVD
1401 FQKTMKVTGV TTQGVKSLLT SMYVKEFLIS SSQDGHQWTL FFQNGKVKVF
1451 QGNQDSFTPV VNSLDPPLLT RYLRIHPQSW VHQIALRMEV LGCEAQDLYD
1501 KTHTCPPCPA PELLGGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSHEDP

1551 EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC
1601 KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN QVSLTCLVKG
1651 FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN
1701 VFSCSVMHEA LHNHYTQKSL SLSPGK*

pSYN FVIII蛋白質序列272 (在胺基酸18處具有144 AE XTEN且在B域中具有244 AE XTEN的FVIII-無 Fc) SEQ ID NO: 85)

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQGAP TSESATPESG
51 PGSEPATSGS ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
101 TSTEPSEGSA PGSPAGSPTS TEEGTSESAT PESGPGSEPA TSGSETPGTS
151 ESATPESGPG SPAGSPTSTE EGSPAGSPTS TEEGASSSDL GELPVDARFP
201 PRVPKSFPFN TSVVYKKTLF 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
451 RQASLEISPI TFLTAQTLLM DLGQFLLFCH ISSHQHDGME AYVKVDSCPE
501 EPQLRMKNNE EAEDYDDDLT DSEMDVVRFD DDNSPSFIQI RSVAKKHPKT
551 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
601 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
651 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
701 YYSSFVNMER 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 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
1201 EGSAPASSPP VLKRHQAEIT RTTLQSDQEE IDYDDTISVE MKKEDFDIYD
1251 EDENQSPRSF QKKTRHYFIA AVERLWDYGM SSSPHVLRNR AQSGSVPQFK
1301 KVVFQEFTDG SFTQPLYRGE LNEHLGLLGP YIRAEVEDNI MVTFRNQASR
1351 PYSFYSSLIS YEEDQRQGAE PRKNFVKPNE TKTYFWKVQH HMAPTKDEFD
1401 CKAWAYFSDV DLEKDVHSGL IGPLLVCHTN TLNPAHGRQV TVQEFALFFT
1451 IFDETKSWYF TENMERNCRA PCNIQMEDPT FKENYRFHAI NGYIMDTLPG
1501 LVMAQDQRIR WYLLSMGSNE NIHSIHFSGH VFTVRKKEEY KMALYNLYPG
1551 VFETVEMLPS KAGIWRVECL IGEHLHAGMS TLFLVYSNKC QTPLGMASGH
1601 IRDFQITASG QYGQWAPKLA RLHYSGSINA WSTKEPFSWI KVDLLAPMII
1651 HGIKTQGARQ KFSSLYISQF IIMYSLDGKK WQTYRGNSTG TLMVFFGNVD
1701 SSGIKHNIFN PPIIARYIRL HPTHYSIRST LRMELMGCDL NSCSMPLGME
1751 SKAISDAQIT ASSYFTNMFA TWSPSKARLH LQGRSNAWRP QVNNPKEWLQ

1801 VDFQKTMKVT GVTTQGVKSL LTSMYVKEFL ISSSQDGHQW TLFFQNGKVK

1851 VFQGNQDSFT PVVNSLDPPL LTRYLRIHPQ SWVHQIALRM EVLGCEAQDL

1901 Y*

pSYN-FVIII-161 蛋白質序列(SEQ ID NO: 69) (FVIII 序列胺基酸位置 1-1457；底線區表示 Fc 區域；彎曲底線表示第一 Fc 和 VWF 片段之間的可切割連接子；加雙底線區表示 VWF 片段；粗體區表示 VWF 片段和 Fc 之間的可切割連接子)。

1 MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQSDL GELPVDARFP

51 PRVPKSFPFN TSVVYKKTLF 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

401 WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY

451 TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT

501 DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR

551 YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE

601 NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL

651 HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS

701 MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED SYEDISAYLL

751 SKNNAIEPRS FSQNPPVLKR HQREITRTTL QSDQEEIDYD DTISVEMKKE

801 DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP HVLRNRAQSG

851 SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA EVEDNIMVTF

901 RNQASRPYSF YSSLISYEED QRQGAEPRKN FVKPNETKTY FWKVQHHMAP

951 TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP AHGRQVTVQE

1001 FALFFTIFDE TKSWYFTENM ERNCRAPCNI QMEDPTFKEN YRFHAINGYI

1051 MDTLPGLVMA QDQRIRWYLL SMGSNENIHS IHFSGHVFTV RKKEEYKMAL

1101 YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL VYSNKCQTPL

1151 GMASGHIRDF QITASGQYGQ WAPKLARLHY SGSINAWSTK EPFSWIKVDL

1201 LAPMIIHGIK TQGARQKFSS LYISQFIIMY SLDGKKWQTY RGNSTGTLMV

1251 FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME LMGCDLNSCS

1301 MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR SNAWRPQVNN

1351 PKEWLQVDFQ KTMKVTGVTT QGVKSLLTSM YVKEFLISSS QDGHQWTLFF

1401 QNGKVKVFQG NQDSFTPVVN SLDPPLLTRY LRIHPQSWVH QIALRMEVLG

1451 CEAQDLYDKT HTCPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV

1501 VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW

1551 LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV

1601 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD

1651 KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGKRRRRSG GGGSGGGGSG

1701 GGGSGGGGSG GGGSGGGGSR KRRKRSLSCR PPMVKLVCPA DNLRAEGLEC

1751 TKTCQNYDLE CMSMGCVSGC LCPPGMVRHE NRCVALERCP CFHQGKEYAP

1801 GETVKIGCNT CVCRDRKWNC TDHVCDATCS TIGMAHYLTF DGLKYLFPGE
1851 CQYVLVQDYC GSNPGTFRIL VGNKGCSHPS VKCKKRVTIL VEGGEIELFD
1901 GEVNVKRPMK DETHFEVVES GRYIILLLGK ALSVVWDRHL SISVVLKQTY
1951 QEKVCGLCGN FDGIQNNDLT SSNLQVEEDP VDFGNSWKVS SQCADTRKVP
2001 LDSSPATCHN NIMKQTMVDS SCRILTSDVF QDCNKLVDPE PYLDVCIYDT
2051 CSCESIGDCA AFCDTIAAYA HVCAQHGKVV TWRTATLCPQ SCEERNLREN
2101 GYEAEWRYNS CAPACQVTCQ HPEPLACPVQ CVEGCHAHCP PGKILDELLQ
2151 TCVDPEDCPV CEVAGRRFAS GKKVTLNPSD PEHCQICHCD VVNLTCEACQ
2201 **EPISGTSESA TPESGPGSEP ATSGSETPGT SESATPESGP GSEPATSGSE**
2251 **TPGTSESATP ESGPGTSTEP SEGSAPGSPA GSPTSTEEGT SESATPESGP**
2301 **GSEPATSGSE TPGTSESATP ESGPGSPAGS PTSTEEGSPA GSPTSTEEGT**
2351 **STEPSEGSAP GTSESATPES GPGTSESATP ESGPGTSESA TPESGPGSEP**
2401 **ATSGSETPGS EPATSGSETP GSPAGSPTST EEGTSTEPSE GSAPGTSTEP**
2451 **SEGSAPGSEP ATSGSETPGT SESATPESGP GTSTEPSEGS APDSGGGGSG**
2501 **GGGSGGGGSG GGGSGGGGSL VPRGSG**DKT HTCPPCPAPE LLGGPSVFLF
2551 PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE
2601 EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQP
2651 REPQVYTLPP SRDELTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT
2701 TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL
2751 SPGK

pSYN-FVIII-170 蛋白質序列(SEQ ID NO: 71)

1 SLSCRPPMVK LVCPADNLRA EGLECTKTCQ NYDLECMSMG CVSGCLCPPG
51 MVRHENRCVA LERCPCFHQG KEYAPGETVK IGCNTCVCRD RKWNCTDHVC
101 DATCSTIGMA HYLTFDGLKY LFPGECQYVL VQDYCGSNPG TFRILVGNKG
151 CSHPSVKCKK RVTILVEGGE IELFDGEVNV KRPMKDETHF EVVESGRYII
201 LLLGKALSVV WDRHLSISVV LKQTYQEKVC GLCGNFDGIQ NNDLTSSNLQ
251 VEEDPVDFGN SWKVSSQCAD TRKVPLDSSP ATCHNNIMKQ TMVDSSCRIL
301 TSDVFQDCNK LVDPEPYLDV CIYDTCSCES IGDCAAFCDT IAAYAHVCAQ
351 HGKVVTWRTA TLCPQSCEER NLRENGYEAE WRYNSCAPAC QVTCQHPEPL
401 ACPVQCVEGC HAHCPPGKIL DELLQTCVDP EDCPVCEVAG RRFASGKKVT
451 LNPSDPEHCQ ICHCDVVNLT CEACQEPISG TSESATPESG PGSEPATSGS
501 ETPGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG TSTEPSEGSA
551 PGSPAGSPTS TEEGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG
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 KKTLFVEFTD HLFNIAKPRP PWMGLLGPTI QAEVYDTVVI TLKNMASHPV
901 SLHAVGVSYW KASEGAEYDD QTSQREKEDD KVFPGGSHTY VWQVLKENGP
951 MASDPLCLTY SYLSHVDLVK DLNSGLIGAL LVCREGSLAK EKTQTLHKFI
1001 LLFAVFDEGK SWHSETKNSL MQDRDAASAR AWPKMHTVNG YVNRSLPGLI

1051 GCHRKSVYWH VIGMGTTPEV HSIFLEGHTF LVRNHRQASL EISPITFLTA
1101 QTLLMDLGQF LLFCHISSHQ HDGMEAYVKV DSCPEEPQLR MKNNEEAEDY
1151 DDDLTDSEMD VVRFDDDNSP SFIQIRSVAK KHPKTWVHYI AAEEEDWDYA
1201 PLVLAPDDRS YKSQYLNNGP QRIGRKYKKV RFMAYTDETF KTREAIQHES
1251 GILGPLLYGE VGDTLLIIFK NQASRPYNIY PHGITDVRPL YSRRLPKGVK
1301 HLKDFPILPG EIFKYKWTVT VEDGPTKSDP RCLTRYYSSF VNMERDLASG
1351 LIGPLLICYK ESVDQRGNQI MSDKRNVILF SVFDENRSWY LTENIQRFLP
1401 NPAGVQLEDP EFQASNIMHS INGYVFDSLQ LSVCLHEVAY WYILSIGAQT
1451 DFLSVFFSGY TFKHKMVYED TLTLFPFSGE TVFMSMENPG LWILGCHNSD
1501 FRNRGMTALL KVSSCDKNTG DYYEDSYEDI SAYLLSKNNA IEPRSFSQNP
1551 PVLKRHQREI TRTTLQSDQE EIDYDDTISV EMKKEDFDIY DEDENQSPRS
1601 FQKKTRHYFI AAVERLWDYG MSSSPHVLRN RAQSGSVPQF KKVVFQEFTD
1651 GSFTQPLYRG ELNEHLGLLG PYIRAEVEDN IMVTFRNQAS RPYSFYSSLI
1701 SYEEDQRQGA EPRKNFVKPN ETKTYFWKVQ HHMAPTKDEF DCKAWAYFSD
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
2001 QKFSSLYISQ FIIMYSLDGK KWQTYRGNST GTLMVFFGNV DSSGIKHNIF
2051 NPPIIARYIR LHPTHYSIRS TLRMELMGCD LNSCSMPLGM ESKAISDAQI
2101 TASSYFTNMF ATWSPSKARL HLQGRSNAWR PQVNNPKEWL QVDFQKTMKV
2151 TGVTTQGVKS LLTSMYVKEF LISSSQDGHQ WTLFFQNGKV KVFQGNQDSF
2201 TPVVNSLDPP LLTRYLRIHP QSWVHQIALR MEVLGCEAQD LY

pSYN FVIII 310 核苷酸序列(編碼 FVIII，其具有除 2 個胺基酸殘基以外的完整 B 域缺失和在 aa 742 後插入有 288 AE-XTEN) (SEQ ID NO:170)

1 ATGCAAATAG AGCTCTCCAC CTGCTTCTTT CTGTGCCTTT TGCGATTCTG
51 CTTTAGTGCC ACCAGAAGAT ACTACCTGGG TGCAGTGGAA CTGTCATGGG
101 ACTATATGCA AAGTGATCTC GGTGAGCTGC CTGTGGACGC AAGATTTCCT
151 CCTAGAGTGC CAAAATCTTT TCCATTCAAC ACCTCAGTCG TGTACAAAAA
201 GACTCTGTTT GTAGAATTCA CGGATCACCT TTTCAACATC GCTAAGCCAA
251 GGCCACCCTG GATGGGTCTG CTAGGTCCTA CCATCCAGGC TGAGGTTTAT
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
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

801 CCACAGGAAA TCAGTCTATT GGCATGTGAT TGGAATGGGC ACCACTCCTG
851 AAGTGCACTC AATATTCCTC GAAGGTCACA CATTTCTTGT GAGGAACCAT
901 CGCCAGGCGT CCTTGGAAAT 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
1151 CTCCTTCCTT TATCCAAATT CGCTCAGTTG CCAAGAAGCA TCCTAAAACT
1201 TGGGTACATT ACATTGCTGC TGAAGAGGAG GACTGGGACT ATGCTCCCTT
1251 AGTCCTCGCC CCCGATGACA GAAGTTATAA AAGTCAATAT TTGAACAATG
1301 GCCCTCAGCG GATTGGTAGG AAGTACAAAA AAGTCCGATT TATGGCATAC
1351 ACAGATGAAA CCTTTAAGAC TCGTGAAGCT ATTCAGCATG AATCAGGAAT
1401 CTTGGGACCT TTACTTTATG GGGAAGTTGG 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
1651 TATTACTCTA GTTTCGTTAA 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
1901 ACAGCATCAA TGGCTATGTT TTTGATAGTT TGCAGTTGTC AGTTTGTTTG
1951 CATGAGGTGG CATACTGGTA CATTCTAAGC ATTGGAGCAC AGACTGACTT
2001 CCTTTCTGTC TTCTTCTCTG GATATACCTT CAAACACAAA ATGGTCTATG
2051 AAGACACACT CACCCTATTC CCATTCTCAG GAGAAACTGT CTTCATGTCG
2101 ATGGAAAACC CAGGTCTATG GATTCTGGGG TGCCACAACT CAGACTTTCG
2151 GAACAGAGGC ATGACCGCCT TACTGAAGGT TTCTAGTTGT GACAAGAACA
2201 CTGGTGATTA TTACGAGGAC AGTTATGAAG ATATTTCAGC ATACTTGCTG
2251 AGTAAAAACA ATGCCATTGA ACCAAGAAGC TTCGGTACCT CAGAGTCTGC
2301 TACCCCCGAG TCAGGGCCAG GATCAGAGCC AGCCACCTCC GGGTCTGAGA
2351 CACCCGGGAC TTCCGAGAGT GCCACCCCTG AGTCCGGACC CGGGTCCGAG
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 GACACCAGGC ACCTCTGAGT CCGCCACACC AGAGTCCGGA CCCGGATCTC
2651 CCGCTGGGAG CCCCACCTCC ACTGAGGAGG GATCTCCTGC TGGCTCTCCA
2701 ACATCTACTG AGGAAGGTAC CTCAACCGAG CCATCCGAGG GATCAGCTCC
2751 CGGCACCTCA GAGTCGGCAA CCCCGGAGTC TGGACCCGGA ACTTCCGAAA
2801 GTGCCACACC AGAGTCCGGT CCCGGGACTT CAGAATCAGC AACACCCGAG
2851 TCCGGCCCTG GGTCTGAACC CGCCACAAGT GGTAGTGAGA CACCAGGATC
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
3151 TCGAGCGAAA TAACTCGTAC TACTCTTCAG TCAGATCAAG AGGAAATCGA
3201 TTATGATGAT ACCATATCAG TTGAAATGAA GAAGGAAGAT TTTGACATTT
3251 ATGATGAGGA TGAAAATCAG AGCCCCCGCA GCTTTCAAAA GAAAACACGA
3301 CACTATTTTA TTGCTGCAGT GGAGAGGCTC TGGGATTATG GGATGAGTAG
3351 CTCCCCACAT GTTCTAAGAA ACAGGGCTCA GAGTGGCAGT GTCCCTCAGT
3401 TCAAGAAAGT TGTTTTCCAG GAATTTACTG ATGGCTCCTT TACTCAGCCC
3451 TTATACCGTG GAGAACTAAA TGAACATTTG GGACTCCTGG GGCCATATAT
3501 AAGAGCAGAA GTTGAAGATA ATATCATGGT AACTTTCAGA AATCAGGCCT
3551 CTCGTCCCTA TTCCTTCTAT TCTAGCCTTA TTTCTTATGA GGAAGATCAG
3601 AGGCAAGGAG CAGAACCTAG AAAAAACTTT GTCAAGCCTA ATGAAACCAA
3651 AACTTACTTT TGGAAAGTGC AACATCATAT GGCACCCACT AAAGATGAGT
3701 TTGACTGCAA AGCCTGGGCT TATTTCTCTG ATGTTGACCT GGAAAAAGAT
3751 GTGCACTCAG GCCTGATTGG ACCCCTTCTG GTCTGCCACA CTAACACACT
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
4051 ATGGGCAGCA ATGAAAACAT CCATTCTATT CATTTCAGTG GACATGTGTT
4101 CACTGTACGA AAAAAAGAGG AGTATAAAAT GGCACTGTAC AATCTCTATC
4151 CAGGTGTTTT TGAGACAGTG GAAATGTTAC CATCCAAAGC TGGAATTTGG
4201 CGGGTGGAAT GCCTTATTGG CGAGCATCTA CATGCTGGGA TGAGCACACT
4251 TTTTCTGGTG TACAGCAATA AGTGTCAGAC TCCCCTGGGA ATGGCTTCTG
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
4551 GACTTATCGA GGAAATTCCA CTGGAACCTT AATGGTCTTC TTTGGCAATG
4601 TGGATTCATC TGGGATAAAA CACAATATTT TTAACCCTCC AATTATTGCT
4651 CGATACATCC GTTTGCACCC AACTCATTAT AGCATTCGCA GCACTCTTCG
4701 CATGGAGTTG ATGGGCTGTG ATTTAAATAG TTGCAGCATG CCATTGGGAA
4751 TGGAGAGTAA AGCAATATCA GATGCACAGA TTACTGCTTC ATCCTACTTT
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
5051 TAAAGGTTTT TCAGGGAAAT CAAGACTCCT TCACACCTGT GGTGAACTCT
5101 CTAGACCCAC CGTTACTGAC TCGCTACCTT CGAATTCACC CCCAGAGTTG
5151 GGTGCACCAG ATTGCCCTGA GGATGGAGGT TCTGGGCTGC GAGGCACAGG

5201 ACCTCTACGA CAAAACTCAC ACATGCCCAC CGTGCCCAGC TCCAGAACTC
5251 CTGGGCGGAC CGTCAGTCTT CCTCTTCCCC CCAAAACCCA AGGACACCCT
5301 CATGATCTCC CGGACCCCTG AGGTCACATG CGTGGTGGTG GACGTGAGCC
5351 ACGAAGACCC TGAGGTCAAG TTCAACTGGT ACGTGGACGG CGTGGAGGTG
5401 CATAATGCCA AGACAAAGCC GCGGGAGGAG CAGTACAACA GCACGTACCG
5451 TGTGGTCAGC GTCCTCACCG TCCTGCACCA GGACTGGCTG AATGGCAAGG
5501 AGTACAAGTG CAAGGTCTCC AACAAAGCCC TCCCAGCCCC CATCGAGAAA
5551 ACCATCTCCA AAGCCAAAGG GCAGCCCCGA GAACCACAGG TGTACACCCT
5601 GCCCCCATCC CGGGATGAGC TGACCAAGAA CCAGGTCAGC CTGACCTGCC
5651 TGGTCAAAGG CTTCTATCCC AGCGACATCG CCGTGGAGTG GGAGAGCAAT
5701 GGGCAGCCGG AGAACAACTA CAAGACCACG CCTCCCGTGT TGGACTCCGA
5751 CGGCTCCTTC TTCCTCTACA GCAAGCTCAC CGTGGACAAG AGCAGGTGGC
5801 AGCAGGGGAA CGTCTTCTCA TGCTCCGTGA TGCATGAGGC TCTGCACAAC
5851 CACTACACGC AGAAGAGCCT CTCCCTGTCT CCGGGTAAAT GA

pSYN FVIII 310 蛋白質序列(FVIII，其具有除 2 個胺基酸以外的完整 B 域缺失和在 aa 742 後插入有 288 AE-XTEN) (SEQ ID NO:171)

1 ATRRYYLGAV ELSWDYMQSD LGELPVDARF PPRVPKSFPF NTSVVYKKTL
51 FVEFTDHLFN IAKPRPPWMG LLGPTIQAEV YDTVVITLKN MASHPVSLHA
101 VGVSYWKASE GAEYDDQTSQ REKEDDKVFP GGSHTYVWQV LKENGPMASD
151 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
401 APDDRSYKSQ YLNNGPQRIG RKYKKVRFMA YTDETFKTRE AIQHESGILG
451 PLLYGEVGDT LLIIFKNQAS RPYNIYPHGI TDVRPLYSRR LPKGVKHLKD
501 FPILPGEIFK YKWTVTVEDG PTKSDPRCLT RYYSSFVNME RDLASGLIGP
551 LLICYKESVD QRGNQIMSDK RNVILFSVFD ENRSWYLTEN IQRFLPNPAG
601 VQLEDPEFQA SNIMHSINGY VFDSLQLSVC LHEVAYWYIL SIGAQTDFLS
651 VFFSGYTFKH KMVYEDTLTL FPFSGETVFM SMENPGLWIL GCHNSDFRNR
701 GMTALLKVSS CDKNTGDYYE DSYEDISAYL LSKNNAIEPR SFGTSESATP
751 ESGPGSEPAT SGSETPGTSE SATPESGPGS EPATSGSETP GTSESATPES
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
1051 DTISVEMKKE DFDIYDEDEN QSPRSFQKKT RHYFIAAVER LWDYGMSSSP
1101 HVLRNRAQSG SVPQFKKVVF QEFTDGSFTQ PLYRGELNEH LGLLGPYIRA
1151 EVEDNIMVTF RNQASRPYSF YSSLISYEED QRQGAEPRKN FVKPNETKTY
1201 FWKVQHHMAP TKDEFDCKAW AYFSDVDLEK DVHSGLIGPL LVCHTNTLNP
1251 AHGRQVTVQE FALFFTIFDE TKSWYFTENM ERNCRAPCNI QMEDPTFKEN

1301 YRFHAINGYI MDTLPGLVMA QDQRIRWYLL SMGSNENIHS IHFSGHVFTV
1351 RKKEEYKMAL YNLYPGVFET VEMLPSKAGI WRVECLIGEH LHAGMSTLFL
1401 VYSNKCQTPL GMASGHIRDF QITASGQYGQ WAPKLARLHY SGSINAWSTK
1451 EPFSWIKVDL LAPMIIHGIK TQGARQKFSS LYISQFIIMY SLDGKKWQTY
1501 RGNSTGTLMV FFGNVDSSGI KHNIFNPPII ARYIRLHPTH YSIRSTLRME
1551 LMGCDLNSCS MPLGMESKAI SDAQITASSY FTNMFATWSP SKARLHLQGR
1601 SNAWRPQVNN PKEWLQVDFQ KTMKVTGVTT QGVKSLLTSM YVKEFLISSS
1651 QDGHQWTLFF QNGKVKVFQG NQDSFTPVVN SLDPPLLTRY LRIHPQSWVH
1701 QIALRMEVLG CEAQDLYDKT HTCPPCPAPE LLGGPSVFLF PPKPKDTLMI
1751 SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV
1801 SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP
1851 SRDELTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS
1901 FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPGK*

pSYN FVIII 312 核苷酸序列(編碼 FVIII，其具有除 5 個胺基酸殘基以外的完整 B 域缺失和在 aa 745 至 B5 版本後插入有 288 AE-XTEN) (SEQ ID NO:172)

1 ATGCAAATAG AGCTCTCCAC CTGCTTCTTT CTGTGCCTTT TGCGATTCTG
51 CTTTAGTGCC ACCAGAAGAT ACTACCTGGG TGCAGTGGAA CTGTCATGGG
101 ACTATATGCA AAGTGATCTC GGTGAGCTGC CTGTGGACGC AAGATTTCCT
151 CCTAGAGTGC CAAAATCTTT TCCATTCAAC ACCTCAGTCG TGTACAAAAA
201 GACTCTGTTT GTAGAATTCA CGGATCACCT TTTCAACATC GCTAAGCCAA
251 GGCCACCCTG GATGGGTCTG CTAGGTCCTA CCATCCAGGC TGAGGTTTAT
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
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
801 CCACAGGAAA TCAGTCTATT GGCATGTGAT TGGAATGGGC ACCACTCCTG
851 AAGTGCACTC AATATTCCTC GAAGGTCACA CATTTCTTGT GAGGAACCAT
901 CGCCAGGCGT CCTTGGAAAT 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
1151 CTCCTTCCTT TATCCAAATT CGCTCAGTTG CCAAGAAGCA TCCTAAAACT
1201 TGGGTACATT ACATTGCTGC TGAAGAGGAG GACTGGGACT ATGCTCCCTT
1251 AGTCCTCGCC CCCGATGACA GAAGTTATAA AAGTCAATAT TTGAACAATG
1301 GCCCTCAGCG GATTGGTAGG AAGTACAAAA AAGTCCGATT TATGGCATAC

1351 ACAGATGAAA CCTTTAAGAC TCGTGAAGCT ATTCAGCATG AATCAGGAAT
1401 CTTGGGACCT TTACTTTATG GGGAAGTTGG 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
1651 TATTACTCTA GTTTCGTTAA 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
1901 ACAGCATCAA TGGCTATGTT TTTGATAGTT TGCAGTTGTC AGTTTGTTTG
1951 CATGAGGTGG CATACTGGTA CATTCTAAGC ATTGGAGCAC AGACTGACTT
2001 CCTTTCTGTC TTCTTCTCTG GATATACCTT CAAACACAAA ATGGTCTATG
2051 AAGACACACT CACCCTATTC CCATTCTCAG GAGAAACTGT CTTCATGTCG
2101 ATGGAAAACC CAGGTCTATG GATTCTGGGG TGCCACAACT CAGACTTTCG
2151 GAACAGAGGC ATGACCGCCT TACTGAAGGT TTCTAGTTGT GACAAGAACA
2201 CTGGTGATTA TTACGAGGAC AGTTATGAAG ATATTTCAGC ATACTTGCTG
2251 AGTAAAAACA ATGCCATTGA ACCAAGAAGC TTCTCTCAAA ACGGTACCTC
2301 AGAGTCTGCT ACCCCCGAGT CAGGGCCAGG ATCAGAGCCA GCCACCTCCG
2351 GGTCTGAGAC ACCCGGGACT TCCGAGAGTG CCACCCCTGA GTCCGGACCC
2401 GGGTCCGAGC CCGCCACTTC CGGCTCCGAA ACTCCCGGCA CAAGCGAGAG
2451 CGCTACCCCA 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 CCCACCTCCA CTGAGGAGGG ATCTCCTGCT
2701 GGCTCTCCAA CATCTACTGA GGAAGGTACC 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 CCACCCCCGA GAGTGGCCCA GGCACTAGTA CCGAGCCCTC TGAAGGCAGT
3151 GCGCCAGCCT CGAGCGAAAT AACTCGTACT ACTCTTCAGT CAGATCAAGA
3201 GGAAATCGAT 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 GACTCCTGGG
3501 GCCATATATA AGAGCAGAAG TTGAAGATAA TATCATGGTA ACTTTCAGAA

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 CATTCTATTC ATTTCAGTGG
4101 ACATGTGTTC 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 GGATTCATCT GGGATAAAAC ACAATATTTT TAACCCTCCA
4651 ATTATTGCTC GATACATCCG TTTGCACCCA ACTCATTATA GCATTCGCAG
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 TTTTTTCAGA
5051 ATGGCAAAGT AAAGGTTTTT CAGGGAAATC AAGACTCCTT CACACCTGTG
5101 GTGAACTCTC TAGACCCACC GTTACTGACT CGCTACCTTC GAATTCACCC
5151 CCAGAGTTGG GTGCACCAGA TTGCCCTGAG GATGGAGGTT CTGGGCTGCG
5201 AGGCACAGGA CCTCTACGAC AAAACTCACA CATGCCCACC GTGCCCAGCT
5251 CCAGAACTCC TGGGCGGACC GTCAGTCTTC CTCTTCCCCC CAAAACCCAA
5301 GGACACCCTC ATGATCTCCC GGACCCCTGA GGTCACATGC GTGGTGGTGG
5351 ACGTGAGCCA CGAAGACCCT GAGGTCAAGT TCAACTGGTA CGTGGACGGC
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
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 蛋白質序列(FVIII，其具有除 5 個胺基酸殘基以外的完整 B 域缺失和在 aa 745 至 B5 版本後插入有 288 AE-XTEN) (SEQ ID NO:173)

1 ATRRYYLGAV ELSWDYMQSD LGELPVDARF PPRVPKSFPF NTSVVYKKTL
51 FVEFTDHLFN IAKPRPPWMG LLGPTIQAEV YDTVVITLKN MASHPVSLHA
101 VGVSYWKASE GAEYDDQTSQ REKEDDKVFP GGSHTYVWQV LKENGPMASD
151 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
401 APDDRSYKSQ YLNNGPQRIG RKYKKVRFMA YTDETFKTRE AIQHESGILG
451 PLLYGEVGDT LLIIFKNQAS RPYNIYPHGI TDVRPLYSRR LPKGVKHLKD
501 FPILPGEIFK YKWTVTVEDG PTKSDPRCLT RYYSSFVNME RDLASGLIGP
551 LLICYKESVD QRGNQIMSDK RNVILFSVFD ENRSWYLTEN IQRFLPNPAG
601 VQLEDPEFQA SNIMHSINGY VFDSLQLSVC LHEVAYWYIL SIGAQTDFLS
651 VFFSGYTFKH KMVYEDTLTL FPFSGETVFM SMENPGLWIL GCHNSDFRNR
701 GMTALLKVSS CDKNTGDYYE DSYEDISAYL LSKNNAIEPR SFSQNGTSES
751 ATPESGPGSE PATSGSETPG TSESATPESG PGSEPATSGS ETPGTSESAT
801 PESGPGTSTE PSEGSAPGSP AGSPTSTEEG TSESATPESG PGSEPATSGS
851 ETPGTSESAT PESGPGSPAG SPTSTEEGSP AGSPTSTEEG TSTEPSEGSA
901 PGTSESATPE SGPGTSESAT PESGPGTSES ATPESGPGSE PATSGSETPG
951 SEPATSGSET PGSPAGSPTS TEEGTSTEPS EGSAPGTSTE PSEGSAPGSE
1001 PATSGSETPG TSESATPESG PGTSTEPSEG SAPASSEITR TTLQSDQEEI
1051 DYDDTISVEM KKEDFDIYDE DENQSPRSFQ KKTRHYFIAA VERLWDYGMS
1101 SSPHVLRNRA QSGSVPQFKK VVFQEFTDGS FTQPLYRGEL NEHLGLLGPY
1151 IRAEVEDNIM VTFRNQASRP YSFYSSLISY EEDQRQGAEP RKNFVKPNET
1201 KTYFWKVQHH MAPTKDEFDC KAWAYFSDVD LEKDVHSGLI GPLLVCHTNT
1251 LNPAHGRQVT VQEFALFFTI FDETKSWYFT ENMERNCRAP CNIQMEDPTF
1301 KENYRFHAIN GYIMDTLPGL VMAQDQRIRW YLLSMGSNEN IHSIHFSGHV
1351 FTVRKKEEYK MALYNLYPGV FETVEMLPSK AGIWRVECLI GEHLHAGMST
1401 LFLVYSNKCQ TPLGMASGHI RDFQITASGQ YGQWAPKLAR LHYSGSINAW
1451 STKEPFSWIK VDLLAPMIIH GIKTQGARQK FSSLYISQFI IMYSLDGKKW
1501 QTYRGNSTGT LMVFFGNVDS SGIKHNIFNP PIIARYIRLH PTHYSIRSTL
1551 RMELMGCDLN SCSMPLGMES KAISDAQITA SSYFTNMFAT WSPSKARLHL
1601 QGRSNAWRPQ VNNPKEWLQV DFQKTMKVTG VTTQGVKSLL TSMYVKEFLI
1651 SSSQDGHQWT LFFQNGKVKV FQGNQDSFTP VVNSLDPPLL TRYLRIHPQS
1701 WVHQIALRME VLGCEAQDLY DKTHTCPPCP APELLGGPSV FLFPPKPKDT
1751 LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY
1801 RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT

1851 LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS

1901 DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK*

pSYN VWF059 核苷酸序列(編碼 VWF D'D3-Fc，其在連接子中具有酸性區 2(a2)凝血酶位點) (SEQ ID NO: 196)

1 ATGATTCCTG CCAGATTTGC CGGGGTGCTG CTTGCTCTGG CCCTCATTTT

51 GCCAGGGACC CTTTGTGCAG AAGGAACTCG CGGCAGGTCA TCCACGGCCC

101 GATGCAGCCT TTCGGAAGT 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 TTGCCCGCTG CCACCCTCTG GTGGACCCCG AGCCTTTTGT GGCCCTGTGT

751 GAGAAGACTT TGTGTGAGTG TGCTGGGGGG CTGGAGTGCG CCTGCCCTGC

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

1201 AACAGATACT TCACCTTCAG TGGGATCTGC CAGTACCTGC TGGCCCGGGA

1251 TTGCCAGGAC CACTCCTTCT CCATTGTCAT TGAGACTGTC CAGTGTGCTG

1301 ATGACCGCGA CGCTGTGTGC ACCCGCTCCG TCACCGTCCG GCTGCCTGGC

1351 CTGCACAACA GCCTTGTGAA ACTGAAGCAT GGGGCAGGAG TTGCCATGGA

1401 TGGCCAGGAC ATCCAGCTCC CCCTCCTGAA AGGTGACCTC CGCATCCAGC

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

1701 CGATCCCTGC GCCCTCAACC CGCGCATGAC CAGGTTCTCC GAGGAGGCGT

1751 GCGCGGTCCT GACGTCCCCC ACATTCGAGG CCTGCCATCG TGCCGTCAGC

1801 CCGCTGCCCT ACCTGCGGAA CTGCCGCTAC GACGTGTGCT CCTGCTCGGA

1851 CGGCCGCGAG TGCCTGTGCG GCGCCCTGGC CAGCTATGCC GCGGCCTGCG

1901 CGGGGAGAGG CGTGCGCGTC GCGTGGCGCG AGCCAGGCCG CTGTGAGCTG
1951 AACTGCCCGA AAGGCCAGGT GTACCTGCAG TGCGGGACCC CCTGCAACCT
2001 GACCTGCCGC TCTCTCTCTT ACCCGGATGA GGAATGCAAT GAGGCCTGCC
2051 TGGAGGGCTG CTTCTGCCCC CCAGGGCTCT ACATGGATGA GAGGGGGGAC
2101 TGCGTGCCCA AGGCCCAGTG CCCCTGTTAC TATGACGGTG AGATCTTCCA
2151 GCCAGAAGAC ATCTTCTCAG ACCATCACAC CATGTGCTAC TGTGAGGATG
2201 GCTTCATGCA CTGTACCATG AGTGGAGTCC CCGGAAGCTT GCTGCCTGAC
2251 GCTGTCCTCA 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 CACTTGTGTC
2551 TGTCGGGACC GGAAGTGGAA CTGCACAGAC CATGTGTGTG ATGCCACGTG
2601 CTCCACGATC GGCATGGCCC ACTACCTCAC CTTCGACGGG CTCAAATACC
2651 TGTTCCCCGG GGAGTGCCAG TACGTTCTGG TGCAGGATTA CTGCGGCAGT
2701 AACCCTGGGA CCTTTCGGAT CCTAGTGGGG AATAAGGGAT GCAGCCACCC
2751 CTCAGTGAAA TGCAAGAAAC GGGTCACCAT CCTGGTGGAG GGAGGAGAGA
2801 TTGAGCTGTT TGACGGGGAG GTGAATGTGA AGAGGCCCAT GAAGGATGAG
2851 ACTCACTTTG AGGTGGTGGA GTCTGGCCGG 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 CGATGGTGGA 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 TCAGCACCCT 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 ATATCGGGCG CGCCAACATC AGAGAGCGCC
3751 ACCCCTGAAA 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
4001 CCACCCCGGA GTCAGGGCCA GGATCTGAAC CCGCTACCTC AGGCAGTGAG
4051 ACGCCAGGAA CGAGCGAGTC CGCTACACCG GAGAGTGGGC CAGGGAGCCC

4101 TGCTGGATCT CCTACGTCCA CTGAGGAAGG GTCACCAGCG GGCTCGCCCA
4151 CCAGCACTGA AGAAGGTGCC TCGATATCTG ACAAGAACAC TGGTGATTAT
4201 TACGAGGACA GTTATGAAGA TATTTCAGCA TACTTGCTGA GTAAAAACAA
4251 TGCCATTGAA CCAAGAAGCT TCTCTGACAA AACTCACACA TGCCCACCGT
4301 GCCCAGCTCC AGAACTCCTG GGCGGACCGT CAGTCTTCCT CTTCCCCCCA
4351 AAACCCAAGG ACACCCTCAT GATCTCCCGG ACCCCTGAGG TCACATGCGT
4401 GGTGGTGGAC GTGAGCCACG AAGACCCTGA GGTCAAGTTC AACTGGTACG
4451 TGGACGGCGT GGAGGTGCAT AATGCCAAGA CAAAGCCGCG GGAGGAGCAG
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
4751 TGGAGTGGGA GAGCAATGGG CAGCCGGAGA ACAACTACAA GACCACGCCT
4801 CCCGTGTTGG ACTCCGACGG CTCCTTCTTC CTCTACAGCA AGCTCACCGT
4851 GGACAAGAGC AGGTGGCAGC AGGGGAACGT CTTCTCATGC TCCGTGATGC
4901 ATGAGGCTCT GCACAACCAC TACACGCAGA AGAGCCTCTC CCTGTCTCCG
4951 GGTAAATGA

pSYN VWF059 蛋白質序列(VWF D'D3-Fc，其在連接子中具有 FVIII 凝血酶位點的 a2 區) – 粗體加底線區表示 a2 區(SEQ ID NO: 197)

1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFVNTFDGSM
51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
101 TVTQGDQRVS 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 IQLPLLKGDL RIQHTVTASV RLSYGEDLQM
501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
551 NAWKLHGDCQ DLQKQHSDPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCEL
651 NCPKGQVYLQ CGTPCNLTCR 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 CKKRVTILVE GGEIELFDGE VNVKRPMKDE
951 THFEVVESGR YIILLLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
1051 MKQTMVDSSC RILTSDVFQD CNKLVDPEPY LDVCIYDTCS CESIGDCAAF

1101 CDTIAAYAHV CAQHGKVVTW 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
1351 TPGTSESATP ESGPGSPAGS PTSTEEGSPA GSPTSTEEGA SIS**DKNTGDY**
1401 **YEDSYEDISA YLLSKNNAIE PRSFS**DKTHT CPPCPAPELL GGPSVFLFPP
1451 KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ
1501 YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE
1551 PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP
1601 PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP
1651 GK*

pSYN VWF062 核苷酸序列(編碼 VWF D'D3-Fc，其在連接子中不具有凝血酶位點) (SEQ ID NO: 198)

1 ATGATTCCTG CCAGATTTGC CGGGGTGCTG CTTGCTCTGG CCCTCATTTT
51 GCCAGGGACC CTTTGTGCAG AAGGAACTCG CGGCAGGTCA TCCACGGCCC
101 GATGCAGCCT TTCGGAAGT 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 TTGCCCGCTG CCACCCTCTG GTGGACCCCG AGCCTTTTGT GGCCCTGTGT
751 GAGAAGACTT TGTGTGAGTG TGCTGGGGGG CTGGAGTGCG CCTGCCCTGC
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
1201 AACAGATACT TCACCTTCAG TGGGATCTGC CAGTACCTGC TGGCCCGGGA
1251 TTGCCAGGAC CACTCCTTCT CCATTGTCAT TGAGACTGTC CAGTGTGCTG
1301 ATGACCGCGA CGCTGTGTGC ACCCGCTCCG TCACCGTCCG GCTGCCTGGC
1351 CTGCACAACA GCCTTGTGAA ACTGAAGCAT GGGGCAGGAG TTGCCATGGA
1401 TGGCCAGGAC ATCCAGCTCC CCCTCCTGAA AGGTGACCTC CGCATCCAGC

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
1701 CGATCCCTGC GCCCTCAACC CGCGCATGAC CAGGTTCTCC GAGGAGGCGT
1751 GCGCGGTCCT GACGTCCCCC ACATTCGAGG CCTGCCATCG TGCCGTCAGC
1801 CCGCTGCCCT ACCTGCGGAA CTGCCGCTAC GACGTGTGCT CCTGCTCGGA
1851 CGGCCGCGAG TGCCTGTGCG GCGCCCTGGC CAGCTATGCC GCGGCCTGCG
1901 CGGGGAGAGG CGTGCGCGTC GCGTGGCGCG AGCCAGGCCG CTGTGAGCTG
1951 AACTGCCCGA AAGGCCAGGT GTACCTGCAG TGCGGGACCC CCTGCAACCT
2001 GACCTGCCGC TCTCTCTCTT ACCCGGATGA GGAATGCAAT GAGGCCTGCC
2051 TGGAGGGCTG CTTCTGCCCC CCAGGGCTCT ACATGGATGA GAGGGGGGAC
2101 TGCGTGCCCA AGGCCCAGTG CCCCTGTTAC TATGACGGTG AGATCTTCCA
2151 GCCAGAAGAC ATCTTCTCAG ACCATCACAC CATGTGCTAC TGTGAGGATG
2201 GCTTCATGCA CTGTACCATG AGTGGAGTCC CCGGAAGCTT GCTGCCTGAC
2251 GCTGTCCTCA 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 CACTTGTGTC
2551 TGTCGGGACC GGAAGTGGAA CTGCACAGAC CATGTGTGTG ATGCCACGTG
2601 CTCCACGATC GGCATGGCCC ACTACCTCAC CTTCGACGGG CTCAAATACC
2651 TGTTCCCCGG GGAGTGCCAG TACGTTCTGG TGCAGGATTA CTGCGGCAGT
2701 AACCCTGGGA CCTTTCGGAT CCTAGTGGGG AATAAGGGAT GCAGCCACCC
2751 CTCAGTGAAA TGCAAGAAAC GGGTCACCAT CCTGGTGGAG GGAGGAGAGA
2801 TTGAGCTGTT TGACGGGGAG GTGAATGTGA AGAGGCCCAT GAAGGATGAG
2851 ACTCACTTTG AGGTGGTGGA GTCTGGCCGG 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 CGATGGTGGA 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 TCAGCACCCT 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 ATATCGGGCG CGCCAACATC AGAGAGCGCC
3751 ACCCCTGAAA 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
4001 CCACCCCGGA GTCAGGGCCA GGATCTGAAC CCGCTACCTC AGGCAGTGAG
4051 ACGCCAGGAA CGAGCGAGTC CGCTACACCG GAGAGTGGGC CAGGGAGCCC
4101 TGCTGGATCT CCTACGTCCA CTGAGGAAGG GTCACCAGCG GGCTCGCCCA
4151 CCAGCACTGA AGAAGGTGCC TCGAGCGACA AAACTCACAC ATGCCCACCG
4201 TGCCCAGCTC CAGAACTCCT GGGCGGACCG TCAGTCTTCC TCTTCCCCCC
4251 AAAACCCAAG GACACCCTCA TGATCTCCCG GACCCCTGAG GTCACATGCG
4301 TGGTGGTGGA CGTGAGCCAC GAAGACCCTG AGGTCAAGTT CAACTGGTAC
4351 GTGGACGGCG TGGAGGTGCA TAATGCCAAG ACAAAGCCGC GGGAGGAGCA
4401 GTACAACAGC ACGTACCGTG TGGTCAGCGT CCTCACCGTC CTGCACCAGG
4451 ACTGGCTGAA TGGCAAGGAG TACAAGTGCA AGGTCTCCAA CAAAGCCCTC
4501 CCAGCCCCCA TCGAGAAAAC CATCTCCAAA GCCAAAGGGC AGCCCCGAGA
4551 ACCACAGGTG TACACCCTGC CCCCATCCCG GGATGAGCTG ACCAAGAACC
4601 AGGTCAGCCT GACCTGCCTG GTCAAAGGCT TCTATCCCAG CGACATCGCC
4651 GTGGAGTGGG AGAGCAATGG GCAGCCGGAG AACAACTACA AGACCACGCC
4701 TCCCGTGTTG GACTCCGACG GCTCCTTCTT CCTCTACAGC AAGCTCACCG
4751 TGGACAAGAG CAGGTGGCAG CAGGGGAACG TCTTCTCATG CTCCGTGATG
4801 CATGAGGCTC TGCACAACCA CTACACGCAG AAGAGCCTCT CCCTGTCTCC
4851 GGGTAAATGA

pSYN VWF062 蛋白質序列(VWF D'D3-Fc，其在連接子中不具有凝血酶位點) (SEQ ID NO: 199)

1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFVNTFDGSM
51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
101 TVTQGDQRVS 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 IQLPLLKGDL RIQHTVTASV RLSYGEDLQM
501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
551 NAWKLHGDCQ DLQKQHSDPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCEL
651 NCPKGQVYLQ CGTPCNLTCR 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 CKKRVTILVE GGEIELFDGE VNVKRPMKDE
951 THFEVVESGR YIILLLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
1051 MKQTMVDSSC RILTSDVFQD CNKLVDPEPY LDVCIYDTCS CESIGDCAAF
1101 CDTIAAYAHV CAQHGKVVTW 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
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 NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM
1601 HEALHNHYTQ KSLSLSPGK*

pSYN VWF073核苷酸序列- (其編碼VWFD1D2D'D3- 144 AE XTEN- FVIII經截切的a2凝血酶位點-Fc) (SEQ ID NO:174)

1 ATGATTCCTG CCAGATTTGC CGGGGTGCTG CTTGCTCTGG CCCTCATTTT
51 GCCAGGGACC CTTTGTGCAG AAGGAACTCG CGGCAGGTCA TCCACGGCCC
101 GATGCAGCCT TTCGGAAGT 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 TTGCCCGCTG CCACCCTCTG GTGGACCCCG AGCCTTTTGT GGCCCTGTGT
751 GAGAAGACTT TGTGTGAGTG TGCTGGGGGG CTGGAGTGCG CCTGCCCTGC
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
1201 AACAGATACT TCACCTTCAG TGGGATCTGC CAGTACCTGC TGGCCCGGGA
1251 TTGCCAGGAC CACTCCTTCT CCATTGTCAT TGAGACTGTC CAGTGTGCTG
1301 ATGACCGCGA CGCTGTGTGC ACCCGCTCCG TCACCGTCCG GCTGCCTGGC
1351 CTGCACAACA GCCTTGTGAA ACTGAAGCAT GGGGCAGGAG TTGCCATGGA
1401 TGGCCAGGAC ATCCAGCTCC CCCTCCTGAA AGGTGACCTC CGCATCCAGC
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
1701 CGATCCCTGC GCCCTCAACC CGCGCATGAC CAGGTTCTCC GAGGAGGCGT
1751 GCGCGGTCCT GACGTCCCCC ACATTCGAGG CCTGCCATCG TGCCGTCAGC
1801 CCGCTGCCCT ACCTGCGGAA CTGCCGCTAC GACGTGTGCT CCTGCTCGGA
1851 CGGCCGCGAG TGCCTGTGCG GCGCCCTGGC CAGCTATGCC GCGGCCTGCG
1901 CGGGGAGAGG CGTGCGCGTC GCGTGGCGCG AGCCAGGCCG CTGTGAGCTG
1951 AACTGCCCGA AAGGCCAGGT GTACCTGCAG TGCGGGACCC CCTGCAACCT
2001 GACCTGCCGC TCTCTCTCTT ACCCGGATGA GGAATGCAAT GAGGCCTGCC
2051 TGGAGGGCTG CTTCTGCCCC CCAGGGCTCT ACATGGATGA GAGGGGGGAC
2101 TGCGTGCCCA AGGCCCAGTG CCCCTGTTAC TATGACGGTG AGATCTTCCA
2151 GCCAGAAGAC ATCTTCTCAG ACCATCACAC CATGTGCTAC TGTGAGGATG
2201 GCTTCATGCA CTGTACCATG AGTGGAGTCC CCGGAAGCTT GCTGCCTGAC
2251 GCTGTCCTCA 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 CACTTGTGTC
2551 TGTCGGGACC GGAAGTGGAA CTGCACAGAC CATGTGTGTG ATGCCACGTG
2601 CTCCACGATC GGCATGGCCC ACTACCTCAC CTTCGACGGG CTCAAATACC
2651 TGTTCCCCGG GGAGTGCCAG TACGTTCTGG TGCAGGATTA CTGCGGCAGT
2701 AACCCTGGGA CCTTTCGGAT CCTAGTGGGG AATAAGGGAT GCAGCCACCC
2751 CTCAGTGAAA TGCAAGAAAC GGGTCACCAT CCTGGTGGAG GGAGGAGAGA
2801 TTGAGCTGTT TGACGGGGAG GTGAATGTGA AGAGGCCCAT GAAGGATGAG
2851 ACTCACTTTG AGGTGGTGGA GTCTGGCCGG 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 CGATGGTGGA 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 TCAGCACCCT 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 GGCGCGCCAA CATCAGAGAG CGCCACCCCT
3751 GAAAGTGGTC CCGGGAGCGA GCCAGCCACA TCTGGGTCGG AAACGCCAGG
3801 CACAAGTGAG TCTGCAACTC CCGAGTCCGG ACCTGGCTCC GAGCCTGCCA
3851 CTAGCGGCTC CGAGACTCCG GGAACTTCCG AGAGCGCTAC ACCAGAAAGC
3901 GGACCCGGAA CCAGTACCGA ACCTAGCGAG GGCTCTGCTC CGGGCAGCCC
3951 AGCCGGCTCT CCTACATCCA CGGAGGAGGG CACTTCCGAA TCCGCCACCC
4001 CGGAGTCAGG GCCAGGATCT GAACCCGCTA CCTCAGGCAG TGAGACGCCA
4051 GGAACGAGCG AGTCCGCTAC ACCGGAGAGT 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
4301 CTCACACATG CCCACCGTGC CCAGCTCCAG AACTCCTGGG CGGACCGTCA
4351 GTCTTCCTCT TCCCCCCAAA ACCCAAGGAC ACCCTCATGA TCTCCCGGAC
4401 CCCTGAGGTC ACATGCGTGG TGGTGGACGT GAGCCACGAA GACCCTGAGG
4451 TCAAGTTCAA CTGGTACGTG GACGGCGTGG AGGTGCATAA TGCCAAGACA
4501 AAGCCGCGGG AGGAGCAGTA CAACAGCACG TACCGTGTGG TCAGCGTCCT
4551 CACCGTCCTG CACCAGGACT GGCTGAATGG CAAGGAGTAC AAGTGCAAGG
4601 TCTCCAACAA AGCCCTCCCA GCCCCCATCG AGAAAACCAT CTCCAAAGCC
4651 AAAGGGCAGC CCCGAGAACC ACAGGTGTAC ACCCTGCCCC CATCCCGGGA
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
4951 AGCCTCTCCC TGTCTCCGGG TAAATGA

pSYN VWF073 蛋白質序列- (VWFD1D2D'D3- 144 AE XTEN-經截切的 a2 凝血酶位點-Fc) (SEQ ID NO:175)

1 MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFVNTFDGSM
51 YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
101 TVTQGDQRVS 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 IQLPLLKGDL RIQHTVTASV RLSYGEDLQM
501 DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
551 NAWKLHGDCQ DLQKQHSDPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
601 PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCEL
651 NCPKGQVYLQ CGTPCNLTCR 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 CKKRVTILVE GGEIELFDGE VNVKRPMKDE
951 THFEVVESGR YIILLLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
1001 GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
1051 MKQTMVDSSC RILTSDVFQD CNKLVDPEPY LDVCIYDTCS CESIGDCAAF
1101 CDTIAAYAHV CAQHGKVVTW RTATLCPQSC EERNLRENGY EAEWRYNSCA
1151 PACQVTCQHP EPLACPVQCV EGCHAHCPPG KILDELLQTC VDPEDCPVCE
1201 VAGRRFASGK KVTLNPSDPE 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
1451 VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT
1501 KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA
1551 KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN
1601 NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK
1651 SLSLSPGK*

表18：示例性的嵌合多肽序列

FVIII-XTEN-Fc：SEQ ID NO: 201
TRRYYLGAVELSWDYMQSDLGELPVDARFPPRVPKSFPFNTSVVYKKTLFVEFTDHLFNIAKP RPPWMGLLGPTIQAEVYDTVVITLKNMASHPVSLHAVGVSYWKASEGAEYDDQTSQREKEDD KVFPGGSHTYVWQVLKENGPMASDPLCLTYSYLSHVDLVKDLNSGLIGALLVCREGSLAKEK TQTLHKFILLFAVFDEGKSWHSETKNSLMQDRDAASARAWPKMHTVNGYVNRSLPGLIGCHR KSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQASLEISPITFLTAQTLLMDLGQFLLFCHISSH QHDGMEAYVKVDSCPEEPQLRMKNNEEAEDYDDDLTDSEMDVVRFDDDNSPSFIQIRSVAKK HPKTWVHYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQRIGRKYKKVRFMAYTDETFKTR EAIQHESGILGPLLYGEVGDTLLIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDFPILP GEIFKYKWTVTVEDGPTKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQIMSD KRNVILFSVFDENRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEV AYWYILSIGAQTDFLSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFR NRGMTALLKVSSCDKNTGDYYEDSYEDISAYLLSKNNAIEPRSFSQNGTSESATPESGPGSEPA TSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEE GTSESATPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSE GSAPGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSP AGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEPSEGS APASSEITRTTLQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSPRSFQKKTRHYFIAAVERLWD YGMSSSPHVLRNRAQSGSVPQFKKVVFQEFTDGSFTQPLYRGELNEHLGLLGPYIRAEVEDNIM

VTFRNQASRPYSFYSSLISYEEDQRQGAEPRKNFVKPNETKTYFWKVQHHMAPTKDEFDCKA
WAYFSDVDLEKDVHSGLIGPLLVCHTNTLNPAHGRQVTVQEFALFFTIFDETKSWYFTENMER
NCRAPCNIQMEDPTFKENYRFHAINGYIMDTLPGLVMAQDQRIRWYLLSMGSNENIHSIHFSGH
VFTVRKKEEYKMALYNLYPGVFETVEMLPSKAGIWRVECLIGEHLHAGMSTLFLVYSNKCQT
PLGMASGHIRDFQITASGQYGQWAPKLARLHYSGSINAWSTKEPFSWIKVDLLAPMIIHGIKTQ
GARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGNVDSSGIKHNIFNPPIIARYIRLHP
THYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSYFTNMFATWSPSKARLHLQGRS
NAWRPQVNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTSMYVKEFLISSSQDGHQWTLFFQN
GKVKVFQGNQDSFTPVVNSLDPPLLTRYLRIHPQSWVHQIALRMEVLGCEAQDLYDKTHTCPP
CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPG

VWF(D'D3)-XTEN-a2 連接子-Fc：SEQ ID NO: 202

SLSCRPPMVKLVCPADNLRAEGLECTKTCQNYDLECMSMGCVSGCLCPPGMVRHENRCVALE
RCPCFHQGKEYAPGETVKIGCNTCVCRDRKWNCTDHVCDATCSTIGMAHYLTFDGLKYLFPG
ECQYVLVQDYCGSNPGTFRILVGNKGCSHPSVKCKKRVTILVEGGEIELFDGEVNVKRPMKDE
THFEVVESGRYIILLLGKALSVVWDRHLSISVVLKQTYQEKVCGLCGNFDGIQNNDLTSSNLQV
EEDPVDFGNSWKVSSQCADTRKVPLDSSPATCHNNIMKQTMVDSSCRILTSDVFQDCNKLVDP
EPYLDVCIYDTCSCESIGDCAAFCDTIAAYAHVCAQHGKVVTWRTATLCPQSCEERNLRENGY
EAEWRYNSCAPACQVTCQHPEPLACPVQCVEGCHAHCPPGKILDELLQTCVDPEDCPVCEVAG
RRFASGKKVTLNPSDPEHCQICHCDVVNLTCEACQEPGTSESATPESGPGSEPATSGSETPGTSE
SATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESG
PGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGASSDKNTGDYYEDSYE
DISAYLLSKNNAIEPRSFSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

FVIII 蛋白(312A)的胺基酸序列: SEQ ID NO: 203

1	MQIELSTCFF LCLLRFCFSA TRRYYLGAVE LSWDYMQSDL GELPVDARFP
51	PRVPKSFPFN TSVVYKKTLF 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
401	WVHYIAAEEE DWDYAPLVLA PDDRSYKSQY LNNGPQRIGR KYKKVRFMAY
451	TDETFKTREA IQHESGILGP LLYGEVGDTL LIIFKNQASR PYNIYPHGIT
501	DVRPLYSRRL PKGVKHLKDF PILPGEIFKY KWTVTVEDGP TKSDPRCLTR
551	YYSSFVNMER DLASGLIGPL LICYKESVDQ RGNQIMSDKR NVILFSVFDE
601	NRSWYLTENI QRFLPNPAGV QLEDPEFQAS NIMHSINGYV FDSLQLSVCL
651	HEVAYWYILS IGAQTDFLSV FFSGYTFKHK MVYEDTLTLF PFSGETVFMS
701	MENPGLWILG CHNSDFRNRG MTALLKVSSC DKNTGDYYED 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 SPHVLRNRAQ SGSVPQFKKV VFQEFTDGSF
1151	TQPLYRGELN EHLGLLGPYI RAEVEDNIMV TFRNQASRPY SFYSSLISYE
1201	EDQRQGAEPR KNFVKPNETK TYFWKVQHHM APTKDEFDCK AWAYFSDVDL
1251	EKDVHSGLIG PLLVCHTNTL NPAHGRQVTV QEFALFFTIF DETKSWYFTE
1301	NMERNCRAPC NIQMEDPTFK ENYRFHAING YIMDTLPGLV MAQDQRIRWY
1351	LLSMGSNENI HSIHFSGHVF TVRKKEEYKM ALYNLYPGVF ETVEMLPSKA

1401	GIWRVECLIG EHLHAGMSTL FLVYSNKCQT PLGMASGHIR DFQITASGQY
1451	GQWAPKLARL HYSGSINAWS TKEPFSWIKV DLLAPMIIHG IKTQGARQKF
1501	SSLYISQFII MYSLDGKKWQ TYRGNSTGTL MVFFGNVDSS GIKHNIFNPP
1551	IIARYIRLHP THYSIRSTLR MELMGCDLNS CSMPLGMESK AISDAQITAS
1601	SYFTNMFATW SPSKARLHLQ GRSNAWRPQV NNPKEWLQVD FQKTMKVTGV
1651	TTQGVKSLLT SMYVKEFLIS SSQDGHQWTL FFQNGKVKVF QGNQDSFTPV
1701	VNSLDPPLLT RYLRIHPQSW VHQIALRMEV LGCEAQDLYD KTHTCPPCPA
1751	PELLGGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG
1801	VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP
1851	IEKTISKAKG QPREPQVYTL PPSRDELTKN QVSLTCLVKG FYPSDIAVEW
1901	ESNGQPENNY KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA
1951	LHNHYTQKSL SLSPG*

編碼 FVIII 312A 的核苷酸序列：SEQ ID NO: 204

1	ATGCAAATAG AGCTCTCCAC CTGCTTCTTT CTGTGCCTTT TGCGATTCTG
51	CTTTAGTGCC ACCAGAAGAT ACTACCTGGG TGCAGTGGAA CTGTCATGGG
101	ACTATATGCA AAGTGATCTC GGTGAGCTGC CTGTGGACGC AAGATTTCCT
151	CCTAGAGTGC CAAAATCTTT TCCATTCAAC ACCTCAGTCG TGTACAAAAA
201	GACTCTGTTT GTAGAATTCA CGGATCACCT TTTCAACATC GCTAAGCCAA
251	GGCCACCCTG GATGGGTCTG CTAGGTCCTA CCATCCAGGC TGAGGTTTAT
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
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
801	CCACAGGAAA TCAGTCTATT GGCATGTGAT TGGAATGGGC ACCACTCCTG
851	AAGTGCACTC AATATTCCTC GAAGGTCACA CATTTCTTGT GAGGAACCAT
901	CGCCAGGCGT CCTTGGAAAT 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
1151	CTCCTTCCTT TATCCAAATT CGCTCAGTTG CCAAGAAGCA TCCTAAAACT
1201	TGGGTACATT ACATTGCTGC TGAAGAGGAG GACTGGGACT ATGCTCCCTT
1251	AGTCCTCGCC CCCGATGACA GAAGTTATAA AAGTCAATAT TTGAACAATG
1301	GCCCTCAGCG GATTGGTAGG AAGTACAAAA AAGTCCGATT TATGGCATAC
1351	ACAGATGAAA CCTTTAAGAC TCGTGAAGCT ATTCAGCATG AATCAGGAAT
1401	CTTGGGACCT TTACTTTATG GGGAAGTTGG 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
1651	TATTACTCTA GTTTCGTTAA 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
1901	ACAGCATCAA TGGCTATGTT TTTGATAGTT TGCAGTTGTC AGTTTGTTTG
1951	CATGAGGTGG CATACTGGTA CATTCTAAGC ATTGGAGCAC AGACTGACTT
2001	CCTTTCTGTC TTCTTCTCTG GATATACCTT CAAACACAAA ATGGTCTATG
2051	AAGACACACT CACCCTATTC CCATTCTCAG GAGAAACTGT CTTCATGTCG
2101	ATGGAAAACC CAGGTCTATG GATTCTGGGG TGCCACAACT CAGACTTTCG
2151	GAACAGAGGC ATGACCGCCT TACTGAAGGT TTCTAGTTGT GACAAGAACA
2201	CTGGTGATTA TTACGAGGAC AGTTATGAAG ATATTTCAGC ATACTTGCTG
2251	AGTAAAAACA ATGCCATTGA ACCAAGAAGC TTCTCTCAAA ACGGTACCTC

2301 AGAGTCTGCT ACCCCCGAGT CAGGGCCAGG ATCAGAGCCA GCCACCTCCG
2351 GGTCTGAGAC ACCCGGGACT TCCGAGAGTG CCACCCCTGA GTCCGGACCC
2401 GGGTCCGAGC CCGCCACTTC CGGCTCCGAA ACTCCCGGCA CAAGCGAGAG
2451 CGCTACCCCA 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 CCCACCTCCA 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 CCACCCCCGA GAGTGGCCCA GGCACTAGTA CCGAGCCCTC TGAAGGCAGT
3151 GCGCCAGCCT CGAGCGAAAT AACTCGTACT 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 GACTCCTGGG
3501 GCCATATATA AGAGCAGAAG TTGAAGATAA TATCATGGTA ACTTTCAGAA
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 CATTCTATTC ATTTCAGTGG
4101 ACATGTGTTC 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 GGATTCATCT GGGATAAAAC ACAATATTTT TAACCCTCCA
4651 ATTATTGCTC GATACATCCG TTTGCACCCA ACTCATTATA GCATTCGCAG
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 TTTTTTCAGA
5051 ATGGCAAAGT AAAGGTTTTT CAGGGAAATC AAGACTCCTT CACACCTGTG
5101 GTGAACTCTC TAGACCCACC GTTACTGACT CGCTACCTTC GAATTCACCC
5151 CCAGAGTTGG GTGCACCAGA TTGCCCTGAG GATGGAGGTT CTGGGCTGCG
5201 AGGCACAGGA CCTCTACGAC AAAACTCACA CATGCCCACC GTGCCCAGCT
5251 CCAGAACTCC 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 CCCCCATCCC GGGATGAGCT GACCAAGAAC CAAGTTAGCC
5651	TGACCTGCCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG
5701	GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGTT
5751	GGACTCCGAC GGCTCCTTCT TCCTCTACTC CAAGCTCACC GTGGACAAGA
5801	GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT GCTCCGTGAT GCATGAGGCT
5851	CTGCACAACC ACTACACGCA GAAGAGCCTC TCCCTGTCTC CGGGTTGA

VWF059A 蛋白的胺基酸序列：SEQ ID NO: 205

1	MIPARFAGVL LALALILPGT LCAEGTRGRS STARCSLFGS DFVNTFDGSM
51	YSFAGYCSYL LAGGCQKRSF SIIGDFQNGK RVSLSVYLGE FFDIHLFVNG
101	TVTQGDQRVS 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 IQLPLLKGDL RIQHTVTASV RLSYGEDLQM
501	DWDGRGRLLV KLSPVYAGKT CGLCGNYNGN QGDDFLTPSG LAEPRVEDFG
551	NAWKLHGDCQ DLQKQHSDPC ALNPRMTRFS EEACAVLTSP TFEACHRAVS
601	PLPYLRNCRY DVCSCSDGRE CLCGALASYA AACAGRGVRV AWREPGRCEL
651	NCPKGQVYLQ CGTPCNLTCR 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 CKKRVTILVE GGEIELFDGE VNVKRPMKDE
951	THFEVVESGR YIILLLGKAL SVVWDRHLSI SVVLKQTYQE KVCGLCGNFD
1001	GIQNNDLTSS NLQVEEDPVD FGNSWKVSSQ CADTRKVPLD SSPATCHNNI
1051	MKQTMVDSSC RILTSDVFQD CNKLVDPEPY LDVCIYDTCS CESIGDCAAF
1101	CDTIAAYAHV CAQHGKVVTW 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 NTGDYYEDSY
1401	EDISAYLLSK NNAIEPRSFS DKTHTCPPCP APELLGGPSV FLFPPKPKDT
1451	LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY
1501	RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT
1551	LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS
1601	DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPG*

編碼 VWF059A 蛋白的核苷酸序列：SEQ ID NO: 206

1	ATGATTCCTG CCAGATTTGC CGGGGTGCTG CTTGCTCTGG CCCTCATTTT
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 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	TTGCCCGCTG CCACCCTCTG GTGGACCCCG AGCCTTTTGT GGCCCTGTGT
751	GAGAAGACTT TGTGTGAGTG TGCTGGGGGG CTGGAGTGCG CCTGCCCTGC
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
1201	AACAGATACT TCACCTTCAG TGGGATCTGC CAGTACCTGC TGGCCCGGGA
1251	TTGCCAGGAC CACTCCTTCT CCATTGTCAT TGAGACTGTC CAGTGTGCTG
1301	ATGACCGCGA CGCTGTGTGC ACCCGCTCCG TCACCGTCCG GCTGCCTGGC
1351	CTGCACAACA GCCTTGTGAA ACTGAAGCAT GGGGCAGGAG TTGCCATGGA
1401	TGGCCAGGAC ATCCAGCTCC CCCTCCTGAA AGGTGACCTC CGCATCCAGC
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
1701	CGATCCCTGC GCCCTCAACC CGCGCATGAC CAGGTTCTCC GAGGAGGCGT
1751	GCGCGGTCCT GACGTCCCCC ACATTCGAGG CCTGCCATCG TGCCGTCAGC
1801	CCGCTGCCCT ACCTGCGGAA CTGCCGCTAC GACGTGTGCT CCTGCTCGGA
1851	CGGCCGCGAG TGCCTGTGCG GCGCCCTGGC CAGCTATGCC GCGGCCTGCG
1901	CGGGGAGAGG CGTGCGCGTC GCGTGGCGCG AGCCAGGCCG CTGTGAGCTG
1951	AACTGCCCGA AAGGCCAGGT GTACCTGCAG TGCGGGACCC CCTGCAACCT
2001	GACCTGCCGC TCTCTCTCTT ACCCGGATGA GGAATGCAAT GAGGCCTGCC
2051	TGGAGGGCTG CTTCTGCCCC CCAGGGCTCT ACATGGATGA GAGGGGGGAC
2101	TGCGTGCCCA AGGCCCAGTG CCCCTGTTAC TATGACGGTG AGATCTTCCA
2151	GCCAGAAGAC ATCTTCTCAG ACCATCACAC CATGTGCTAC TGTGAGGATG
2201	GCTTCATGCA CTGTACCATG AGTGGAGTCC CCGGAAGCTT GCTGCCTGAC
2251	GCTGTCCTCA 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 CACTTGTGTC
2551	TGTCGGGACC GGAAGTGGAA CTGCACAGAC CATGTGTGTG ATGCCACGTG
2601	CTCCACGATC GGCATGGCCC ACTACCTCAC CTTCGACGGG CTCAAATACC
2651	TGTTCCCCGG GGAGTGCCAG TACGTTCTGG TGCAGGATTA CTGCGGCAGT
2701	AACCCTGGGA CCTTTCGGAT CCTAGTGGGG AATAAGGGAT GCAGCCACCC
2751	CTCAGTGAAA TGCAAGAAAC GGGTCACCAT CCTGGTGGAG GGAGGAGAGA
2801	TTGAGCTGTT TGACGGGGAG GTGAATGTGA AGAGGCCCAT GAAGGATGAG
2851	ACTCACTTTG AGGTGGTGGA GTCTGGCCGG 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 CGATGGTGGA 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 TCAGCACCCT 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	GGTCCCGGGA GCGAGCCAGC CACATCTGGG TCGGAAACGC 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

ATRRYYLGAVELSWDYMQSDLGELPVDARFPPRVPKSFPFNTSVVYKKTLFVEFTDHLFNIAKP
RPPWMGLLGPTIQAEVYDTVVITLKNMASHPVSLHAVGVSYWKASEGAEYDDQTSQREKEDD
KVFPGGSHTYVWQVLKENGPMASDPLCLTYSYLSHVDLVKDLNSGLIGALLVCREGSLAKEKT
QTLHKFILLFAVFDEGKSWHSETKNSLMQDRDAASARAWPKMHTVNGYVNRSLPGLIGCHRK
SVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQASLEISPITFLTAQTLLMDLGQFLLFCHISSHQ
HDGMEAYVKVDSCPEEPQLRMKNNEEAEDYDDDLTDSEMDVVRFDDDNSPSFIQIRSVAKKH
PKTWVHYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQRIGRKYKKVRFMAYTDETFKTRE
AIQHESGILGPLLYGEVGDTLLIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDFPILPGE
IFKYKWTVTVEDGPTKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQIMSDKR
NVILFSVFDENRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAY
WYILSIGAQTDFLSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNR
GMTALLKVSSCDKNTGDYYEDSYEDISAYLLSKNNAIEPRSFSQNGTSESATPESGPGSEPATSG
SETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSE
SATPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGSAP
GTSESATPESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSP
TSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPASS
EITRTTLQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSPRSFQKKTRHYFIAAVERLWDYGMS
SSPHVLRNRAQSGSVPQFKKVVFQEFTDGSFTQPLYRGELNEHLGLLGPYIRAEVEDNIMVTFR
NQASRPYSFYSSLISYEEDQRQGAEPRKNFVKPNETKTYFWKVQHHMAPTKDEFDCKAWAYF
SDVDLEKDVHSGLIGPLLVCHTNTLNPAHGRQVTVQEFALFFTIFDETKSWYFTENMERNCRAP
CNIQMEDPTFKENYRFHAINGYIMDTLPGLVMAQDQRIRWYLLSMGSNENIHSIHFSGHVFTVR
KKEEYKMALYNLYPGVFETVEMLPSKAGIWRVECLIGEHLHAGMSTLFLVYSNKCQTPLGMA
SGHIRDFQITASGQYGQWAPKLARLHYSGSINAWSTKEPFSWIKVDLLAPMIIHGIKTQGARQK
FSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGNVDSSGIKHNIFNPPIIARYIRLHPTHYSIR
STLRMELMGCDLNSCSMPLGMESKAISDAQITASSYFTNMFATWSPSKARLHLQGRSNAWRPQ
VNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTSMYVKEFLISSSQDGHQWTLFFQNGKVKVFQ
GNQDSFTPVVNSLDPPLLTRYLRIHPQSWVHQIALRMEVLGCEAQDLYDKTHTCPPCPAPELLG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC
SVMHEALHNHYTQKSLSLSPG

表19. 另外的嵌合多肽之序列

描述/ SEQ ID NO.	序列
AE288 SEQ ID NO: 8	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 EPSEGSAP 288
pSYN VWF059 SEQ ID NO: 13	TSTEEGASIS DKNTGDYYED SYEDISAYLL SKNNAIEPRS FSDKTH
pSYN VWF059A SEQ ID NO: 22	TSTEEGASSD KNTGDYYEDS YEDISAYLLS KNNAIEPRSF SDKTH
pSYN FVIII 312 SEQ ID NO: 173	ATRRYYLGAV ELSWDYMQSD LGELPVDARF PPRVPKSFPF NTSVVYKKTL FVEFTDHLFN 60 IAKPRPPWMG LLGPTIQAEV YDTVVITLKN MASHPVSLHA VGVSYWKASE GAEYDDQTSQ 120 REKEDDKVFP GGSHTYVWQV LKENGPMASD PLCLTYSYLS HVDLVKDLNS GLIGALLVCR 180 EGSLAKEKTQ TLHKFILLFA VFDEGKSWHS ETKNSLMQDR DAASARAWPK MHTVNGYVNR 240 SLPGLIGCHR KSVYWHVIGM GTTPEVHSIF LEGHTFLVRN HRQASLEISP ITFLTAQTLL 300 MDLGQFLLFC HISSHQHDGM EAYVKVDSCP EEPQLRMKNN EEAEDYDDDL TDSEMDVVRF 360 DDDNSPSFIQ IRSVAKKHPK TWVHYIAAEE EDWDYAPLVL APDDRSYKSQ YLNNGPQRIG 420 RKYKKVRFMA YTDETFKTRE AIQHESGILG PLLYGEVGDT LLIIFKNQAS RPYNIYPHGI 480 TDVRPLYSRR LPKGVKHLKD FPILPGEIFK YKWTVTVEDG PTKSDPRCLT RYYSSFVNME 540 RDLASGLIGP LLICYKESVD QRGNQIMSDK RNVILFSVFD ENRSWYLTEN IQRFLPNPAG 600 VQLEDPEFQA SNIMHSINGY VFDSLQLSVC LHEVAYWYIL SIGAQTDFLS VFFSGYTFKH 660 KMVYEDTLTL 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 TSTEPSEGSA 900 PGTSESATPE SGPGTSESAT PESGPGTSES ATPESGPGSE PATSGSETPG SEPATSGSET 960 PGSPAGSPTS TEEGTSTEPS EGSAPGTSTE PSEGSAPGSE PATSGSETPG TSESATPESG 1020 PGTSTEPSEG SAPASSEITR TTLQSDQEEI DYDDTISVEM KKEDFDIYDE DENQSPRSFQ 1080 KKTRHYFIAA VERLWDYGMS SSPHVLRNRA QSGSVPQFKK VVFQEFTDGS FTQPLYRGEL 1140 NEHLGLLGPY IRAEVEDNIM VTFRNQASRP YSFYSSLISY EEDQRQGAEP RKNFVKPNET 1200 KTYFWKVQHH MAPTKDEFDC KAWAYFSDVD LEKDVHSGLI GPLLVCHTNT LNPAHGRQVT 1260 VQEFALFFTI FDETKSWYFT ENMERNCRAP CNIQMEDPTF KENYRFHAIN GYIMDTLPGL 1320 VMAQDQRIRW YLLSMGSNEN IHSIHFSGHV FTVRKKEEYK MALYNLYPGV FETVEMLPSK 1380 AGIWRVECLI GEHLHAGMST LFLVYSNKCQ TPLGMASGHI RDFQITASGQ YGQWAPKLAR 1440 LHYSGSINAW STKEPFSWIK VDLLAPMIIH GIKTQGARQK FSSLYISQFI IMYSLDGKKW 1500 QTYRGNSTGT LMVFFGNVDS SGIKHNIFNP PIIARYIRLH PTHYSIRSTL RMELMGCDLN 1560 SCSMPLGMES KAISDAQITA SSYFTNMFAT WSPSKARLHL QGRSNAWRPQ VNNPKEWLQV 1620 DFQKTMKVTG VTTQGVKSLL TSMYVKEFLI SSSQDGHQWT LFFQNGKVKV FQGNQDSFTP 1680 VVNSLDPPLL TRYLRIHPQS WVHQIALRME VLGCEAQDLY DKTHTCPPCP APELLGGPSV 1740 FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY 1800 RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSRDELTK 1860 NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG 1920 NVFSCSVMHE ALHNHYTQKS LSLSPGK
XTEN_AE288_2 SEQ ID NO: 54	GSPAGSPTST EEGTSESATP ESGPGSEPAT SGSETPGTSE SATPESGPGT STEPSEGSAP 60 GTSTEPSEGS APGTSTEPSE 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 TSTEPSEGSA PGSPAGSPTS TEEGTSESAT PESGPGSEPA TSGSETPGTS ESATPESGPG 120 SPAGSPTSTE EGSPAGSPTS TEEG
嵌合多肽的 a2 連接子 SEQ ID NO: 88	DKNTGDYYED SYEDISAYLL SKNNAIEPRS FS 32
FVIII 的信號肽	MQIELSTCFFLCLLRFCFS

SEQ ID NO: 64	
嵌合多肽的 FVIII 片段 1 SEQ ID NO. 215	ATRRYYLGAV ELSWDYMQSD LGELPVDARF PPRVPKSFPF NTSVVYKKTL FVEFTDHLFN 60 IAKPRPPWMG LLGPTIQAEV YDTVVITLKN MASHPVSLHA VGVSYWKASE GAEYDDQTSQ 120 REKEDDKVFP GGSHTYVWQV LKENGPMASD PLCLTYSYLS HVDLVKDLNS GLIGALLVCR 180 EGSLAKEKTQ TLHKFILLFA VFDEGKSWHS ETKNSLMQDR DAASARAWPK MHTVNGYVNR 240 SLPGLIGCHR KSVYWHVIGM GTTPEVHSIF LEGHTFLVRN HRQASLEISP ITFLTAQTLL 300 MDLGQFLLFC HISSHQHDGM EAYVKVDSCP EEPQLRMKNN EEAEDYDDDL TDSEMDVVRF 360 DDDNSPSFIQ IRSVAKKHPK TWVHYIAAEE EDWDYAPLVL APDDRSYKSQ YLNNGPQRIG 420 RKYKKVRFMA YTDETFKTRE AIQHESGILG PLLYGEVGDT LLIIFKNQAS RPYNIYPHGI 480 TDVRPLYSRR LPKGVKHLKD FPILPGEIFK YKWTVTVEDG PTKSDPRCLT RYYSSFVNME 540 RDLASGLIGP LLICYKESVD QRGNQIMSDK RNVILFSVFD ENRSWYLTEN IQRFLPNPAG 600 VQLEDPEFQA SNIMHSINGY VFDSLQLSVC LHEVAYWYIL SIGAQTDFLS VFFSGYTFKH 660 KMVYEDTLTL FPFSGETVFM SMENPGLWIL GCHNSDFRNR GMTALLKVSS CDKNTGDYYE 720 DSYEDISAYL LSKNNAIEPR SFSQN
嵌合多肽的 FVIII 片段 2 SEQ ID NO. 216	EITRTTLQSD QEEIDYDDTI SVEMKKEDFD IYDEDENQSP RSFQKKTRHY FIAAVERLWD 60 YGMSSSPHVL RNRAQSGSVP QFKKVVFQEF TDGSFTQPLY RGELNEHLGL LGPYIRAEVE 120 DNIMVTFRNQ ASRPYSFYSS LISYEEDQRQ GAEPRKNFVK PNETKTYFWK VQHHMAPTKD 180 EFDCKAWAYF SDVDLEKDVH SGLIGPLLVC HTNTLNPAHG RQVTVQEFAL FFTIFDETKS 240 WYFTENMERN CRAPCNIQME DPTFKENYRF HAINGYIMDT LPGLVMAQDQ RIRWYLLSMG 300 SNENIHSIHF SGHVFTVRKK EEYKMALYNL YPGVFETVEM LPSKAGIWRV ECLIGEHLHA 360 GMSTLFLVYS NKCQTPLGMA SGHIRDFQIT ASGQYGQWAP KLARLHYSGS INAWSTKEPF 420 SWIKVDLLAP MIIHGIKTQG ARQKFSSLYI SQFIIMYSLD GKKWQTYRGN STGTLMVFFG 480 NVDSSGIKHN IFNPPIIARY IRLHPTHYSI RSTLRMELMG CDLNSCSMPL GMESKAISDA 540 QITASSYFTN MFATWSPSKA RLHLQGRSNA WRPQVNNPKE WLQVDFQKTM KVTGVTTQGV 600 KSLLTSMYVK EFLISSSQDG HQWTLFFQNG KVKVFQGNQD SFTPVVNSLD PPLLTRYLRI 660 HPQSWVHQIA LRMEVLGCEA QDLY
VWF 信號肽 SEQ ID NO: 208	MIPARFAGVL LALALILPGT LC
嵌合多肽的 VWF D1D2 域 SEQ ID NO: 209	AEGTRGRSST ARCSLFGSDF VNTFDGSMYS FAGYCSYLLA GGCQKRSFSI IGDFQNGKRV 60 SLSVYLGEFF DIHLFVNGTV TQGDQRVSMP 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 ERCVDGCSCP EGQLLDEGLC VESTECPCVH SGKRYPPGTS LSRDCNTCIC RNSQWICSNE 360 ECPGECLVTG QSHFKSFDNR YFTFSGICQY LLARDCQDHS FSIVIETVQC ADDRDAVCTR 420 SVTVRLPGLH NSLVKLKHGA GVAMDGQDIQ LPLLKGDLRI QHTVTASVRL SYGEDLQMDW 480 DGRGRLLVKL SPVYAGKTCG LCGNYNGNQG DDFLTPSGLA EPRVEDFGNA WKLHGDCQDL 540 QKQHSDPCAL NPRMTRFSEE ACAVLTSPTF EACHRAVSPL PYLRNCRYDV CSCSDGRECL 600 CGALASYAAA CAGRGVRVAW REPGRCELNC PKGQVYLQCG TPCNLTCRSL SYPDEECNEA 660 CLEGCFCPPG LYMDERGDCV PKAQCPCYYD GEIFQPEDIF SDHHTMCYCE DGFMHCTMSG 720 VPGSLLPDAV LSSPLSHRSK R
嵌合多肽的 VWF D' 域 SEQ ID NO: 210	SLSCRPPMVK LVCPADNLRA EGLECTKTCQ NYDLECMSMG CVSGCLCPPG MVRHENRCVA 60 LERCPCFHQG KEYAPGETVK IGCNTCVCRD RKWNCTDHVC DAT 103
嵌合多肽的 VWF D3 域 SEQ ID NO: 214	CSTIGMAHYL TFDGLKYLFP GECQYVLVQD YCGSNPGTFR ILVGNKGCSH PSVKCKKRVT 60 ILVEGGEIEL FDGEVNVKRP MKDETHFEVV ESGRYIILLL GKALSVVWDR HLSISVVLKQ 120 TYQEKVCGLC GNFDGIQNND LTSSNLQVEE DPVDFGNSWK VSSQCADTRK VPLDSSPATC 180 HNNIMKQTMV DSSCRILTSD VFQDCNKLVD PEPYLDVCIY DTCSCESIGD CAAFCDTIAA 240 YAHVCAQHGK VVTWRTATLC PQSCEERNLR ENGYEAEWRY NSCAPACQVT CQHPEPLACP 300 VQCVEGCHAH CPPGKILDEL LQTCVDPEDC PVCEVAGRRF ASGKKVTLNP SDPEHCQICH 360 CDVVNLTCEA CQEP 374
Fc 區 SEQ ID NO: 217	DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD 60 GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK 120 GQPREPQVYT LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 180 DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPG
XTEN AE288_3	GTSESATPES GPGSEPATSG SETPGTSESA TPESGPGSEP ATSGSETPGT SESATPESGP 60

SEQ ID NO: 218	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】 具體的實施例的前述描述將充分地揭示本公開的一般性質，使得其他人可通過應用本領域技術範圍內的知識，在不脫離本公開的一般概念的情況下，針對各種應用容易地修改和/或改編此類具體實施例，而無需過度實驗。因此，基於本文呈現的教導和指導，此類改編和修改旨在落入所公開實施例的等同物的含義和範圍內。應理解，本文中的詞組或術語是出於描述而非限制性目的，使得本說明書的術語或詞組將由本領域技術人員根據教導和指導來解釋。

【0388】 考慮到本文公開的說明書和實踐，本公開的其他實施例對於本領域技術人員而言是顯而易見的。說明書和實例旨在僅被視為示例性的，本公開的真實範圍和精神由所附申請專利範圍指示。

【0389】 本文引用的所有專利和出版物均通過提述以其整體併入本文。

【符號說明】

無

【序列表】

<110> 美商百歐維拉提夫治療公司(Bioverativ Therapeutics Inc.)

<120> 治療 A 型血友病的方法

<130> 609832: SA9-461-4

<160> 218

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130 135 140

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

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50 55 60

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130 135 140

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195 200 205

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210 215 220

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225 230 235 240

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500 505 510

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530 535 540

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

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

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ggccagttct gggaggaggg ctgcgatgtg tgcacctgca ccgacatgga ggatgccgtg 7380

atgggcctcc gcgtggccca gtgctcccag aagccctgtg aggacagctg tcggtcgggc 7440

ttcacttacg ttctgcatga aggcgagtgc tgtggaaggt gcctgccatc tgcctgtgag 7500

gtggtgactg gctcaccgcg gggggactcc cagtcttcct ggaagagtgt cggctcccag 7560

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gcctgcatgc tcaatggcac tgtcattggg cccgggaaga ctgtgatgat cgatgtgtgc 7800

acgacctgcc gctgcatggt gcaggtgggg gtcatctctg gattcaagct ggagtgcagg 7860

aagaccacct gcaacccctg ccccctgggt tacaaggaag aaaataacac aggtgaatgt 7920

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ctgaagcgtg atgagacgct ccaggatggc tgtgatactc acttctgcaa ggtcaatgag 8040

agaggagagt acttctggga gaagagggtc acaggctgcc cacccttga tgaacacaag 8100

tgtcttgctg agggaggtaa aattatgaaa attccaggca cctgctgtga cacatgtgag 8160

gagcctgagt gcaacgacat cactgccagg ctgcagtatg tcaaggtggg aagctgtaag 8220

tctgaagtag aggtggatat ccactactgc cagggcaaat gtgccagcaa agccatgtac 8280

tccattgaca tcaacgatgt gcaggaccag tgctcctgct gctctccgac acggacggag 8340

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<213> 智人

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<222> (2016)..(2016)
<223> Xaa 可為任何天然存在的胺基酸

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Met Ile Pro Ala Arg Phe Ala Gly Val Leu Leu Ala Leu Ala Leu Ile
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Leu Pro Gly Thr Leu Cys Ala Glu Gly Thr Arg Gly Arg Ser Ser Thr
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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 Cys Gly Cys Arg Trp Thr Cys Pro Cys Val Cys Thr Gly Ser
1940 1945 1950

Ser Thr Arg His Ile Val Thr Phe Asp Gly Gln Asn Phe Lys Leu
1955 1960 1965

Thr Gly Ser Cys Ser Tyr Val Leu Phe Gln Asn Lys Glu Gln Asp
1970 1975 1980

Leu Glu Val Ile Leu His Asn Gly Ala Cys Ser Pro Gly Ala Arg
1985 1990 1995

Gln Gly Cys Met Lys Ser Ile Glu Val Lys His Ser Ala Leu Ser
2000 2005 2010

Val Glu Xaa His Ser Asp Met Glu Val Thr Val Asn Gly Arg Leu
2015 2020 2025

Val Ser Val Pro Tyr Val Gly Gly Asn Met Glu Val Asn Val Tyr
2030 2035 2040

Gly Ala Ile Met His Glu Val Arg Phe Asn His Leu Gly His Ile
2045 2050 2055

Phe Thr Phe Thr Pro Gln Asn Asn Glu Phe Gln Leu Gln Leu Ser
2060 2065 2070

Pro Lys Thr Phe Ala Ser Lys Thr Tyr Gly Leu Cys Gly Ile Cys
2075 2080 2085

Asp Glu Asn Gly Ala Asn Asp Phe Met Leu Arg Asp Gly Thr Val
2090 2095 2100

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

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Thr Ser Thr Glu Glu Gly Ala Ser Ser Asp Lys Asn Thr Gly Asp Tyr
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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

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<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
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<400> 24

Gly Glu Ser Pro Gly Gly Ser Ser Gly Ser Glu Ser
1 5 10

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<400> 25

Gly Ser Glu Gly Ser Ser Gly Pro Gly Glu Ser Ser
1 5 10

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<400> 26

Gly Ser Ser Glu Ser Gly Ser Ser Glu Gly Gly Pro
1 5 10

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<400> 27

Gly Ser Gly Gly Glu Pro Ser Glu Ser Gly Ser Ser
1 5 10

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<400> 28

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

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

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<400> 30

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

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

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1 5 10

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

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<400> 34

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

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

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

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<400> 37

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

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<400> 38

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

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<400> 39

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

<210> 40
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<400> 40

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

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<400> 41

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

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<400> 42

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

<210> 43
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<400> 43

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

<210> 44
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<400> 44

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

<210> 45
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<400> 45

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

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<400> 46

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

<210> 47
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Gly Ser Glu Pro Ala Thr Ser Gly Thr Glu Pro Ser
1 5 10

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<400> 48

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

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<212> PRT
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<220>
<223> XTEN 家族基序 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> 人工序列

<220>
<223> XTEN 基序家族 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> 人工序列

<220>

<223> XTEN 基序家族 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> 人工序列

<220>
<223> XTEN 基序家族 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> 人工序列

<220>
<223> XTEN 基序家族 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> 人工序列

<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> 人工序列

<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> 人工序列

<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> 人工序列

<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> 人工序列

<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> 人工序列

<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> 人工序列

<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> 人工序列

<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> 人工序列

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

Ser Gly Thr Ala Ser Ser Ser 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 Ala Ser Pro Gly Thr Ser Ser Thr Gly 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> 63
<211> 144
<212> PRT
<213> 人工序列

<220>
<223> AG144_F

<400> 63

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> 人工序列

<220>
<223> FVIII 信號肽

<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> 人工序列

<220>
<223> 成熟因子 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> 人工序列

<220>
<223> 全長 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 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 aaacaggtct 780

ctgccaggtc tgattggatg ccacaggaaa tcagtctatt ggcatgtgat tggaatgggc 840

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cgccaggcgt ccttggaaat ctcgccaata actttcctta ctgctcaaac actcttgatg 960

gaccttggac agtttctact gttttgtcat atctcttccc accaacatga tggcatggaa 1020

gcttatgtca aagtagacag ctgtccagag gaaccccaac tacgaatgaa aaataatgaa 1080

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tgggtacatt acattgctgc tgaagaggag gactgggact atgctccctt agtcctcgcc 1260

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aagtacaaaa aagtccgatt tatggcatac acagatgaaa cctttaagac tcgtgaagct 1380

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gatgtccgtc ctttgtattc aaggagatta ccaaaaggtg taaaacattt gaaggatttt 1560

ccaattctgc caggagaaat attcaaatat aaatggacag tgactgtaga agatgggcca 1620

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gatctagctt caggactcat tggccctctc ctcatctgct acaaagaatc tgtagatcaa 1740

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aaccgaagct ggtacctcac agagaatata caacgctttc tccccaatcc agctggagtg 1860

cagcttgagg atccagagtt ccaagcctcc aacatcatgc acagcatcaa tggctatgtt 1920

tttgatagtt tgcagttgtc agtttgtttg catgaggtgg catactggta cattctaagc 1980

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atggaaaacc caggtctatg gattctgggg tgccacaact cagactttcg gaacagaggc 2160

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ggactcaaag agatggtttt 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

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agccagcaga attttgtcac gcaacgtagt aagagagctt tgaaacaatt cagactccca 4020

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aaaaacatga aacatttgac cccgagcacc ctcacacaga tagactacaa tgagaaggag 4140

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ccctgcaata tccagatgga agatcccact tttaaagaga attatcgctt ccatgcaatc 5820

aatggctaca taatggatac actacctggc ttagtaatgg ctcaggatca aaggattcga 5880

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gtttttgaga cagtggaaat gttaccatcc aaagctggaa tttggcgggt ggaatgcctt 6060

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accttaatgg tcttctttgg caatgtggat tcatctggga taaaacacaa tatttttaac 6480

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agtaaagcaa tatcagatgc acagattact gcttcatcct actttaccaa tatgtttgcc 6660

acctggtctc 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 cctgtggtga actctctaga cccaccgtta 6960

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<210> 67
<211> 1438
<212> PRT
<213> 人工序列

<220>
<223> BDD FVIII

<400> 67

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

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

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

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

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

Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser Glu Gly Ala

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 68
<211> 1429
<212> PRT
<213> 人工序列

<220>
<223> B 域缺失的因子 VIII 的胺基酸序列(除 5 個胺基酸殘基外的 B 域缺失)

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

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
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Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
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Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
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Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
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Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro
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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
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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
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Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
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2435 2440 2445

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser
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Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
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Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Asp
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Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
2495 2500 2505

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Val Pro Arg
2510 2515 2520

Gly Ser Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
2525 2530 2535

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
2540 2545 2550

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
2555 2560 2565

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
2570 2575 2580

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
2585 2590 2595

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
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Ser Leu Ser Pro Gly Lys
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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

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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 Phe Thr Ile Phe Asp Glu Thr Lys Ser Trp Tyr Phe Thr Glu
1790 1795 1800

Asn Met Glu Arg Asn Cys Arg Ala Pro Cys Asn Ile Gln Met Glu
1805 1810 1815

Asp Pro Thr Phe Lys Glu Asn Tyr Arg Phe His Ala Ile Asn Gly
1820 1825 1830

Tyr Ile Met Asp Thr Leu Pro Gly Leu Val Met Ala Gln Asp Gln
1835 1840 1845

Arg Ile Arg Trp Tyr Leu Leu Ser Met Gly Ser Asn Glu Asn Ile
1850 1855 1860

His Ser Ile His Phe Ser Gly His Val Phe Thr Val Arg Lys Lys
1865 1870 1875

Glu Glu Tyr Lys Met Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe
1880 1885 1890

Glu Thr Val Glu Met Leu Pro Ser Lys Ala Gly Ile Trp Arg Val
1895 1900 1905

Glu Cys Leu Ile Gly Glu His Leu His Ala Gly Met Ser Thr Leu
1910 1915 1920

Phe Leu Val Tyr Ser Asn Lys Cys Gln Thr Pro Leu Gly Met Ala
1925 1930 1935

Ser Gly His Ile Arg Asp Phe Gln Ile Thr Ala Ser Gly Gln Tyr
1940 1945 1950

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

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35 40 45

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

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

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

85 90 95

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

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

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

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

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

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

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

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

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

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

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

260 265 270

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

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

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

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

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

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

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

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

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

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

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

435 440 445

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

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

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

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

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

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

Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu Ser 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 Ala Pro Gly Thr Ser Glu
740 745 750

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
755 760 765

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
770 775 780

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

785 790 795 800

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu
805 810 815

Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
820 825 830

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
835 840 845

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
850 855 860

Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
865 870 875 880

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr
885 890 895

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> 人工序列

<220>
<223> FVIII 195 (在胺基酸 1656 和 1900 處具有兩個 144 AE XTEN 的雙鏈 FVIIIFc)

<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
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 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> 人工序列

<220>
<223> FVIII 196 (在胺基酸 26、1656 和 1900 處具有三個 144 AE XTEN 的雙鏈 FVIIIFc)

<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 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 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> 人工序列

<220>
<223> FVIII 199 (在胺基酸 1656 和 1900 處具有三個 144 AE XTEN 的單鏈 FVIIIFc)

<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 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> 76
<211> 2134
<212> PRT
<213> 人工序列

<220>

<223> FVIII 201 (在胺基酸 26, 1656 和 1900 處具有三個 144 AE XTEN 的單鏈 FVIIIFc)

<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
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 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 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> 77
<211> 2128
<212> PRT
<213> 人工序列

<220>
<223> FVIII 203 (具有兩個 AE XTEN 的單鏈 FVIIIFc；一個為 B 域中的 288AE XTEN，一個為在胺基酸 1900 處的 144 AE XTEN)

<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 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> 78
<211> 2128
<212> PRT
<213> 人工序列

<220>
<223> FVIII 204 (具有兩個 AE XTEN 的單鏈 FVIIIFc；一個為 B 域中的 288AE XTEN，且一個為在胺基酸 403 處的 144 AE XTEN)

<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> 人工序列

<220>
<223> FVIII 205 (具有兩個 AE XTEN 的單鏈 FVIIIFc；一個為 B 域中的 288AE XTEN，且一個為在胺基酸 18 處的 144 AE XTEN)

<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 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> 80
<211> 2020
<212> PRT
<213> 人工序列

<220>
<223> pSYN FVIII 266 (FVIII Fc，其在胺基酸 18 處具有 42 AE-XTEN 且在 B 域中具有 288 AE XTEN)

<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> 人工序列

<220>
<223> pSYN FVIII 267 (FVIII Fc，其在胺基酸 18 處具有 72 AE-XTEN 且在 B 域中具有 288 AE XTEN)

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

1625 1630 1635

Pro Pro Ile Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr
1640 1645 1650

Ser Ile Arg Ser Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu
1655 1660 1665

Asn Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser
1670 1675 1680

Asp Ala Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala
1685 1690 1695

Thr Trp Ser Pro Ser Lys Ala Arg Leu His Leu Gln Gly Arg Ser
1700 1705 1710

Asn Ala Trp Arg Pro Gln Val Asn Asn Pro Lys Glu Trp Leu Gln
1715 1720 1725

Val Asp Phe Gln Lys Thr Met Lys Val Thr Gly Val Thr Thr Gln
1730 1735 1740

Gly Val Lys Ser Leu Leu Thr Ser Met Tyr Val Lys Glu Phe Leu
1745 1750 1755

Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr Leu Phe Phe Gln
1760 1765 1770

Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp Ser Phe Thr
1775 1780 1785

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> 人工序列

<220>
<223> pSYN FVIII 268 (FVIII Fc，其在胺基酸 18 處具有 144 AE-XTEN)

<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> 人工序列

<220>
<223> pSYN FVIII 269 (FVIII Fc，其在胺基酸 18 處具有 72 AE-XTEN)

<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> 人工序列

<220>
<223> pSYNFVIII 271 (FVIII Fc，其在胺基酸 18 處具有 42 AE-XTEN)

<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> 人工序列

<220>
<223> pSYN FVIII 272 (FVIII，其在胺基酸 18 處具有 144 AE XTEN 且在 B 域中具有 244 AE XTEN-無 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> 人工序列

<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> 人工序列

<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> 人工序列

<220>
<223> 可切割連接子

<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> 人工序列

<220>
<223> Ig 恆定區部分

<400> 89

Pro Lys Asn Ser Ser Met Ile Ser Asn Thr Pro
1 5 10

<210> 90
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> Ig 恆定區部分

<400> 90

His Gln Ser Leu Gly Thr Gln
1 5

<210> 91
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> Ig 恆定區部分

<400> 91

His Gln Asn Leu Ser Asp Gly Lys
1 5

<210> 92
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> Ig恆定區部分

<400> 92

His Gln Asn Ile Ser Asp Gly Lys
1 5

<210> 93
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> Ig恆定區部分

<400> 93

Val Ile Ser Ser His Leu Gly Gln
1 5

<210> 94
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 連接子, 其中該序列可重複 1 至 20 次

<400> 94

Gly Gly Gly Gly Ser
1 5

<210> 95
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 連接子, 其中該序列可重複 1 至 100 次或 1 至 20 次

<400> 95

Gly Gly Ser Gly Gly Gly Gly Ser
1 5

<210> 96
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 96

Ser Gly Gly Ser Gly Gly Ser
1 5

<210> 97
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<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> 人工序列

<220>
<223> 連接子

<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> 人工序列

<220>
<223> 連接子

<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> 人工序列

<220>
<223> 連接子

<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> 人工序列

<220>
<223> 連接子, 其中該序列可重複 1 至 00 次或 1 至 20 次

<400> 101

Gly Gly Gly Ser
1

<210> 102
<211> 4
<212> PRT
<213> 人工序列

<220>
<223> 切割位點

<400> 102

Arg Arg Arg Arg
1

<210> 103
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> 切割位點

<400> 103

Arg Lys Arg Arg Lys Arg
1 5

<210> 104
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 切割位點

<400> 104

Arg Arg Arg Arg Ser
1 5

<210> 105
<211> 4
<212> PRT
<213> 人工序列

<220>
<223> 凝血酶可切割位點

<220>
<221> misc_feature
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Xaa Val Pro Arg
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<400> 106

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

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<223> 可切割連接子

<400> 107

Ile Ser Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp Leu
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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

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<223> 可切割連接子

<400> 108

Ile Ser Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile
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Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp
20 25 30

Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln
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Ser Phe Leu Leu Arg Asn
1 5

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<223> PAR1 位點外相互作用基序

<400> 111

Pro Asn Asp Lys Tyr
1 5

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<223> PAR1 位點外相互作用基序

<400> 112

Pro Asn Asp Lys Tyr Glu
1 5

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<223> PAR1 位點外相互作用基序

<400> 113

Pro Asn Asp Lys Tyr Glu Pro
1 5

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<223> PAR1 位點外相互作用基序

<400> 114

Pro Asn Asp Lys Tyr Glu Pro Phe
1 5

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Pro Asn Asp Lys Tyr Glu Pro Phe Trp
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Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu
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<223> PAR1 位點外相互作用基序

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Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp
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Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu
1 5 10

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Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu
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Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser
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Lys Leu Thr Arg Ala Glu Thr
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Asp Phe Thr Arg Val Val Gly
1 5

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Thr Met Thr Arg Ile Val Gly Gly
1 5

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<223> 激肽釋放酶切割位點

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Ser Pro Phe Arg Ser Thr Gly Gly
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<400> 125

Leu Gln Val Arg Ile Val Gly Gly
1 5

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Pro Leu Gly Arg Ile Val Gly Gly
1 5

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Ile Glu Gly Arg Thr Val Gly Gly
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<223> FIIa (凝血酶)切割位點

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Leu Thr Pro Arg Ser Leu Leu Val
1 5

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Leu Gly Pro Val Ser Gly Val Pro
1 5

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<400> 130

Val Ala Gly Asp Ser Leu Glu Glu
1 5

<210> 131
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<223> MMP-12 切割位點

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Gly Pro Ala Gly Leu Gly Gly Ala
1 5

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<223> MMP-13 切割位點

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Gly Pro Ala Gly Leu Arg Gly Ala
1 5

<210> 133
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<223> MMP-17 切割位點

<400> 133

Ala Pro Leu Gly Leu Arg Leu Arg
1 5

<210> 134
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<223> MMP-20 切割位點

<400> 134

Pro Ala Leu Pro Leu Val Ala Gln
1 5

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<223> TEV 切割位點

<400> 135

Glu Asn Leu Tyr Phe Gln Gly
1 5

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<400> 136

Asp Asp Asp Lys Ile Val Gly Gly
1 5

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Leu Glu Val Leu Phe Gln Gly Pro
1 5

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<223> 分選酶 A 切割位點

<400> 138

Leu Pro Lys Thr Gly Ser Glu Ser
1 5

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<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
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<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

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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

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<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
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<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
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<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
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<223> 凝血酶切割位點

<400> 145

Ala Leu Arg Pro Arg Val Val Gly Gly Ala
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<212> PRT
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Thr Leu Asp Pro Arg Ser Phe Leu Leu Arg Asn Pro Asn Asp Lys Tyr
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Glu Pro Phe Trp Glu Asp Glu Glu Lys

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

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35 40 45

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

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885 890 895

Tyr Cys Gly Ser Asn Pro Gly Thr Phe Arg Ile Leu Val Gly Asn Lys
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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
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Gln Asp Cys Asn Lys Leu Val Asp Pro Glu Pro Tyr Leu Asp Val
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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
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Ser Cys Glu Glu Arg Asn Leu Arg Glu Asn Gly Tyr Glu Ala Glu
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Trp Arg Tyr Asn Ser Cys Ala Pro Ala Cys Gln Val Thr Cys Gln
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His Pro Glu Pro Leu Ala Cys Pro Val Gln Cys Val Glu Gly Cys
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His Ala His Cys Pro Pro Gly Lys Ile Leu Asp Glu Leu Leu Gln
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Thr Cys Val Asp Pro Glu Asp Cys Pro Val Cys Glu Val Ala Gly
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Arg Arg Phe Ala Ser Gly Lys Lys Val Thr Leu Asn Pro Ser Asp
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Pro Glu His Cys Gln Ile Cys His Cys Asp Val Val Asn Leu Thr
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Cys Glu Ala Cys Gln Glu Pro Ile Ser Gly Ala Pro Thr Ser Glu
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Cys Gln Lys Arg Ser Phe Ser Ile Ile Gly Asp Phe Gln Asn Gly Lys
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Arg Val Ser Leu Ser Val Tyr Leu Gly Glu Phe Phe Asp Ile His Leu
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Phe Val Asn Gly Thr Val Thr Gln Gly Asp Gln Arg Val Ser Met Pro
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Ser Cys Asn Ile Ser Ser Gly Glu Met Gln Lys Gly Leu Trp Glu Gln
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Cys Gln Leu Leu Lys Ser Thr Ser Val Phe Ala Arg Cys His Pro Leu
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Val Asp Pro Glu Pro Phe Val Ala Leu Cys Glu Lys Thr Leu Cys Glu
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Asp Cys Gln Asp His Ser Phe Ser Ile Val Ile Glu Thr Val Gln Cys
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Pro Gly Leu His Asn Ser Leu Val Lys Leu Lys His Gly Ala Gly Val
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Cys Pro Pro Gly Leu Tyr Met Asp Glu Arg Gly Asp Cys Val Pro Lys
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Arg Pro Met Lys Asp Glu Thr His Phe Glu Val Val Glu Ser Gly Arg
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980 985 990

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

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

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Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
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945 950 955 960

Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala
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Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val
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Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe
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gtttttcagg gaaatcaaga ctccttcaca cctgtggtga actctctaga cccaccgtta 5160

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gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca 5460

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<400> 161

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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

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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

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gagaaagaag atgataaagt cttccctggt ggaagccata catatgtctg gcaggtcctg 480

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gctgcatctg ctcgggcctg gcctaaaatg cacacagtca atggttatgt aaacaggtct 780

ctgccaggtc tgattggatg ccacaggaaa tcagtctatt ggcatgtgat tggaatgggc 840

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cgccaggcgt ccttggaaat ctcgccaata actttcctta ctgctcaaac actcttgatg 960

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gcttatgtca aagtagacag ctgtccagag gaaccccaac tacgaatgaa aaataatgaa 1080

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<213> 人工序列

<220>
<223> pSYNFVIII 010 (雙鏈 FVIIIFc)

<400> 163

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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> 人工序列

<220>
<223> 連接子, 其中該序列可重複 1 至 10 次

<400> 164
Ser Gly Gly Gly Gly Ser
1 5

<210> 165
<211> 20
<212> PRT

<213> 人工序列

<220>
<223> 連接子

<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> 人工序列

<220>
<223> 連接子

<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> 人工序列

<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> 人工序列

<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> 人工序列

<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> 人工序列

<220>
<223> pSYN FVIII 310 (編碼 FVIII，其具有除 2 個胺基酸殘基之外的完整 B 域缺失和在 aa 742 後插入有 288 AE-XTEN)

<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 tgaggtttat 300

gatacagtgg tcattacact taagaacatg gcttcccatc ctgtcagtct tcatgctgtt 360

ggtgtatcct 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 aaacaggtct 780

ctgccaggtc tgattggatg ccacaggaaa tcagtctatt ggcatgtgat tggaatgggc 840

accactcctg aagtgcactc aatattcctc gaaggtcaca catttcttgt gaggaaccat 900

cgccaggcgt ccttggaaat ctcgccaata actttcctta ctgctcaaac actcttgatg 960

gaccttggac agtttctact gttttgtcat atctcttccc accaacatga 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 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 atcctcggtg cctgacccgc 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 tggctatgtt 1920

tttgatagtt tgcagttgtc agtttgtttg catgaggtgg catactggta cattctaagc 1980

attggagcac agactgactt cctttctgtc ttcttctctg gatatacctt caaacacaaa 2040

atggtctatg 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

ttcggtacct cagagtctgc taccccccgag tcagggccag gatcagagcc agccacctcc 2340

gggtctgaga cacccgggac ttccgagagt gccacccctg agtccggacc cgggtccgag 2400

cccgccactt ccggctccga aactcccggc acaagcgaga gcgctacccc agagtcagga 2460

ccaggaacat ctacagagcc ctctgaaggc tccgctccag ggtccccagc cggcagtccc 2520

actagcaccg aggagggaac ctctgaaagc gccacacccg aatcagggcc agggtctgag 2580

cctgctacca gcggcagcga gacaccaggc acctctgagt ccgccacacc agagtccgga 2640

cccggatctc ccgctgggag ccccacctcc actgaggagg gatctcctgc tggctctcca 2700

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gagtcggcaa ccccggagtc tggacccgga acttccgaaa gtgccacacc agagtccggt 2820

cccgggactt cagaatcagc aacacccgag tccggccctg ggtctgaacc cgccacaagt 2880

ggtagtgaga caccaggatc agaacctgct acctcagggt cagagacacc cggatctccg 2940

gcaggctcac caacctccac tgaggagggc accagcacag aaccaagcga gggctccgca 3000

cccggaacaa gcactgaacc cagtgagggt 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 agccccccgca 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 atatcatggt aactttcaga 3540

aatcaggcct ctcgtcccta ttccttctat tctagcctta tttcttatga ggaagatcag 3600

aggcaaggag cagaacctag aaaaaacttt gtcaagccta atgaaaccaa aacttacttt 3660

tggaaagtgc aacatcatat ggcacccact aaagatgagt ttgactgcaa agcctgggct 3720

tatttctctg atgttgacct ggaaaaagat gtgcactcag gcctgattgg acccccttctg 3780

gtctgccaca ctaacacact gaaccctgct catgggagac aagtgacagt acaggaattt 3840

gctctgtttt tcaccatctt tgatgagacc aaaagctggt 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 gacatgtgtt cactgtacga aaaaaagagg agtataaaat ggcactgtac 4140

aatctctatc caggtgtttt tgagacagtg gaaatgttac catccaaagc tggaatttgg 4200

cgggtggaat gccttattgg cgagcatcta catgctggga tgagcacact ttttctggtg 4260

tacagcaata agtgtcagac tcccctggga atggcttctg gacacattag agattttcag 4320

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gcaccaatga ttattcacgg catcaagacc cagggtgccc gtcagaagtt ctccagcctc 4500

tacatctctc agtttatcat catgtatagt cttgatggga agaagtggca gacttatcga 4560

ggaaattcca ctggaacctt aatggtcttc 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 ctttttcag 5040

aatggcaaag taaaggtttt tcagggaaat caagactcct tcacacctgt ggtgaactct 5100

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cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc 5460

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc 5520

aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga 5580

gaaccacagg tgtacaccct gcccccatcc cgggatgagc tgaccaagaa ccaggtcagc 5640

ctgacctgcc tggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat 5700

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ccgggtaaat ga 5892

<210> 171
<211> 1944
<212> PRT
<213> 人工序列

<220>
<223> pSYN FVIII 310 (FVIII，其具有除 2 個胺基酸以外的完整 B 域缺失和在 aa 742 後插入有 288 AE-XTEN)

<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> 人工序列

<220>
<223> pSYN FVIII 312 (編碼 FVIII，其具有除 5 個胺基酸殘基之外的完全 B 域缺失和在 aa 745-B5 版本後插入有 288 AE-XTEN)

<400> 172
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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 cttccctggt ggaagccata catatgtctg gcaggtcctg 480

aaagagaatg gtccaatggc ctctgaccca ctgtgcctta cctactcata tctttctcat 540

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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 ccttggaaat ctcgccaata actttcctta ctgctcaaac actcttgatg 960

gaccttggac agtttctact gttttgtcat atctcttccc accaacatga tggcatggaa 1020

gcttatgtca aagtagacag ctgtccagag gaaccccaac tacgaatgaa aaataatgaa 1080

gaagcggaag actatgatga tgatcttact gattctgaaa tggatgtggt caggtttgat 1140

gatgacaact ctccttcctt tatccaaatt cgctcagttg ccaagaagca tcctaaaact 1200

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aagtacaaaa aagtccgatt tatggcatac acagatgaaa cctttaagac tcgtgaagct 1380

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gatgtccgtc ctttgtattc aaggagatta ccaaaaggtg taaaacattt gaaggatttt 1560

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agaggaaacc agataatgtc agacaagagg aatgtcatcc tgttttctgt atttgatgag 1800

aaccgaagct ggtacctcac agagaatata caacgctttc tccccaatcc agctggagtg 1860

cagcttgagg atccagagtt ccaagcctcc aacatcatgc acagcatcaa tggctatgtt 1920

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<210> 173
<211> 1947
<212> PRT
<213> 人工序列

<220>
<223> pSYN FVIII 312 (FVIII，其具有除 5 個胺基酸殘基之外的完全 B 域缺失和在 aa 745 至 FVIII B5 版本後插入有 288 AE-XTEN)

<400> 173

Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser Trp Asp Tyr
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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
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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

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<211> 4977
<212> DNA
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<220>
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ctggcagggg gctgccagaa acgctccttc tcgattattg gggacttcca gaatggcaag 240

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<400> 175

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

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<211> 25
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<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
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<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
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<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
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<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
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<210> 180
<211> 21
<212> PRT
<213> 人工序列

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<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> 人工序列

<220>
<223> 可切割連接子

<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
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<220>
<223> 可切割連接子

<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
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<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
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<220>
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<400> 184

Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe
1 5 10 15

Ser

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<211> 16
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<400> 185

Ala Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
1 5 10 15

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<400> 186

Tyr Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser

1 5 10 15

<210> 187
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<400> 187

Leu Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
1 5 10

<210> 188
<211> 13
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<400> 188

Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
1 5 10

<210> 189
<211> 12
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<400> 189

Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
1 5 10

<210> 190
<211> 11
<212> PRT
<213> 人工序列

<220>
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<400> 190

Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
1 5 10

<210> 191
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 可切割連接子

<400> 191

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser
1 5 10

<210> 192
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<400> 192

Asn Ala Ile Glu Pro Arg Ser Phe Ser
1 5

<210> 193

<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 可切割連接子

<400> 193
Ala Ile Glu Pro Arg Ser Phe Ser
1 5

<210> 194
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 可切割連接子

<400> 194
Ile Glu Pro Arg Ser Phe Ser
1 5

<210> 195
<211> 6
<212> PRT
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<220>
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<400> 195
Glu Pro Arg Ser Phe Ser
1 5

<210> 196
<211> 4959
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<220>
<223> pSYN VWF059 (在連接子中具有酸性區 2 (a2)凝血酶位點的 VWF D'D3-Fc)

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ctttgtgcag aaggaactcg cggcaggtca tccacggccc gatgcagcct tttcggaagt 120

gacttcgtca acacctttga tgggagcatg tacagctttg cgggatactg cagttacctc 180

ctggcagggg gctgccagaa acgctccttc tcgattattg gggacttcca gaatggcaag 240

agagtgagcc tctccgtgta tcttggggaa ttttttgaca tccatttgtt 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 tgacccaaga agggaccttg 540

acctcggacc cttatgactt tgccaactca tgggctctga gcagtggaga acagtggtgt 600

gaacgggcat ctcctcccag cagctcatgc aacatctcct ctggggaaat gcagaagggc 660

ctgtgggagc agtgccagct tctgaagagc acctcggtgt ttgcccgctg ccaccctctg 720

gtggaccccg agcctttttgt ggccctgtgt gagaagactt tgtgtgagtg tgctgggggg 780

ctggagtgcg cctgccctgc cctcctggag tacgcccgga 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 actggtcaat cccacttcaa gagctttgac 1200

aacagatact tcaccttcag tgggatctgc cagtacctgc tggcccggga ttgccaggac 1260

cactccttct ccattgtcat tgagactgtc cagtgtgctg atgaccgcga cgctgtgtgc 1320

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ggggcaggag ttgccatgga tggccaggac atccagctcc ccctcctgaa aggtgacctc 1440

cgcatccagc 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

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

tgcgtgccca aggcccagtg cccctgttac tatgacggtg agatcttcca gccagaagac 2160

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aaccctggga cctttcggat cctagtgggg aataagggat gcagccaccc ctcagtgaaa 2760

tgcaagaaac gggtcaccat cctggtggag ggaggagaga ttgagctgtt tgacggggag 2820

gtgaatgtga agaggcccat gaaggatgag actcactttg aggtggtgga gtctggccgg 2880

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tttgggaact cctggaaagt gagctcgcag tgtgctgaca ccagaaaagt gcctctggac 3120

tcatcccctg ccacctgcca taacaacatc atgaagcaga cgatggtgga ttcctcctgt 3180

agaatcctta ccagtgacgt cttccaggac tgcaacaagc tggtggaccc 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 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 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

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gagagtgggc cagggagccc tgctggatct cctacgtcca ctgaggaagg gtcaccagcg 4140

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tacgaggaca gttatgaaga tatttcagca tacttgctga gtaaaaacaa tgccattgaa 4260

ccaagaagct tctctgacaa aactcacaca tgcccaccgt gcccagctcc agaactcctg 4320

ggcggaccgt cagtcttcct cttccccca aaacccaagg acaccctcat gatctcccgg 4380

acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 4440

aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 4500

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ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccat cgagaaaacc 4620

atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 4680

gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc 4740

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cccgtgttgg 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> 人工序列

<220>
<223> pSYN VWF059 (在連接子中具有 LVPR 凝血酶位點的 VWF D'D3-Fc)

<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> 人工序列

<220>
<223> pSYN VWF062 (在連接子中不具有凝血酶位點的 VWF D'D3-Fc)

<400> 198

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gacttcgtca acacctttga tgggagcatg tacagctttg cgggatactg cagttacctc 180

ctggcagggg gctgccagaa acgctccttc tcgattattg gggacttcca gaatggcaag 240

agagtgagcc tctccgtgta tcttggggaa ttttttgaca tccatttgtt 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 tgacccaaga 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 cctcctggag tacgcccgga cctgtgccca ggagggaatg 840

gtgctgtacg gctggaccga ccacagcgcg tgcagcccag tgtgccctgc tggtatggag 900

tataggcagt gtgtgtcccc ttgcgccagg acctgccaga gcctgcacat caatgaaatg 960

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gactgggatg gccgcgggag gctgctggtg aagctgtccc ccgtctatgc cgggaagacc 1560

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gcgtggcgcg agccaggccg ctgtgagctg aactgcccga aaggccaggt gtacctgcag 1980

tgcgggaccc cctgcaacct gacctgccgc tctctctctt acccggatga ggaatgcaat 2040

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tgcgtgccca aggcccagtg cccctgttac tatgacggtg agatcttcca gccagaagac 2160

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agcaaaagga gcctatcctg tcggcccccc atggtcaagc tggtgtgtcc cgctgacaac 2340

ctgcgggctg aagggctcga gtgtaccaaa acgtgccaga actatgacct ggagtgcatg 2400

agcatgggct gtgtctctgg ctgcctctgc cccccgggca tggtccggca tgagaacaga 2460

tgtgtggccc tggaaaggtg tccctgcttc catcagggca aggagtatgc ccctggagaa 2520

acagtgaaga ttggctgcaa cacttgtgtc tgtcgggacc ggaagtggaa ctgcacagac 2580

catgtgtgtg atgccacgtg ctccacgatc ggcatggccc actacctcac cttcgacggg 2640

ctcaaatacc tgttccccgg ggagtgccag tacgttctgg tgcaggatta ctgcggcagt 2700

aaccctggga cctttcggat cctagtgggg aataagggat gcagccaccc ctcagtgaaa 2760

tgcaagaaac gggtcaccat cctggtggag ggaggagaga ttgagctgtt tgacggggag 2820

gtgaatgtga agaggcccat gaaggatgag actcactttg aggtggtgga gtctggccgg 2880

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ggcatccaga acaatgacct caccagcagc aacctccaag tggaggaaga ccctgtggac 3060

tttgggaact cctggaaagt gagctcgcag tgtgctgaca ccagaaaagt gcctctggac 3120

tcatcccctg ccacctgcca taacaacatc atgaagcaga cgatggtgga ttcctcctgt 3180

agaatcctta ccagtgacgt cttccaggac tgcaacaagc tggtggaccc cgagccatat 3240

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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

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gtggctggcc ggcgttttgc ctcaggaaag aaagtcacct tgaatcccag tgaccctgag 3660

cactgccaga tttgccactg tgatgttgtc aacctcacct gtgaagcctg ccaggagccg 3720

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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

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gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac 4320

gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag 4380

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tacaccctgc ccccatcccg ggatgagctg accaagaacc aggtcagcct gacctgcctg 4620

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aacaactaca agaccacgcc tcccgtgttg gactccgacg gctccttctt cctctacagc 4740

aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg 4800

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<210> 199
<211> 1619
<212> PRT
<213> 人工序列

<220>
<223> pSYN VWF062 (在連接子中不具有凝血酶位點的 VWF D'D3-Fc)

<400> 199

Met Ile Pro Ala Arg Phe Ala Gly Val Leu Leu Ala Leu Ala Leu Ile
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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> 人工序列

<220>
<223> 可切割連接子

<400> 200

Ile Glu Pro Arg
1

<210> 201
<211> 1945
<212> PRT
<213> 人工序列

<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

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<400> 202

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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> 人工序列

<220>
<223> FVIII 312A 的最終胺基酸序列

<400> 203

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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

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<213> 人工序列

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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 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 aaacaggtct 780

ctgccaggtc tgattggatg ccacaggaaa tcagtctatt ggcatgtgat tggaatgggc 840

accactcctg aagtgcactc aatattcctc gaaggtcaca catttcttgt gaggaaccat 900

cgccaggcgt ccttggaaat ctcgccaata actttcctta ctgctcaaac actcttgatg 960

gaccttggac agtttctact gttttgtcat atctcttccc accaacatga 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 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 atcctcggtg cctgacccgc 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 tggctatgtt 1920

tttgatagtt tgcagttgtc agtttgtttg catgaggtgg catactggta cattctaagc 1980

attggagcac agactgactt cctttctgtc ttcttctctg gatatacctt caaacacaaa 2040

atggtctatg 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

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

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

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

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His Pro Glu Pro Leu Ala Cys Pro Val Gln Cys Val Glu Gly Cys
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His Ala His Cys Pro Pro Gly Lys Ile Leu Asp Glu Leu Leu Gln
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<220>
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<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 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
1940 1945

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<211> 22
<212> PRT
<213> 智人

<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> 智人

<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> 智人

<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
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
100

<210> 211
<211> 374
<212> PRT
<213> 智人

<400> 211

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 Cys 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 Cys 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> 212
<211> 239
<212> PRT
<213> 智人

<400> 212

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> 智人

<220>
<221> misc_feature
<222> (537)..(537)
<223> Xaa 可為任何天然存在的胺基酸

<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

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> 人工序列

<220>
<223> VWF D3 區 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> 人工序列

<220>
<223> FVIII的1至745

<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> 人工序列

<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> 人工序列

<220>
<223> Fc區

<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> 人工序列

<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

【發明申請專利範圍】

【第1項】 一種治療有需要的人類個體的 A 型血友病的方法，該方法包括以給藥間隔向該個體施用多劑量的嵌合多肽，該嵌合多肽包含(i) 因子 VIII (FVIII) 多肽和(ii) 包含 VWF 的 D'域和 VWF 的 D3 域的馮威里氏因子(von Willebrand factor，VWF)片段，

其中該多劑量中的至少一個為約 15 IU/kg 至約 100 IU/kg，且該給藥間隔為至少約 7 天。

【第2項】 如請求項 1 的方法，其中該 FVIII 多肽通過共價鍵與該 VWF 片段締合。

【第3項】 如請求項 1 或 2 的方法，其中該共價鍵是肽鍵或雙硫鍵。

【第4項】 如請求項 1 至 3 中任一項的方法，其中該 FVIII 多肽包含第一延長半衰期的部分。

【第5項】 如請求項 4 的方法，其中該第一延長半衰期的部分與該 FVIII 多肽的 C 端或 N 端融合。

【第6項】 如請求項 4 的方法，其中該第一延長半衰期的部分被插入在該 FVIII 多肽內。

【第7項】 如請求項 5 或 6 的方法，其中該第一延長半衰期的部分被插入在該 FVIII 多肽的 B 域內。

【第8項】 如請求項 7 的方法，其中該第一延長半衰期的部分被插入在 FVIII 多肽內，緊鄰對應於 SEQ ID NO: 65 的胺基酸殘基 745 的胺基酸的下游。

【第9項】 如請求項 4 至 8 中任一項的方法，其中該第一延長半衰期的部分通過連接子與該 FVIII 多肽融合。

【第10項】 如請求項 4 至 9 中任一項的方法，其中該 VWF 片段包含第二延長半衰期的部分。

【第11項】 如請求項 10 的方法，其中該第二延長半衰期的部分與該 VWF 片段的 C 端或 N 端融合。

【第12項】 如請求項 10 的方法，其中該第二延長半衰期的部分被插入在該 VWF 片段內。

【第13項】 如請求項 10 或 11 的方法，其中該第二延長半衰期的部分與該 VWF 片段的 C 端融合。

【第14項】 如請求項 10 至 13 中任一項的方法，其中該第二延長半衰期的部分通過連接子與該 VWF 片段融合。

【第15項】 如請求項 4 至 14 中任一項的方法，其中該第一延長半衰期的部分、該第二延長半衰期的部分、或二者，係選自下列群組：白蛋白、免疫球蛋白 Fc 區、XTEN 序列、人絨毛膜促性腺激素的 β 次單元的 C 端肽(CTP)、PAS 序列、HAP 序列、轉鐵蛋白、白蛋白結合部分、或其任何片段、衍生物、變異體、和任何組合。

【第16項】 如請求項 4 至 15 中任一項的方法，其中該第一延長半衰期的部分包含第一 XTEN。

【第17項】 如請求項 16 的方法，其中該第一 XTEN 被插入在該 FVIII 多肽內，緊鄰對應於 SEQ ID NO: 65 的胺基酸殘基 745 的胺基酸的下游。

【第18項】 如請求項 10 至 17 中任一項的方法，其中該第二延長半衰期的部分包含第二 XTEN。

【第19項】 如請求項 18 的方法，其中該第二 XTEN 與該 VWF 片段的 C 端融合。

【第20項】 如請求項 1 至 19 中任一項的方法，其中該 FVIII 多肽包含第一免疫球蛋白(Ig)恆定區或其部分。

【第21項】 如請求項 20 的方法，其中該第一 Ig 恆定區或其部分與該 FVIII 多肽的 C 端或 N 端融合。

【第22項】 如請求項 20 的方法，其中該第一 Ig 恆定區或其部分被插入至該 FVIII 多肽內。

【第23項】 如請求項 20 或 21 的方法，其中該第一 Ig 恆定區或其部分與該 FVIII 多肽的 C 端融合。

【第24項】 如請求項 20 至 23 中任一項的方法，其中該第一 Ig 恆定區或其部分通過連接子與該 FVIII 多肽融合。

【第25項】 如請求項 20 至 24 中任一項的方法，其中該第一 Ig 恆定區或其部分包含第一 Fc 域或其部分。

【第26項】 如請求項 1 至 25 中任一項的方法，其中該 VWF 片段包含第二 Ig 恆定區或其部分。

【第27項】 如請求項 26 的方法，其中該第二 Ig 恆定區或其部分與該 VWF 片段的 C 端或 N 端融合。

【第28項】 如請求項 26 的方法，其中該第二 Ig 恆定區或其部分被插入在該 VWF 片段內。

【第29項】 如請求項 26 或 27 的方法，其中該第二 Ig 恆定區或其部分與該 VWF 片段的 C 端融合。

【第30項】 如請求項 26 至 29 中任一項的方法，其中該第二 Ig 恆定區或其部分通過連接子與該 VWF 片段融合。

【第31項】 如請求項 30 的方法，其中該連接子是可切割的連接子。

【第32項】 如請求項 26 至 31 中任一項的方法，其中該第二 Ig 恆定區或其部分包含第二 Fc 域或其部分。

【第33項】 如請求項 32 的方法，其中該 FVIII 蛋白和該 VWF 片段通過該第一 Fc 域和該第二 Fc 域之間的共價鍵彼此締合。

【第34項】 如請求項 33 的方法，其中該 FVIII 蛋白和該 VWF 片段進一步通過該 FVIII 蛋白和該 VWF 片段之間的非共價相互作用彼此締合。

【第35項】 一種治療人類個體的 A 型血友病的方法，該方法包括以給藥間隔向有需要的該個體施用多劑量的嵌合多肽，其中該嵌合多肽包含：

(i) FVIII 蛋白，其包含：

(a) 第一 FVIII 多肽片段，其包含 SEQ ID NO: 215 的胺基酸序列；

(b) 第一 XTEN 序列，其包含 SEQ ID NO: 8 (AE288)的胺基酸序列；

(c) 第二 FVIII 多肽片段，其包含 SEQ ID NO: 216 的胺基酸序列；和

(d) 第一 Fc 區，其包含 SEQ ID NO: 217 的胺基酸序列；

(ii) VWF 蛋白，其包含：

(a) VWF 的 D'域，其包含 SEQ ID NO: 210 的胺基酸序列；

(b) VWF 的 D3 域，其包含 SEQ ID NO: 214 的胺基酸序列；

(c) 第二 XTEN 序列，其包含 SEQ ID NO: 58 (AE144_5A)的胺基酸序列；

(d) a2 連接子，其包含 SEQ ID NO: 88 的胺基酸序列；和

(e) 第二 Fc 區，其包含 SEQ ID NO: 217 的胺基酸序列；

其中該第一 Fc 區通過雙硫鍵與該第二 Fc 區共價連接。

【第36項】 如請求項35的方法，其中該FVIII蛋白進一步包含FVIII信號肽，該 FVIII 信號肽包含 SEQ ID NO: 64 的胺基酸序列。

【第37項】 如請求項35的方法，其中該VWF蛋白進一步包含VWF信號肽，該 VWF 信號肽包含 SEQ ID NO: 208 的胺基酸序列。

【第38項】 如請求項 35 的方法，其中該 VWF 蛋白進一步包含 VWF 的 D1D2 域，該 D1D2 域包含 SEQ ID NO: 209 的胺基酸序列。

【第39項】 一種治療人類個體的 A 型血友病的方法，該方法包括以給藥間隔向有需要的該個體施用多劑量的嵌合多肽，其中該嵌合多肽包含：

(i) FVIII蛋白，其包含與SEQ ID NO: 173、SEQ ID NO: 201、SEQ ID NO: 203、或 SEQ ID NO: 207 至少約 80%、90%、95%、或 100%相同的胺基酸序列；和

(ii) VWF 蛋白，其包含與 SEQ ID NO: 197、SEQ ID NO: 202、或 SEQ ID NO: 205 至少約 80%、90%、95%、或 100%相同的胺基酸序列。

【第40項】 一種治療人類個體的 A 型血友病的方法，該方法包括以給藥間隔向有需要的該個體施用多劑量的嵌合多肽，其中該嵌合多肽包含：

(i) FVIII 蛋白，其包含 SEQ ID NO: 203 的胺基酸序列；和

(ii) VWF 蛋白，其包含 SEQ ID NO: 205 的胺基酸序列。

【第41項】 一種治療人類個體的 A 型血友病的方法，該方法包括以給藥間隔向有需要的該個體施用多劑量的嵌合多肽，其中該嵌合多肽包含：

(i) FVIII 蛋白，其包含與選自以下的序列至少約 80%、90%、95%、或 100% 相同的胺基酸序列：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)、FVIII199 (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)、或 FVIII-312A (SEQ ID NO: 203)；和

(ii) VWF 蛋白，其包含與選自以下的序列至少約 80%、90%、95%、或 100% 相同的胺基酸序列：VWF031 (SEQ ID NO: 86)、VWF034 (SEQ ID NO: 87)、VWF059 (SEQ ID NO: 197)、VWF059A (SEQ ID NO: 202)、或 VWF036。

【第42項】 如請求項 39-41 中任一項的方法，其中該多劑量中的至少一個為約 15 IU/kg 至約 100 IU/kg，且該給藥間隔為至少約 7 天。

【第43項】 如請求項 39-41 中任一項的方法，其中該多劑量中的至少一個為約 50 IU/kg 或約 65 IU/kg，且該給藥間隔為至少約 5 天或約 7 天。

【第44項】 如請求項 1-41 中任一項的方法，其中該多劑量包含至少兩個劑量、至少三個劑量、至少四個劑量、至少五個劑量、至少六個劑量、至少七個劑量、至少八個劑量、至少九個劑量、至少十個劑量、至少十一個劑量、至少十二個劑量、至少十三個劑量、至少十四個劑量、至少十五個劑量、至少十六個劑量、至少十七個劑量、至少十八個劑量、至少十九個劑量、至少二十個劑量、或更多個。

【第45項】 如請求項 1-41 中任一項的方法，其中 A 型血友病的治療包括控制或降低有需要的人類個體的出血事件的發生率或頻率。

【第46項】 如請求項 1-41 中任一項的方法，其中 A 型血友病的治療包括預防或治療有需要的人類個體的出血事件。

【第47項】 如請求項 1-41 中任一項的方法，其中該多劑量中的至少一個為約 20 IU/kg 至約 95 IU/kg、約 20 IU/kg 至約 90 IU/kg、約 20 IU/kg 至約 85 IU/kg、約 20 IU/kg 至約 80 IU/kg、約 20 IU/kg 至約 75 IU/kg、約 20 IU/kg 至約 70 IU/kg、約 20 IU/kg 至約 65 IU/kg、約 20 IU/kg 至約 60 IU/kg，、約 20 IU/kg 至約 55 IU/kg、約 20 IU/kg 至約 50 IU/kg、約 20 IU/kg 至約 45 IU/kg、約 20 IU/kg 至約 40 IU/kg、約 20 IU/kg 至約 35 IU/kg、約 20 IU/kg 至約 30 IU/kg、或約 20 IU/kg 至約 25 IU/kg。

【第48項】 如請求項 1-415 中任一項的方法，其中該多劑量中的至少一個為約 20 IU/kg 至約 100 IU/kg、約 25 IU/kg 至約 100 IU/kg、約 30 IU/kg 至約 100 IU/kg、約 35 IU/kg 至約 100 IU/kg、約 40 IU/kg 至約 100 IU/kg、約 45 IU/kg 至約 100 IU/kg、約 50 IU/kg 至約 100 IU/kg、約 55 IU/kg 至約 100 IU/kg、約 60 IU/kg 至約 100 IU/kg、約 65 IU/kg 至約 100 IU/kg、約 70 IU/kg 至約 100 IU/kg、約 75 IU/kg 至約 100 IU/kg、約 80 IU/kg 至約 100 IU/kg、約 85 IU/kg 至約 100 IU/kg、或約 90 IU/kg 至至約 100 IU/kg。

【第49項】 如請求項 1-41 中任一項的方法，其中該多劑量中的至少一個為約 20 IU/kg 至約 80 IU/kg、約 25 IU/kg 至約 75 IU/kg、約 30 IU/kg 至約 70 IU/kg、約 35 IU/kg 至約 65 IU/kg、約 40 IU/kg 至約 60 IU/kg、或約 45 IU/kg 至約 55 IU/kg。

【第50項】 如請求項 1-41 中任一項的方法，其中該多劑量中的至少一個為約 25 IU/kg 至約 65 IU/kg。

【第51項】 如請求項 1-41 中任一項的方法，其中該多劑量中的至少一個為約 20 IU/kg、約 25 IU/kg、約 30 IU/kg、約 35 IU/kg、約 40 IU/kg、約 45 IU/kg、約 50 IU/kg、約 55 IU/kg、約 60 IU/kg、約 65 IU/kg、約 70 IU/kg、約 75 IU/kg、約 80 IU/kg、約 85 IU/kg、約 90 IU/kg、約 95 IU/kg、或約 100 IU/kg。

【第52項】 如請求項 1-41 中任一項的方法，其中該多劑量中的至少一個為約 25 IU/kg。

【第53項】 如請求項 1-41 中任一項的方法，其中該多劑量中的至少一個為約 65 IU/kg。

【第54項】 如請求項 1-41 中任一項的方法，其中該多劑量中的至少一個為約 80 IU/kg。

【第55項】 如請求項 1-41 中任一項的方法，其中該給藥間隔為至少約 7 天、至少約 8 天、至少約 9 天、至少約 10 天、至少約 11 天、至少約 12 天、至少約 13 天、至少約 14 天、至少約 15 天、至少約 16 天、至少約 17 天、至少約 18 天、至少約 19 天、至少約 20 天、至少約 21 天、至少約 22 天、至少約 23 天、至少約 24 天、至少約 25 天、至少約 26 天、至少約 27 天、至少約 28 天、至少約 29 天、至少約 30 天、或至少約 31 天。

【第56項】 如請求項 1-41 中任一項的方法，其中該劑量的頻率為至少每週一次、至少每 2 週一次、至少每 3 週一次、或至少每 4 週一次。

【第57項】 如請求項 1-41 中任一項的方法，其中該劑量的頻率為至少每週一次。

【第58項】 如請求項 1-41 中任一項的方法，其中該劑量的頻率為至少每兩週一次。

【第59項】 如請求項 1-41 中任一項的方法，其中施用該嵌合多肽用於預防性治療。

【第60項】 如請求項 1-41 中任一項的方法，其中該嵌合多肽通過選自下列群組的途徑施用：靜脈內注射、靜脈內輸注、皮下施用、肌肉內施用、口服施用、鼻腔施用、和肺部施用。

【第61項】 如請求項 1-41 中任一項的方法，其中該嵌合多肽在該施用後導致 FVIII 血漿活性水平為至少約 1%、至少約 2%、至少約 3%、至少約 4%、至少約 5%、至少約 6%、至少約 7%、至少約 8%、至少約 9%、或至少約 10%。

【第62項】 如請求項 61 的方法，其中該 FVIII 血漿活性水平為至少約 3%。

【第63項】 如請求項 61 的方法，其中該 FVIII 血漿活性水平為至少約 5%。

【第64項】 如請求項 1 至 41 中任一項的方法，其中該嵌合多肽在該施用後導致 FVIII 血漿活性水平為至少約 1 IU/dL、至少約 2 IU/dL、至少約 3 IU/dL、

至少約4 IU/dL、至少約5 IU/dL、至少約6 IU/dL、至少約7 IU/dL、至少約8 IU/dL、至少約 9 IU/dL、或至少約 10 IU/dL。

【第65項】如請求項 64 的方法，其中該 FVIII 血漿活性水平為至少約 3 IU/dL。

【第66項】如請求項 64 的方法，其中該 FVIII 血漿活性水平為至少約 5 IU/dL。

【第67項】如請求項 1 至 41 中任一項的方法，其中在施用該嵌合多肽後至少約 5 天，該 FVIII 血漿活性水平為至少約 10 IU/dL。

【第68項】如請求項 1 至 41 中任一項的方法，其中在施用該嵌合多肽後至少約 7 天，該 FVIII 血漿活性水平為至少約 5 IU/dL。

【第69項】如請求項 1 至 41 中任一項的方法，其中在施用嵌合多肽後至少約 8 天，該 FVIII 血漿活性水平為至少約 3 IU/dL。

【第70項】如請求項 1 至 41 中任一項的方法，其中在施用嵌合多肽後至少約 10 天，該 FVIII 血漿活性水平為至少約 1 IU/dL。

【第71項】如請求項 1-41 中任一項的方法，其中該多劑量中的至少一個為約 50 IU/kg。

【第72項】如請求項 1-41 中任一項的方法，其中該多劑量為約 50 IU/kg，且該給藥間隔為約 7 天。

【第73項】如請求項 1-41 中任一項的方法，其中該嵌合多肽的施用在該施用的約 7 天、約 10 天、約 11 天、約 12 天、約 13 天、約 14 天、約 15 天、約 20 天、約 24 天、約 25 天、約 28 天、約 30 天、或約 35 天後不誘發 FVIII 抑制因子。

【第74項】如請求項 1-41 中任一項的方法，其中該嵌合多肽的施用在該施用的約 28 天後不誘發 FVIII 抑制因子。

【第75項】如請求項 1-41 中任一項的方法，其中該多劑量中的至少一個為約 50 IU/kg 至約 80 IU/kg。

【第76項】 如請求項 1-41 中任一項的方法，其中該多劑量中的至少一個為約 50 IU/kg 至約 65 IU/kg。

【第77項】 如請求項 1-41 中任一項的方法，其中該多劑量中的至少一個為約 65 IU/kg 至約 80 IU/kg。

【第78項】 如請求項 1-41 中任一項的方法，其中該給藥間隔為至少約 7 天。

【第79項】 如請求項 1-41 中任一項的方法，其中該給藥間隔為約 7 天至約 14 天。

【第80項】 如請求項 1-41 中任一項的方法，其中該給藥間隔為至少約 10 天。

【第81項】 如請求項 1-41 中任一項的方法，其中該給藥間隔為約 10 天至約 21 天。

【第82項】 如請求項 1-41 中任一項的方法，其中該給藥間隔為約 14 天至約 21 天。

【第83項】 如請求項 1-41 中任一項的方法，其中該給藥間隔為約 14 天。

【第84項】 如請求項 1-41 中任一項的方法，其中該人受試者是女性。

【第85項】 如請求項 1-41 中任一項的方法，其中該人受試者是兒童。

【第86項】 如請求項 85 的方法，其中該人受試者是小於或等於約 12 歲、小於約 11 歲、小於約 10 歲、小於約 9 歲、小於約 8 歲、小於約 7 歲、小於約 6 歲、小於約 5 歲、小於約 4 歲、小於約 3 歲、小於約 2 歲、或小於約 1 歲的兒童。

【第87項】 如請求項 1-41 中任一項的方法，其中該施用在該人受試者中誘發對 FVIII 的免疫耐受。

【第88項】 如請求項 1-41 中任一項的方法，其中該施用在該人受試者中誘發對 FVIII 的抑制性免疫反應。

【第89項】 如請求項 88 的方法，其中該對 FVIII 的抑制性免疫反應包含在該個體人類個體中高效價（titer）的抗 FVIII 抗體。

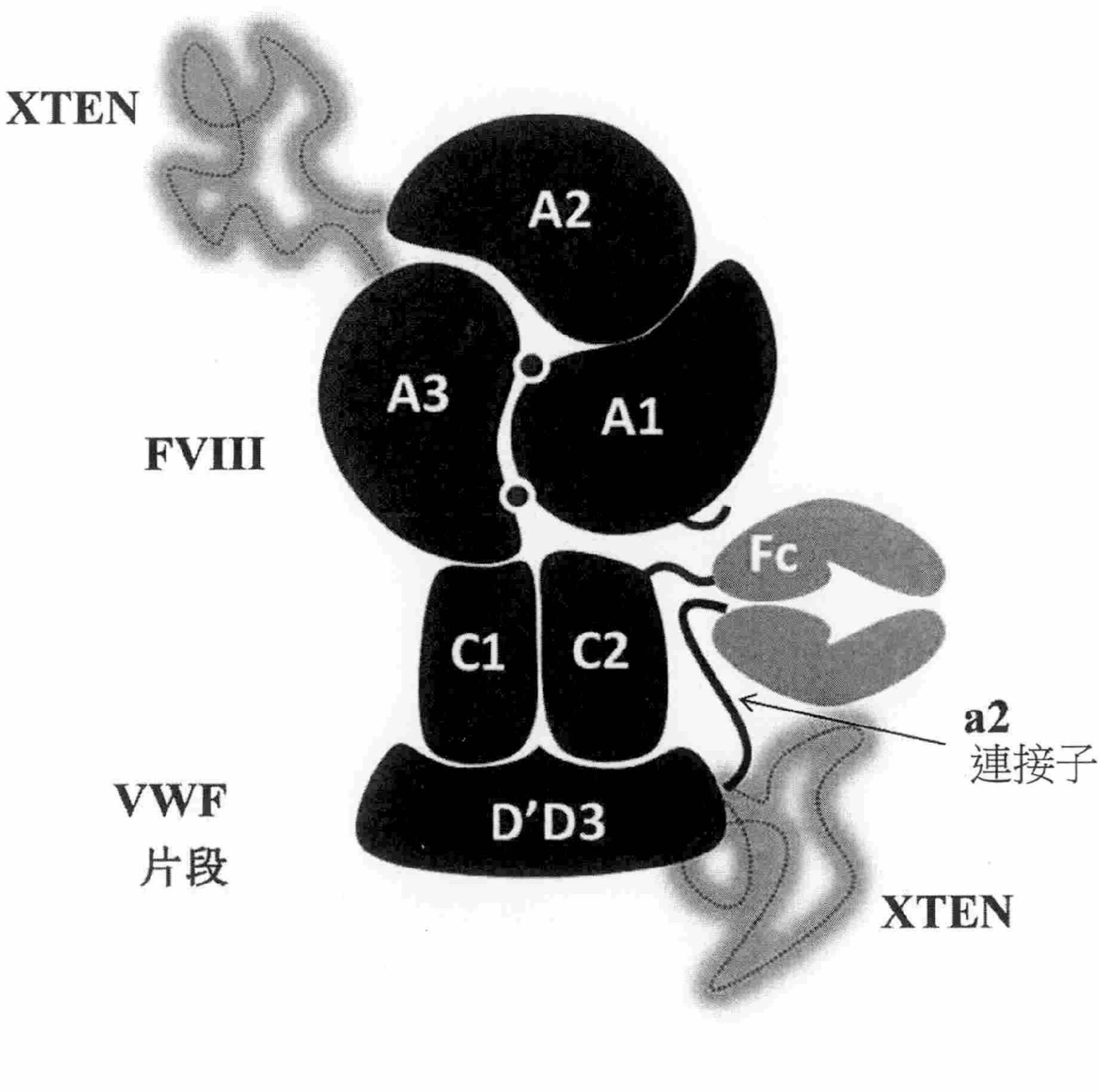


圖1

低劑量隊列

rFVIII

rFVIII-Fc-VWF-XTEN

第14天
抑制因子
測試

第28天
抑制因子
測試

篩選和洗脫 28天[a]	rFVIII PK (3天)	洗脫 (3天)[b]	rFVIIIFc-VWF-XTEN PK (10天)	殘餘安全性觀察 (18天)

圖2A

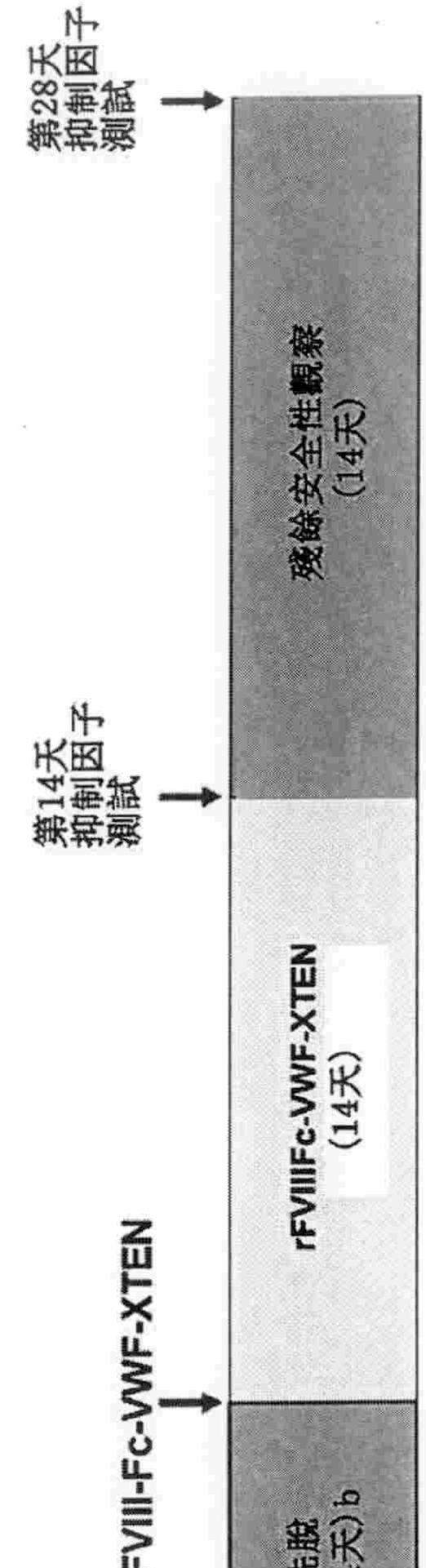

高劑量隊列
rFVIII
篩選和洗脫
28天a
rFVIII PK
(3天)
rFVIII-Fc-VWF-XTEN
洗脫
(4天) b
rFVIIIFc-VWF-XTEN
(14天)
第14天
抑制因子
測試
殘餘安全性觀察
(14天)
第28天
抑制因子
測試

圖2B

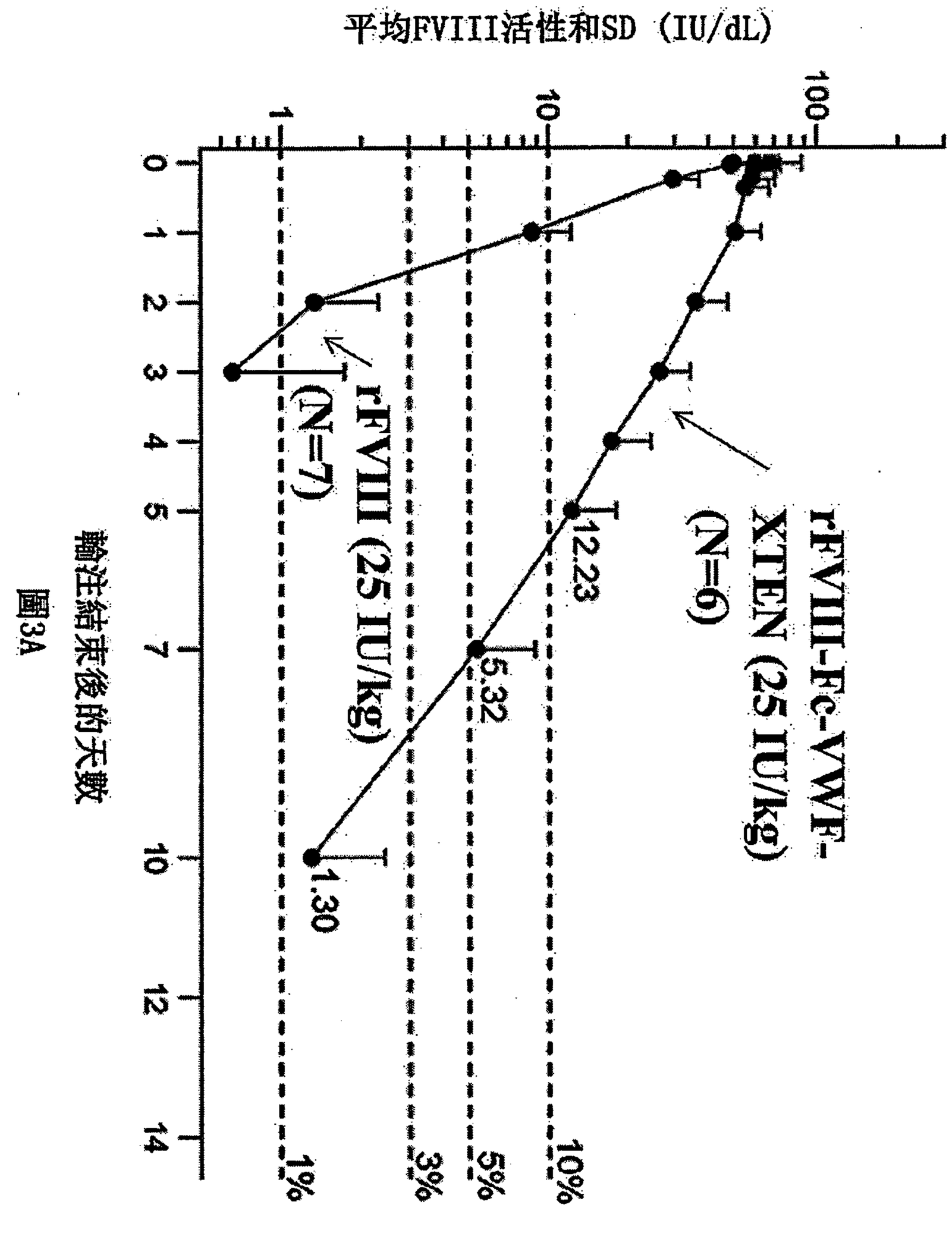

平均FVIII活性和SD (IU/dL)
100
10
1
0 1 2 3 4 5 7 10 12 14
輸注結束後的天數
rFVIII-Fc-VWF-XTEN (25 IU/kg)
(N=6)
rFVIII (25 IU/kg)
(N=7)
5.32
1.30
12
23
10%
5%
3%
1%

圖3A

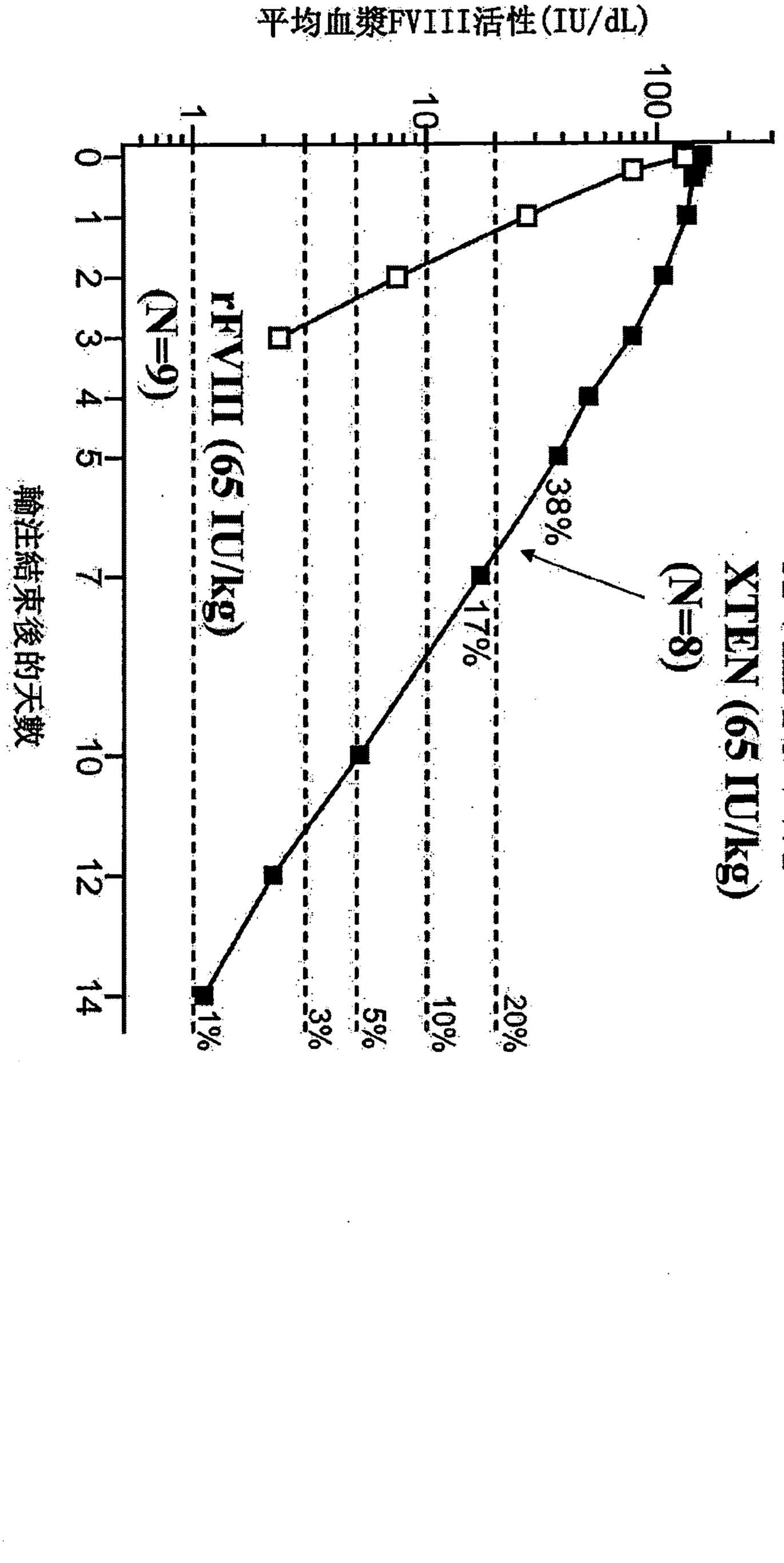

平均血漿FVIII活性(IU/dL)
100
10
1
0
1
2
3
4
5
rFVIII (65 IU/kg)
(N=9)
rFVIII-Fc-VWF-XTEN (65 IU/kg)
(N=8)
38%
17%
1%
20%
10%
5%
3%
1%
7
10
12
14
輸注結束後的天數

圖3B

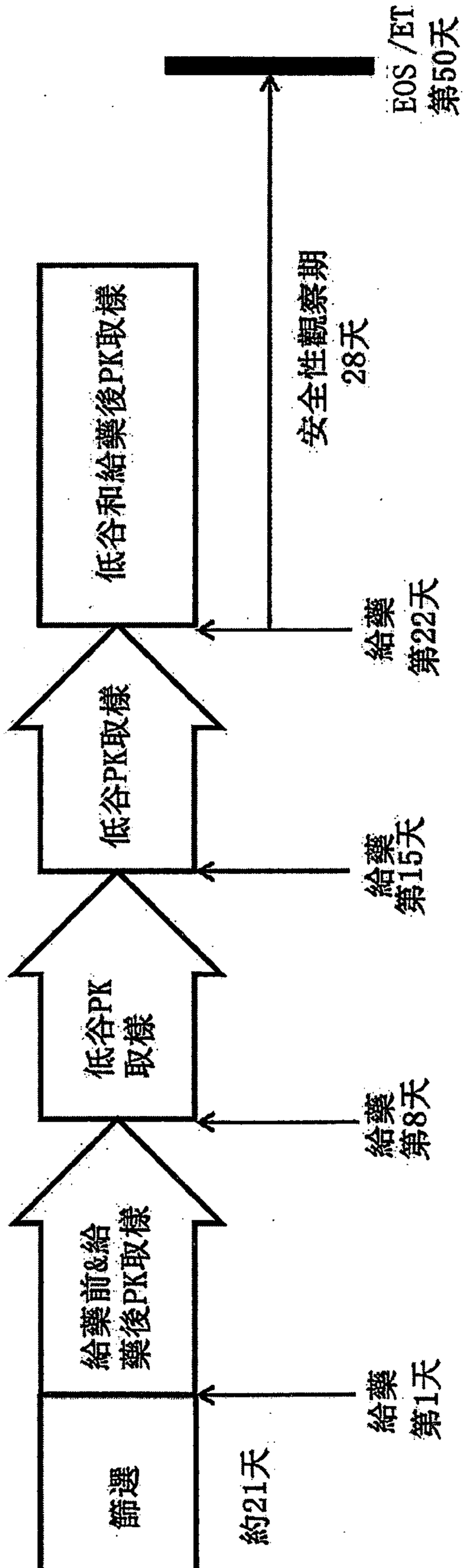

篩選
約21天
給藥
第1天
給藥前&給藥後PK取樣
給藥
第8天
低谷PK
取樣
給藥
第15天
低谷PK取樣
給藥
第22天
低谷和給藥後PK取樣
安全性觀察期
28天
EOS /ET
第50天

圖4