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(54)名稱

因子ＩＸ融合蛋白以及其製備及使用方法

(57)摘要

本發明提供包含至少一個諸如 XTEN 之異源部分的因子 IX(FIX)融合蛋白。本發明另外揭示製備及使用該等 FIX 融合蛋白之方法。

The present invention provides Factor IX (FIX) fusion proteins comprising at least one heterologous moiety, such as an XTEN. The present invention further discloses methods of making and using the FIX fusion proteins.

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公告本

發明摘要

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【發明名稱】(中文/英文)

因子 IX 融合蛋白以及其製備及使用方法

Factor IX fusion proteins and methods of making and using same

【中文】

本發明提供包含至少一個諸如 XTEN 之異源部分的因子 IX (FIX)融合蛋白。本發明另外揭示製備及使用該等 FIX 融合蛋白之方法。

【英文】

The present invention provides Factor IX (FIX) fusion proteins comprising at least one heterologous moiety, such as an XTEN. The present invention further discloses methods of making and using the FIX fusion proteins.

【代表圖】

【本案指定代表圖】：無

【本代表圖之符號簡單說明】：無

【本案若有化學式時，請揭示最能顯示發明特徵的化學式】：無

發明專利說明書

（本說明書格式、順序，請勿任意更動）

【發明名稱】(中文/英文)

因子 IX 融合蛋白以及其製備及使用方法

Factor IX fusion proteins and methods of making and using same

〔對以電子方式提交之序列表之參照〕

[0001] 與本申請案一起提交之 ASCII 正文檔案(名稱：2159_466PC03_SeqListing_ST25.txt；大小：688,114 位元組；且創建日期：2016 年 8 月 2 日)中以電子方式提交之序列表之內容以全文引用之方式併入本文中。

【技術領域】

本發明關於因子 IX 融合蛋白以及其製備及使用方法。

【先前技術】

[0002] B 型血友病(亦稱為克里斯馬斯病(Christmas disease))係世界上最常見的一種遺傳性出血病症。其導致活體內及活體外血液凝結活性降低且需要受影響個體終生進行廣泛醫學監測。在不存在干預情況下，患病個體將經受自發性關節出血，由此產生嚴重疼痛且逐漸衰弱而行動不便；肌肉內出血導致血液在該等組織中累積；咽喉及頸部自發性出血若不立即治療，則會引起窒息；腎出血；且

在手術、微小意外損傷或拔牙之後嚴重出血亦相當普遍。

[0003] 正常活體內血液凝固最少需要絲胺酸蛋白酶因子 II (凝血酶原(prothrombin))、因子 VII、因子 IX、因子 X 及因子 XI (可溶血漿蛋白)；輔因子，包括跨膜蛋白組織因子及血漿蛋白因子 V 及因子 VIII；纖維蛋白原、轉麩醯胺酶(transglutaminase)因子 XIII、磷脂(包括活性血小板)及鈣。一些活體外凝結測試需要包括血管舒素、高分子量激肽原及因子 XII 在內之其他蛋白質，且其可在病理條件下在活體內起作用。

[0004] 就血友病而言，血液凝結由於缺乏某些血漿血液凝結因子而受到干擾。B 型血友病係由因子 IX (FIX)之缺乏引起，因子 IX 之缺乏可由 FIX 蛋白合成減少或不存在，或者活性降低之缺陷分子導致。血友病係藉由用高度富含 FIX 之外源性因子濃縮物替代缺失之凝血因子進行治療。然而，如下所述，自血液產生此類濃縮物存在技術難題。

[0005] 自血漿純化 FIX(血漿源性 FIX；pdFIX)幾乎僅得到全-γ-羧基化之 FIX。然而，此種自血漿純化 FIX 極為困難，因為 FIX 僅以低濃度存在於血漿中(5 μg/mL)。Andersson, Thrombosis Research 7: 451 459 (1975)。另外，自血液進行純化需要將諸如 HIV 及 HCV 之感染源移除或去活。此外，pdFIX 之半衰期短且因此需要頻繁給藥。重組因子 IX (rFIX)亦為可用的，但與 pdFIX 一樣，其半衰期短且需要頻繁給藥(例如就預防而言，每週 2-3

次)。

[0006] 死亡率降低、關節損傷之預防及生活品質之改善係由開發血漿源性 FIX 及重組 FIX 帶來的重要成就。長期防止出血將代表治療 B 型血友病受試者之另一關鍵進步。因此，仍需要具有較長半衰期，同時保持有效活性的改良之重組 FIX。

【發明內容】

[0007] 本發明揭示包括至少一個 XTEN 之特定因子 IX 融合蛋白。在一個態樣中，本發明提供一種因子 IX (FIX)融合蛋白，其包含 FIX 多肽及至少一個 XTEN，該 XTEN 插入該 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 2 之胺基酸 103、SEQ ID NO: 2 之胺基酸 105、SEQ ID NO: 2 之胺基酸 142、SEQ ID NO: 2 之胺基酸 149、SEQ ID NO: 2 之胺基酸 162、SEQ ID NO: 2 之胺基酸 166、SEQ ID NO: 2 之胺基酸 174、SEQ ID NO: 2 之胺基酸 224、SEQ ID NO: 2 之胺基酸 226、SEQ ID NO: 2 之胺基酸 228、SEQ ID NO: 2 之胺基酸 413 及其任何組合，且其中該 FIX 融合蛋白展現促凝血活性。

[0008] 本發明亦提供一種 FIX 融合蛋白，其包含 FIX 多肽及包含 XTEN 之異源部分，其中該 XTEN 與該 FIX 多肽之 C 末端融合且包含長度超過 42 個胺基酸且少於 144 個胺基酸的胺基酸序列。

[0009] 本發明之 FIX 融合蛋白具有若干用途，包括提供一種預防、治療、改善或管理有需要患者之凝血疾病或病症之方法。在一個實施例中，該方法包括投與有效量的本文所描述之 FIX 融合蛋白(例如藉由皮下投與)之步驟。

[0010] 本發明亦提供一種延長 FIX 多肽之半衰期的方法，其包含將 XTEN 插入該 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 2 之胺基酸 103、SEQ ID NO: 2 之胺基酸 105、SEQ ID NO: 2 之胺基酸 142、SEQ ID NO: 2 之胺基酸 149、SEQ ID NO: 2 之胺基酸 162、SEQ ID NO: 2 之胺基酸 166、SEQ ID NO: 2 之胺基酸 174、SEQ ID NO: 2 之胺基酸 224、SEQ ID NO: 2 之胺基酸 226、SEQ ID NO: 2 之胺基酸 228、SEQ ID NO: 2 之胺基酸 413 及其任何組合，由此構築 FIX 融合蛋白，且其中該 FIX 融合蛋白展現促凝血活性。

[0011] 自以下說明及附圖將易於瞭解其他發明實施例。

〔以引用方式之併入〕

[0012] 本文中揭示之所有出版物、專利及專利申請案均以引用之方式併入本文中，其引用程度就如同具體且個別地指示每一個別出版物、專利或專利申請案以引用之方式併入本文中一般。

【圖式簡單說明】

[0013] 圖 1 為描繪 FIX 融合蛋白之活性的圖，該等 FIX 融合蛋白包含插入各種插入位點(例如，胺基酸 52、胺基酸 59、胺基酸 66、胺基酸 80、胺基酸 85、胺基酸 89、胺基酸 103、胺基酸 105、胺基酸 113、胺基酸 129、胺基酸 142、胺基酸 149、胺基酸 162、胺基酸 166、胺基酸 174、胺基酸 188、胺基酸 202、胺基酸 224、胺基酸 226、胺基酸 228、胺基酸 230、胺基酸 240、胺基酸 257、胺基酸 265、胺基酸 277、胺基酸 283、胺基酸 292、胺基酸 316、胺基酸 341、胺基酸 354、胺基酸 392、胺基酸 403 及胺基酸 413，對應於 SEQ ID NO: 2 之胺基酸)或與該 FIX 多肽之 C 末端(C-terminus)(C 末端(C-term))融合的具有 42 個胺基酸(例如 AE42)之 XTEN。C 末端融合之 XTEN 在 FIX 與 C 末端融合物之間含有凝血酶可裂解位點。Y 軸顯示 FIX 活性，以藉由發色分析測定的基礎構築體(FIX-R338L)在條件培養基中之活性百分比表示。X 軸以胺基酸編號(對應於 SEQ ID NO: 2)及單字母胺基酸縮寫顯示具體插入位點。FIX 之相應結構域(例如，GLA、EGF1、EGF2、連接子、AP 及催化結構域)、連接子區及 C 末端(C-terminus)(「C 末端(C-term)」)在 X 軸下方指出。

[0014] 圖 2 係描繪 FIX 融合蛋白之活性的圖，該等 FIX 融合蛋白包含插入各種插入位點(例如，胺基酸 103、胺基酸 105、胺基酸 142、胺基酸 149、胺基酸 162、胺基

酸 166、胺基酸 174、胺基酸 224 及胺基酸 413，對應於 SEQ ID NO: 2 之胺基酸)或與 FIX 多肽之 C 末端 (C-terminus) (C 末端(C-term)，胺基酸 415)融合的具有 42 個胺基酸(AE42)、72 個胺基酸(AE72)、144 個胺基酸(AE144)、288 個胺基酸(AE288)及 864 個胺基酸(AE864)之 XTEN。Y 軸顯示 FIX 活性，以藉由發色分析測定的基礎構築體(FIX-R338L)在條件培養基中之活性百分比表示。X 軸以胺基酸編號(對應於 SEQ ID NO: 2)顯示每個插入位點之結構域(例如 EGF2、AP 及催化結構域)或區域(例如，連接子及 C 末端)及具體插入位點。箭頭指示選擇用於進一步實驗(參見圖 3A-3B)之插入位點。

[0015] 圖 3A 為 R338L FIX 變異體之區域及結構域之示意性表示。突出顯示作為潛在異源部分(例如 XTEN)插入位點之特定胺基酸殘基(例如 N105、D166 及 E224)及 C 末端。圖 3B 顯示自三個不同角度得到的豬 FIX (PDB:1PFX)之三維結構的圖解。標出插入位點 N105、D166 及 E224；C 末端；及 R338L 突變(例如在 R338L FIX 變異體中)之位置。

[0016] 圖 4 概述包含一個或兩個 XTEN(例如，具有 42 個、72 個、144 個及 288 個胺基酸之 XTEN)，或包含一個 XTEN 及一個 Fc 結構域或 FIXFc 之 FIX 融合蛋白的相對活性。Y 軸顯示 FIX 活性，以藉由發色分析測定的基礎構築體(FIX-R338L)在條件培養基中之活性百分比表示。X 軸顯示構築體編號，且 X 軸下方之表格顯示所測試

的每一構築體中 XTEN 及 Fc 之組成。EGF2 (105)、AP (166)、60 環(224)及 C 末端 XTEN 或 Fc 指示 XTEN 或 Fc 插入或融合之位置。X 軸下方之表格中每一格中之數字(例如，42、72、144 及 288，指示 XTEN 之大小)及「Fc」指示哪一部分插入 FIX 多肽內或與 FIX 多肽之 C 末端融合。

[0017] 圖 5A 提供描繪如在 B 型血友病小鼠中單次靜脈內推注給藥後所量測，相較於 rFIX 及 rFIXFc，對於具有各種長度之凝血酶可裂解 C 末端 XTEN 融合之各種 FIX 融合蛋白(例如，FIX-CT.288 (具有 288 個胺基酸之 XTEN，例如 AE288)及 FIX-CT.864 (具有 864 個胺基酸之 XTEN，例如 AE864)，給予 FIX 凝血活性劑之血漿百分含量隨時間變化的圖。圖 5B 提供描繪如在 B 型血友病小鼠中單次靜脈內推注給藥之後所量測，相較於 rFIX 及 rFIXFc，對於在活化肽(AP)結構域中插入各種長度之 XTEN 的各種 FIX 融合蛋白(例如，FIX-AP.144、FIX-AP.72 及 FIX-AP.42)，給予之 FIX 凝血活性劑之血漿百分含量隨時間變化的圖。圖 5C 提供圖 5A 及 5B 中所示之單次靜脈內推注給予 FIX 融合蛋白的藥物動力學參數計算值之圖解編輯。Y 軸上指示每一指定分子之血漿活性劑回收百分含量。X 軸顯示平均滯留時間(MRT，以小時為單位)計算值，且圓點區域表示在劑量曲線下面積之相對計算值(AUC/D，以 h/kg/mL 為單位)。

[0018] 圖 6A 提供描繪如在 B 型血友病小鼠中單次靜

脈內推注給藥之後所量測，相較於 rFIX 及 rFIXFc，對於在活化肽(AP)結構域(例如 FIXFc-AP.72 及 FIXFc-AP.42)或 EGF2 結構域(例如 FIXFc-EGF.42)中插入各種長度之 XTEN 融合物的各種 FIX 融合蛋白，給予之 FIX 凝血活性劑之血漿百分含量隨時間變化的圖。圖 6B 提供圖 6A 中所示之單次靜脈內推注給予 FIX 融合蛋白的藥物動力學參數計算值之圖解編輯。Y 軸上指示每一指定分子之血漿活性劑回收百分含量。X 軸指示平均滯留時間(MRT，以小時為單位)計算值。圓點區域表示在劑量曲線下面積之相對計算值(AUC/D，以 h/kg/mL 為單位)。

[0019] 圖 7A 提供描繪如在 B 型血友病小鼠中單次皮下推注給藥之後所量測，相較於 rFIX 及 rFIXFc，對於包含與 FIX 多肽之 C 末端融合的具有 288 個胺基酸之凝血酶可裂解 XTEN 之 FIX 融合蛋白(rFIX-CT.288)、包含插入 FIX 多肽之 AP 結構域內的具有 72 個胺基酸之 XTEN 之 FIX 融合蛋白(rFIXFc-AP.72)及包含插入 FIX 多肽之 EGF2 結構域內的具有 42 個胺基酸之 XTEN 之 FIX 融合蛋白(rFIXFc-EGF2.42)，給予之 FIX 凝血活性劑之血漿百分含量隨時間變化的圖。圖 7B 提供圖 7A 中所示之單次皮下推注給予 FIX 融合蛋白的藥物動力學參數計算值之圖解編輯。Y 軸上指示每一指定分子之生物利用率百分含量。X 軸指示平均滯留時間(MRT，以小時為單位)計算值。圓點區域表示在劑量曲線下面積之相對計算值(AUC/D，以 h/kg/mL 為單位)。

[0020] 圖 8A 提供在人 B 型血友病血液中藉由旋轉式血栓彈力測定法(rotational thromboelastometry，ROTEM)量測的 rFIXFc 及包含插入 FIX 之 AP 結構域內的具有 72 個胺基酸的 XTEN 之 FIX 融合蛋白(例如 rFIXFc-AP-XTEN.72)之凝血時間(以秒為單位)的圖解描繪。圖 8B 提供在人 B 型血友病血液中 rFIXFc 及 FIX 融合蛋白(例如 rFIXFc-AP-XTEN.72)之 α 角(以度為單位)的圖解描繪。圖 8C 提供在人 B 型血友病血液中 rFIXFc 及 FIX 融合蛋白(例如 rFIXFc-AP-XTEN.72)之最大凝塊強度(以 mm 為單位)的圖解描繪。

[0021] 圖 9 係顯示 rFIXFc-AP.72 與 rFIXFc 在尾截割出血模型中之急性功效之比較的圖。呈現之結果為在 30 分鐘治療期內給藥後 5 分鐘之個別及平均失血量(μl)及所指示之劑量。星號指示媒劑相對於所有其他治療組之顯著性 p 值。資料指示相較於 rFIXFc，給予小鼠 rFIXFc-AP.72 具有類似或改善之功效。

[0022] 圖 10 係顯示 HemB 小鼠存活率百分比(Y 軸)隨尾靜脈切斷後時間(以小時為單位；X 軸)之變化的圖。所有小鼠在尾靜脈切斷之前 72 小時以指定 IU/kg 經靜脈內預先給予 FIXFc(點劃線)或皮下預先給予 FIXFc-AP.72(FIXFc-AP.72：100 IU/kg(實心黑色圓圈)、50 IU/kg(實心灰色三角形)及 15 IU/kg(實心倒轉之灰色三角形)；rFIXFc：100 IU/kg (空心圓圈)、50 IU/kg (空心三角形)及 15 IU/kg (空心倒轉三角形))；及媒劑(實心灰色圓

圈)。當與媒劑治療之小鼠相比較時，給予 rFIXFc 或 FIXFc-AP.72 之小鼠的存活率曲線均顯著不同($p < 0.0001$，對數秩(Mantel-Cox)測試)。

[0023] 圖 11A 係顯示在藉由靜脈內(虛線)或皮下注射(實線)給予單次推注(200 IU/kg)之 rFIX(灰色)或 rFIXFc-AP.72 融合蛋白(黑色)之 B 型血友病小鼠中如藉由一級血漿分析量測之 FX 活性劑之血漿含量隨時間變化的圖。圖 11B 顯示如使用非房室分析(NCA)，使用 Phoenix WinNonLin 6.2.1 軟體(Pharsight, Certara)測定的藥物動力學參數。

[0024] 圖 12A 係說明 rFIXFc-AP.72 單鏈 Fc 之結構域結構的示意圖。圖 12B 係說明 rFIXFc-AP.72 雙鏈 Fc 之結構域結構的示意圖。「FIX HC」係指 FIX 之重鏈；「FIX LC」係指 FIX 之輕鏈，其包括 FIX 之 EGF 及 GLA 結構域；且 AP 係指 FIX 之活化肽。

[0025] 圖 13 係概述實例中使用之 FIX-XTEN 構築體及相配之序列標識符、說明及質體代碼之表格。

【實施方式】

[0026] 本發明提供一種包含 FIX 多肽及至少一個異源部分之 FIX 融合蛋白以及其製備及使用方法。在某些態樣中，FIX 融合蛋白包含插入 FIX 多肽內、與 FIX 多肽之 C 末端融合或兩者之至少一個異源部分，其中 FIX 融合蛋白展現促凝血活性。在一特定態樣中，該異源部分為

XTEN。

I. 定義

[0027] 在本發明通篇，術語「一個(種)」實體係指一或多個(種)該實體；舉例而言，「一個聚核苷酸」應理解為表示一或多個聚核苷酸。因此，術語「一個(種)」、「一或多個(種)」及「至少一個(種)」在本文中可互換使用。

[0028] 此外，「及/或」在本文中使用時應視為對兩個指定特徵或組分中之每一者在存在或不存在另一者之情況下的具體揭示。因此，如本文中在諸如「A及/或B」之片語中使用之術語「及/或」意欲包括「A及B」、「A或B」、「A」(單獨)及「B」(單獨)。同樣，如在諸如「A、B及/或C」之片語中使用之術語「及/或」意欲涵蓋以下態樣中之每一者：A、B及C；A、B或C；A或C；A或B；B或C；A及C；A及B；B及C；A(單獨)；B(單獨)；及C(單獨)。

[0029] 應理解，當在本文中用語言「包含」描述各態樣時，亦提供以「由...組成」及/或「實質上由...組成」之術語描述之其他相似態樣。

[0030] 除非另外定義，否則本文所使用之所有技術及科學術語皆具有與本發明所屬領域之一般技術人員通常所理解相同的含義。舉例而言，Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 第2

版，2002, CRC Press；The Dictionary of Cell and Molecular Biology, 第 3 版, 1999, Academic Press；及 Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press，向技術人員提供本發明所使用之許多術語的大體解釋。

[0031] 單位、前綴及符號皆以其國際單位制(Système International de Unites, (SI))公認形式表示。數字範圍包括界定該範圍之數字在內。除非另外指明，否則胺基酸序列係自左至右以胺基至羧基取向書寫。本文中提供之標題不限制本發明之各種態樣，該等態樣可藉由參考整個說明書得出。因此，即將在下文定義之術語藉由參照說明書全文進行更完整地定義。

[0032] 術語「約」在本文中用於意謂近似、大致、大約或在.....左右。當術語「約」與數字範圍結合使用時，其藉由使邊界擴展高於及低於所陳述之數字來修飾該範圍。一般而言，術語「約」可藉由例如向上或向下(增大或降低) 10%之變化來修飾高於或低於所述值之數值。

[0033] 術語「聚核苷酸」或「核苷酸」意欲涵蓋單個核酸以及複數個核酸，且係指分離之核酸分子或構築體，例如信使 RNA(mRNA)或質體 DNA(pDNA)。在某些實施例中，聚核苷酸包含習知磷酸二酯鍵或非習知鍵(例如醯胺鍵，諸如在肽核酸(PNA)中所發現的之醯胺鍵)。術語「核酸」係指聚核苷酸中存在的任一個或多個核酸區段，例如 DNA 或 RNA 片段。「分離之」核酸或聚核苷酸意欲

指已自其天然環境移出之核酸分子，即 DNA 或 RNA。舉例而言，出於本發明之目的，載體中所包含的編碼 FIX 多肽之重組聚核苷酸被視為分離之聚核苷酸。分離之聚核苷酸之其他實例包括維持在異源宿主細胞中或在溶液中自其他聚核苷酸純化(部分或實質上純化)之重組聚核苷酸。分離之 RNA 分子包括本發明之聚核苷酸之活體內或活體外 RNA 轉錄物。根據本發明之分離之聚核苷酸或核酸進一步包括以合成方式產生的此等分子。此外，聚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。

[0034] 如本文所用之「編碼區」或「編碼序列」為由可轉譯成胺基酸之密碼子組成的聚核苷酸之一部分。儘管「終止密碼子」(TAG、TGA 或 TAA)通常不轉譯成胺基酸，但其可被視為編碼區之一部分，不過任何側接序列，例如啟動子、核糖體結合位點、轉錄終止子、內含子及其類似序列，不為編碼區之一部分。編碼區之邊界通常由在 5'末端處之編碼所得多肽之胺基末端的起始密碼子及在 3'末端處編碼所得多肽之羧基末端之轉譯終止密碼子來確定。本發明之兩個或超過兩個編碼區可存在於單個聚核苷酸構築體中，例如在單個載體上；或存在於獨立聚核苷酸構築體中，例如在獨立(不同)載體上。單個載體又可僅含有單個編碼區，或包含兩個或超過兩個編碼區，例如單個載體可獨立地編碼如下文所描述之結合結構域 A 及結合結構域 B。此外，本發明之載體、聚核苷酸或核酸可編碼融

合或未融合至編碼本發明結合結構域之核酸的異源編碼區。異源編碼區包括(但不限於)特殊元件或基元，諸如分泌信號肽或異源功能結構域。

[0035] 哺乳動物細胞分泌之某些蛋白質與分泌信號肽締合，一旦逐漸增長之蛋白質鏈開始跨粗糙內質網輸出，該信號肽即自成熟蛋白質裂解。一般熟習此項技術者應明白，信號肽一般與多肽之 N 末端融合，且自完整或「全長」多肽裂解以產生該多肽之分泌或「成熟」形式。在某些實施例中，使用天然信號肽、或該序列之保留引導與其可操作地締合之多肽分泌之能力的功能性衍生物。或者，可使用異源哺乳動物信號肽，例如人類組織纖維蛋白溶酶原活化物(TPA)或小鼠 β-葡萄醣醛酸酶信號肽，或其功能性衍生物。

[0036] 術語「下游」係指位於參考核苷酸序列之 3' 方向之核苷酸序列。在某些實施例中，下游核苷酸序列係針對在轉錄起始點之後之序列。舉例而言，基因之轉譯起始密碼子位於轉錄起始位點之下游。「下游」亦可指位於參考肽序列之 C 末端的肽序列。

[0037] 術語「上游」係指位於參考核苷酸序列之 5' 方向之核苷酸序列。在某些實施例中，上游核苷酸序列係針對位於編碼區或轉錄起始點之 5'側之序列。舉例而言，大多數啟動子位於轉錄起始位點之上游。「上游」亦可指位於參考肽序列之 N 末端的肽序列。

[0038] 如本文所用，術語「調控區」係指位於編碼

區之上游(5'非編碼序列)、內部或下游(3'非編碼序列)，且影響所締合之編碼區之轉錄、RNA 加工、穩定性或轉譯之核苷酸序列。調控區可包括啟動子、轉譯前導序列、內含子、聚腺苷酸化識別序列、RNA 加工位點、效應物結合位點及莖-環結構。若編碼區意欲在真核細胞中表現，則聚腺苷酸化信號及轉錄終止序列通常將位於編碼序列之3'方向。

[0039] 編碼基因產物(例如多肽)之聚核苷酸可包括與一或多個編碼區可操作地締合之啟動子及/或其他轉錄或轉譯控制元件。在一可操作締合中，基因產物(例如多肽)之編碼區以將該基因產物之表現置於調控區之影響或控制下的方式與一或多個調控區締合。舉例而言，若誘導啟動子功能引起編碼由編碼區編碼之基因產物之 mRNA 的轉錄，且若啟動子與編碼區之間之鍵聯的性質不干擾啟動子引導基因產物表現之能力或不干擾轉錄 DNA 模板之能力，則編碼區及啟動子係「可操作地締合」。除啟動子之外的其他轉錄控制元件，例如增強子、操縱子、阻遏子及轉錄終止信號，亦可與編碼區可操作地締合以引導基因產物表現。

[0040] 熟習此項技術者已知多個轉錄控制區。該等轉錄控制區包括(但不限於)，在脊椎動物細胞中起作用之轉錄控制區，諸如但不限於，來自細胞巨大病毒(立即早期啟動子與內含子 A 之組合)、猿猴病毒 40(早期啟動子)及反轉錄病毒(諸如勞斯肉瘤病毒)之啟動子及增強子區

段。其他轉錄控制區包括源於脊椎動物基因，諸如肌動蛋白(actin)、熱休克蛋白、牛生長激素及兔 β-球蛋白之彼等控制區，以及能夠控制真核細胞中之基因表現之其他序列。其他適合的轉錄控制區包括組織特異性啟動子及增強子，以及淋巴因子(lymphokine)誘導性啟動子(例如可由干擾素或介白素誘導之啟動子)。

[0041] 類似地，一般熟習此項技術者已知多種轉譯控制元件。該等元件包括(但不限於)，核糖體結合位點、轉譯起始及終止密碼子，及源自於細小核糖核酸病毒之元件(特別是內部核糖體進入位點，或 IRES，又稱為 CITE 序列)。

[0042] 如本文所用，術語「表現」係指聚核苷酸藉以產生基因產物(例如 RNA 或多肽)之過程。其包括(但不限於)，聚核苷酸轉錄成信使 RNA(mRNA)、轉移 RNA(tRNA)、小髮夾 RNA(shRNA)、小干擾 RNA(siRNA)或任何其他 RNA 產物，及 mRNA 轉譯成多肽。表現產生「基因產物」。如本文所用，基因產物可為核酸(例如藉由基因轉錄產生之信使 RNA)或自轉錄物轉譯之多肽。本文所述之基因產物進一步包括具有轉錄後修飾(例如聚腺苷酸化或剪接)之核酸，或具有轉譯後修飾(例如甲基化、糖基化、添加脂質、與其他蛋白質次單元締合，或蛋白水解裂解)之多肽。

[0043] 「載體」係指用於將核酸選殖及/或轉移至宿主細胞中之任何媒介物。載體可為可與另一核酸區段連接

以使所連接區段複製之複製子。「複製子」係指在活體內充當自主複製單元，亦即，能夠在自身控制下複製之任何遺傳元件(例如質體、噬菌體、黏質體、染色體、病毒)。術語「載體」包括用於在活體外、離體或在活體內將核酸引入細胞中之病毒載體與非病毒載體。此項技術中已知且使用許多載體，包括例如質體、經修飾真核病毒或經修飾細菌病毒。將聚核苷酸插入適合載體中可藉由將適當聚核苷酸片段連接至具有互補黏性末端之所選載體中來達成。

[0044] 載體可經工程改造以編碼提供對已併有載體之細胞之選擇或鑑別的可選擇標記物或報導體。可選擇標記或報導體之表現允許鑑別及/或選擇併有且表現載體上含有之其他編碼區之宿主細胞。此項技術中已知且使用之可選擇標記物基因之實例包括：提供對胺苄青黴素(ampicillin)、鏈黴素(streptomycin)、健他黴素(gentamycin)、康黴素(kanamycin)、潮黴素(hygromycin)、新黴素(neomycin)、嘌呤黴素(puromycin)、雙丙胺膦(bialaphos)除草劑、磺醯胺及其類似物之抗性之基因；及用作表型標記物之基因，亦即，花青素(anthocyanin)調控基因、異戊基轉移酶基因及其類似物。此項技術中已知且使用之報導體之實例包括：螢光素酶(luciferase，Luc)、綠色螢光蛋白(GFP)、氯黴素乙醯轉移酶(CAT)、-半乳糖苷酶(galactosidase，LacZ)、-葡糖醛酸酶(glucuronidase，Gus)及其類似物。可選擇標記物亦可視為報導體。

[0045] 術語「質體」係指染色體外元件，其常攜帶

不為細胞之重要代謝之部分的基因，且通常呈環狀雙股DNA分子形式。此等元件可為源於任何來源之具有單股或雙股DNA或RNA之線性、環狀或超螺旋自主複製序列、基因組整合序列、噬菌體或核苷酸序列，其中許聚核苷酸序列已接合或重組成能夠將啟動子片段及所選基因產物之DNA序列連同適當3'未轉譯序列一起引入細胞中之獨特構造。

[0046] 可使用之真核病毒載體包括(但不限於)腺病毒載體、逆轉錄病毒載體、腺相關病毒載體及痘病毒(例如牛痘病毒)載體、桿狀病毒載體或皰疹病毒載體。非病毒載體包括質體、脂質體、帶電荷脂質(細胞轉染劑)、DNA-蛋白質複合物及生物聚合物。

[0047] 「選殖載體」係指一種「複製子」，其為依序複製且包含複製起點的單位長度之核酸(諸如質體、噬菌體或黏質體)，另一核酸區段可與其連接以達成所連接區段之複製。某些選殖載體能夠在一個細胞類型(例如細菌)中複製且在另一細胞類型(例如真核細胞)中表現。選殖載體通常包含一或多種可用於選擇包含載體之細胞之序列及/或一或多個用於插入相關核酸序列之多選殖位點。

[0048] 術語「表現載體」係指設計成使插入之核酸序列能夠在插入宿主細胞中之後表現之載體。插入之核酸序列係以與如上所述之調控區可操作締合之方式置放。

[0049] 藉由此項技術中熟知之方法將載體引入宿主細胞中，該等方法例如轉染、電穿孔、顯微注射、轉導、

細胞融合、DEAE 葡聚糖、磷酸鈣沈澱、脂質體轉染(溶酶體融合)、使用基因槍、或 DNA 載體轉運體(transporter)。

[0050] 如本文所用之「培養」意謂在允許細胞生長或分裂之活體外條件下培育細胞或意謂使細胞維持存活狀態。如本文所用之「培養細胞」意謂在活體外繁殖之細胞。

[0051] 如本文所用，術語「多肽」意欲涵蓋單數「多肽」以及複數「多肽」，且係指由醯胺鍵(亦稱為肽鍵)線性聯結之單體(胺基酸)所組成的分子。術語「多肽」係指具有兩個或超過兩個胺基酸之任何一或多條鏈，且不指代特定長度的產物。因此，肽、二肽、三肽、寡肽、「蛋白質」、「胺基酸鏈」或用於表示具有兩個或超過兩個胺基酸之一或多個鏈之任何其他術語均包括在「多肽」之定義內且術語「多肽」可替代任何此等術語使用或可與任何此等術語互換使用。術語「多肽」亦意欲代表具有多肽之表現後修飾之產物，該等修飾不加限制地包括糖基化、乙醯化、磷酸化、醯胺化、由已知保護/阻隔基團達成之衍生化、蛋白水解裂解、或由非天然存在之胺基酸達成之修飾。多肽可源於天然生物來源或藉由重組技術產生，但未必自指定核酸序列轉譯。其可以任何方式產生，包括藉由化學合成產生。

[0052] 「經分離」多肽或其片段、變異體或衍生物係指不在天然環境中之多肽。不要求特定純化程度。舉例

而言，經分離多肽可僅自其原生或天然環境移除。出於本發明之目的，在寄主細胞中表現的重組產生之多肽及蛋白質視為分離的，已藉由任何適合技術分離、分餾或部分地或實質上純化之天然或重組多肽亦視為分離的。

[0053] 如本文所用，術語「宿主細胞」係指帶有或能夠帶有重組核酸之細胞或細胞群體。宿主細胞可為原核細胞(例如大腸桿菌(*E. coli*))，或者，宿主細胞可為真核細胞，例如真菌細胞(例如酵母細胞，諸如釀酒酵母(*Saccharomyces cerevisiae*)、畢赤酵母(*Pichia pastoris*)或粟酒裂殖酵母(*Schizosaccharomyces pombe*))，及各種動物細胞，諸如昆蟲細胞(例如 Sf-9)或哺乳動物細胞(例如 HEK293F、CHO、COS-7、NIH-3T3)。

[0054] 本發明中亦包括多肽之片段或變異體及其任何組合。術語「片段」或「變異體」在關於本發明之多肽結合結構域或結合分子時包括保留參照多肽之至少一些特性(例如對 FcRn 結合結構域或 Fc 變異體之 FcRn 結合親和力或 FIX 變異體之凝血活性)之任何多肽。除在本文中其他地方論述之特定抗體片段之外，多肽之片段亦包括蛋白水解片段以及缺失片段，但不包括天然存在之全長多肽(或成熟多肽)。本發明之多肽結合結構域或結合分子之變異體包括如上所述之片段以及胺基酸序列歸因於胺基酸取代、缺失或插入而改變之多肽。變異體可為天然存在的或非天然存在的。非天然存在之變異體可使用此項技術已知之突變誘發技術來產生。變異多肽可包含保守或非保守胺

基酸取代、缺失或添加。本文所揭示之一個特定 FIX 變異體為 R338L FIX (Padua)變異體(SEQ ID NO: 2)。參見例如，Simioni, P.等人，「X-Linked Thrombophilia with a Mutant Factor IX (Factor IX Padua),」 *NEJM 361*:1671-75 (2009 年 10 月)，以全文引用之方式併入本文中。

[0055] 「保守胺基酸取代」為用具有相似側鏈之胺基酸殘基置換胺基酸殘基的取代。具有類似側鏈之胺基酸殘基之家族已在此項技術中加以定義，包括鹼性側鏈(例如離胺酸、精胺酸、組胺酸)、酸性側鏈(例如天冬胺酸、麩胺酸)、不帶電荷極性側鏈(例如甘胺酸、天冬醯胺、麩醯胺酸、絲胺酸、酥胺酸、酪胺酸、半胱胺酸)、非極性側鏈(例如丙胺酸、纈胺酸、白胺酸、異白胺酸、脯胺酸、苯丙胺酸、甲硫胺酸、色胺酸)、β-分支側鏈(例如酥胺酸、纈胺酸、異白胺酸)及芳族側鏈(例如酪胺酸、苯丙胺酸、色胺酸、組胺酸)。因此，若多肽中之胺基酸用來自同一側鏈家族之另一胺基酸置換，則將取代視為保守的。在另一實施例中，可將一連串胺基酸用側鏈家族成員之順序及/或組成不同的結構上相似的胺基酸串保守地置換。

[0056] 兩個聚核苷酸或多肽序列之間使用的術語「序列一致性百分比」係指在比較窗口上由該等序列共用的一致匹配位置數，其考慮到為進行兩個序列之最佳比對必須引入的添加或缺失(亦即間隙)。匹配位置為靶序列及參考序列二者中存在相同核苷酸或胺基酸的任何位置。靶

序列中存在的間隙不做計數，因為間隙不為核苷酸或胺基酸。同樣，參考序列中存在的間隙不做計數，因為對靶序列核苷酸或胺基酸計數，而不對來自參考序列之核苷酸或胺基酸計數。

[0057] 藉由以下方式來計算序列一致性百分比：測定兩個序列中存在相同胺基酸殘基或核酸鹼基之位置的數目以產生匹配位置之數目，用匹配位置之數目除以比較窗中位置之總數且將結果乘以 100 以產生序列一致性百分比。兩個序列之間序列之比較及序列一致性百分比的測定可使用供線上使用與下載兩者之可易於得到之軟體完成。適合軟體程式可自各種來源獲得，且可用於比對蛋白質及核苷酸序列。一種適於測定序列一致性百分比之程式為bl2seq，其為可自美國政府之國家生物技術資訊中心(National Center for Biotechnology Information)BLAST 網站(blast.ncbi.nlm.nih.gov)獲得之 BLAST 程式套件之一部分。Bl2seq 使用 BLASTN 或 BLASTP 算法進行兩個序列之間的比較。BLASTN 用於比較核酸序列，而 BLASTP 用於比較胺基酸序列。其他適合程式為例如 Needle、Stretcher、Water 或 Matcher，其為生物資訊程式之 EMBOSS 套件之部分，且亦可獲自歐洲生物資訊研究所(EBI)之 www.ebi.ac.uk/Tools/psa。

[0058] 與聚核苷酸或多肽參考序列比對的單個聚核苷酸或多肽靶序列內的不同區可各自具有其自身的序列一致性百分比。應注意，將序列一致性百分比值捨入至最接

近的十分位。舉例而言，將 80.11、80.12、80.13 及 80.14 向下捨入至 80.1，而將 80.15、80.16、80.17、80.18 及 80.19 向上捨入至 80.2。亦注意，長度值將始終為整數。

[0059] 熟習此項技術者將理解，產生用於計算序列一致性百分比的序列比對不限於唯一地由原始序列資料驅動之二進制序列-序列比較。序列比對可來源於多重序列比對。一種產生多序列比對之適合程式為 ClustalW2，可獲自 www.clustal.org。另一適合程式為 MUSCLE，可獲自 www.drive5.com/muscle/。ClustalW2 及 MUSCLE 可替代地獲自例如 EBI。

[0060] 亦應理解，序列比對可藉由序列資料與異質來源之資料的整合產生，該等異質來源之資料諸如結構資料(例如結晶蛋白結構)、功能資料(例如突變位置)或譜系學資料。整合異質資料以產生多重序列比對的適合程式為 T-Coffee，其獲自 www.tcoffee.org 且可替代地獲自例如 EBI。亦應瞭解用於計算序列一致性百分比之最終比對可自動或手動策劃。

[0061] 如本文所用，在因子 IX 蛋白質序列中「對應於……之胺基酸」、「對應於……之位點」或「等效胺基酸」係藉由對準以使第一 FIX 序列與第二 FIX 序列之間之一致性或相似性最大來鑑別。用於鑑別第二 FIX 序列中之等效胺基酸之編號係基於用於鑑別第一 FIX 序列中之相應胺基酸之編號。

[0062] 如本文所用，術語「插入位點」係指 aFIX 多

肽(通常為成熟 FIX 多肽)或其片段、變異體或衍生物中緊靠可插入異源部分之位置之上游的位置。以編號指定「插入位點」，該編號為 R388L FIX(Padua)變異體(SEQ ID NO: 2)中由插入位點所對應之胺基酸的編號，該胺基酸緊靠插入位置之 N 末端。舉例而言，片語「EGF2 結構域在對應於 SEQ ID NO: 2 之胺基酸 105 之插入位點處包含 XTEN」指示異源部分位於對應於 SEQ ID NO: 2 之胺基酸 105 及胺基酸 106 之兩個胺基酸之間。然而，熟習此項技術者將能夠容易地鑑別任何 FIX 變異體中之相應位置，且本發明不局限於僅在 R338L FIX (Padua)變異體中進行之插入。相反，本文所揭示之插入可在任何 FIX 變異體或其具有促凝血活性之片段中對應於 R338L FIX 變異體之位置處進行。

[0063] 如本文所用，片語「緊靠胺基酸之下游」係指緊接於胺基酸之末端羧基之位置。類似地，片語「緊靠胺基酸之上游」係指緊接於胺基酸之末端胺基之位置。因此，如本文所用，片語「在插入位點之兩個胺基酸之間」係指 XTEN 或任何其他多肽插入在兩個相鄰胺基酸之間所處之位置。

[0064] 如本文所用，術語「插入」、「經插入」、「插入...中」或語法相關術語係指相對於 R338L FIX(Padua)變異體(SEQ ID NO: 2)中之類似位置，XTEN 在融合多肽中之位置。本領域技術人員應理解如何鑑別與其他 FIX 多肽序列(如 SEQ ID NO:1 所示之序列)相應之插

入位置。如本文所用，該等術語係指重組 FIX 多肽相對於 R338L FIX(Padua)變異體之特徵，且不指示、暗示或意指製備融合多肽之任何方法或過程。舉例而言，對於本文提供之融合多肽，片語「將 XTEN 插入緊鄰 FIX 多肽之殘基 105 下游之 EGF2 結構域中」意謂該融合多肽在緊鄰對應於 R338L FIX 變異體(SEQ ID NO: 2)中之胺基酸 105 之胺基酸的下游包含 XTEN，其例如由對應於 R338L FIX 變異體之胺基酸 105 及 106 之胺基酸所界定。

[0065] 「融合」或「嵌合」蛋白包含第一胺基酸序列連接於在自然界中其未天然連接之第二胺基酸序列。通常存在於各別蛋白質中之胺基酸序列可集合在一起形成融合多肽，或通常存在於同一蛋白質中之胺基酸序列可以新排列安置在融合多肽中，該融合多肽例如為本發明之 FIX 結構域與 Ig Fc 結構域之融合物。融合蛋白係例如藉由化學合成，或藉由產生並轉譯肽區域以所需關係編碼之聚核苷酸來產生。融合蛋白可進一步包含藉由共價非肽鍵或非共價鍵與第一胺基酸序列締合之第二胺基酸序列。

[0066] 術語「異源」及「異源部分」意謂聚核苷酸、多肽或其他部分源於與其所比較之實體不同之實體。舉例而言，異源多肽可為合成多肽，或源於不同物種、個體之不同細胞類型或不同個體之相同或不同類型之細胞。在一個態樣中，異源部分係與另一多肽融合以產生融合多肽或蛋白質之多肽。在另一態樣中，異源部分係與多肽或蛋白質偶聯之非多肽部分，諸如 PEG。

[0067] 如本文所用，術語「半衰期」係指特定多肽在活體內之生物半衰期。半衰期可由向個體投與之一半數量自動物中之循環及/或其他組織清除所需的時間表示。當構築既定多肽隨時間而變之清除曲線時，曲線通常為雙相的，即快速 α 相及較長 β 相。α 相通常表示投與之多肽在血管內空間與血管外空間之間達到平衡且部分地由多肽之尺寸決定。β-相通常表示多肽於血管內空間中的分解代謝。在一些實施例中，FIX 及包含 FIX 之融合蛋白為單相的，且因此不具有 α 相，而僅具有單一 β 相。因此，在某些實施例中，如本文所用，術語半衰期係指多肽在 β 相中之半衰期。人體中人類抗體之典型 β 相半衰期為 21 日。

[0068] 如本文所用，術語「連接」及「融合」係指第一胺基酸序列或核苷酸序列分別共價或非共價接合至第二胺基酸序列或核苷酸序列。第一胺基酸或核苷酸序列可直接接合或相鄰於第二胺基酸或核苷酸序列，或者介入序列可將第一序列共價接合於第二序列。術語「連接」不僅意謂第一胺基酸序列在 C 末端或 N 末端融合於第二胺基酸序列，而且亦包括將整個第一胺基酸序列(或第二胺基酸序列)插入第二胺基酸序列(或相應地第一胺基酸序列)中之任何兩個胺基酸中。在一個實施例中，第一胺基酸序列係藉由肽鍵或連接子連接至第二胺基酸序列。第一核苷酸序列可藉由磷酸二酯鍵或連接子連接於第二核苷酸序列。連接子可為肽或多肽(用於多肽鏈)或核苷酸或核苷酸鏈(用於核苷酸鏈)或任何化學部分(用於多肽與聚核苷酸鏈兩

者)。術語「連接」亦藉由連字符(-)加以指示。

[0069] 如本文所用，術語「與...締合」係指第一條胺基酸鏈與第二條胺基酸鏈之間形成的共價鍵或非共價鍵。在一個實施例中，術語「與...締合」意謂共價非肽鍵或非共價鍵。此締合可由冒號，亦即(:)指示。在另一實施例中，其意謂除肽鍵之外的共價鍵。舉例而言，胺基酸半胱胺酸包含可與第二半胱胺酸殘基上之硫醇基形成二硫鍵或二硫橋之硫醇基。在大多數天然存在之 IgG 分子中，CH1 區與 CL 區藉由二硫鍵締合且兩個重鏈藉由兩個二硫鍵在對應於 239 及 242 之位置處締合，該等位置係使用 Kabat 編號系統(位置 226 或 229，EU 編號系統)。共價鍵之實例包括(但不限於)肽鍵、金屬鍵、氫鍵、二硫鍵、ζ 鍵、π 鍵、δ 鍵、糖苷鍵、抓氫鍵、彎曲鍵、偶極鍵、π 反向鍵、雙鍵、參鍵、四鍵、五鍵、六鍵、結合、超結合、芳香性、哈普托數(hapticity)或反鍵結。非共價鍵之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、二氫複合物、低障壁氫鍵或對稱氫鍵)、凡得瓦力(van der Walls force)、倫敦分散力(London dispersion force)、機械鍵(mechanical bond)、鹵素鍵、親金作用(aurophilicity)、嵌入、堆積作用、熵力(entropic force)或化學極性。

[0070] 如本文所用，術語「裂解位點」或「酶促裂解位點」係指由酶識別之位點。某些酶促裂解位點包含細胞內加工位點。在一個實施例中，多肽具有由在凝結級聯

期間活化之酶裂解之酶促裂解位點，因此此等位點之裂解發生在凝塊形成之部位處。示範性此類位點包括例如由凝血酶、因子 XIa 或因子 Xa 識別者。示範性 FXIa 裂解位點包括例如 TQSFNDFTR(SEQ ID NO: 166)及 SVSQTSKLTR (SEQ ID NO: 167)。示範性凝血酶裂解位點包括例如 DFLAEGGGVR(SEQ ID NO: 168)、TTKIKPR(SEQ ID NO: 169)、LVPRG(SEQ ID NO: 170)及 ALRPR(SEQ ID NO: 171)。其他酶促裂解位點在此項技術中為已知的。

[0071] 如本文所用，術語「加工位點」或「細胞內加工位點」係指多肽中一種類型之酶促裂解位點，其為在該多肽轉譯之後起作用之酶的目標。在一個實施例中，此等酶在自高爾基體腔(Golgi lumen)轉運至反面高爾基體(trans-Golgi)區室期間起作用。細胞內加工酶在蛋白質自細胞分泌之前裂解多肽。此等加工位點之實例包括例如由內肽酶之 PACE/弗林蛋白酶(furin)(其中 PACE 為成對鹼性胺基酸裂解酶(Paired basic Amino acid Cleaving Enzyme)之頭字語)家族所靶向者。此等酶定位於高爾基體膜且在序列基元 Arg-[任何殘基]-(Lys 或 Arg)-Arg 之羧基端側上裂解蛋白質。如本文所用，「弗林蛋白酶」酶家族包括例如 PCSK1(亦稱為 PC1/Pc3)、PCSK2(亦稱為 PC2)、PCSK3(亦稱為弗林蛋白酶或 PACE)、PCSK4(亦稱為 PC4)、PCSK5(亦稱為 PC5 或 PC6)、PCSK6(亦稱為 PACE4)、或 PCSK7(亦稱為 PC7/LPC、PC8 或 SPC7)。其他加工位點係此項技術中已知的。本文中提及之術語「可

加工連接子」意謂包含細胞內加工位點之連接子。

[0072] 在包括一個以上加工或裂解位點之構築體中，應瞭解此等位點可相同或不同。

[0073] 如本文所用，「可加工連接子」係指包含至少一個在本文中其他地方描述之細胞內加工位點的連接子。

[0074] 如本文所用，「基線」為在投與劑量之前受試者中之最低量測血漿 FIX 含量。FIX 血漿含量可在給藥之前之兩個時間點量測：在篩檢訪視時及即將給藥之前。或者，(a)治療前 FIX 活性<1%、不具有可偵測 FIX 抗原且具有無意義基因型之受試者之基線可定義為 0%，(b)治療前 FIX 活性<1%且具有可偵測 FIX 抗原之受試者之基線可設置為 0.5%，(c)治療前 FIX 活性在 1-2%之間的受試者之基線為 Cmin (在整個 PK 研究期間之最低活性)，及(d)治療前 FIX 活性≥2%之受試者之基線可設置為 2%。

[0075] 如本文所用之「受試者」意謂人類。如本文所用之受試者包括以下個體：已知發生過至少一次不受控制之出血事件；已診斷有與不受控制之出血事件相關之疾病或病症例如出血疾病或病症，例如 B 型血友病；易患不受控制之出血事件例如血友病；或其任何組合。受試者亦可包括在某一活動例如手術、運動活動或任何劇烈活動之前處於一或多個不可控制出血事件之危險中的個體。受試者之基線 FIX 活性可小於 1%、小於 0.5%、小於 2%、小於 2.5%、小於 3%或小於 4%。受試者亦包括兒童。兒童

受試者之年齡為出生至 20 歲、較佳為出生至 18 歲、出生至 16 歲、出生至 15 歲、出生至 12 歲、出生至 11 歲、出生至 6 歲、出生至 5 歲、出生至 2 歲、及 2 至 11 歲。

[0076] 如本文所用之治療係指例如減輕疾病或病狀之嚴重性；降低疾病病程之持續時間；改善與疾病或病狀相關之一或多種症狀；向患有疾病或病狀之個體提供有益效應，未必治癒該疾病或病狀；或防治與疾病或病狀相關之一或多種症狀。在一個實施例中，術語「治療(treating/treatment)」意謂藉由投與本發明之融合蛋白來使受試者之 FIX 谷底含量維持在至少約 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。在另一實施例中，治療意謂維持 FIX 谷底含量在以下之間：約 1 與約 20 IU/dL、約 2 與約 20 IU/dL、約 3 與約 20 IU/dL、約 4 與約 20 IU/dL、約 5 與約 20 IU/dL、約 6 與約 20 IU/dL、約 7 與約 20 IU/dL、約 8 與約 20 IU/dL、約 9 與約 20 IU/dL、或約 10 與約 20 IU/dL。治療疾病或病狀亦可包括維持受試者體內之 FIX 活性在相當於非血友病受試者體內 FIX 活性之至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、11%、12%、13%、14%、15%、16%、17%、18%、19%或 20%水準。治療所需之最小谷底含量可藉由一或多種已知方法加以量測且可針對每個人加以調整(增加或減

少)。

[0077] 如本文所用之止血障礙意謂特徵在於由於形成纖維蛋白凝塊之能力受損或不能形成纖維蛋白凝塊而有自發出血或由於創傷而出血之傾向的基因遺傳性或獲得性病狀。此等病症之實例包括血友病。三種主要形式為 A 型血友病(因子 VIII 缺乏)、B 型血友病(因子 IX 缺乏或「克雷司馬斯病(Christmas disease)」)及 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範威爾邦德病；因子 XI 缺乏症(PTA 缺乏症)；因子 XII 缺乏症；纖維蛋白原、凝血酶原、因子 V、因子 VII、因子 X 或因子 XIII 缺乏症或結構異常；伯納德-蘇里爾症候群(Bernard-Soulier syndrome)，其為一種 GPIb 缺陷症或缺乏症。VWF 之受體 GPIb 可為有缺陷的且導致缺乏初級凝塊形成(初級止血)及流血傾向增加、以及格蘭茨曼(Glanzman) 及內格利 (Naegeli) 血小板無力症(thrombasthenia)(格蘭茨曼血小板無力症)。在肝衰竭(急性及慢性形式)中，由肝產生之凝血因子存在不足；此可增加流血風險。

[0078] 如本文所用，術語「急性流血」係指無論潛伏原因如何之流血事件。舉例而言，受試者可具有創傷、尿毒症、遺傳性出血病症(例如因子 VII 缺乏症)、血小板病症，或由於產生針對凝血因子之抗體而具有抗性。

II. FIX 融合蛋白

[0079] 本發明係針對一種包含 FIX 多肽及至少一個異源部分之 FIX 融合蛋白，該至少一個異源部分插入該 FIX 多肽內、與該 FIX 多肽之 C 末端融合或兩者。在異源部分插入或與異源部分融合之後，FIX 融合蛋白可保持一或多種 FIX 活性。在一個實施例中，FIX 活性為促凝血活性。「促凝血活性」意謂本發明之 FIX 蛋白能夠替代原生 FIX 參與血液中之凝血級聯。舉例而言，當本發明之重組 FIX 蛋白在因子 VIII(FVIII)存在下將因子 X(FX)轉化成活化因子 X(FXa)時具有促凝血活性，如例如在發色分析中所測試。在另一實施例中，FIX 活性係產生因子 X 活化酶(tenase)複合體的能力。在其他實施例中，FIX 活性係產生凝血酶(或凝塊)的能力。

[0080] 本發明之重組 FIX 蛋白無需展現原生成熟人類 FIX 之 100%促凝血活性。實際上，在某些態樣中，插入本發明之 FIX 多肽中之異源部分可使蛋白質之半衰期顯著延長或穩定性顯著增強，因此較低活性係完全可接受。因此，在某些態樣中，本發明之 FIX 融合蛋白具有原生 FIX 之至少約 10%、約 20%、約 30%、約 40%、約 50%、約 60%、約 70%、約 80%、約 90%或約 100%促凝血活性。然而，在本發明之一些實施例中，對於含有 FIX Padua R338L 高活性變異體之蛋白質，本發明之重組 FIX 蛋白可具有超過 100%之原生 FIX 活性，例如該活性之至少約 105%、110%、120%、130%、140%、150%、160%、170%、180%、190%或 200%。

[0081] 促凝血活性可藉由任何適合之活體外或活體內分析加以量測。FIX 之活性可在凝血級聯之下游藉由監測凝塊產生(凝血分析)或在上游藉由直接量測 FX 在藉由 FVIII-FIX 複合物活化之後的酶活性(發色分析)來加以量測(參見例如 Barrowcliffe 等人, *Semin. Thromb. Haemost.* 28: 247-56 (2002)；Lee 等人, *Thromb. Haemost.* 82: 1644-47 (1999)；Lippi 等人, *Clin. Chem. Lab. Med.* 45: 2-12 (2007)；Matsumoto 等人, J. *Thromb. Haemost.* 4: 377-84 (2006))。因此，促凝血活性可使用發色受質分析、凝血分析(例如單級或兩級凝血分析)或兩者加以量測。發色分析機制係基於凝血級聯之原理，其中活化之 FIX 在活化 FVIII、磷脂及鈣離子存在下將 FX 轉化成 FX_a。藉由使針對 FX_a 具有特異性之對硝基醯苯胺(pNA)受質水解來評估 FX_a 活性。在 405 nM 下量測的對硝基苯胺之初始釋放速率與 FX_a 活性成正比且因此與樣品中之 FIX 活性成正比。顯色分析由國際血栓暨止血學會(ISTH)之科學及標準化委員會(SSC)之因子 VIII 及因子 IX 小組委員會所推薦。

[0082] 適用於測定促凝血活性之其他適合分析包括例如 Scheiflinger 及 Dockal 之美國申請公開案第 2010/0022445 號中所揭示者，該公開案以全文引用的方式併入本文中。

[0083] 在某些態樣中，將本發明之重組 FIX 蛋白之促凝血活性與原生成熟 FIX 相比較，在某些態樣中，將其與國際標準相比較。

[0084] 該至少一個異源部分(如以下更詳細地描述)可包含任何異源部分，或可為能使 FIX 蛋白具有改善之特性的部分。舉例而言，在一個態樣中，可用於本發明之異源部分可為能夠延長 FIX 蛋白之半衰期的部分，或能夠改善 FIX 蛋白之穩定性的部分。本發明之 FIX 融合蛋白可具有超過一個異源部分插入 FIX 多肽中或與 FIX 多肽融合。在一個實施例中，該超過一個異源部分係相同的。在另一實施例中，該超過一個異源部分係不同的。在其他實施例中，該異源部分係選自由以下組成之群：XTEN、白蛋白、白蛋白結合肽、白蛋白小結合分子、Fc 結構域、FcRn 結合搭配物、PAS、CTP、PEG、HES、PSA 或其任何組合。

[0085] 在一些實施例中，將至少一個異源部分插入 FIX 多肽的一個結構域內，而非多個結構域之間。FIX 多肽包含多個結構域，例如，γ-羧基麩胺酸(GLA)結構域、類表皮生長因子 1(EGF1)結構域、類表皮生長因子 2(EGF2)結構域、活化肽(AP)結構域、在 EGF2 結構域與 AP 結構域之間之連接子，及催化結構域(例如，絲胺酸蛋白酶結構域)。FIX 酶原包含 461 個胺基酸：胺基酸 1-28 (對應於 SEQ ID NO: 3)為信號肽；胺基酸 29-46 (對應於 SEQ ID NO: 3)為前肽；隨後為 415 個胺基酸之 FIX 蛋白質序列。此具有 415 個胺基酸之經加工 FIX 包含胺基酸 1-145 (對應於 SEQ ID NO: 1 或 SEQ ID NO: 2)為 FIX 輕鏈；胺基酸 146-180 為活化肽；且胺基酸 181 至 415 (對

應於 SEQ ID NO: 1 或 SEQ ID NO: 2)為催化性 FIX 重鏈。在輕鏈及重鏈內，GLA 結構域對應於 SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 1 至 46；EGF1 結構域對應於 SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 47 至 84；EGF2 結構域對應於 SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 85 至 127；在 EGF2 結構域與 AP 結構域之間之連接子對應於 SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 128 至 145；AP 結構域對應於 SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 146 至 180；且催化結構域對應於 SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 181 至 415。

[0086] 在某些實施例中，將至少一個異源部分插入 FIX 多肽之一或多個結構域內。舉例而言，至少一個異源部分，例如 XTEN，可插入選自由以下組成之群之結構域內：GLA 結構域、EGF1 結構域、EGF2 結構域、AP 結構域、在 EGF2 結構域與 AP 結構域之間之連接子、催化結構域及其任何組合。在一個特定實施例中，將該至少一個異源部分，例如 XTEN，插入 GLA 結構域內，例如 SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 1 至 46 內。在一個特定實施例中，將該至少一個異源部分，例如 XTEN，插入 EGF1 結構域內，例如 SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 47 至 83 內。在一個特定實施例中，將該至少一個異源部分，例如 XTEN，插入 EGF2 結構域內，例如 SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 84 至 125 內。在一些實施例中，將該至少一個異源部分，例如 XTEN，插入在

EGF2 結構域與 AP 結構域之間之連接子內，例如 SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 132 至 145 內。在一個特定實施例中，將該至少一個異源部分，例如 XTEN，插入 AP 結構域內，例如 SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 146 至 180 內。在一些實施例中，將該至少一個異源部分，例如 XTEN，插入催化結構域內，例如 SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 181 至 415 內。

[0087] 在一些實施例中，可將一或多個異源部分插入各種插入位點內。在某些實施例中，在該等位點中之一或多個處插入至少一個異源部分，例如 XTEN，不會引起 FIX 活性之損失及/或誘導 FIX 蛋白質特性之改善。舉例而言，可將至少一個異源部分插入 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 2 之胺基酸 103(亦即，緊靠對應於 SEQ ID NO: 2 之胺基酸 103 之胺基酸的下游)、SEQ ID NO: 2 之胺基酸 105 (亦即，緊靠對應於 SEQ ID NO: 2 之胺基酸 105 之胺基酸的下游)、SEQ ID NO: 2 之胺基酸 142 (亦即，緊靠對應於 SEQ ID NO: 2 之胺基酸 142 之胺基酸的下游)、SEQ ID NO: 2 之胺基酸 149 (亦即，緊靠對應於 SEQ ID NO: 2 之胺基酸 149 之胺基酸的下游)、SEQ ID NO: 2 之胺基酸 162 (亦即，緊靠對應於 SEQ ID NO: 2 之胺基酸 162 之胺基酸的下游)、SEQ ID NO: 2 之胺基酸 166 (亦即，緊靠對應於 SEQ ID NO: 2 之胺基酸 166 之胺基酸的下游)、SEQ ID NO: 2 之胺基酸 174 (亦即，緊靠對應於 SEQ ID NO: 2 之

胺基酸 174 之胺基酸的下游)、SEQ ID NO: 2 之胺基酸 224 (亦即，緊靠對應於 SEQ ID NO: 2 之胺基酸 224 之胺基酸的下游)、SEQ ID NO: 2 之胺基酸 226 (亦即，緊靠對應於 SEQ ID NO: 2 之胺基酸 226 之胺基酸的下游)、SEQ ID NO: 2 之胺基酸 228 (亦即，緊靠對應於 SEQ ID NO: 2 之胺基酸 228 之胺基酸的下游)、SEQ ID NO: 2 之胺基酸 413 (亦即，緊靠對應於 SEQ ID NO: 2 之胺基酸 413 之胺基酸的下游)及其任何組合，其中 FIX 融合蛋白展現促凝血活性。

[0088] 在一個實施例中，將異源部分，例如 XTEN，插入 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 149、SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 162、SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 166、SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 174，及其任何組合。在一個實施例中，將異源部分，例如 XTEN，插入 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 224、SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 226、SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 228、SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 413，及其任何組合。在其他實施例中，將異源部分，例如 XTEN，插入 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 103、SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 105 及

二者。在另一實施例中，將異源部分，例如 XTEN，插入 FIX 多肽內對應於 SEQ ID NO: 1 或 SEQ ID NO: 2 之胺基酸 142 的插入位點。

[0089] 如以下更詳細地論述，異源部分可為具有不同長度之 XTEN。舉例而言，XTEN 可包含至少約 42 個胺基酸、至少約 72 個胺基酸、至少約 144 個胺基酸、至少約 288 個胺基酸或至少約 864 個胺基酸。在一些實施例中，XTEN 係選自由以下組成之群：AE42、AG42、AE72、AG72、AE144、AG144、AE288、AG288、AE864 及 AG864。可插入 FIX 多肽中或與 FIX 多肽融合之 XTEN 的非限制性實例包括在本文別處。

[0090] 在一些實施例中，將包含 42 個胺基酸之 XTEN，例如 AE42 或 AG42，插入 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 1 或 2 之胺基酸 103、SEQ ID NO: 1 或 2 之胺基酸 105、SEQ ID NO: 1 或 2 之胺基酸 142、SEQ ID NO: 1 或 2 之胺基酸 149、SEQ ID NO: 1 或 2 之胺基酸 162、SEQ ID NO: 1 或 2 之胺基酸 166、SEQ ID NO: 1 或 2 之胺基酸 174、SEQ ID NO: 1 或 2 之胺基酸 224、SEQ ID NO: 1 或 2 之胺基酸 226、SEQ ID NO: 1 或 2 之胺基酸 228、SEQ ID NO: 1 或 2 之胺基酸 413 及其任何組合，其中 FIX 融合蛋白展現促凝血活性。

[0091] 在一些實施例中，將包含 72 個胺基酸之 XTEN，例如 AE72 或 AG72，插入 FIX 多肽內對應於選自

由以下組成之群之胺基酸的插入位點：SEQ ID NO: 1 或 2 之胺基酸 149、SEQ ID NO: 1 或 2 之胺基酸 162、SEQ ID NO: 1 或 2 之胺基酸 166、SEQ ID NO: 1 或 2 之胺基酸 174、SEQ ID NO: 1 或 2 之胺基酸 224、SEQ ID NO: 1 或 2 之胺基酸 226、SEQ ID NO: 1 或 2 之胺基酸 228、SEQ ID NO: 1 或 2 之胺基酸 413 及其任何組合，或 XTEN 與 C 末端融合，其中 FIX 融合蛋白展現促凝血活性。

[0092] 在一些實施例中，將包含 144 個胺基酸之 XTEN，例如 AE144 或 AG144，插入 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 1 或 2 之胺基酸 149、SEQ ID NO: 1 或 2 之胺基酸 162、SEQ ID NO: 1 或 2 之胺基酸 166、SEQ ID NO: 1 或 2 之胺基酸 174、SEQ ID NO: 1 或 2 之胺基酸 224、SEQ ID NO: 1 或 2 之胺基酸 226、SEQ ID NO: 1 或 2 之胺基酸 228、SEQ ID NO: 1 或 2 之胺基酸 413 及其任何組合，其中 FIX 融合蛋白展現促凝血活性。

[0093] 在一些實施例中，將包含 288 個胺基酸之 XTEN，例如 AE288 或 AG288，插入 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 1 或 2 之胺基酸 149、SEQ ID NO: 1 或 2 之胺基酸 162、SEQ ID NO: 1 或 2 之胺基酸 166、SEQ ID NO: 1 或 2 之胺基酸 174、SEQ ID NO: 1 或 2 之胺基酸 224、SEQ ID NO: 1 或 2 之胺基酸 226、SEQ ID NO: 1 或 2 之胺基酸 228、SEQ ID NO: 1 或 2 之胺基酸 413 及其任何組合，其中 FIX 融合

蛋白展現促凝血活性。

[0094] 在又其他實施例中，將包含 864 個胺基酸之 XTEN，例如 AE864 或 AG8648，插入 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 1 或 2 之胺基酸 149、SEQ ID NO: 1 或 2 之胺基酸 162、SEQ ID NO: 1 或 2 之胺基酸 166、SEQ ID NO: 1 或 2 之胺基酸 174、SEQ ID NO: 1 或 2 之胺基酸 224、SEQ ID NO: 1 或 2 之胺基酸 224、SEQ ID NO: 1 或 2 之胺基酸 226、SEQ ID NO: 1 或 2 之胺基酸 228、SEQ ID NO: 1 或 2 之胺基酸 413 及其任何組合，其中 FIX 融合蛋白展現促凝血活性。

[0095] 本發明之 FIX 融合蛋白可另外包含插入 FIX 內、與 FIX 之 C 末端融合或兩者的第二異源部分，例如第二 XTEN。該第二異源部分可插入 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 1 或 2 之胺基酸 103、SEQ ID NO: 1 或 2 之胺基酸 105、SEQ ID NO: 1 或 2 之胺基酸 142、SEQ ID NO: 1 或 2 之胺基酸 149、SEQ ID NO: 1 或 2 之胺基酸 162、SEQ ID NO: 1 或 2 之胺基酸 166、SEQ ID NO: 1 或 2 之胺基酸 174、SEQ ID NO: 1 或 2 之胺基酸 224、SEQ ID NO: 1 或 2 之胺基酸 226、SEQ ID NO: 1 或 2 之胺基酸 228、SEQ ID NO: 1 或 2 之胺基酸 413 及其任何組合，或其中該第二 XTEN 與 FIX 多肽之 C 末端融合。在一些實施例中，將第一 XTEN 及第二 XTEN 分別插入 FIX 多肽內對應於選自由以下組成

之群的 SEQ ID NO: 1 或 2 之胺基酸的插入位點及/或與 FIX 多肽之 C 末端融合：SEQ ID NO: 1 或 2 之胺基酸 105 及 SEQ ID NO: 1 或 2 之胺基酸 166；SEQ ID NO: 1 或 2 之胺基酸 105 及 SEQ ID NO: 1 或 2 之胺基酸 224；SEQ ID NO: 1 或 2 之胺基酸 105 及與 C 末端融合；SEQ ID NO: 1 或 2 之胺基酸 166 及 SEQ ID NO: 1 或 2 之胺基酸 224；SEQ ID NO: 1 或 2 之胺基酸 166 及與 C 末端融合；以及 SEQ ID NO: 1 或 2 之胺基酸 224 及與 C 末端融合。在一個實施例中，將第一 XTEN 插入 FIX 多肽內對應於 SEQ ID NO: 1 或 2 之胺基酸 166 的插入位點，且第二 XTEN 與 FIX 多肽之 C 末端融合。

[0096] 該第二 XTEN 可包含至少約 6 個胺基酸、至少約 12 個胺基酸、至少約 36 個胺基酸、至少約 42 個胺基酸、至少約 72 個胺基酸、至少約 144 個胺基酸或至少約 288 個胺基酸。在一些實施例中，該第二 XTEN 包含 6 個胺基酸、12 個胺基酸、36 個胺基酸、42 個胺基酸、72 個胺基酸、144 個胺基酸或 288 個胺基酸。該第二 XTEN 可選自由以下組成之群：AE42、AE72、AE864、AE576、AE288、AE144、AG864、AG576、AG288、AG144 及其任何組合。在一特定實施例中，該第二 XTEN 為 AE72 或 AE144。

[0097] 在一特定實施例中，該第二 XTEN 包含與選自由以下組成之群之氨基酸序列具有至少約 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%一致性的胺基酸序列：SEQ ID NO: 34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49、50、51、52、53及其任何組合。

[0098] 在一些實施例中，FIX 融合蛋白另外包含第三、第四、第五及/或第六 XTEN。

[0099] 在一些實施例中，FIX 融合蛋白包含與選自由不含信號肽及前肽序列之 SEQ ID NO: 54 至 SEQ ID NO: 153 組成之群的序列具有至少約 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%一致性的胺基酸序列。在某些實施例中，FIX 融合蛋白包含選自由不含信號肽及前肽序列之 SEQ ID NO: 54 至 SEQ ID NO: 153 組成之群的胺基酸序列。在一些實施例中，FIX 融合蛋白包含與選自由不含信號肽及前肽序列之 SEQ ID NO: 119、120、121 及 123 組成之群的序列具有至少約 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%一致性的胺基酸序列。在另一實施例中，FIX 融合蛋白包含選自由不含信號肽及前肽序列之 SEQ ID NO: 119、120、123、121 及 226 或 122 組成之群的胺基酸序列。在一些實施例中，FIX 融合蛋白係選自由以下組成之群：FIX-AP.72、FIX-AP.144、FIX-CT.72、FIX-CT.144、FIX-AP.288 及 FIX-CT.288，該等融合蛋白不含信號肽及前肽序列。

[0100] 在一些實施例中，FIX融合蛋白包含兩種不同類型之異源部分。在一些實施例中，FIX 融合蛋白包含FIX 多肽、XTEN 及 Fc 結構域(或 FcRn 結合搭配物)或其片段。在一些實施例中，XTEN 插入 FIX 內，且 Fc 結構域(或 FcRn 結合搭配物)或其片段與 FIX 之 C 末端融合。在一些實施例中，XTEN 插入 FIX 多肽內選自表 3 中所列插入位點之一或多個插入位點。在一個實施例中，XTEN 插入 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 1 或 2 之胺基酸 103、SEQ ID NO: 1 或 2 之胺基酸 105、SEQ ID NO: 1 或 2 之胺基酸 142、SEQ ID NO: 1 或 2 之胺基酸 149、SEQ ID NO: 1 或 2 之胺基酸 162、SEQ ID NO: 1 或 2 之胺基酸 166、SEQ ID NO: 1 或 2 之胺基酸 174、SEQ ID NO: 1 或 2 之胺基酸 224、SEQ ID NO: 1 或 2 之胺基酸 226、SEQ ID NO: 1 或 2 之胺基酸 228、SEQ ID NO: 1 或 2 之胺基酸 413 及其任何組合；且 Fc 結構域(或 FcRn 結合搭配物)或其片段與 FIX 之 C 末端融合。在某些實施例中，XTEN 插入 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 1 或 2 之胺基酸 105、SEQ ID NO: 1 或 2 之胺基酸 166 及 SEQ ID NO: 1 或 2 之胺基酸 224；且 Fc 結構域(或 FcRn 結合搭配物)或其片段與 FIX 之 C 末端融合。在一些實施例中，XTEN 係選自 AE42、AE72 及 AE144。

[0101] 在本發明某些態樣中，FIX 融合蛋白包含一條或兩條多肽鏈。在一個實施例中，FIX 融合蛋白包含兩條

多肽鏈，其中第一多肽鏈包含與 Fc 結構域(或 FcRn 結合搭配物)融合之 FIX 多肽，且第二多肽鏈包含第二 Fc 結構域，其中第一 Fc 結構域(或 FcRn 結合搭配物)與第二 Fc 結構域(或 FcRn 結合搭配物)藉由共價鍵締合。

[0102] 在另一實施例中，FIX 融合蛋白包含單一多肽鏈，該多肽鏈包含 FIX 多肽及 Fc 結構域(或 FcRn 結合搭配物)。在一特定實施例中，FIX 融合蛋白另外包含連接子，該連接子連接 FIX 多肽及 Fc 結構域(或 FcRn 結合搭配物)。在另一實施例中，FIX 融合蛋白包含 FIX 多肽、Fc 結構域及第二 Fc 結構域(或 FcRn 結合搭配物)。在一特定實施例中，FIX 融合蛋白另外包含連接子，該連接子連接 Fc 結構域(或 FcRn 結合搭配物)與第二 Fc 結構域(或 FcRn 結合搭配物)。在另一實施例中，FIX 融合蛋白包含 FIX 多肽、Fc 結構域(或 FcRn 結合搭配物)及第二 Fc 結構域(或 FcRn 結合搭配物)，其中 FIX 多肽藉由連接子連接至 Fc 結構域(或 FcRn 結合搭配物)。在另一實施例中，FIX 融合蛋白包含 FIX 多肽、Fc 結構域(或 FcRn 結合搭配物)及第二 Fc 結構域(或 FcRn 結合搭配物)，其中 FIX 多肽藉由第一連接子連接至 Fc 結構域(或 FcRn 結合搭配物)，且其中該 Fc 結構域(或 FcRn 結合搭配物)藉由連接子連接至第二 Fc 結構域(或 FcRn 結合搭配物)。在某些實施例中，FIX 融合蛋白包含選自由以下組成之群之式：

(i) FIX(X)-F1；

(ii) FIX(X)-L1-F1；

(iii) FIX(X)-F1-F2；

(iv) FIX(X)-L1-F1-F2；

(v) FIX(X)-L1-F1-L2-F2；

(vi) FIX(X)-F1-L1-F2；

(vii) FIX(X)-F1:F2；

(viii) FIX(X)-L1-F1:F2；及

(ix) 其任何組合，

其中 FIX(X)為具有 XTEN 插入一或多個本文所描述之插入位點之 FIX 多肽；L1 及 L2 各自為連接子；F1 為 Fc 結構域或 FcRn 結合搭配物；F2 為第二 Fc 結構域或第二 FcRn 結合搭配物；(-)為肽鍵或者一或多個胺基酸；且(:)為共價鍵，例如二硫鍵。

[0103] 該等連接子(L1 及 L2)可相同或不同。連接子可為可裂解或不可裂解連接子，且連接子可包含一或多個細胞內加工位點。連接子之非限制性實例在本文中其他地方描述。可使用任何連接子將 FIX 與異源部分(例如 XTEN 或 Fc)組合或將第一異源部分(例如第一 Fc)與第二異源部分(例如第二 Fc)組合。

[0104] 在某些實施例中，連接子包含凝血酶裂解位點。在一特定實施例中，凝血酶裂解位點包含 XVPR，其中 X 為任何脂族胺基酸(例如甘胺酸、丙胺酸、纈胺酸、白胺酸或異白胺酸)。在一特定實施例中，凝血酶裂解位點包含 LVPR。在一些實施例中，連接子包含 PAR1 外結合位點相互作用基元，其包含 SFLLRN (SEQ ID NO:

190)。在一些實施例中，PAR1 外結合位點相互作用基元另外包含選自以下之胺基酸序列：P、PN、PND、PNDK (SEQ ID NO: 191)、PNDKY (SEQ ID NO: 192)、PNDKYE (SEQ ID NO: 193)、PNDKYEP (SEQ ID NO: 194)、PNDKYEPF (SEQ ID NO: 195)、PNDKYEPFW (SEQ ID NO: 196)、PNDKYEPFWE (SEQ ID NO: 197)、PNDKYEPFWED (SEQ ID NO: 198)、PNDKYEPFWEDE (SEQ ID NO: 199)、PNDKYEPFWEDEE (SEQ ID NO: 200)、PNDKYEPFWEDEES (SEQ ID NO: 201)或其任何組合。在其他實施例中，連接子包含 FXIa 裂解位點 LDPR。

[0105] 在一特定實施例中，FIX 融合蛋白包含 FIX 多肽及異源部分，該異源部分包含 XTEN，其中 XTEN 在存在或不存在連接子(該連接子可為可裂解或不可裂解的)情況下與 FIX 多肽之 C 末端融合，且包含長度超過 42 個胺基酸且短於 864 個胺基酸，較佳長度短於 144 個胺基酸之胺基酸序列。XTEN 包含的胺基酸序列可超過 42、43、44、45、46、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、63、64、65、66、67、68、69、70 或 71 個胺基酸且短於 140、139、138、137、136、135、134、133、132、131、130、129、128、127、126、125、124、123、122、121、120、119、118、117、116、115、114、113、112、111、110、109、108、107、106、105、104、103、102、101、100、99、98、97、

96、95、94、93、92、91、90、89、88、87、86、85、84、83、82、81、80、79、78、76、75、74 或 73 個胺基酸等，或其任何組合。在一些實施例中，XTEN 為 72 個胺基酸長。在一特定實施例中，XTEN 為 AE72。在另一實施例中，XTEN 包含與 SEQ ID NO: 35 具有至少約 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%一致性的胺基酸序列。

[0106] 在一些實施例中，FIX 融合蛋白包括含有至少一個插入之 XTEN 序列之 FIX 多肽及包含 XTEN 之異源部分，其中 XTEN 在存在或不存在連接子(該連接子可為可裂解或不可裂解的)情況下與 FIX 多肽之 C 末端融合。在一些實施例中，XTEN 之長度短於 864 個胺基酸，較佳短於 144 個胺基酸。在其他實施例中，XTEN 包含長度短於 244、140、130、120、110、100、90、80 或 75 個胺基酸之胺基酸序列。

[0107] 在其他實施例中，FIX 融合蛋白包含選自由以下組成之群之式：

(i) FIX-X

(ii) FIX-L1-X

(iii) FIX(X)-X

(iv) FIX(X)-L1-X

(v) FIX(X)-L1:X

(vi) 其任何組合，

其中 FIX 為 FIX 多肽；FIX(X)為具有至少一個 XTEN 插入一或多個本文所描述之插入位點之 FIX 多肽；(X)為超過 42 個胺基酸且短於 144 個胺基酸之 XTEN；X 為超過 42 個胺基酸且短於 864 個胺基酸，諸如 288 個胺基酸，較佳短於 144 個胺基酸之 XTEN(例如具有 72 個胺基酸之 XTEN)；L1 為連接子；(-)為肽鍵或者一或多個胺基酸；且(:)為共價鍵，例如二硫鍵。

[0108] 連接子(L1)可相同或不同。必要時，連接子可為可裂解或不可裂解連接子，且連接子可包含一或多個細胞內加工位點。連接子之非限制性實例在本文中其他地方描述。可使用任何連接子將 FIX 與異源部分(例如 XTEN 或 Fc)組合。以下為適於許多發明實施例之連接子的非限制性實例：

a) GPEGPS**KLTRAET**GAGSPGAETAEQKLISEEDLSPATGHHHHHHHH (SEQ ID NO: 219，凝血酶)；

b) GAGSPGAE**TALVPR**GAGSPGAETAG (SEQ ID NO: 220，凝血酶-PAR1)；

c) GAGSPGAETA**LVPRSFLLRNPNDKYEPFWEDEE**SGAGSPGAETA (SEQ ID NO: 221)；

d) GPEGPS**KLTRAET**GAGSPGAETA (SEQ ID NO: 222)

e) GGGGA**LRPRV**VGGAGSPGAETA (SEQ ID NO: 223)

f) GGGGT**LDPRSFLLRNPNDKYEPFWEDEE**KGGAGSPGAETA (SEQ ID NO: 224)

g) GGAGSPGAETA (SEQ ID NO: 225)

[0109] 在某些實施例中，連接子包含凝血酶裂解位點。在一特定實施例中，凝血酶裂解位點包含 XVPR，其中 X 為任何脂族胺基酸(例如甘胺酸、丙胺酸、纈胺酸、白胺酸或異白胺酸)。在一特定實施例中，凝血酶裂解位點包含 LVPR。在一些實施例中，連接子包含 PAR1 外結合位點相互作用基元，其包含 SFLLRN (SEQ ID NO: 190)。在一些實施例中，PAR1 外結合位點相互作用基元另外包含選自以下之胺基酸序列：P、PN、PND、PNDK (SEQ ID NO: 191)、PNDKY (SEQ ID NO: 192)、PNDKYE (SEQ ID NO: 193)、PNDKYEP (SEQ ID NO: 194)、PNDKYEPF (SEQ ID NO: 195)、PNDKYEPFW (SEQ ID NO: 196)、PNDKYEPFWE (SEQ ID NO: 197)、PNDKYEPFWED (SEQ ID NO: 198)、PNDKYEPFWEDE (SEQ ID NO: 199)、PNDKYEPFWEDEE (SEQ ID NO: 200)、PNDKYEPFWEDEES (SEQ ID NO: 201)或其任何組合。在某些其他實施例中，連接子包括含 LDPR 之 FXIa 裂解位點，其可與 PAR1 外結合位點相互作用基元組合。

[0110] 在某些實施例中，在 C 末端與 XTEN 融合之 FIX 多肽可另外包含第二 XTEN。該第二 XTEN 可融合於或插入 FIX 融合蛋白之任何部分，包括(但不限於)本文所揭示之插入位點。FIX 融合蛋白可另外包含第三 XTEN、第四 XTEN、第五 XTEN 或第六 XTEN。

[0111] 本發明之 FIX 融合蛋白保持與原生 FIX 相當之活性水準。在一些實施例中，FIX 融合蛋白具有原生

FIX 之至少約 10%、至少約 20%、至少約 30%、至少約 40%、至少約 50%、至少約 60%、至少約 70%、至少約 80%、至少約 90%或 100%之促凝血活性。促凝血活性可藉由此項技術中已知之任何方法量測，包括(但不限於)發色基質分析、單級凝結分析或兩者。

II.A. 因子 IX

[0112] 人因子 IX(FIX)係一種絲胺酸蛋白酶，其為血液凝固級聯之固有路徑中的重要組分。如本文所用，「因子 IX」或「FIX」係指凝血因子蛋白質及其種類及序列變異體，且包括(但不限於)人 FIX 前體多肽之具有 461 個胺基酸之單鏈序列(「前原」)、成熟人 FIX 之具有 415 個胺基酸之單鏈序列(SEQ ID NO: 1)及 R338L FIX (Padua)變異體(SEQ ID NO: 2)。FIX 包括具有凝血 FIX 之典型特徵的任何形式之 FIX 分子。如本文所用，「因子 IX」及「FIX」意欲涵蓋包含結構域 Gla(含有 γ-羧基麩胺酸殘基之區域)、EGF1 及 EGF2(含有與人表皮生長因子同源之序列的區域)、活化肽(「AP」，由成熟 FIX 之殘基 R136-R180 形成)及 C 末端蛋白酶結構域(「Pro」)，或此項技術中已知的該等結構域之同義詞，或可為保持原生蛋白質之至少一部分生物活性的截短片段或序列變異體。FIX 或序列變異體已經選殖，如美國專利第 4,770,999 號及第 7,700,734 號中所描述，且編碼人因子 IX 之 cDNA 已經分離，表徵且被選殖至表現載體中(參見例如，Choo 等人，

Nature 299:178-180 (1982)；Fair 等人，Blood 64:194-204 (1984)；及 Kurachi 等人，Proc. Natl. Acad. Sci., U.S.A. 79:6461-6464 (1982))。一個特定 FIX 變異體為由 Simioni 等人，2009 表徵之 R338L FIX (Padua)變異體(SEQ ID NO: 2)，其包含功能獲得突變，該突變與 Padua 變異體活性相對於原生 FIX 有近 8 倍增加相關(表 1)。FIX 變異體亦可包括具有一或多個保守胺基酸取代之任何 FIX 多肽，該一或多個取代不會影響 FIX 多肽之 FIX 活性。

表 1：示範性 FIX 序列

SEQ ID NO: 1 (成熟 FIX 多肽)
1:YNSGKLEEFV QGNLERECME EKCSFEEARE VFENTERTTE FWKQYVDGDQ CESNPCLNGG 61:SCKDDINSYE CWCPFGFEGK NCELDVTCNI KNGRCEQFCK NSADNKVVCS CTEGYRLAEN 121:QKSCEPAVPF PCGRVSVSQT SKLTRAETVF PDVDYVNSTE AETILDNITQ STQSFNDFTR 181:VVGGEDAKPG QFPWQVVLNG KVDAFCGGSI VNEKWIVTAA HCVETGVKIT VVAGEHNIEE 241:TEHTEQKRNV IRIIPHHNYN AAINKYNHDI ALLELDEPLV LNSYVTPICI ADKEYTNIFL 301:KFGSGYVSGW GRVFHKGRSA LVLQYLRVPL VDRATCLRST KFTIYNNMFC AGFHEGGRDS 361:CQGDSGGPHV TEVEGTSFLT GIISWGEECA MKGKYGIYTK VSRYVNWIKE KTKLT
SEQ ID NO: 2 (成熟 Padua(R338L)FIX 多肽)
1:YNSGKLEEFV QGNLERECME EKCSFEEARE VFENTERTTE FWKQYVDGDQ CESNPCLNGG 61:SCKDDINSYE CWCPFGFEGK NCELDVTCNI KNGRCEQFCK NSADNKVVCS CTEGYRLAEN 121:QKSCEPAVPF PCGRVSVSQT SKLTRAETVF PDVDYVNSTE AETILDNITQ STQSFNDFTR 181:VVGGEDAKPG QFPWQVVLNG KVDAFCGGSI VNEKWIVTAA HCVETGVKIT VVAGEHNIEE 241:TEHTEQKRNV IRIIPHHNYN AAINKYNHDI ALLELDEPLV LNSYVTPICI ADKEYTNIFL 301:KFGSGYVSGW GRVFHKGRSA LVLQYLRVPL VDRATCLLST KFTIYNNMFC AGFHEGGRDS 361:CQGDSGGPHV TEVEGTSFLT GIISWGEECA MKGKYGIYTK VSRYVNWIKE KTKLT
SEQ ID NO: 3 (FIX 信號肽及前肽)
1: MQRVNMIMAE SPGLITICLL GYLLSAEC*TV FLDHENANKI LNRPKR*

[0113] FIX 多肽為 55 kDa，以由以下三個區構成之前體多肽原鏈(SEQ ID NO: 1)形式合成：具有 28 個胺基酸之信號肽(SEQ ID NO: 3 之胺基酸 1 至 28)、麩胺酸殘基 γ-羧基化所需的具有 18 個胺基酸之前肽(胺基酸 29 至 46)及具有 415 個胺基酸之成熟因子 IX (SEQ ID NO: 1 或 2)。前肽係在 γ-羧基麩胺酸結構域 N 末端之具有 18 個胺基酸殘基之序列。前肽結合維生素 K 依賴性 γ 羧化酶，且接著經內源蛋白酶，最可能是 PACE(成對鹼性胺基酸裂解酶，又稱為弗林蛋白酶(furin)或 PCSK3)自 FIX 之前體多肽裂解。若不發生 γ 羧基化，則 Gla 結構域無法結合鈣以呈現將蛋白質錨定於帶負電之磷脂表面所需之正確構形，由此使因子 IX 沒有功能。即使其經羧基化，Gla 結構域亦取決於前肽之裂解而獲得適當功能，因為保留之前肽干擾 Gla 結構域與鈣及磷脂最佳結合所需之構形變化。在人體中，所得成熟因子 IX 係由肝細胞以無活性酶原形式分泌至血流中，該酶原為以重量計含有約 17%碳水化合物的具有 415 個胺基酸殘基之單鏈蛋白質(Schmidt, A. E.等人(2003) Trends Cardiovasc Med, 13: 39)。

[0114] 成熟 FIX 係由若干結構域構成，該等結構域以 N 末端至 C 末端配置為：GLA 結構域、EGF1 結構域、EGF2 結構域、活化肽(AP)結構域及蛋白酶(催化)結構域。短連接子將 EGF2 結構域與 AP 結構域相連接。FIX 含有分別由 R145-A146 及 R180-V181 形成之兩個活化肽。活化後，單鏈 FIX 變為具有 2 條鏈之分子，其中該兩

條鏈係藉由二硫鍵連接。凝血因子可藉由置換其活化肽引起活化特異性之改變來進行工程改造。在哺乳動物中，成熟 FIX 必須由活化因子 XI 活化以得到因子 IXa。在 FIX 活化成 FIXa 之後，蛋白酶結構域提供 FIX 之催化活性。活化因子 VIII(FVIIIa)係完整表現 FIXa 活性之特定輔因子。

[0115] 在其他實施例中，FIX 多肽包含血漿源性因子 IX 之 Thr148 等位基因形式且具有與內源因子 IX 類似之結構及功能特徵。

[0116] 已知許多功能性 FIX 變異體。國際公開案第 WO 02/040544 A3 號在第 4 頁第 9-30 列及第 15 頁第 6-31 列揭示了對肝素抑制作用之展現較高抗性的突變體。國際公開案第 WO 03/020764 A2 號在表 2 及表 3 (第 14-24 頁)中及在第 12 頁第 1-27 列揭示 T 細胞免疫原性降低之 FIX 突變體。國際公開案第 WO 2007/149406 A2 號在第 4 頁第 1 列至第 19 頁第 11 列揭示展現較高蛋白質穩定性、較長活體內及活體外半衰期及較高的對蛋白酶之抗性的功能性突變 FIX 分子。WO 2007/149406 A2 亦在第 19 頁第 12 列至第 20 頁第 9 列揭示嵌合及其他變異體 FIX 分子。國際公開案第 WO 08/118507 A2 號在第 5 頁第 14 列至第 6 頁第 5 列揭示展現較高凝血活性之 FIX 突變體。國際公開案第 WO 09/051717 A2 號在第 9 頁第 11 列至第 20 頁第 2 列揭示具有使半衰期及/或回收率增加之增加數目之 N-連接及/或 O-連接糖基化位點的 FIX 突變體。國際公開案第

WO 09/137254 A2 號亦在第 2 頁第[006]段至第 5 頁第[011]段及第 16 頁第[044]段至第 24 頁第[057]段揭示糖基化位點數增加之因子 IX 突變體。國際公開案第 WO 09/130198 A2 號在第 4 頁第 26 列至第 12 頁第 6 行揭示具有使半衰期增加之增加數目之糖基化位點的功能性突變 FIX 分子。國際公開案第 WO 09/140015 A2 號在第 11 頁第[0043]段至第 13 頁第[0053]段揭示可用於聚合物(例如 PEG)偶聯之 Cys 殘基之數目增加的功能性 FIX 突變體。2011 年 7 月 11 日申請且在 2012 年 1 月 12 日以 WO 2012/006624 公開之國際申請案第 PCT/US2011/043569 號中所述之 FIX 多肽亦以全文引用的方式併入本文中。

[0117] 此外，已在血友病受試者中鑑別出數百種 FIX 非功能性突變，其中許多揭示於國際公開案第 WO 09/137254 A2 號第 11-14 頁之表 5 中。此等非功能性突變不包括在本發明中，但提供有關哪些突變很可能或不太可能產生功能性 FIX 多肽之額外指導。

[0118] 在一個實施例中，FIX 多肽(或融合多肽之因子 IX 部分)包含與 SEQ ID NO: 1 或 2 中所陳述之序列(SEQ ID NO: 1 或 2 之胺基酸 1 至 415)具有至少 70%、至少 80%、至少 85%、至少 90%、至少 95%、至少 96%、至少 97%、至少 98%、至少 99%或 100%一致性的胺基酸序列，或者具有前肽序列，或具有前肽及信號序列(全長 FIX)。在另一實施例中，FIX 包含與 SEQ ID NO: 2 中所陳述之序列具有至少 70%、至少 80%、至少 85%、至少

90%、至少 95%、至少 96%、至少 97%、至少 98%、至少 99%或 100%一致性的胺基酸序列。

[0119] 因子 IX 凝血活性係以國際單位(IU)表示。一個 IU 之 FIX 活性近似對應於一毫升正常人類血漿中 FIX 之量。若干分析可用於量測因子 IX 活性，包括單級凝結分析(部分活化凝血激酶時間；aPTT)、凝血酶產生時間(TGA)及旋轉式血栓彈力分析儀(ROTEM®)。本發明涵蓋與 FIX 序列具有同源性之序列、天然序列片段(諸如來自人類；非人類靈長類動物；哺乳動物，包括家養動物)，及保持 FIX 之至少一部分生物活性或生物功能及/或可用於預防、治療、介導或改善凝血因子相關疾病、缺乏、病症或病狀(例如與外傷、手術或凝血因子缺乏相關之出血事件)的非天然序列變異體。與人 FIX 同源之序列可藉由標準同源性搜索技術，諸如 NCBI BLAST 發現。

II.B. 異源部分

[0120] 本發明之 FIX 融合蛋白可包含插入 FIX 多肽內之一或多個位點、與 C 末端融合或兩者之至少一個異源部分，其中 FIX 融合蛋白具有促凝血活性且可在宿主細胞中活體內或活體外表現。「異源部分」可包含異源多肽或非多肽部分或兩者。在某些態樣中，異源部分為 XTEN。在一些態樣中，本發明之 FIX 融合蛋白包含插入 FIX 多肽內之一或多個位點的至少一個 XTEN。在其他態樣中，FIX 融合蛋白包含插入 FIX 多肽內之一或多個位點的至少

一個異源部分，其中該異源部分為半衰期延長部分(例如活體內半衰期延長部分)。

[0121] 咸信 FIX 保留至少一部分其促凝血活性之插入位點的發現亦將允許將具有與在融合於 FIX 蛋白時延長半衰期相關之非結構化或結構化特徵的其他肽及多肽插入於彼等位點中之一或多者中。異源部分(例如半衰期延長部分)之非限制性實例包括白蛋白；白蛋白片段；免疫球蛋白之 Fc 片段；FcRn 結合搭配物；人類絨毛膜促性腺素 β 次單位之 C 末端肽(CTP)；HAP 序列；轉鐵蛋白(transferrin)；美國專利申請案第 20100292130 號之 PAS 多肽；聚甘胺酸連接子；聚絲胺酸連接子；具有 6-40 個選自甘胺酸(G)、丙胺酸(A)、絲胺酸(S)、酥胺酸(T)、麩胺酸(E)及脯胺酸(P)之兩種類型胺基酸之胺基酸且具有小於 50%至大於 50%之不同程度之二級結構的肽及短多肽，將尤其適於插入於所鑑別之 FIX 活性插入位點中。

[0122] 在某些態樣中，異源部分使重組 FIX 蛋白之活體內或活體外半衰期延長。在其他態樣中，異源部分有助於可視化或定位 FIX 融合蛋白。FIX 融合蛋白之可視化及/或定位可在活體內、活體外、離體或以其組合方式進行。在其他態樣中，異源部分使 FIX 融合蛋白之穩定性增強。如本文所用，術語「穩定性」係指 FIX 融合蛋白響應於環境條件(例如溫度升高或降低)而保持一或多種物理特性的此項技術公認之量度。在某些態樣中，物理特性為維持 FIX 融合蛋白之共價結構(例如不存在蛋白水解裂解、

不必要之氧化或脫醯胺)。在其他態樣中，物理特性亦可為呈適當折疊狀態之 FIX 融合蛋白之存在(例如不存在可溶性或不溶性聚集物或沈澱物)。在一個態樣中，藉由分析 FIX 融合蛋白之生物物理特性，例如熱穩定性、pH 展開型態、聚醣之穩定移除、溶解性、生物化學功能(例如結合至另一蛋白質之能力)等及/或其組合來量測 FIX 融合蛋白之穩定性。在另一態樣中，生物化學功能係藉由相互作用之結合親和力來說明。在一個態樣中，蛋白質穩定性之量度為熱穩定性，亦即，對熱激發之抗性。穩定性可使用此項技術中已知之方法量測，諸如 HPLC(高效液相層析)、SEC(尺寸排阻層析)、DLS(動態光散射)等。量測熱穩定性之方法包括(但不限於)差示掃描量熱法(DSC)、差示掃描螢光測定法(DSF)、圓偏光二色性(CD)及熱激發分析。

[0123] 在一特定態樣中，插入 FIX 融合蛋白中一或多個插入位點中之異源部分保留 FIX 融合蛋白之生物化學活性。在某些實施例中，異源部分為 XTEN。在一個實施例中，生物化學活性為可藉由發色分析量測之 FIX 活性。

[0124] 在一些實施例中，至少一個異源部分係經由位於異源部分之 N 末端、C 末端或 N 末端與 C 末端兩者處之連接子間接插入於插入位點中。在異源部分之 N 末端及 C 末端處之連接子可相同或不同。在一些實施例中，多個連接子可串聯側接異源部分之一個或兩個末端。在一些實施例中，連接子為「Gly-Ser 肽連接子」。術語「Gly-

Ser肽連接子」係指包含甘胺酸及絲胺酸殘基之肽。

[0125] 示範性 Gly/Ser 肽連接子包括(但不限於)胺基酸序列$(Gly_4Ser)_n$ (SEQ ID NO: 161)，其中 n 為與以下相同或高於以下的整數 1、2、3、4、5、6、7、8、9、10、15、20、25、30、35、40、46、50、55、60、70、80、90 或 100。在一個實施例中，n=1，亦即連接子為(Gly_4Ser) (SEQ ID NO: 161)。在一個實施例中，n=2，亦即，連接子為$(Gly_4Ser)_2$ (SEQ ID NO:162)。在另一實施例中，n=3，亦即，連接子為$(Gly_4Ser)_3$ (SEQ ID NO:172)。在另一實施例中，n=4，亦即，連接子為$(Gly_4Ser)_4$ (SEQ ID NO:173)。在另一實施例中，n=5，亦即，連接子為$(Gly_4Ser)_5$ (SEQ ID NO:174)。在另一實施例中，n=6，亦即，連接子為$(Gly_4Ser)_6$ (SEQ ID NO:175)。在另一實施例中，n=7，亦即，連接子為$(Gly_4Ser)_7$ (SEQ ID NO:176)。在另一實施例中，n=8，亦即，連接子為$(Gly_4Ser)_8$ (SEQ ID NO:177)。在另一實施例中，n=9，亦即，連接子為$(Gly_4Ser)_9$ (SEQ ID NO:178)。在另一實施例中，n=10，亦即，連接子為$(Gly_4Ser)_{10}$ (SEQ ID NO:179)。

[0126] 另一示範性 Gly/Ser 肽連接子包含胺基酸序列$Ser(Gly_4Ser)_n$ (SEQ ID NO: 180)，其中 n 為與以下相同或高於以下的整數 1、2、3、4、5、6、7、8、9、10、15、20、25、30、35、40、46、50、55、60、70、80、90 或 100。在一個實施例中，n=1，亦即，連接子為$Ser(Gly_4Ser)$ (SEQ ID NO: 180)。在一個實施例中，n=2，

亦即，連接子為 $Ser(Gly_4Ser)_2$ (SEQ ID NO:181)。在另一實施例中，n=3，亦即，連接子為 $Ser(Gly_4Ser)_3$ (SEQ ID NO:182)。在另一實施例中，n=4，亦即，連接子為 $Ser(Gly_4Ser)_4$ (SEQ ID NO:183)。在另一實施例中，n=5，亦即，連接子為 $Ser(Gly_4Ser)_5$ (SEQ ID NO:184)。在另一實施例中，n=6，亦即，連接子為 $Ser(Gly_4Ser)_6$ (SEQ ID NO:185)。在另一實施例中，n=7，亦即，連接子為 $Ser(Gly_4Ser)_7$ (SEQ ID NO:186)。在另一實施例中，n=8，亦即，連接子為 $Ser(Gly_4Ser)_8$ (SEQ ID NO:187)。在另一實施例中，n=9，亦即，連接子為 $Ser(Gly_4Ser)_9$ (SEQ ID NO:188)。在另一實施例中，n=10，亦即，連接子為 $Ser(Gly_4Ser)_{10}$ (SEQ ID NO:189)。

[0127] 在某些態樣中，FIX 融合蛋白包含插入表 7 中所列之插入位點的一個異源部分。在其他態樣中，FIX 融合蛋白包含插入表 7 中所列兩個插入位點中之兩個異源部分。在一特定實施例中，該兩個異源部分插入表 8 中所列之兩個插入位點中。在某些態樣中，FIX 融合蛋白包含插入表 7 中所列三個個插入位點中之三個異源部分。在某些態樣中，FIX 融合蛋白包含插入表 7 中所列四個個插入位點中之四個異源部分。在某些態樣中，FIX 融合蛋白包含插入表 7 中所列五個個插入位點中之五個異源部分。在某些態樣中，FIX 融合蛋白包含插入表 7 中所列六個個插入位點中之六個異源部分。在一些態樣中，所有插入之異源部分皆相同。在其他態樣中，至少一個插入之異源部分不

同於其餘插入之異源部分。

[0128] FIX 多肽與至少一個異源部分(例如 XTEN)融合可影響本發明之融合蛋白的物理或化學特性，例如藥物動力學。在一特定實施例中，連接至 FIX 蛋白之異源部分增加藥物動力學特性，諸如延長終末半衰期或增加曲線下面積(AUC)，以使本文所述之融合蛋白在活體內停留之時間相較於野生型 FIX 或缺乏異源部分之相應 FIX 有所增加。在其他實施例中，用於本發明中之 XTEN 序列增加至少一種藥物動力學特性，例如增加終末半衰期、增加回收率及/或增加皮下給藥之生物利用率、增加曲線下面積(AUC)，以使 FIX 蛋白在活體內停留之時間相較於野生型 FIX 或缺乏異源部分之相應 FIX 有所增加。

[0129] 在某些態樣中，使本發明之 FIX 融合蛋白之半衰期延長的異源部分包含(但不限於)異源多肽，諸如白蛋白、免疫球蛋白 Fc 區、XTEN 序列、人類絨毛膜促性腺素 β 次單位之 C 末端肽(CTP)、PAS 序列、HAP 序列、轉鐵蛋白、白蛋白結合部分，或此等多肽之任何片段、衍生物、變異體或組合。在某些態樣中，本發明之 FIX 融合蛋白包含使半衰期延長之異源多肽，其中該異源多肽為 XTEN 序列。在其他相關態樣中，異源部分可包括諸如聚乙二醇(PEG)、羥乙基澱粉(HES)、聚唾液酸或此等部分之任何衍生物、變異體或組合之非多肽部分的連接位點。

[0130] 在其他實施例中，本發明之 FIX 融合蛋白與一或多種聚合物偶聯。聚合物可為水溶性的或非水溶性

的。聚合物可共價或非共價連接至 FIX 或連接至與 FIX 偶聯之其他部分。聚合物之非限制性實例可為聚(氧化烯)、聚(乙烯基吡咯啶酮)、聚(乙烯醇)、聚噁唑啉或聚(丙烯醯基嗎啉)。

[0131] 在某些態樣中，本發明之 FIX 融合蛋白包含一個、兩個、三個或多於三個異源部分，該等異源部分可各自為相同或不同分子。在一些實施例中，FIX 融合蛋白包含一或多個 XTEN。在其他實施例中，FIX 融合蛋白包含一或多個 XTEN 及一或多個 Fc 結構域。在一特定實施例中，FIX 融合蛋白可包含插入 FIX 內之 XTEN 及與 FIX 之 C 末端融合之 Fc。

[0132] 本發明之 FIX 融合蛋白相較於原生 FIX、rFIXFc 或 FIX R338L 可惡具有增加之活體內半衰期。在一些實施例中，該 FIX 融合蛋白之活體內半衰期可為缺乏異源部分之原生 FIX 或缺乏異源部分之 FIX R338L 的至少約 1.5 倍、至少約 2 倍、至少約 3 倍或至少約 4 倍。在一特定實施例中，FIX 融合蛋白的活體內半衰期為不含異源部分之 FIX 多肽之超過 2 倍。

[0133] 在其他實施例中，FIX 融合蛋白之活體內半衰期可比缺乏異源部分之 FIX 多肽之活體內半衰期長至少約 5 小時、至少約 6 小時、至少約 7 小時、至少約 8 小時、至少約 9 小時、至少約 10 小時、至少約 11 小時、至少約 12 小時、至少約 13 小時、至少約 14 小時、至少約 15 小時、至少約 16 小時、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、至少約小時或至少約 34 小時。

II.B.1. XTEN

[0134] 在一些實施例中，至少一個異源部分為 XTEN。如此處所用，「XTEN 序列」係指具有非天然存在、實質上非重複、主要由小親水性胺基酸組成之序列的長度延長之多肽，該序列在生理條件下具有較低程度之二級或三級結構或無二級或三級結構。作為融合蛋白搭配物，XTEN 可充當載體，以在連接至本發明之 FIX 序列以產生融合蛋白時，賦予某些合乎需要之藥物動力學、物理化學及醫藥特性。該等合乎需要之特性包括(但不限於)增強的藥物動力學參數及可溶性特徵。如本文所用，「XTEN」明確排除抗體或抗體片段，諸如單鏈抗體，或者輕鏈或重鏈之 Fc 片段。

[0135] 在某些態樣中，本發明之 FIX 融合蛋白包含至少一個插入 FIX 中之 XTEN 或其片段、變異體或衍生物，其中該 FIX 融合蛋白具有促凝血活性且可在宿主細胞中在活體內或活體外表現。在某些態樣中，該等異源部分中之兩者為 XTEN 序列。在一些態樣中，該等異源部分中

之三者為 XTEN 序列。在一些態樣中，該等異源部分中之四者為 XTEN 序列。在一些態樣中，該等異源部分中之五者為 XTEN 序列。在一些態樣中，該等異源部分中之六者或六者以上為 XTEN 序列。

[0136] 在一些實施例中，可用於本發明之 XTEN 序列為具有超過約 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 個胺基酸殘基之肽或多肽。在某些實施例中，XTEN 為具有超過約 20 至約 3000 個胺基酸殘基、超過 30 至約 2500 個殘基、超過 40 至約 2000 個殘基、超過 50 至約 1500 個殘基、超過 60 至約 1000 個殘基、超過 70 至約 900 個殘基、超過 80 至約 800 個殘基、超過 90 至約 700 個殘基、超過 100 至約 600 個殘基、超過 110 至約 500 個殘基或超過 120 至約 400 個殘基之肽或多肽。在一特定實施例中，XTEN 包含長度超過 42 個胺基酸且短於 144 個胺基酸之氨基酸序列。

[0137] 本發明之 XTEN 序列可包含一或多個具有 5 至 14 個(例如 9 至 14 個)胺基酸殘基之序列基元或與該序列基元至少 80%、90%、91%、92%、93%、94%、95%、96%、97%、98%或 99%一致之胺基酸序列，其中該基元包含以下、基本上由以下組成或由以下組成：選自由甘胺酸(G)、丙胺酸(A)、絲胺酸(S)、酥胺酸(T)、麩胺酸(E)及脯胺酸(P)組成之群的 4 至 6 種類型之胺基酸(例如 5 個胺

基酸)。參見 US 2010-0239554 A1。

[0138] 在一些實施例中，XTEN 包含不重疊序列基元，其中約 80%、或至少約 85%、或至少約 90%、或約 91%、或約 92%、或約 93%、或約 94%、或約 95%、或約 96%、或約 97%、或約 98%、或約 99%或約 100%之序列由多個選自由表 2A 選擇之單一基元家族之不重疊序列之單元組成，從而產生家族序列。如本文所用，「家族」意謂 XTEN 具有僅選自表 2A 中之單一基元類別的基元；亦即，AD、AE、AF、AG、AM、AQ、BC 或 BD XTEN，且選擇 XTEN 中之不來自家族基元之任何其他胺基酸以達成所需特性，諸如允許藉由編碼核苷酸併入限制位點、併入裂解序列，或達成與 FIX 之更佳連接。在 XTEN 家族之一些實施例中，XTEN 序列包含以下者之非重疊序列基元之多個單元：AD 基元家族、或 AE 基元家族、或 AF 基元家族、或 AG 基元家族、或 AM 基元家族、或 AQ 基元家族、或 BC 家族、或 BD 家族，所得 XTEN 顯示上文所述之同源性範圍。在其他實施例中，XTEN 包含來自表 2A 之兩個或超過兩個基元家族之多個基元序列單元。此等序列可經選擇以達成所需物理/化學特徵，包括諸如淨電荷、親水性、缺乏二級結構或缺乏重複性之特性，該等特性係由基元之胺基酸組成賦予，下文將更全面地描述。在以上本段描述之實施例中，併入 XTEN 中之基元可使用本文所述之方法選擇及組裝以獲得具有約 36 至約 3000 個胺基酸殘基之 XTEN。

表 2A. 具有 12 個胺基酸之 XTEN 序列基元及基元家族

基元家族*	基元序列	SEQ ID NO:
AD	GESPGGSSGSES	4
AD	GSEGSSGPGESS	5
AD	GSSESGSSEGGP	6
AD	GSGGEPSESGSS	7
AE、AM	GSPAGSPTSTEE	8
AE、AM、AQ	GSEPATSGSETP	9
AE、AM、AQ	GTSESATPESGP	10
AE、AM、AQ	GTSTEPSEGSAP	11
AF、AM	GSTSESPSGTAP	12
AF、AM	GTSTPESGSASP	13
AF、AM	GTSPSGESSTAP	14
AF、AM	GSTSSTAESPGP	15
AG、AM	GTPGSGTASSSP	16
AG、AM	GSSTPSGATGSP	17
AG、AM	GSSPSASTGTGP	18
AG、AM	GASPGTSSTGSP	19
AQ	GEPAGSPTSTSE	20
AQ	GTGEPSSTPASE	21
AQ	GSGPSTESAPTE	22
AQ	GSETPSGPSETA	23
AQ	GPSETSTSEPGA	24
AQ	GSPSEPTEGTSA	25
BC	GSGASEPTSTEP	26
BC	GSEPATSGTEPS	27
BC	GTSEPSTSEPGA	28
BC	GTSTEPSEPGSA	29
BD	GSTAGSETSTEA	30
BD	GSETATSGSETA	31
BD	GTSESATSESGA	32
BD	GTSTEASEGSAS	33

*表示當以各種排列一起使用時產生「家族序列」之個別基元序列

[0139] XTEN 可具有不同長度以供插入 FIX 中或與 FIX 連接。在一個實施例中，基於欲在融合蛋白中達成之特性或功能選擇 XTEN 序列之長度。取決於預期特性或功能，XTEN 可為可充當載劑的短或中等長度序列或較長序列。在某些實施例中，XTEN 包括具有約 6 至約 99 個胺基酸殘基的短區段、具有約 100 至約 399 個胺基酸殘基的中等長度區段，及具有約 400 至約 1000 個且高達約 3000 個胺基酸殘基的長度較長之區段。因此，插入 FIX 中或連接至 FIX 之 XTEN 之長度可為約 6、約 12、約 36、約 40、約 42、約 72、約 96、約 144、約 288、約 400、約 500、約 576、約 600、約 700、約 800、約 864、約 900、約 1000、約 1500、約 2000、約 2500 或至多約 3000 個胺基酸殘基長。在其他實施例中，XTEN 序列長度為約 6 至約 50、約 50 至約 100、約 100 至 150、約 150 至 250、約 250 至 400、約 400 至約 500、約 500 至約 900、約 900 至 1500、約 1500 至 2000 或約 2000 至約 3000 個胺基酸殘基。插入 FIX 中或連接至 FIX 之 XTEN 之精確長度可不同，而不會不利地影響 FIX 之活性。在一個實施例中，本文使用之一或多個 XTEN 具有 42 個胺基酸、72 個胺基酸、144 個胺基酸、288 個胺基酸、576 個胺基酸或 864 個胺基酸長度且可選自一或多個 XTEN 家族序列；亦即，AD、AE、AF、AG、AM、AQ、BC 或 BD。

[0140] 在一些實施例中，本發明中使用之 XTEN 序列與選自由以下組成之群之序列至少 60%、70%、80%、

85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或 100%一致：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、AG2004 及其任何組合。參見 US 2010-0239554 A1。在一特定實施例中，XTEN 包含 AE42、AE72、AE144、AE288、AE576、AE864、AG42、AG72、AG144、AG288、AG576、AG864 或其任何組合。

[0141] 在一個實施例中，XTEN 序列與選自由以下組成之群之胺基酸序列至少 60%、70%、80%、90%、95%、96%、97%、98%、99%或 100%一致：AE36 (SEQ ID NO: 217)、AE42 (SEQ ID NO: 34)、AE72 (SEQ ID NO: 35)、

AE78 (SEQ ID NO: 218)、AE144 (SEQ ID NO: 36)、AE144_2A (SEQ ID NO: 37)、AE144_3B (SEQ ID NO: 38)、AE144_4A (SEQ ID NO: 39)、AE144_5A (SEQ ID NO: 40)、AE144_6B (SEQ ID NO: 41)、AG144 (SEQ ID NO: 42)、AG144_A (SEQ ID NO: 43)、AG144_B (SEQ ID NO: 44)、AG144_C (SEQ ID NO: 45)、AG144_F (SEQ ID NO: 46)、AE288 (SEQ ID NO: 47)、AE288_2 (SEQ ID NO: 48)、AG288 (SEQ ID NO: 49)、AE576 (SEQ ID NO: 50)、AG576 (SEQ ID NO: 51)、AE864 (SEQ ID NO: 52)、AG864 (SEQ ID NO: 53)、XTEN_AE72_2A_1 (SEQ ID NO: 202)、XTEN_AE72_2A_2 (SEQ ID NO: 203)、XTEN_AE72_3B_1 (SEQ ID NO: 204)、XTEN_AE72_3B_2 (SEQ ID NO: 205)、XTEN_AE72_4A_2 (SEQ ID NO: 206)、XTEN_AE72_5A_2 (SEQ ID NO: 207)、XTEN_AE72_6B_1 (SEQ ID NO: 208)、XTEN_AE72_6B_2 (SEQ ID NO: 209)、XTEN_AE72_1A_1 (SEQ ID NO: 210)、XTEN_AE72_1A_2 (SEQ ID NO: 211)、XTEN_AE144_1A (SEQ ID NO: 212)、AE150 (SEQ ID NO: 213)、AG150 (SEQ ID NO: 214)、AE294 (SEQ ID NO: 215)、AG294 (SEQ ID NO: 216)及其任何組合。

[0142] 在一些實施例中，XTEN 中少於 100%之胺基酸係選自甘胺酸(G)、丙胺酸(A)、絲胺酸(S)、蘇胺酸(T)、麩胺酸(E)及脯胺酸(P)，或少於 100%之序列由來自表 2A 之序列基元或表 2B 之 XTEN 序列組成。在此類實

施例中，XTEN 之其餘胺基酸殘基係選自其他 14 個天然 L-胺基酸中之任一個，但可優先選自親水性胺基酸，以使 XTEN 序列含有至少約 90%、91%、92%、93%、94%、95%、96%、97%、98%或至少約 99%之親水性胺基酸。偶聯構築體中使用之 XTEN 中疏水性胺基酸之含量可低於 5%，或低於 2%，或低於 1%之疏水性胺基酸含量。較少用於構築 XTEN 之疏水性殘基包括色胺酸、苯丙胺酸、酪胺酸、白胺酸、異白胺酸、纈胺酸及甲硫胺酸。另外，XTEN 序列可含有少於 5%，或少於 4%，或少於 3%，或少於 2%，或少於 1%，或無以下胺基酸：甲硫胺酸(例如用以避免氧化)，或天冬醯胺及麩醯胺酸(用以避免脫醯胺)。

[0143] 在另一實施例中，XTEN 序列係選自由以下組成之群：AE36 (SEQ ID NO: 217)、AE42 (SEQ ID NO: 34)、AE72 (SEQ ID NO: 35)、AE78 (SEQ ID NO: 218)、AE144 (SEQ ID NO: 36)、AE144_2A (SEQ ID NO: 37)、AE144_3B (SEQ ID NO: 38)、AE144_4A (SEQ ID NO: 39)、AE144_5A (SEQ ID NO: 40)、AE144_6B (SEQ ID NO: 41)、AG144 (SEQ ID NO: 42)、AG144_A (SEQ ID NO: 43)、AG144_B (SEQ ID NO: 44)、AG144_C (SEQ ID NO: 45)、AG144_F (SEQ ID NO: 46)、AE288 (SEQ ID NO: 47)、AE288_2 (SEQ ID NO: 48)、AG288 (SEQ ID NO: 49)、AE576 (SEQ ID NO: 50)、AG576 (SEQ ID NO: 51)、AE864 (SEQ ID NO: 52)、AG864 (SEQ ID NO: 53)、

XTEN_AE72_2A_1 (SEQ ID NO: 202)、XTEN_AE72_2A_2 (SEQ ID NO: 203)、XTEN_AE72_3B_1 (SEQ ID NO: 204)、XTEN_AE72_3B_2 (SEQ ID NO: 205)、XTEN_AE72_4A_2 (SEQ ID NO: 206)、XTEN_AE72_5A_2 (SEQ ID NO: 207)、XTEN_AE72_6B_1 (SEQ ID NO: 208)、XTEN_AE72_6B_2 (SEQ ID NO: 209)、XTEN_AE72_1A_1 (SEQ ID NO: 210)、XTEN_AE72_1A_2 (SEQ ID NO: 211)、XTEN_AE144_1A (SEQ ID NO: 212)、AE150 (SEQ ID NO: 213)、AG150 (SEQ ID NO: 214)、AE294 (SEQ ID NO: 215)、AG294 (SEQ ID NO: 216)及其任何組合。在一特定實施例中，XTEN 序列係選自由以下組成之群：AE72、AE144 及 AE288。本發明之某些 XTEN 序列之胺基酸序列顯示於表 2B 中。

表 2B. XTEN 序列

XTEN	胺基酸序列
AE36 SEQ ID NO: 217	GSPAGSPTSTEEGTSESATPESGPGSEPATSGSETP
AE42 SEQ ID NO:34	GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSG SETPASS
AE72 SEQ ID NO:35	GAPTSESATPESGPGSEPATSGSETPGTSESATPES GPGSEPATSGSETPGTSESATPESGPGTSTEPSEGS APGASS
AE78 SEQ ID NO: 218	GAPTSESATPESGPGSEPATSGSETPGTSESATPES GPGSEPATSGSETPGTSESATPESGPGTSTEPSEGS APGASS
AE144 SEQ ID NO:36	GSEPATSGSETPGTSESATPESGPGSEPATSGSETP GSPAGSPTSTEEGTSTEPSEGSAPGSEPATSGSETP GSEPATSGSETPGSEPATSGSETPGTSTEPSEGSAP GTSESAPESGPGSEPATSGSETPGTSTEPSEGSAP
AE144_2A SEQ ID NO:37	TSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPG TSTEPSEGSAPGTSESATPESGPGTSTEPSEGSAPG TSESATPESGPGSEPATSGSETPGTSTEPSEGSAPG TSTEPSEGSAPGTSESATPESGPGTSESATPESGPG
AE144_3B SEQ ID NO:38	SPAGSPTSTEEGTSESATPESGPGSEPATSGSETPG TSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPG TSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPG TSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPG
AE144_4A SEQ ID NO:39	TSESATPESGPGSEPATSGSETPGTSESATPESGPG SEPATSGSETPGTSESATPESGPGTSTEPSEGSAPG TSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEG SPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPG
AE144_5A SEQ ID NO:40	TSESATPESGPGSEPATSGSETPGTSESATPESGPG SEPATSGSETPGTSESATPESGPGTSTEPSEGSAPG SPAGSPTSTEEGTSESATPESGPGSEPATSGSETPG TSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEG
AE144_6B SEQ ID NO:41	TSTEPSEGSAPGTSESATPESGPGTSESATPESGPG TSESATPESGPGSEPATSGSETPGSEPATSGSETPG SPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPG

	SEPATSGSETPGTSESATPESGPGTSTEPSEGSAPG
AG144 SEQ ID NO:42	GTPGSGTASSSPGSSTPSGATGSPGSSPSASTGTG PGSSPSASTGTGPGASPGTSSTGSPGASPGTSSTG SPGSSTPSGATGSPGSSPSASTGTGPGASPGTSST GSPGSSPSASTGTGPGTPGSGTASSSPGSSTPSGA TGSP
AG144_A SEQ ID NO:43	GASPGTSSTGSPGSSPSASTGTGPGSSPSASTGTG PGTPGSGTASSSPGSSTPSGATGSPGSSPSASTGT GPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGAT GSPGTPGSGTASSSPGASPGTSSTGSPGASPGTSS TGSP
AG144_B SEQ ID NO:44	GTPGSGTASSSPGSSTPSGATGSPGASPGTSSTGS PGTPGSGTASSSPGSSTPSGATGSPGSSPSASTGT GPGSSPSASTGTGPGSSTPSGATGSPGSSTPSGAT GSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSS TGSP
AG144_C SEQ ID NO:45	GTPGSGTASSSPGASPGTSSTGSPGASPGTSSTGS PGASPGTSSTGSPGSSPSASTGTGPGTPGSGTASS SPGASPGTSSTGSPGASPGTSSTGSPGASPGTSST GSPGSSTPSGATGSPGSSTPSGATGSPGASPGTSS TGSP
AG144_F SEQ ID NO:46	GSSPSASTGTGPGSSPSASTGTGPGASPGTSSTGS PGASPGTSSTGSPGSSTPSGATGSPGSSPSASTGT GPGASPGTSSTGSPGSSPSASTGTGPGTPGSGTAS SSPGSSTPSGATGSPGSSTPSGATGSPGASPGTSST GSP
AE288 SEQ ID NO:47	GTSESATPESGPGSEPATSGSETPGTSESATPESGP GSEPATSGSETPGTSESATPESGPGTSTEPSEGSAP GSPAGSPTSTEEGTSESATPESGPGSEPATSGSETP GTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEE GTSTEPSEGSAPGTSESATPESGPGTSESATPESGP GTSESATPESGPGSEPATSGSETPGSEPATSGSETP GSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAP GSEPATSGSETPGTSESATPESGPGTSTEPSEGSAP
AE288_2	GSPAGSPTSTEEGTSESATPESGPGSEPATSGSETP

SEQ ID NO:48	GTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAP GTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAP GTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAP GTSESATPESGPGSEPATSGSETPGTSESATPESGP GSEPATSGSETPGTSESATPESGPGTSTEPSEGSAP GTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEE GSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAP
AG288 SEQ ID NO:49	PGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASS SPGSSTPSGATGSPGTPGSGTASSSPGSSTPSGAT GSPGTPGSGTASSSPGSSTPSGATGSPGSSTPSGA TGSPGSSPSASTGTGPGSSPSASTGTGPGASPGTS STGSPGTPGSGTASSSPGSSTPSGATGSPGSSPSAS TGTGPGSSPSASTGTGPGASPGTSSTGSPGASPGT SSTGSPGSSTPSGATGSPGSSPSASTGTGPGASPG TSSTGSPGSSPSASTGTGPGTPGSGTASSSPGSSTP SGATGS
AE576 SEQ ID NO:50	GSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAP GSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAP GTSESATPESGPGSEPATSGSETPGSEPATSGSETP GSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAP GTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAP GTSTEPSEGSAPGTSESATPESGPGTSTEPSEGSAP GTSESATPESGPGSEPATSGSETPGTSTEPSEGSAP GTSTEPSEGSAPGTSESATPESGPGTSESATPESGP GSPAGSPTSTEEGTSESATPESGPGSEPATSGSETP GTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAP GTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAP GTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAP GTSESATPESGPGSEPATSGSETPGTSESATPESGP GSEPATSGSETPGTSESATPESGPGTSTEPSEGSAP GTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEE GSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAP
AG576 SEQ ID NO:51	PGTPGSGTASSSPGSSTPSGATGSPGSSPSASTGT GPGSSPSASTGTGPGSSTPSGATGSPGSSTPSGAT GSPGASPGTSSTGSPGASPGTSSTGSPGASPGTSS

	TGSPGTPGSGTASSSPGASPGTSSTGSPGASPGTS STGSPGASPGTSSTGSPGSSPSASTGTGPGTPGSG TASSSPGASPGTSSTGSPGASPGTSSTGSPGASPG TSSTGSPGSSTPSGATGSPGSSTPSGATGSPGASP GTSSTGSPGTPGSGTASSSPGSSTPSGATGSPGSS TPSGATGSPGSSTPSGATGSPGSSPSASTGTGPGA SPGTSSTGSPGASPGTSSTGSPGTPGSGTASSSPG ASPGTSSTGSPGASPGTSSTGSPGASPGTSSTGSP GASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGS PGTPGSGTASSSPGSSTPSGATGSPGTPGSGTASS SPGSSTPSGATGSPGSSTPSGATGSPGSSPSASTGT GPGSSPSASTGTGPGASPGTSSTGSPGTPGSGTAS SSPGSSTPSGATGSPGSSPSASTGTGPGSSPSASTG TGPGASPGTSSTGS
AE864 SEQ ID NO:52	GSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAP GSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAP GTSESATPESGPGSEPATSGSETPGSEPATSGSETP GSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAP GTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAP GTSTEPSEGSAPGTSESATPESGPGTSTEPSEGSAP GTSESATPESGPGSEPATSGSETPGTSTEPSEGSAP GTSTEPSEGSAPGTSESATPESGPGTSESATPESGP GSPAGSPTSTEEGTSESATPESGPGSEPATSGSETP GTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAP GTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAP GTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAP GTSESATPESGPGSEPATSGSETPGTSESATPESGP GSEPATSGSETPGTSESATPESGPGTSTEPSEGSAP GTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEE GSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAP GTSESATPESGPGSEPATSGSETPGTSESATPESGP GSEPATSGSETPGTSESATPESGPGTSTEPSEGSAP GSPAGSPTSTEEGTSESATPESGPGSEPATSGSETP GTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEE GTSTEPSEGSAPGTSESATPESGPGTSESATPESGP

	GTSESATPESGPGSEPATSGSETPGSEPATSGSETP GSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAP GSEPATSGSETPGTSESATPESGPGTSTEPSEGSAP
AG864 SEQ ID NO:53	GASPGTSSTGSPGSSPSASTGTGPGSSPSASTGTG PGTPGSGTASSSPGSSTPSGATGSPGSSPSASTGT GPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGAT GSPGTPGSGTASSSPGASPGTSSTGSPGASPGTSS TGSPGTPGSGTASSSPGSSTPSGATGSPGASPGTS STGSPGTPGSGTASSSPGSSTPSGATGSPGSSPSAS TGTGPGSSPSASTGTGPGSSTPSGATGSPGSSTPS GATGSPGASPGTSSTGSPGASPGTSSTGSPGASPG TSSTGSPGTPGSGTASSSPGASPGTSSTGSPGASP GTSSTGSPGASPGTSSTGSPGSSPSASTGTGPGTP GSGTASSSPGASPGTSSTGSPGASPGTSSTGSPGA SPGTSSTGSPGSSTPSGATGSPGSSTPSGATGSPG ASPGTSSTGSPGTPGSGTASSSPGSSTPSGATGSP GSSTPSGATGSPGSSTPSGATGSPGSSPSASTGTG PGASPGTSSTGSPGASPGTSSTGSPGTPGSGTASS SPGASPGTSSTGSPGASPGTSSTGSPGASPGTSST GSPGASPGTSSTGSPGTPGSGTASSSPGSSTPSGA TGSPGTPGSGTASSSPGSSTPSGATGSPGTPGSGT ASSSPGSSTPSGATGSPGSSTPSGATGSPGSSPSAS TGTGPGSSPSASTGTGPGASPGTSSTGSPGTPGSG TASSSPGSSTPSGATGSPGSSPSASTGTGPGSSPSA STGTGPGASPGTSSTGSPGASPGTSSTGSPGSSTP SGATGSPGSSPSASTGTGPGASPGTSSTGSPGSSP SASTGTGPGTPGSGTASSSPGSSTPSGATGSPGSS TPSGATGSPGASPGTSSTGSP
XTEN_AE72_2A_1 SEQ ID NO: 202	TSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPG TSTEPSEGSAPGTSESATPESGPGTSTEPSEGSAPG
XTEN_AE72_2A_2 SEQ ID NO: 203	TSESATPESGPGSEPATSGSETPGTSTEPSEGSAPG TSTEPSEGSAPGTSESATPESGPGTSESATPESGPG
XTEN_AE72_3B_1 SEQ ID NO: 204	SPAGSPTSTEEGTSESATPESGPGSEPATSGSETPG TSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPG
XTEN_AE72_3B_2	TSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPG

SEQ ID NO: 205	TSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPG
XTEN_AE72_4A_2 SEQ ID NO: 206	TSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEG SPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPG
XTEN_AE72_5A_2 SEQ ID NO: 207	SPAGSPTSTEEGTSESATPESGPGSEPATSGSETPG TSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEG
XTEN_AE72_6B_1 (SEQ ID NO: 208)	TSTEPSEGSAPGTSESATPESGPGTSESATPESGPG TSESATPESGPGSEPATSGSETPGSEPATSGSETPG
XTEN_AE72_6B_2 SEQ ID NO: 209	SPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPG SEPATSGSETPGTSESATPESGPGTSTEPSEGSAPG
XTEN_AE72_1A_1 SEQ ID NO: 210	SPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPG SPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPG
XTEN_AE72_1A_2 SEQ ID NO: 211	TSESATPESGPGSEPATSGSETPGSEPATSGSETPG SPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPG
XTEN_AE144_1A SEQ ID NO: 212	SPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPG SPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPG TSESATPESGPGSEPATSGSETPGSEPATSGSETPG SPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPG
AE150 SEQ ID NO: 213	GAPGSEPATSGSETPGTSESATPESGPGSEPATSG SETPGSPAGSPTSTEEGTSTEPSEGSAPGSEPATSG SETPGSEPATSGSETPGSEPATSGSETPGTSTEPSE GSAPGTSESATPESGPGSEPATSGSETPGTSTEPSE GSAPASS
G150 SEQ ID NO: 214	GAPGTPGSGTASSSPGSSTPSGATGSPGSSPSAST GTGPGSSPSASTGTGPGASPGTSSTGSPGASPGTS STGSPGSSTPSGATGSPGSSPSASTGTGPGASPGT SSTGSPGSSPSASTGTGPGTPGSGTASSSPGSSTPS GATGSPASS
AE294 SEQ ID NO: 215	GAPGTSESATPESGPGSEPATSGSETPGTSESATP ESGPGSEPATSGSETPGTSESATPESGPGTSTEPSE GSAPGSPAGSPTSTEEGTSESATPESGPGSEPATS GSETPGTSESATPESGPGSPAGSPTSTEEGSPAGS PTSTEEGTSTEPSEGSAPGTSESATPESGPGTSESA TPESGPGTSESATPESGPGSEPATSGSETPGSEPAT SGSETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEP SEGSAPGSEPATSGSETPGTSESATPESGPGTSTEP

	SEGSAPASS
AG294 SEQ ID NO: 216	GAPPGASPGTSSTGSPGASPGTSSTGSPGTPGSGT ASSSPGSSTPSGATGSPGTPGSGTASSSPGSSTPSG ATGSPGTPGSGTASSSPGSSTPSGATGSPGSSTPS GATGSPGSSPSASTGTGPGSSPSASTGTGPGASPG TSSTGSPGTPGSGTASSSPGSSTPSGATGSPGSSPS ASTGTGPGSSPSASTGTGPGASPGTSSTGSPGASP GTSSTGSPGSSTPSGATGSPGSSPSASTGTGPGAS PGTSSTGSPGSSPSASTGTGPGTPGSGTASSSPGSS TPSGATGSASS

[0144] 在其他實施例中，本發明中使用之 XTEN 序列影響本發明之融合蛋白之物理或化學特性，例如藥物動力學特性。用於本發明中的 XTEN 序列可顯示以下一或多個有利特性：構形可撓性、增強的水溶解性、高程度的蛋白酶抗性、低免疫原性、對哺乳動物受體的較低結合或增加的流體動力學(或 Stokes)半徑。在一特定實施例中，連接至本發明中之 FIX 蛋白之 XTEN 序列增加藥物動力學特性，諸如延長終末半衰期或增加曲線下面積(AUC)，以使本文所述之蛋白質在活體內停留之時間相較於野生型 FIX 有所增加。在其他實施例中，本發明中使用之 XTEN 序列增加藥物動力學特性，諸如延長終末半衰期或增加曲線下面積(AUC)，以使 FIX 蛋白質在活體內停留之時間相較於野生型 FIX 有所增加。

[0145] 在一些實施例中，FIX 蛋白質展現的活體內半衰期為原生 FIX、rFIXFc、FIX R338L 或缺乏 XTEN 之相應 FIX 蛋白質的至少約 1.5 倍、至少約 2 倍、至少約 3 倍

或至少約 4 倍。在一特定實施例中，FIX 融合蛋白的活體內半衰期可為不含異源部分之 FIX 多肽之超過 2 倍。

[0146] 在其他實施例中，FIX 融合蛋白展現的活體內半衰期比缺乏異源部分之 FIX 多肽之活體內半衰期長至少約 5 小時、至少約 6 小時、至少約 7 小時、至少約 8 小時、至少約 9 小時、至少約 10 小時、至少約 11 小時、至少約 12 小時、至少約 13 小時、至少約 14 小時、至少約 15 小時、至少約 16 小時、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、至少約小時或至少約 34 小時。

[0147] 多種方法及分析可用於測定包含 XTEN 序列之蛋白質之物理/化學特性。該等方法包括(但不限於)分析性離心、EPR、HPLC-離子交換、HPLC-尺寸排阻、反相 HPLC、光散射、毛細管電泳、圓偏光二色性、差示掃描量熱法、螢光、HPLC-離子交換、HPLC-尺寸排阻、IR、NMR、拉曼光譜、折射量測法及 UV/可見光譜學。其他方法揭示於 Amau 等人, *Prot Expr and Purif* 48, 1-13 (2006)中。

[0148] 可根據本發明使用之 XTEN 序列的其他實例揭示於美國專利公開案號 2010/0239554 A1、2010/0323956

A1、2011/0046060 A1、2011/0046061 A1、2011/0077199 A1 或 2011/0172146 A1；或國際專利公開案號 WO 2010091122 A1、WO 2010144502 A2、WO 2010144508 A1、WO 2011028228 A1、WO 2011028229 A1、WO 2011028344 A2、WO 2014/011819 A2 或 WO 2015/023891 中。

[0149] 在一些態樣中，FIX 融合蛋白包含插入 FIX 內、與 FIX 之 C 末端融合或兩者的一或多個 XTEN 序列。在一個實施例中，一或多個 XTEN 序列插入 GLA 結構域內。在另一實施例中，一或多個 XTEN 序列插入 EGF1 結構域內。在其他實施例中，一或多個 XTEN 序列插入 EGF2 內。在又其他實施例中，一或多個 XTEN 序列插入 AP 內。在其他實施例中，一或多個 XTEN 序列插入催化結構域內。在一些實施例中，一或多個 XTEN 序列與 FIX 之 C 末端融合。

[0150] 在某些態樣中，FIX 融合蛋白包含插入表 7 中所列之插入位點之一個 XTEN 序列。在其他態樣中，FIX 融合蛋白包含插入表 7 中所列兩個插入位點中之兩個 XTEN 序列。在一特定實施例中，兩個 XTEN 序列插入表 8 中所列之兩個插入位點中。在某些態樣中，FIX 融合蛋白包含插入表 7 中所列三個插入位點中之三個 XTEN 序列。在某些態樣中，FIX 融合蛋白包含插入表 7 中所列四個插入位點中之四個 XTEN 序列。在某些態樣中，FIX 融合蛋白包含插入表 7 中所列五個插入位點中之五個 XTEN

序列。在某些態樣中，FIX 融合蛋白包含插入表 7 中所列六個插入位點中之六個 XTEN 序列。在一些態樣中，所有插入之 XTEN 序列皆相同。在其他態樣中，至少一個插入之 XTEN 序列不同於其餘插入之 XTEN 序列。

[0151] 在一些態樣中，FIX 融合蛋白包含插入 FIX 多肽內對應於選自由以下組成之群之胺基酸之插入位點的一個 XTEN 序列：SEQ ID NO: 2 之胺基酸 103、SEQ ID NO: 2 之胺基酸 105、SEQ ID NO: 2 之胺基酸 142、SEQ ID NO: 2 之胺基酸 149、SEQ ID NO: 2 之胺基酸 162、SEQ ID NO: 2 之胺基酸 166、SEQ ID NO: 2 之胺基酸 174、SEQ ID NO: 2 之胺基酸 224、SEQ ID NO: 2 之胺基酸 226、SEQ ID NO: 2 之胺基酸 228、SEQ ID NO: 2 之胺基酸 413 及其任何組合，其中該 FIX 融合蛋白展現促凝血活性。在一些態樣中，FIX 融合蛋白包含在 FIX 多肽內對應於選自由以下組成之群之胺基酸之插入位點的第二 XTEN 序列：SEQ ID NO: 2 之胺基酸 103、SEQ ID NO: 2 之胺基酸 105、SEQ ID NO: 2 之胺基酸 142、SEQ ID NO: 2 之胺基酸 149、SEQ ID NO: 2 之胺基酸 162、SEQ ID NO: 2 之胺基酸 166、SEQ ID NO: 2 之胺基酸 174、SEQ ID NO: 2 之胺基酸 224、SEQ ID NO: 2 之胺基酸 226、SEQ ID NO: 2 之胺基酸 228、SEQ ID NO: 2 之胺基酸 413 及其任何組合，或其中該第二 XTEN 與 FIX 多肽之 C 末端融合，其中該 FIX 融合蛋白展現促凝血活性。在一特定態樣中，FIX 融合蛋白包含與 FIX 之 C 末端融合的一個

XTEN 序列，其中 XTEN 包含長度超過 42 個胺基酸且短於 144 個胺基酸之胺基酸序列。

II.B.2 Fc 區或 FcRn 結合搭配物

[0152] 在一些實施例中，該至少一個異源部分為 Fc 區(例如 FcRn 結合搭配物)或其片段。在某些態樣中，本發明之 FIX 融合蛋白包含插入於 FIX 內、與 FIX 之 C 末端融合或兩者之至少一個 Fc 區(例如 FcRn 結合搭配物)，其中該 FIX 融合蛋白具有促凝血活性且可在宿主細胞中在活體內或活體外表現。除非另外規定，否則如本文所用，「Fc」或「Fc 區」可為包含 Fc 結構域、其變異體或片段之功能性新生兒 Fc 受體(FcRn)結合搭配物。FcRn 結合搭配物為可由 FcRn 受體特異性結合，從而藉由 FcRn 結合搭配物之 FcRn 受體主動運輸之任何分子。因此，術語 Fc 包括 IgG Fc 之任何功能性變異體。IgG 之 Fc 部分中結合至 FcRn 受體的區域已基於 X-射線結晶學進行描述(Burmeister 等人, *Nature 372*:379 (1994)，其以全文引用之方式併入本文中)。Fc 與 FcRn 之主要接觸區域接近 CH2 結構域與 CH3 結構域之接合點。Fc-FcRn 接觸區全部在單一 Ig 重鏈內。結合搭配物的 FcRn 包括(但不限於)完整 IgG、IgG 之 Fc 片段及 IgG 中包括 FcRn 之完整結合區之其他片段。Fc 可包含免疫球蛋白中具有或不具有免疫球蛋白鉸鏈區之 CH2 域及 CH3 域。亦包括融合蛋白中維持 Fc 區之所需特性(例如延長半衰期，例如活體內半衰

期)之 Fc 片段、變異體或衍生物。許多突變體、片段、變異體及衍生物描述於例如 PCT 公開案第 WO 2011/069164 A2 號、第 WO 2012/006623 A2 號、第 WO 2012/006635 A2 號或第 WO 2012/006633 A2 號中，皆以全文引用的方式併入本文中。

[0153] 該一或多個 Fc 結構域可插入 FIX 多肽內、與該多肽之 C 末端融合或兩者。在一些實施例中，Fc 結構域與 FIX 多肽融合。在一些實施例中，Fc 結構域與另一異源部分，諸如 XTEN 融合，Fc 結構域插入 FIX 內或與 XTEN 之 C 末端融合。在一些實施例中，FIX 融合蛋白包含第二 Fc 結構域。該第二 Fc 結構域可例如經由一或多個共價鍵與第一 Fc 結構域締合。

II.B.3. 白蛋白

[0154] 在一些實施例中，該至少一個異源部分為白蛋白、白蛋白結合結構域或白蛋白結合小分子，或者其變異體、衍生物或片段。在某些態樣中，本發明之 FIX 融合蛋白包含至少一個插入 FIX 內、與 FIX 之 C 末端融合或兩者之白蛋白多肽或其片段、變異體或衍生物，其中該 FIX 融合蛋白具有促凝血活性且可在宿主細胞中在活體內或活體外表現。人血清白蛋白(HAS 或 HA)係呈全長形式時具有 609 個胺基酸之蛋白質，其負責顯著比例的血清滲透壓且亦充當內源性及外源性配位體之載劑。如本文所用，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之實例揭示於美國專利公開案第 2008/0194481A1 號、第 2008/0004206 A1 號、第 2008/0161243 A1 號、第 2008/0261877 A1 號或第 2008/0153751 A1 號或 PCT 申請公開案第 2008/033413 A2 號、第 2009/058322 A1 號或第 2007/021494 A2 號中，該等公開案以全文引用的方式併入本文中。

[0155] 白蛋白結合多肽(ABP)可包含(但不限於)可結合白蛋白之細菌白蛋白結合結構域、白蛋白結合肽或白蛋白結合抗體片段。如 Kraulis 等人, FEBS Lett. 378:190-194 (1996)及 Linhult 等人, Protein Sci. 11:206-213 (2002)所揭示的來自鏈球菌蛋白質 G 之結構域 3 為細菌白蛋白結合結構域的一個實例。白蛋白結合肽之實例包括一系列具有核心序列 DICLPRWGCLW (SEQ ID NO: 163)之肽。參見例如 Dennis 等人, J. Biol. Chem. 2002, 277: 35035-35043 (2002)。白蛋白結合抗體片段之實例揭示於 Muller 及 Kontermann, *Curr. Opin. Mol. Ther.* 9:319-326 (2007)；Roovers 等人, *Cancer Immunol. Immunother.* 56:303-317 (2007)；及 Holt 等人, Prot. Eng. Design Sci., 21:283-288 (2008)中，該等參考文獻以全文引用的方式併入本文中。

[0156] 在某些態樣中，本發明之 FIX 融合蛋白包含可結合至插入 FIX 中、與 FIX 之 C 末端融合或兩者之白蛋白(例如白蛋白結合小分子)之非多肽小分子、其變異體或衍生物的至少一個連接位點，其中該 FIX 融合蛋白具有

促凝血活性且可在宿主細胞中在活體內或活體外表現。舉例而言，本發明之 FIX 融合蛋白可包括連接於 FIX 內之一或多個插入位點中，或與 FIX 之 C 末端融合，或兩者的一或多個有機白蛋白結合部分，其中該 FIX 融合蛋白具有促凝血活性且可在宿主細胞中在活體內或活體外表現。此等白蛋白結合部分之實例為如由 Trusselet 等人，Bioconjugate Chem. 20:2286-2292 (2009)所揭示之 2-(3-順丁烯二醯亞胺基丙醯胺基)-6-(4-(4-碘苯基)丁醯胺基)己酸酯(「Albu」標籤)。

[0157] 在一些實施例中，白蛋白結合多肽序列係藉由 Gly-Ser 肽連接子序列側接在 C 末端、N 末端或兩端處。在一些實施例中，Gly-Ser 肽連接子為 Gly_4Ser(SEQ ID NO: 161)。在其他實施例中，Gly-Ser 肽連接子為 $(Gly_4Ser)_2$(SEQ ID NO: 162)。

II.B.4. CTP

[0158] 在一些實施例中，至少一個異源部分為人類絨毛膜促性腺素 β 次單位之 C 末端肽(CTP)或其片段、變異體或衍生物。在某些態樣中，本發明之 FIX 融合蛋白包含至少一個插入 FIX 中、與 FIX 之 C 末端融合或兩者之 CTP 或其片段、變異體或衍生物，其中該 FIX 融合蛋白具有促凝血活性且可在宿主細胞中在活體內或活體外表現。已知一或多個插入重組蛋白中之 CTP 肽會延長彼蛋白質之半衰期。參見例如美國專利第 5,712,122 號，以全文引

用之方式併入本文中。示範性 CTP 肽包括 DPRFQDSSSSKAPPPSLPSPSRLPGPSDTPIL (SEQ ID NO: 164)或 SSSSKAPPPSLPSPSRLPGPSDTPILPQ (SEQ ID NO: 165)。參見例如，美國專利申請公開案第 US 2009/0087411 A1 號，以引用之方式併入本文中。在一些實施例中，CTP 序列係藉由 Gly-Ser 肽連接子序列側接在 C 末端、N 末端或兩個末端處。在一些實施例中，Gly-Ser 肽連接子為 Gly_4Ser(SEQ ID NO: 161)。在其他實施例中，Gly-Ser 肽連接子為 $(Gly_4Ser)_2$(SEQ ID NO: 162)。

II.B.5. PAS

[0159] 在一些實施例中，至少一個異源部分為 PAS 肽。在某些態樣中，本發明之 FIX 融合蛋白包含至少一個插入 FIX 中、與 FIX 之 C 末端融合或兩者之 PAS 肽或其片段、變異體或衍生物，其中該 FIX 融合蛋白具有促凝血活性且可在宿主細胞中在活體內或活體外表現。如本文所用，「PAS 肽」或「PAS 序列」意謂主要包含丙胺酸及絲胺酸殘基或主要包含丙胺酸、絲胺酸及脯胺酸殘基之胺基酸序列，該胺基酸序列在生理條件下形成無規捲曲構形。因此，PAS 序列為包含丙胺酸、絲胺酸及脯胺酸；基本上由丙胺酸、絲胺酸及脯胺酸組成或由丙胺酸、絲胺酸及脯胺酸組成的可用作融合蛋白中之異源部分之一部分的構築嵌段、胺基酸聚合物或序列卡匣。當除丙胺酸、絲胺酸及脯胺酸以外之殘基作為次要組分添加於 PAS 序列中時，

胺基酸聚合物亦可形成無規捲曲構形。「次要組分」意謂除丙胺酸、絲胺酸及脯胺酸以外之胺基酸可在某種程度上添加於 PAS 序列中，例如佔該等胺基酸至多約 12%，亦即 PAS 序列之 100 個胺基酸中有約 12 個彼等胺基酸；至多約 10%；至多約 9%；至多約 8%；約 6%；約 5%；約 4%；約 3%；亦即，約 2%或約 1%。不同於丙胺酸、絲胺酸及脯胺酸之胺基酸可選自由以下組成之群：Arg、Asn、Asp、Cys、Gln、Glu、Gly、His、Ile、Leu、Lys、Met、Phe、Thr、Trp、Tyr 及 Val。在生理條件下，PAS 肽形成無規捲曲構形且藉此可介導本發明重組蛋白之活體內及/或活體外穩定性增強，且具有促凝血活性。

[0160] PAS 肽之非限制性實例包括 ASPAAPAPASPAAPAPSAPA (SEQ ID NO: 154)、AAPASPAPAAPSAPAPAAPS (SEQ ID NO: 155)、APSSPSPSAPSSPSPASPSS (SEQ ID NO: 156)、APSSPSPSAPSSPSPASPS (SEQ ID NO: 157)、SSPSAPSPSSPASPSPSSPA (SEQ ID NO: 158)、AASPAAPSAPPAAASPAAPSAPPA (SEQ ID NO: 159)、ASAAAPAAASAAASAPSAAA (SEQ ID NO: 160)或其任何變異體、衍生物、片段或組合。PAS 序列之其他實例根據例如美國專利公開案第 2010/0292130 A1 號及 PCT 申請公開案第 WO 2008/155134 A1 號可知。歐洲頒布之專利 EP2173890。

[0161] 在一些實施例中，PAS 序列係藉由 Gly-Ser 肽連接子序列側接在 C 末端、N 末端或兩個末端處。在一些實施例中，Gly-Ser 肽連接子為 Gly_4Ser(SEQ ID NO:

161)。在其他實施例中，Gly/Ser 肽連接子為$(Gly_4Ser)_2$ (SEQ ID NO: 162)。

II.B.6 HAP

[0162] 在一些實施例中，該至少一個異源部分為高胺基酸聚合物(HAP)肽或其片段、變異體或衍生物。在某些態樣中，本發明之 FIX 融合蛋白包含至少一個插入 FIX 內、與 FIX 之 C 末端融合或兩者之高胺基酸聚合物(HAP)肽或其片段、變異體或衍生物，其中該 FIX 融合蛋白具有促凝血活性且可在宿主細胞中在活體內或活體外表現。HAP 肽可包含甘胺酸重複序列，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 序列能夠延長融合於或連接至 HAP 序列之部分的半衰期。HAP 序列之非限制性實例包括(但不限於)$(Gly)_n$、$(Gly_4Ser)_n$ 或 $S(Gly_4Ser)_n$，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。在一個實施例中，n 為 20、21、22、23、24、25、26、26、28、29、30、31、32、33、34、35、36、37、38、39 或 40。在一個實施例中，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 等人，Protein Eng. Design Selection, 20: 273-284

(2007)。

II.B.7. 有機聚合物

[0163] 在一些實施例中，該至少一個異源部分為有機聚合物，例如聚乙二醇、聚唾液酸或羥乙基澱粉。在某些態樣中，本發明之 FIX 融合蛋白包含插入 FIX 中、與 FIX 之 C 末端融合或兩者之非多肽異源部分或其片段、變異體或衍生物的至少一個連接位點，其中該 FIX 融合蛋白具有促凝血活性且可在宿主細胞中在活體內或活體外表現。舉例而言，本發明之 FIX 融合蛋白可包括連接於 FIX 序列內、連接至 FIX 之 C 末端，或兩者的一或多個聚乙二醇(PEG)部分，其中該 FIX 融合蛋白具有促凝血活性且可在宿主細胞中在活體內或活體外表現。

[0164] 聚乙二醇化 FIX 可指 FIX 與至少一個聚乙二醇(PEG)分子之間形成的偶聯物。可購得在多種分子量及平均分子量範圍內的 PEG。PEG 平均分子量範圍之典型實例包括(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 及約 80000 道爾頓。此等平均分子量僅作為實例提供且不意欲以任何方式具有限制性。

[0165] 本發明之 FIX 融合蛋白可經聚乙二醇化以包

括單個或多個(例如 2-4 個)PEG 部分。聚乙二醇化可藉由此項技術中已知之聚乙二醇化反應中之任一種進行。製備聚乙二醇化蛋白質產物之方法一般將包括(i)使多肽與聚乙二醇(諸如 PEG 之反應性酯或醛衍生物)在使本發明之肽連接至一或多個 PEG 基團之條件下反應；及(ii)獲得反應產物。一般而言，反應之最佳反應條件將基於已知參數及所需結果根據具體情況來確定。

[0166] 存在許多可為熟習此項技術者可利用的 PEG 連接方法，例如 Malik F 等人, *Exp. Hematol.* 20:1028-35 (1992)；Francis, *Focus on Growth Factors* 3(2):4-10 (1992)；歐洲專利公開案第 EP0401384 號、第 EP0154316 號及第 EP0401384 號；及國際專利申請公開案第 WO92/16221 號及第 WO95/34326 號。作為非限制性實例，FIX 變異體可在如本文所述之一或多個插入位點處或其附近含有半胱胺酸取代，且半胱胺酸可進一步與 PEG 聚合物偶聯。參見 Mei 等人, *Blood* 116:270-279 (2010)及美國專利第 7,632,921 號，其以全文引用的方式併入本文中。

[0167] 在其他實施例中，有機聚合物為聚唾液酸(PSA)。PSA 為由某些細菌菌株及在哺乳動物中於某些細胞中產生之唾液酸之天然存在之未分支聚合物。參見例如，Roth J.等人(1993) *Polysialic Acid: From Microbes to Man*, Roth J., Rutishauser U., Troy F. A.編(BirkhäuserVerlag, Basel, Switzerland), 第 335–348 頁。PSA 可藉由有限酸水

解或藉由用神經胺糖酸苷酶(neuraminidase)消化或藉由份化聚合物之天然細菌源性形式來以自 n=約 80 個或 80 個以上唾液酸殘基至 n=2 之各種聚合度產生。存在許多可為熟習此項技術者所用之 PSA 連接方法，例如上述相同 PEG 連接方法。在某些態樣中，活化 PSA 亦可連接至 FIX 上之半胱胺酸胺基酸殘基。參見例如美國專利第 5846951 號。

[0168] 在其他實施例中，有機聚合物為羥乙基澱粉(HES)聚合物。在某些態樣中，本發明之 FIX 融合蛋白包含至少一個偶聯於 FIX 內之一或多個位點、與 FIX 之 C 末端融合或兩者之 HES 聚合物，其中該重組 FIX 蛋白具有促凝血活性且可在宿主細胞中在活體內或活體外表現。

III. 聚核苷酸、載體、宿主細胞及製備方法

[0169] 本發明另外提供一種編碼本文所描述之 FIX 融合蛋白之聚核苷酸、包含該聚核苷酸之表現載體、包含該聚核苷酸或該載體之宿主細胞，或製備該 FIX 融合蛋白之方法。

[0170] 編碼 FIX 融合蛋白之聚核苷酸可為單一核苷酸序列、兩個核苷酸序列、三個核苷酸序列或更多核苷酸序列。在一個實施例中，單一核苷酸序列編碼包含 FIX 多肽及異源部分(例如 XTEN)之 FIX 融合蛋白，例如包含 FIX 多肽及插入 FIX 多肽內之 XTEN、與 FIX 多肽之 C 末端融合之 Fc 結構域及藉由可選連接子與 FIX 多肽融合之

第二 Fc 結構域的 FIX 融合蛋白。在另一實施例中，多核苷酸包含兩個核苷酸序列，第一核苷酸序列編碼 FIX 多肽及插入 FIX 多肽內之 XTEN，且第二核苷酸序列編碼異源部分，例如 Fc。在其他實施例中，多核苷酸包含兩個核苷酸序列，第一核苷酸序列編碼 FIX 多肽、插入 FIX 多肽內之 XTEN 及與 FIX 多肽融合之 Fc 結構域，且第二核苷酸序列編碼第二 Fc 結構域。編碼的 Fc 結構域可在表現後形成共價鍵。

[0171] 在一些實施例中，編碼 FIX 融合蛋白之多核苷酸經密碼子優化。

[0172] 如本文所用，表現載體係指含有在引入適當宿主細胞中時插入之編碼序列轉錄及轉譯所必需之元件，或在 RNA 病毒載體之情況下複製及轉譯所必需之元件的任何核酸構築體。表現載體可包括質體、噬菌粒、病毒及其衍生物。

[0173] 如本文所用之基因表現控制序列為有助於可操作地連接之編碼核酸之高效轉錄及轉譯的任何調控性核苷酸序列，諸如啟動子序列或啟動子-增強子組合。基因表現控制序列可例如為哺乳動物或病毒啟動子，諸如組成性或誘導性啟動子。組成性哺乳動物啟動子包括(但不限於)以下基因之啟動子：次黃嘌呤磷酸核糖基轉移酶(HPRT)、腺苷去胺酶、丙酮酸激酶、β-肌動蛋白啟動子及其他組成性啟動子。在真核細胞中組成性起作用之示範性病毒啟動子包括例如來自細胞巨大病毒(CMV)、猿猴病毒

(例如 SV40)、乳頭狀瘤病毒、腺病毒、人類免疫缺陷病毒(HIV)、勞斯肉瘤病毒(Rous sarcoma virus)、細胞巨大病毒、莫洛尼白血病病毒(Moloney leukemia virus)之長末端重複序列(LTR)及其他反轉錄病毒之啟動子、及單純性皰疹病毒之胸苷激酶啟動子。一般熟習此項技術者已知其他組成性啟動子。可用作本發明之基因表現序列之啟動子亦包括誘導性啟動子。誘導性啟動子在誘導劑存在下表現。舉例而言，誘導金屬硫蛋白啟動子以促進在某些金屬離子存在下之轉錄及轉譯。其他誘導性啟動子為一般熟習此項技術者所知。

[0174] 出於本發明之目的，可採用眾多表現載體系統。該等表現載體通常可在宿主生物體中作為游離基因體或作為宿主染色體 DNA 之整體部分複製。表現載體可包括表現控制序列，包括但不限於，啟動子(例如天然締合或異源啟動子)、增強子、信號序列、剪接信號、增強子元件及轉錄終止序列。較佳地，表現控制序列為在能夠轉型或轉染真核宿主細胞之載體中的真核啟動子。表現載體亦可利用來源於動物病毒，諸如牛乳頭瘤病毒、多瘤病毒、腺病毒、牛痘病毒、桿狀病毒、反轉錄病毒(RSV、MMTV 或 MOMLV)、細胞巨大病毒(CMV)或 SV40 病毒之 DNA 元件。其他涉及使用具有內部核糖體結合位點之多順反子系統。

[0175] 通常，表現載體含有選擇標記物(例如胺苄青黴素抗性、潮黴素抗性、四環素抗性或新黴素抗性)以容

許偵測經所需 DNA 序列轉型之細胞(參見例如，Itakura 等人，美國專利第 4,704,362 號)。將 DNA 整合至染色體中之細胞可藉由引入一或多個允許選擇經轉染宿主細胞之標記物來進行選擇。標記物可向具有生物殺滅劑抗性(例如抗生素)或對諸如銅之重金屬具有抗性的營養缺陷型宿主提供原營養。可選擇標記物基因可直接連接至待表現之 DNA 序列，或藉由共轉型引入該細胞中。

[0176] 可用於表現優化之 FIX 序列之載體的實例為 NEOSPLA (美國專利第 6,159,730 號)。該載體含有細胞巨大病毒啟動子/增強子、小鼠 β 球蛋白主要啟動子、SV40 複製起點、牛生長激素聚腺苷酸化序列、新黴素磷酸轉移酶外顯子 1 及外顯子 2、二氫葉酸還原酶基因及前導序列。已發現，該載體在併入可變區及恆定區基因、在細胞中轉染隨後在含 G418 之培養基中選擇並進行甲胺喋呤擴增後以極高水準表現抗體。載體系統亦於美國專利第 5,736,137 號及第 5,658,570 號中教示，其各自以全文引用之方式併入本文中。該系統提供高表現水準，例如> 30 皮克/細胞/天。其他示範性載體系統揭示於例如美國專利第 6,413,777 號中。

[0177] 在其他實施例中，本發明之多肽可使用多順反子構築體表現。在此等表現系統中，可自單個多順反子構築體產生多個所關注基因產物，諸如多聚體結合蛋白質之多個多肽。此等系統宜使用內部核糖體入口位點(IRES)以在真核宿主細胞中提供相對較高含量之多肽。適用

IRES 序列揭示於美國專利第 6,193,980 號，該案亦併入本文中。

[0178] 更一般而言，一旦製備出編碼多肽之載體或 DNA 序列，即可將該表現載體引入適當宿主細胞中。亦即，宿主細胞可經轉型。將質體引入宿主細胞中可藉由如以上所論述的熟習此項技術者熟知之各種技術實現。轉型之細胞在適於產生 FIX 多肽之條件下生長，且針對 FIX 多肽合成進行分析。示範性分析技術包括酶聯結免疫吸附劑分析(ELISA)、放射免疫分析(RIA)或螢光活化細胞分選器分析(FACS)、免疫組織化學及其類似技術。

[0179] 在對用於自重組寄主分離多肽之方法的描述中，除非另外清楚地指明，否則術語「細胞」及「細胞培養物」可互換使用以指示多肽之來源。換言之，自「細胞」回收多肽可意謂自短暫離心之完整細胞或自含有培養基及懸浮細胞之細胞培養物中回收。

[0180] 用於表現蛋白質之宿主細胞較佳為哺乳動物來源；最佳為人類或小鼠來源。示範性宿主細胞株已於上文描述。在產生具有 FIX 活性之多肽之方法的一個實施例中，宿主細胞為 HEK293 細胞。在產生具有 FIX 活性之多肽之方法的另一實施例中，宿主細胞為 CHO 細胞。

[0181] 編碼本發明多肽之基因亦可在非哺乳動物細胞，諸如細菌或真菌或植物細胞中表現。就這一點而言，應理解，各種單細胞非哺乳動物微生物，諸如細菌，亦可經轉型；亦即，能夠在培養或發酵時生長之該等微生物。

易於轉型之細菌包括腸桿菌科成員，諸如大腸桿菌或沙門氏菌屬菌株；芽孢桿菌科，諸如枯草芽孢桿菌(*Bacillus subtilis*)；肺炎球菌屬；鏈球菌屬，及流感嗜血桿菌(*Haemophilus influenzae*)。另外，應理解，當在細菌中表現時，多肽通常變為包涵體之一部分。該等多肽必須加以分離、純化且隨後組裝成功能性分子。

[0182] 或者，本發明之聚核苷酸序列可併入轉殖基因中以引入轉殖基因動物之基因組中且隨後在轉殖基因動物之乳汁中表現(參見例如，Deboer等人，US 5,741,957；Rosen, US 5,304,489；及Meade等人，US 5,849,992)。適合轉殖基因包括與來自乳腺特異性基因，諸如酪蛋白或β乳球蛋白之啟動子及增強子可操作連接之多肽編碼序列。

[0183] 活體外產生允許按比例擴大以得到大量所需多肽。關於在組織培養條件下培養哺乳動物細胞之技術在此項技術中為已知的，且包括均勻懸浮培養，例如在氣升式反應器中或在連續攪拌反應器中的均勻懸浮培養；或固定或截留細胞培養，例如在中空纖維、微囊中，在瓊脂糖微珠或陶瓷匣筒上的培養。必要時及/或需要時，可藉由慣用層析法，例如凝膠過濾、離子交換層析法、經DEAE-纖維素層析或(免疫)親和層析法，例如在合成鉸鏈區多肽之優先生物合成之後或在本文所描述之HIC層析步驟之前或之後，純化多肽之溶液。親和標籤序列(例如 His(6)標籤)可視情況連接或包括在多肽序列內以促進下游純化。

[0184] 一旦表現，即可根據此項技術之標準程序，

包括硫酸銨沉澱、親和管柱層析、HPLC 純化、凝膠電泳及其類似方法純化 FIX 蛋白質(一般參見 Scopes, Protein Purification (Springer-Verlag, N.Y., (1982))。對於醫藥應用，均勻性為至少約 90%或 95%的實質上純之蛋白質較佳，且 98%至 99%或更高均勻性最佳。

[0185] 在一個實施例中，宿主細胞為真核細胞。如本文所用，真核細胞係指具有胚乳原核之任何動物或植物細胞。動物之真核細胞包括脊椎動物(例如哺乳動物)之細胞，及無脊椎動物(例如昆蟲)之細胞。植物之真核細胞特定言之可包括而不限於酵母細胞。真核細胞不同於例如細菌之原核細胞。

[0186] 在某些實施例中，真核細胞為哺乳動物細胞。哺乳動物細胞為源於哺乳動物之任何細胞。哺乳動物細胞特定言之包括(但不限於)哺乳動物細胞株。在一個實施例中，哺乳動物細胞為人類細胞。在另一實施例中，哺乳動物細胞為 HEK 293 細胞，其為一種人類胚腎細胞株。HEK 293 細胞可以 CRL-1533 自 Manassas, VA 之美國典型培養物保藏中心(American Type Culture Collection)及以 293-H 細胞(目錄編號 11631-017)或 293-F 細胞(目錄編號 11625-019)自 Invitrogen (Carlsbad, Calif.)獲得。在一些實施例中，哺乳動物細胞為 PER.C6®細胞，其為一種源於視網膜之人類細胞株。PER.C6®細胞可自 Crucell (Leiden, The Netherlands)獲得。在其他實施例中，哺乳動物細胞為中國倉鼠卵巢(CHO)細胞。CHO 細胞可自美國典

型培養物保藏中心(Manassas, VA.)獲得(例如 CHO-K1；CCL-61)。在其他實施例中，哺乳動物細胞為幼小倉鼠腎(BHK)細胞。BHK 細胞可自美國典型培養物保藏中心(Manassas, Va.)獲得(例如 CRL-1632)。在一些實施例中，哺乳動物細胞為 HKB11 細胞，其為 HEK293 細胞與人類 B 細胞株之雜交細胞株。Mei 等人, Mol. Biotechnol. 34(2): 165-78 (2006)。

[0187] 在其他實施例中，所轉染細胞經穩定轉染。使用熟習此項技術者已知之習知技術，此等細胞可經選擇且維持為穩定細胞株。

[0188] 含有蛋白質之 DNA 構築體之宿主細胞生長在適當生長培養基中。如本文所用，術語「適當生長培養基」意謂含有為細胞生長所需之養分之培養基。為細胞生長所需之養分可包括碳源、氮源、必需胺基酸、維生素、礦物質及生長因子。視情況，培養基可含有一或多種選擇因子。視情況，培養基可含有小牛血清或胎牛血清(FCS)。在一個實施例中，培養基實質上不含有 IgG。生長培養基將通常藉由例如藥物選擇或缺乏必需養分來選擇含有 DNA 構築體之細胞，該必需養分由 DNA 構築體上或與 DNA 構築體共轉染之可選擇標記補充。所培養哺乳動物細胞通常生長在市售含血清或不含血清培養基(例如 MEM、DMEM、DMEM/F12)中。在一個實施例中，培養基為 CD293(Invitrogen, Carlsbad, CA.)。在另一實施例中，培養基為 CD17(Invitrogen, Carlsbad, CA.)。對適於所用特

定細胞株之培養基之選擇屬於一般熟習此項技術者之水準。

[0189] 在一些實施例中，核酸、載體或宿主細胞進一步包含編碼蛋白質轉化酶之另一核苷酸。蛋白質轉化酶可選自由以下組成之群：前蛋白轉化酶枯草桿菌蛋白酶/kexin 5 型(PCSK5 或 PC5)、前蛋白轉化酶枯草桿菌蛋白酶/kexin 7 型(PCSK7 或 PC5)、酵母 Kex 2、前蛋白轉化酶枯草桿菌蛋白酶/kexin 3 型(PACE 或 PCSK3)及其兩種或兩種以上組合。在一些實施例中，蛋白質轉化酶為 PACE、PC5 或 PC7。在一特定實施例中，蛋白質轉化酶為 PC5 或 PC7。參見國際申請公開案第 WO 2012/006623 號，其以引用的方式併入本文中。在另一實施例中，蛋白質轉化酶為 PACE/弗林蛋白酶。

[0190] 在某些態樣中，本發明係關於藉由本文所述之方法產生之 FIX 融合蛋白。

[0191] 在某些態樣中，本發明之宿主細胞可在活體內或活體外表現 FIX 融合蛋白。活體外生產允許按比例擴大以得到大量本發明所需之改變之多肽。可藉由在表現 FIX 融合蛋白之條件下培養本文所描述之宿主細胞來產生 FIX 融合蛋白。有關在組織培養條件下培養哺乳動物細胞之技術在此項技術中為已知的，且包括均勻懸浮培養，例如在氣升式反應器中或在連續攪拌反應器中的均勻懸浮培養；或固定或截留細胞培養，例如在中空纖維、微囊中，在瓊脂糖微珠或陶瓷匣筒上的培養。必要及/或需要時，

多肽之溶液可藉由慣用層析方法，例如凝膠過濾、離子交換層析、疏水性相互作用層析(HIC)、經 DEAE-纖維素層析或親和層析純化。在其他態樣中，宿主細胞在活體內表現 FIX 融合蛋白。

[0192] 在一個實施例中，本發明包括一種製備 FIX 融合蛋白之方法，其包含如本文所描述將異源部分插入於插入位點中、使異源部分與 FIX 之 C 末端融合，或兩者，其中該 FIX 融合蛋白展現促凝血活性。

[0193] 在另一實施例中，本發明包括一種增加 FIX 蛋白質之半衰期，同時不消除或降低 FIX 蛋白質之促凝血活性的方法，其包含如本文所描述將異源部分插入於插入位點中、使異源部分與 FIX 之 C 末端融合，或兩者，其中該 FIX 融合蛋白展現促凝血活性且半衰期相較於不含異源部分之 FIX 蛋白質有所增加。

[0194] 在其他實施例中，本發明提供一種構築 FIX 融合蛋白之方法，其包含設計編碼 FIX 融合蛋白之核苷酸序列，該 FIX 融合蛋白包含如本文所描述的在插入位點中、與 FIX 之 C 末端融合或二者之至少一個異源部分。

[0195] 在某些實施例中，本發明包括一種增加 FIX 融合蛋白之表現的方法，其包含如本文所描述將異源部分插入於插入位點中、使異源部分與 FIX 之 C 末端融合，或兩者，其中該 FIX 融合蛋白展現促凝血活性。

[0196] 在又其他實施例中，本發明包括一種保持 FIX 融合蛋白之促凝血活性的方法，其包含如本文所描述將異

源部分插入於插入位點中、使異源部分與 FIX 之 C 末端融合，或兩者，其中該 FIX 融合蛋白展現促凝血活性。

IV. 醫藥組合物及治療方法

[0197] 本發明另外提供一種使用包含本發明之 FIX 融合蛋白之醫藥組合物預防、治療、改善或管理有需要之人類受試者之凝血疾病或病狀或者出血病狀的方法。示範性方法包含括向有需要之受試者投與治療有效量的包含本發明之 FIX 融合蛋白的醫藥組合物/調配物。在其他態樣中，可向有需要之受試者投與包含編碼本發明之融合蛋白之 DNA 的組合物。在本發明之某些態樣中，可向有需要之受試者投與表現本發明之 FIX 融合蛋白之細胞。在本發明之某些態樣中，醫藥組合物包含(i) FIX 融合蛋白、(ii)編碼 FIX 融合蛋白之分離之核酸、(iii)包含編碼 FIX 融合蛋白質核酸的載體、(iv)包含編碼 FIX 融合蛋白之分離之核酸及/或包含編碼 FIX 融合蛋白之核酸之載體的細胞，或(v)其組合，且醫藥組合物進一步包含可接受之賦形劑或載劑。

[0198] 本發明之 FIX 融合蛋白可靜脈內、皮下或經口投與患者。在某些實施例中，FIX 融合蛋白係藉由靜脈內注射投與受試者。在其他實施例中，FIX 融合蛋白係藉由皮下注射投與受試者。注射可包含單次推注。受試者可接受超過一次注射。

[0199] 本發明之融合蛋白可用於防治目的。如本文

所用，術語「防治性治療」係指在流血事件之前投與分子。在一個實施例中，需要一般性止血劑之個體正經歷或即將經歷手術。本發明之融合蛋白可在手術之前或之後作為防治劑投與。本發明之融合蛋白可在手術期間或之後投與以控制急性出血事件。手術可包括(但不限於)肝移植、肝切除、牙齒程序或幹細胞移植。

[0200] 本發明之融合蛋白亦用於按需治療。術語「按需治療」係指響應於出血事件之症狀或在可能導致出血之活動之前投與融合蛋白。在一個態樣中，按需治療係在出血開始時(諸如在損傷之後)或在預期會出血時(諸如在手術之前)給與個體。在另一態樣中，按需治療係在增加出血風險之活動(諸如接觸性運動)之前給與。

[0201] 在其他實施例中，使用融合蛋白控制、改善或治療急性出血事件。在其他實施例中，相較於不含異源部分之相應 FIX 蛋白質，FIX 融合蛋白展現一或多個藥物動力學參數。PK 參數可基於 FIX 抗原含量(本文中常附帶表示為「抗原」)或 FIX 活性水準(本文中常附帶表示為「活性」)。由於一些受試者之血漿中存在內源性、非活性 FIX，其干擾使用針對 FIX 之抗體量測所投與之(亦即外源性) FIX 之能力，故在文獻中，PK 參數常基於 FIX 活性水準。然而，當如本文所提供將 FIX 作為 Fc 融合蛋白之一部分投與時，所投與之(亦即外源性) FIX 抗原可使用異源性多肽之抗體準確地量測。此外，某些 PK 參數可基於經模型預測之資料(在本文中常附帶表示為「經模型預

測之」)或經觀測之資料(在本文中常附帶表示為「經觀測之」)，且較佳基於經觀測資之料。

[0202] FIX 融合蛋白可經由此項技術中已知之任何方式投與受試者。舉例而言，FIX 融合蛋白可經由局部(例如經皮或眼部)、經口、經頰、經鼻、經陰道、經直腸或非經腸(例如皮下、皮內、血管內/靜脈內、肌肉內、經脊椎、經顱內、經鞘內、經眼內、眼周、眶內、滑膜內及腹膜內注射)投與。在一特定實施例中，FIX 融合蛋白係經由皮下注射投與。皮下注射可包括一或多次推注，包括例如單次推注一劑 FIX 融合蛋白。或者，FIX 融合蛋白可經由靜脈內注射投與。

[0203] FIX 融合蛋白之劑量可取決於特定融合蛋白之性質及受試者病狀之性質而變化。在一些實施例中，FIX 融合蛋白之劑量可包含介於 1 與 1000 IU/kg 之間之 FIX 融合蛋白。

[0204] 出血病狀可由凝血病症引起。凝血病症亦可稱為凝血病。在一個實例中，可用本發明之醫藥組合物治療之凝血病症為血友病。在另一實例中，可用本發明之醫藥組合物治療之凝血病症為 B 型血友病。

[0205] 在一些實施例中，與出血病狀相關之出血類型係選自關節積血、肌肉出血、口腔出血、失血、向肌肉內失血、口腔失血、創傷、頭創傷、胃腸出血、顱內失血、腹內失血、胸內失血、骨折、中樞神經系統出血、咽後間隙中出血、腹膜後間隙中出血及髂腰肌鞘中出血。

[0206] 在其他實施例中，罹患出血病狀之受試者需要手術治療，包括例如手術預防或圍手術期處理。在一個實例中，手術係選自小手術及大手術。示範性手術程序包括拔牙、扁桃體切除術、腹股溝疝切開術、滑膜切除術、開顱術、骨縫合術、創傷手術、顱內手術、腹內手術、胸內手術、關節置換手術(例如全膝關節置換術、髖關節置換術及其類似置換手術)、心臟手術及剖腹生產術。

[0207] 在另一實例中，受試者係用因子 VIII 並行治療。因為本發明化合物能夠活化 FIXa，所以其可用於在向受試者投與 FIXa 之前將 FIXa 多肽預活化。

[0208] 本發明方法可對需要防治性治療或按需治療之受試者實施。

[0209] 包含本發明之 FIX 融合蛋白之醫藥組合物可經調配以用於任何適當投藥方式，包括例如局部(例如經皮或眼部)、經口、經頰、經鼻、經陰道、經直腸或非經腸投藥。

[0210] 如本文所用，術語非經腸包括皮下、皮內、血管內(例如靜脈內)、肌肉內、經脊椎、顱內、鞘內、眼內、眼周、眶內、滑膜內及腹膜內注射以及任何類似注射或輸注技術。特定言之，包含本發明之 FIX 融合蛋白之醫藥組合物可經調配以用於皮下投與。組合物亦可為例如懸浮液、乳液、持續釋放調配物、乳膏劑、凝膠劑或散劑。組合物可用傳統黏合劑及載劑(諸如三酸甘油酯)調配成栓劑。

[0211] 在一個實例中，醫藥調配物為液體調配物，例如緩衝等張水溶液。在另一實例中，醫藥組合物具有生理性或接近於生理性之 pH 值。在其他實例中，水性調配物具有生理性或接近於生理性之容積莫耳滲透濃度及鹽度。其可含有氯化鈉及/或乙酸鈉。在一些實例中，本發明之組合物經凍乾。

[0212] 本發明之融合蛋白可在哺乳動物(例如人類患者)體內活體內產生，使用基因療法方法來治療出血疾病或病症將具有治療上之益處，該出血疾病或病症選自由以下組成之群：出血凝血病症、關節積血、肌肉出血、口腔出血、失血、向肌肉內失血、口腔失血、創傷、頭創傷、胃腸出血、顱內失血、腹內失血、胸內失血、骨折、中樞神經系統出血、咽後間隙中出血、腹膜後間隙中出血及髂腰肌鞘中出血。在一個實施例中，出血疾病或病症為血友病。在另一實施例中，出血疾病或病症為 B 型血友病。此方法涉及投與可操作地連接至適合表現控制序列之適合融合蛋白編碼核酸。在某些實施例中，此等序列併入病毒載體中。適用於此基因療法之病毒載體包括腺病毒載體、慢病毒載體、桿狀病毒載體、艾伯斯坦巴爾病毒載體、乳多泡病毒載體(papovaviral vector)、牛痘病毒載體、單純性皰疹病毒載體、及腺相關病毒(AAV)載體。病毒載體可為複製有缺陷之病毒載體。在其他實施例中，腺病毒載體在其 E1 基因或 E3 基因中具有缺失。當使用腺病毒載體時，哺乳動物可不暴露於編碼可選擇標記基因之核酸。在其他

實施例中，序列併入熟習此項技術者已知之非病毒載體中。

[0213] 除非另外指示，否則本發明之實踐將採用細胞生物學、細胞培養、分子生物學、轉殖基因生物學、微生物學、重組 DNA 及免疫學之習知技術，該等技術係在此項技術之技能範圍內。此類技術完整解釋於文獻中。參見例如，Molecular Cloning A Laboratory Manual, 第 2 版, Sambrook 等人編, Cold Spring Harbor Laboratory Press: (1989)；Molecular Cloning: A Laboratory Manual, Sambrook 等人編, Cold Springs Harbor Laboratory, New York (1992), DNA Cloning, D. N. Glover 編, 第 I 及 II 卷 (1985)；Oligonucleotide Synthesis, M. J. Gait ed., (1984)；Mullis 等人, 美國專利號 4,683,195；Nucleic Acid Hybridization, B. D. Hames & S. J. Higgins 編 (1984)；Transcription And Translation, B. D. Hames & S. J. Higgins 編 (1984)；Culture Of Animal Cells, R. I. Freshney, Alan R. Liss, Inc., (1987)；Immobilized Cells And Enzymes, IRL Press, (1986)；B. Perbal, A Practical Guide To Molecular Cloning (1984)；論文 Methods In Enzymology, Academic Press, Inc., N.Y.；Gene Transfer Vectors For Mammalian Cells, J. H. Miller 及 M. P. Calos 編, Cold Spring Harbor Laboratory (1987)；Methods In Enzymology, 第 154 及 155 卷 (Wu 等人編)；Immunochemical Methods In Cell And Molecular Biology, Mayer 及 Walker

編，Academic Press, London (1987)；Handbook Of Experimental Immunology, 第 I-IV 卷, D. M. Weir 及 C. C. Blackwell 編 (1986)；Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986)；及 Ausubel 等人，Current Protocols in Molecular Biology, John Wiley and Sons, Baltimore, Maryland (1989)。

[0214] 陳述免疫學之基本原理之參考文獻包括 Current Protocols in Immunology, John Wiley & Sons, New York；Klein, J., Immunology: The Science of Self-Nonself Discrimination, John Wiley & Sons, New York (1982)；Roitt, I., Brostoff, J.及 Male D., Immunology, 第 6 版, London: Mosby (2001)；Abbas A., Abul, A.及 Lichtman, A., Cellular and Molecular Immunology, 第 5 版, Elsevier Health Sciences Division (2005)；及 Harlow 及 Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Press (1988)。

[0215] 現已詳細描述本發明，藉由參考以下實例將更明確地瞭解本發明，該等實例係僅出於說明目的包括於此且不意欲限制本發明。

實例

實例 1：鑑別活性 FIX-XTEN 變異體

[0216] 構築 FIX 融合蛋白，其包含 FIX 多肽及一或

多個 XTEN 插入以改善 FIX 蛋白質之活性。不過，可容易地變化 XTEN 修飾之位置、長度、組成及數量，且可評價該等修飾對 FIX 活性及清除率之影響。

[0217] 本實例旨在鑑別 FIX 中可引入 XTEN 而不消除 FIX 活性之位點且將此方法應用於其他未修飾之 FIX 及重組 FIX-Fc 融合蛋白。

方法

[0218] 在緊鄰編碼起始 Met 殘基之 ATG 密碼子 5'端引入 Kozak 轉譯起始序列(GCCGCCACC)之後，將 FIX 多肽編碼序列連接至表現載體 pcDNA4/myc-His C (INVITROGEN™, Carlsbad, CA)中 BsiWI 與 PmeI 位點之間。

[0219] 使用聚乙烯亞胺(PEI, Polysciences Inc., Warrington, PA)，用質體轉染 HEK293F 細胞(INVITROGEN™, Carlsbad, CA)。使短暫轉染之細胞在 FREESTYLE™ 293 培養基或 FREESTYLE™ 293 與 CD OPTICHO™培養基(INVITROGEN™, Carlsbad, CA)之混合物中生長。轉染 5 天後，收集細胞培養基並藉由發色分析或 aPTT FIX 活性分析來分析 FIX 活性。

[0220] 使用來自 Aniara 之 BIOPHEN 因子 IX 套組量測發色 FIX 活性且在震盪下，於 37℃板加熱器上進行所有培育。使用 Tris-BSA 稀釋緩衝液(R4)將自 6 孔盤中含 FIX-XTEN 變異體之短暫轉染培養基收集的細胞培養物稀

釋至所需 FIX 活性範圍。亦在 Tris-BSA 稀釋緩衝液中製備 FIX 標準物。將標準物、稀釋之細胞培養物樣品及彙集之正常人類血漿分析對照物(50 微升/孔)一式兩份添加至 IMMULON® 2HB 96 孔培養盤中。隨後將人類因子 X、FVIII:C 及纖維蛋白聚合抑制劑(50 μL)、50 μL 的因子 XIa 與凝血酶、磷脂及鈣之混合物，及 50 μL 因子 Xa 特異性發色基質(SXa-11)添加至每一孔中，其中在每次添加之間培育 2 分鐘。在與受質一起培育之後，添加 50 μL 20%乙酸以終止顯色反應，且用 SPECTRAMAX® plus (MOLECULAR DEVICES®)儀器量測在 405 nm 下之吸光度。使用 SOFTMAX® Pro 軟體(第 5.2 版)進行資料分析。

[0221] 採用單級部分活化凝血激酶時間(aPTT)凝固分析來評估 FIX 活性。使用 SYSMEX® CA-1500 儀器 (Siemens Healthcare Diagnostics Inc., Tarrytown, NY)量測 FIX-XTEN aPTT 活性。為了建立該分析之標準曲線，用具有匹配之培養基濃度的模擬轉染培養基作為測試樣品稀釋 WHO 因子 IX 標準物。使用模擬轉染培養基將自 6 孔盤中含 FIX-XTEN 變異體之短暫轉染培養基收集的細胞培養物稀釋至所需 FIX 活性範圍。在稀釋之後，使用 Sysmex 儀器如下進行 aPTT 分析：將 50 μl 稀釋之標準物及樣品與 50 μl Siemens 人類 FIX 清除之血漿混合且接著與 50 μl Siemens Actin FSL(鞣花酸)活化劑混合。培育混合物 1 分鐘。隨後，將 50 μl Siemens $CaCl_2$ 添加至混合物中並培育該混合物 240 秒。在此培育之後立即量測凝結時

間。為了測定測試樣品之 FIX 活性，使用 log 標度繪製標準物之凝結時間曲線以外推凝結時間與 FIX 活性之間的等式，且接著針對該標準曲線計算 FIX-XTEN 活性。

選擇插入位點

[0222] 分析來自 Protein Data Bank 之 FIX 結構 1PFX、1IXA、1CFI、1CFH,1EDM、3LC3、3LC5、1RFN、1X7A 及 3KCG，以選出 FIX 中供 XTEN 插入之位點。由於 GLA 結構域在將 FIX 錨定於磷脂表面及內皮下 IV 型膠原蛋白方面之重要作用，避免將 XTEN 插入 GLA 結構域內。藉由結合以下標準分析 Protein Data Bank 中之可用 FIX 結構來選擇 XTEN 插入位點：1)藉由算法軟體 ASA View (http://www.abren.net/asaview/) 及 Get Area (http://curie.utmb.edu/getarea.html)計算之可及表面積；2)藉由氫/氘交換質譜法(H/DX-MS)評估之溶劑可及性；3)排除確定之二級結構元件內之位點；4)優先選擇具有顯著種間蛋白質序列變化性之位置；及 5)排除鄰近已知 B 型血友病突變之位點。

[0223] 選出 EGF1 結構域中之四個位點、EGF2 結構域中之 5 個位點、在 AP 結構域與 EGF2 結構域之間之連接子區中的 2 個位點、AP(活化肽)結構域中之 4 個位點及催化結構域中之 18 個位點插入 XTEN(表 6)。

表 6：供 XTEN 插入 FIX 中之可能位點(插入指定殘基之 c 末端)

FIX 結構域	選定位點
EGF1	E52、G59、I66、K80
EGF2	D85、N89、A103、N105、E113
連接子	P129、K142
AP	V149、E162、D166、S174
催化結構域	K188、V202、E224、G226、K228、T230、E240、H257、K265、E277、S283、D292、K316、K341、H354、K392、R403、K413

具有 42 個胺基酸之 XTEN 插入及 C 末端融合之活性篩選

[0224] 使用高活性 FIX Padua 變體(R338L)作為支架以計算由引入 XTEN 引起之活性降低導致的潛在 FIX 活性損失。將具有 42 個殘基之 XTEN 元件(AE42)插入使用以上標準選擇之位點或在 FIX 之 C 末端融合。在含經轉染 HEK293 細胞中之條件培養基中評價如以上所描述之該等變異體之 FIX 活性。FIX-AE42 之 FIX 活性係以不含 XTEN 之基礎構築體 FIX-R338L 的百分含量顯示(圖 1)。

[0225] 如藉由 FIX 發色分析所測定，在有限位點處插入 XTEN 係容許的(圖 1 及表 7)。選出 FIX 中總計 33 個位點並藉由插入 AE-42 進行評價。其中，EGF2 結構域中之兩個、在 EGF2 結構域與 AP 結構域之間之連接子區中的一個、AP 結構域中之四個及催化結構域中之四個，包括 C 末端在內，經 FIX 活性分析鑑別為容許的位點(圖 1 及表 7)。

表 7：示例 FIX 插入位點

插入位點	結構域	活性 AE42	活性 AE72	活性 AE144	活性 AE288	活性 AE4864
52	EGF1	ND				
59	EGF1	ND				
66	EGF1	ND				
80	EGF1	ND				
85	EGF2	ND				
89	EGF2	ND				
103	EGF2	+	ND	ND	ND	ND
105	EGF2	+	ND	ND	ND	ND
113	EGF2	ND				
129	EGF2-AP 連接子	ND				
142	EGF2-AP 連接子	++	ND	ND	ND	ND
149	AP	+++	+	+	+	ND
162	AP	++	+	+	+	ND
166	AP	+++	+	+	+	ND
174	AP	+++	+	+	+	ND
188	催化結構域	ND				
202	催化結構域	+				
224	催化結構域	+	+	ND	ND	ND
226	催化結構域	+				
228	催化結構域	+				
230	催化結構域	ND				
240	催化結構域	ND				
257	催化結構域	+				
265	催化結構域	ND				
277	催化結構域	ND				
283	催化結構域	ND				
292	催化結構域	ND				
316	催化結構域	ND				
341	催化結構域	ND				
354	催化結構域	ND				
392	催化結構域	ND				
403	催化結構域	ND				
413	催化結構域	++	+	+	+	ND
415	C 末端	+++	+++	++	++	+

注釋：ND =未偵測到活性；(+) = 偵測到低於 30%之活性；(++) =偵測到介於 30%與 70%之間之活性；及(+++) = 偵測到超過 70%活性，均以基礎構築體之百分比計，藉由發色分析偵測(參見圖 5A-5C 及 6A-6B)。

較長 XTEN 插入及 C 末端融合之活性

[0226] 接著，以類似方式測試在經顯示容許 AE42 插入之位點處的較長 XTEN (AE-72、AE-144 及 AE-288)。如先前所描述測定 FIX 活性且以不含 XTEN 之基礎構築體 FIX-R338L 的百分含量顯示(圖 2)。

[0227] 僅 AP 中之位點以及在 FIX 之 C 末端處或其附近之位點容許較長 XTEN(AE144、AE288 或 AE864)(圖 2)。在條件培養基中偵測到的 FIX 活性與引入之 XTEN 之長度反相關(圖 2，表 7)。選出 FIX 之不同結構域中的四個容許插入位點以產生組合文庫。

多個 XTEN 插入

[0228] 基於用單一 XTEN 變體得到的結果，藉由 aPTT 分析，在含經轉染 HEK293 細胞之條件培養基中評價在四個不同位置(參見圖 4 及表 8)插入多個長度不同之 XTEN 的 FIX 變異體之 FIX 活性(表 8-10)。FIX 活性係以不含 XTEN 之基礎構築體 FIX-R338L 的百分含量顯示(圖 4)。

表 8：示例 FIX 雙插入

插入位點 1	XTEN 1 (或 Fc)	插入位點 2	XTEN 2 (或 Fc)	活性
105	AE42			++
166	AE42			++
166	AE72			+
166	AE144			+
224	AE42			+
C 末端	AE72			++
C 末端	AE144			+
C 末端	AE288			+
C 末端	Fc			++
166	AE42	C 末端	AE72	++
166	AE42	C 末端	AE144	+
166	AE42	C 末端	AE288	+
166	AE72	C 末端	AE72	+
166	AE72	C 末端	AE144	+
166	AE72	C 末端	AE288	+
166	AE144	C 末端	AE72	+
166	AE144	C 末端	AE144	+
166	AE144	C 末端	AE288	+
105	AE42	166	AE42	+
105	AE42	166	AE72	+
105	AE42	166	AE144	ND
105	AE42	C 末端	AE72	+
105	AE42	C 末端	AE144	+
105	AE42	C 末端	AE288	+
105	AE42	224	AE42	+
166	AE42	224	AE42	+
166	AE72	224	AE42	+
166	AE144	224	AE42	ND
224	AE42	C 末端	AE72	+
224	AE42	C 末端	AE144	+
224	AE42	C 末端	AE288	+
105	AE42	C 末端	Fc	+
224	AE42	C 末端	Fc	+
166	AE42	C 末端	Fc	+
166	AE72	C 末端	Fc	+
166	AE144	C 末端	Fc	+

注釋：ND =未偵測到活性；(+) = 偵測到低於 30%之活性；(++) =偵測到介於 30%與 70%之間之活性；及(+++) = 偵測到超過 70%活性，均以基礎構築體之百分比計，藉由發色分析偵測(參見圖 8A-8C)。

表 9：插入每一結構域中之 XTEN 元件

位置	元件
EGF2	AE42
AP	AE42、AE72、AE144
催化性 60 環	AE42
C 末端	AE72、AE144、AE288、Fc

表 10：以單個、兩個、三個及四個之組合插入之構築體的總數

組合	#構築體
單個	9
兩個	27
三個	31
四個	12
	總計 79

[0229] 三個組，即具有單一 XTEN 之 FIX、插入兩個 XTEN 之 FIX 及插入單個 XTEN 之 FIX-Fc，顯示可偵測之活性，而在三個或超過三個位點處插入/融合之組合消除 FIX 活性(圖 4)。

[0230] 總之，在 FIX 中存在若干容許 XTEN 插入之位點且選定之 XTEN 插入變異體組合保持 FIX 活性。此處鑑別之活性 FIX-XTEN 變異體為在 B 型血友病小鼠中進行藥物動力學表徵之候選物。

實例 2：FIX 融合蛋白以及其血漿回收率及 AUC/D

[0231] 因子 IX 缺陷型(HemB, B6.129P2-F9tm1Dws/J, MGI:1932297)小鼠(Lin.等人，1997)最初係自 Dr. Darrel

Stafford (University of North Carolina, Chapel Hill)得到。在 t= 0 小時，以 10 mL/kg 之劑量體積藉由單次靜脈內推注對雄性/雌性 HemB 小鼠分別靜脈內注射 50 或 200 IU/kg FIX 融合蛋白(例如 FIX-CT.288(AE288 XTEN 與 FIX 多肽之 C 末端融合)、FIX-CT.864 (AE864 XTEN 與 FIX 多肽之 C 末端融合)、FIX-AP.144 (AE144 XTEN 插入 FIX 多肽之 AP 結構域內的 D166 後)、FIX-AP.72 (AE72 XTEN 插入 FIX 多肽之 AP 結構域內的 D166 後)、FIX-AP.42 (AE42 XTEN 插入 FIX 多肽之 AP 結構域內的 D166 後)、FIXFc 及 FIX)。給藥後 5 分鐘至給藥後 168 小時(7 天)，收集血液。對於每一指定時間點，每一時間點藉由眶後或末段大靜脈抽血自 3-4 只小鼠收集約 100 µl 檸檬酸鹽血液。每只小鼠產生最多 3 個時間點。藉由以 5000 rpm 離心 8 分鐘來分離血漿，且在乾冰乙醇浴中速凍血漿樣品，並在-80℃下儲存，直至在 Sysmex-CA1500 凝固分析儀上，使用 Dade Behring 試劑及肌動蛋白 FSL 作為活化劑並以給藥物質作為活性標準物，利用單極部分活化凝血激酶時間(aPTT)分析對其進行分析。在圖 5A-5B 中，將血漿活性隨注射劑量%變化作圖。使用非房室模型，利用 Phoenix WinNonlin 6.2.1 (Pharsight, Certera by NCA analysis)計算平均滯留時間(MRT)及其他藥物動力學(PK)參數。圖 5C 描繪相對血漿回收率(Y 軸)隨 MRT (X 軸)之變化。加點區域表示劑量曲線下面積(AUC/D，以 h/kg/mL 表示)且顯示，FIX 血漿活性回收率及 AUC/D 隨 XTEN 長

度增加而增加(圖 5C)。該等圖顯示，具有較長 XTEN 長度(在 C 末端處 288 及 864，或在 AP 結構域中 144、72 及 42)之 FIX 融合蛋白在靜脈內推注給藥後，展現血漿回收率之尺寸依賴性增加，最多達 60%，及 AUC/D 增加。

實例 3：FIX 融合蛋白及其半衰期

[0232] 對 FIX 缺陷型小鼠靜脈內給與 50 或 200 IU/kg 以下 FIX 融合蛋白：FIX 與具有 288 個胺基酸之 XTEN(例如 AE288)之融合物；具有 72 個胺基酸之 XTEN (例如 AE72)插入 AP 結構域之 D166 後的 FIX-Fc；具有 42 個胺基酸之 XTEN (例如 AE42)插入 AP 結構域之 D166 後的 FIX-Fc；及對照物(FIXFc 及 FIX)。收集血漿並以與實例 5 中所描述之方法相同之方式進行 FIX 活性及 PK 分析。圖 6A 繪出血漿活性隨注射劑量%之變化。使用 WinNonlin 6.2.1 (Pharsight, Certera by NCA analysis)計算藥物動力學(PK)參數且圖 6B 描繪相對血漿回收率(Y 軸)隨 MRT(X 軸)之變化。加點區域表示劑量曲線下面積(AUC/D，以 h/kg/mL 表示)且顯示，相較於 FIX，在 FIXFc 之活化肽(AP)結構域中插入 XTEN 序列延長平均滯留時間長於單獨 rFIXFc(圖 6B)。此外，血漿活性回收率及 AUC/D 隨 XTEN 長度增加而提高(圖 6A-6B)。相較於 rFIXFc，rFIX-CT.288 (SEQ ID NO: 226)及 rFIXFc-AP.72 (SEQ ID NO: 151)之 AUC/D 分別提高 3.4 倍及 4.5 倍(圖 6A-6B)。此與其 AUC/D 相較於靜脈內給與之 rFIX 分別有

8.5 倍及 14.5 倍提高相符(圖 6A-6B)。因此，相較於 rFIX 及 rFIXFc，AP 結構域中 XTEN 之插入與 rFIXFc-R338L 中 Fc 介導之半衰期延長的組合使半衰期延長並增加血漿回收率及 AUC/劑量。

實例 4：藉由皮下遞送改善 FIX 融合蛋白之藥物動力學。

[0233] t=0 時，對 FIX 缺陷型小鼠皮下給與 50 或 200 IU/kg 以下 FIX 融合蛋白：FIX 與具有 288 個胺基酸之 XTEN(例如 AE288)在 C 末端之融合物(FIX-CT.288)；在 AP 結構域中具有 72 個胺基酸之 XTEN (例如 AE72)的 FIXFc(FIXFc-AP.72)；在 EGF2 結構域中具有 42 個胺基酸之 XTEN (例如 AE42)的 FIXFc(例如 FIXFc-EGF.42)；及對照物(FIXFc 及 FIX)。收集血漿並以與實例 1 中所描述之方法相同之方式進行 FIX 活性及 PK 分析。圖 7A 繪出血漿活性隨注射劑量%之變化。使用 WinNonlin 6.2.1 (Pharsight, Certera by NCA analysis)計算藥物動力學(PK)參數且圖 7B 描繪相對生物利用率(Y 軸)隨 MRT(X 軸)之變化。加點區域表示劑量曲線下面積(AUC/D，以 h/kg/mL 表示)且顯示，在 rFIX 之羧基末端融合 XTEN 多肽序列或在 FIXFc 之活化肽(AP)結構域或 EGF2 結構域中插入 XTEN 序列大幅改善 FIX 融合蛋白之皮下給藥型態(圖 7B)。在皮下給藥之 HemB 小鼠中，相較於 rFIXFc，rFIXFc-AP.72 及 rFIX-CT.288 具有 6 至 9 倍之 AUC/D 改善、1.5 至 2 倍之生物利用率改善及 3 至 10 倍之 C_{max}/D

改善。當與 rFIX 相比較時，FIXFc-AP.72 及 rFIX-CT.288 相較於 rFIX 之藥物動力學參數改善分別為 28 至 40 倍之 AUC/D 改善、3 倍之生物利用率增加及 15 至 30 倍之 C_{max}/D 改善(圖 7A-7B)。

[0234] 總體而言，當與靜脈內給與 rFIXFc 相比較時，FIX 融合蛋白(例如 rFIX-CT.288 及 rFIXFc-AP.72)對於皮下給與顯示 2.6 倍及 1.9 倍之 AUC/D 改善，rFIXFc 在人類中支持每週一次或更不頻繁之靜脈內給藥用於防治目的。

實例 5：FIX 融合蛋白之活體外功效

[0235] 向人 B 型血友病血液中加入 3、10 及 30 IU/dL 之指定劑量之 rFIXFc(空心圓圈、點劃線)或 FIX 融合蛋白(例如 rFIXFc-AP.72)(實心點、實線)或媒劑(空心三角形)(圖 8A-8C)。使用旋轉式血栓彈力測定法(ROTEM)測定全血凝結特徵且藉由使血液再鈣化(NATEM)來起始凝固。在 B 型血友病血液中，rFIXFc-AP.72 在凝結時間(CT，以秒表示)、α 角(以度表示)及最大凝塊強度(MCF，以 mm 表示)方面顯示與 rFIXFc 類似之活性(圖 8A-8C)。每一時間點之資料為 4 至 5 個重複樣品之平均值+/-標準差(圖 8A-8C)。

[0236] 相較於 rFIX 及 rFIXFc，rFIXFc-AP.72 及 rFIX-CT.288 在 HemB 小鼠中顯示皮下藥物動力學之大幅改善。正在進行其他研究以瞭解在臨床前動物模型中之功

效及異速生長尺度規律。

實例 6：rFIXFc-AP.72 在急性鼠類尾截割出血模型中之活體內功效

[0237] 如先前所描述(Dumont 等人, Blood, 119(13):3024–3030, 2012)，在失明鼠類尾截割出血模型中研究急性功效，其中在尾尖切斷術後量測給藥小鼠之總失血量。簡言之，用 50 mg/kg 克他命(ketamine)及 0.5 mg/kg 右美托咪定(dexmedetomidine)之混合液使 8-15 週齡之雄性 B 型血友病小鼠(Lin 等人, Blood (1997) 90: 3962-3966)麻醉。將尾部浸入 37℃ 生理食鹽水中 10 分鐘，以使側靜脈擴張，隨後經靜脈內對尾靜脈注射 50、100 及 200 IU/kg 的媒劑(3.88 g/L L-組胺酸、23.8 g/L 甘露糖醇、11.9 g/L 蔗糖、3.25 g/L 氯化鈉、0.01 % (w/v)聚山梨醇酯 20 (pH 7.1)、3%人血清白蛋白)、rFIXFc-AP.72 或 rFIXFc。給藥後 5 分鐘，截割尾部遠端 5 mm 之尾尖，並將其浸沒於含有 13 mL 生理食鹽水的預先稱重之管中，保持 30 分鐘。藉由重量定量失血量。使用非成對雙尾 t 檢驗，在 GraphPad Prism 6 中計算統計學顯著性。此類雙尾 t 檢驗顯示，50、100 及 200 IU /kg 劑量之 rFIXFc-AP.72 與媒劑顯著不同(p 值 < 0.0001)。此外，資料顯示，較低劑量(例如 50 IU/kg)之 rFIXFc-AP.72 使失血量相較於相同低劑量，即 50 IU/kg 之 rFIXFc 顯著降低。該等結果證實，在此出血模型中，相較於 rFIXFc，rFIXFc-AP.72 具有相

同或改善之急性功效。

實例 7：FIXFc-AP.72 在防治性鼠類尾靜脈切斷出血模型中之活體內功效

[0238] 如先前所描述(Toby 等人，*PLOS One*, DOI:10.1371/journal.pone.0148255, 2016；Pan 等人，*Blood 114*:2802-2822 (2009))，在失明鼠類尾靜脈切斷(TVT)出血模型中研究長期功效，其中在切斷單側尾靜脈之後量測經給藥之 B 型血友病小鼠之存活時間。簡言之，對 8-15 週齡之雄性 B 型血友病小鼠(Lin 等人，*Blood 90*: 3962-3966 (1997))經靜脈內預先給與含 15、50、100 IU/kg FIX 活性劑之 rFIXFc 或相配皮下劑量之 FIXFc-AP.72，並與接受推注劑量媒劑之小鼠相比較。給藥後 72 小時，將所有小鼠麻醉，並在 2.7 mm 尾直徑處切斷單側尾靜脈。在 TVT 後立即 9 至 11 小時及隨後在 24 小時之隔夜時間點期間，監測定性終點並每小時記錄，包括再出血及死亡時間(定義為實施安樂死之時間，如在動物瀕死時測定)。在 24 小時研究結束時，對所有小鼠實施安樂死，同時確定未死亡或瀕死之動物在 24 小時的時候存活。

[0239] 使用 GraphPad Prism 6 將資料對在 TVT 之後之存活率百分比作圖。小鼠皮下給與媒劑(點劃線)、皮下給與 FIXFc-AP.72(實線，實心符號)或靜脈內給與 FIXFc(虛線，空心符號)(15 IU/ kg、50 IU/kg、100 IU/kg；n = 20 只/劑，媒劑劑量除外；n = 30)(圖 10)。比

較用相配 IU/kg 劑量皮下給與 FIXFc-AP.72 及靜脈內給與 rFIXFc 治療的小鼠的存活曲線顯示，皮下給與 FIXFc-AP.72 的 HemB 小鼠在所有測試劑量下之存活率相較於等效靜脈內給與 rFIXFc 改善(圖 10)。

實例 8：在 HemB 小鼠中 FIXFc-AP.72 (FIX-216，雙鏈 Fc)相較於 rFIX 之靜脈內及皮下藥物動力學參數改善。

[0240] 給與 B 型血友病小鼠 200 IU/kg FIXFc-AP.72 (FIX-216，雙鏈 Fc)或 rFIX。在指定時間，藉由眶後抽血來收集血液。使用給藥物質作為活性標準物，藉由單級凝血分析活性來測定 FIX 之血漿含量。在圖 11A 中，將血漿活性對%注射劑量作圖。圖 11B 顯示使用 Phoenix WinNonLin 6.2.1 (Pharsight, Certara)，藉由 NCA(非房室)分析計算之藥物動力學參數的表格。所顯示的 FIX-216 相對於 rFIX 之藥物動力學參數的改善包括平均滯留時間(MRT)、AUC/劑量及其他參數。

[0241] 皮下給與 FIXFc-AP.72 顯示在小鼠中給藥後約 20 小時為 t_{max}，且血漿活性劑含量相較於類似(IU/kg)靜脈內給與之 rFIX 或 rFIXFc 有所改善。在 HemB 小鼠中使用 TVT 出血模型顯示，給藥後 72 小時，皮下給與 FIXFc-AP.72 在所有測試劑量下的活體內功效相較於靜脈內給與之 rFIXFc 有所改善。類似地，在 HemB 小鼠尾截割出血模型中進行的急性功效測試顯示，靜脈內給與 FIXFc-AP.72 的功效相較於 rFIXFc 有所改善。該等資料支

持在人類中每週一次或更不頻繁之皮下防治性給與FIXFc-AP.72的潛力。

[0242] 具體實施例之前文描述將充分地揭露本發明之一般性質，以使得其他人藉由應用此項技術中之知識，在無不當實驗且不背離本發明之一般概念的情況下，可輕易地針對各種應用對此等特定實施例進行修改及/或改變。因此，基於本文呈現之教示及指導，此等改變及修改意欲在所揭示實施例之等效物的含義及範圍內。應瞭解，本文之措辭或術語係出於描述而非限制之目的，以使得本說明書之術語或措辭應由熟習此項技術者根據教示及指導進行解釋。

[0243] 自本文所揭示的本發明之說明書及實踐的考慮，本發明之其他實施例對熟習此項技術者而言將為顯而易見的。意欲將說明書及實例視為僅具示範性，且本發明之真實範疇及精神藉由以下申請專利範圍指示。

[0244] 本申請案要求2015年8月3日申請之美國臨時申請案第62/200,590號及2016年1月22日申請之第62/281,993號的權益，其以全文引用之方式併入本文中。

實施例

[0245] E1. 一種因子IX (FIX)融合蛋白，其包含FIX多肽及至少一個XTEN，該XTEN插入該FIX多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 2之胺基酸103、SEQ ID NO: 2之胺基酸105、SEQ ID

NO: 2 之胺基酸 142、SEQ ID NO: 2 之胺基酸 149、SEQ ID NO: 2 之胺基酸 162、SEQ ID NO: 2 之胺基酸 166、SEQ ID NO: 2 之胺基酸 174、SEQ ID NO: 2 之胺基酸 224、SEQ ID NO: 2 之胺基酸 226、SEQ ID NO: 2 之胺基酸 228、SEQ ID NO: 2 之胺基酸 413 及其任何組合，且其中該 FIX 融合蛋白展現促凝血活性。

[0246] E2. 如 E1 之 FIX 融合蛋白，其中該插入位點對應於選自由以下組成之群之胺基酸：SEQ ID NO: 2 之胺基酸 149、SEQ ID NO: 2 之胺基酸 162、SEQ ID NO: 2 之胺基酸 166、SEQ ID NO: 2 之胺基酸 174 及其任何組合。

[0247] E3. 如 E1 或 E2 之 FIX 融合蛋白，其中該插入位點對應於選自由以下組成之群之胺基酸：SEQ ID NO: 2 之胺基酸 224、SEQ ID NO: 2 之胺基酸 226、SEQ ID NO: 2 之胺基酸 228、SEQ ID NO: 2 之胺基酸 413 及其任何組合。

[0248] E4. 如 E1 至 E3 中任一項之 FIX 融合蛋白，其中該插入位點對應於選自由 SEQ ID NO: 2 之胺基酸 103、SEQ ID NO: 2 之胺基酸 105 及二者組成之群之胺基酸。

[0249] E5. 如 E1 至 E4 中任一項之 FIX 融合蛋白，其中該插入位點對應於 SEQ ID NO: 2 之胺基酸 142。

[0250] E6. 如 E1 至 E5 中任一項之 FIX 融合蛋白，其中該 XTEN 包含至少約 6 個胺基酸、至少約 12 個胺基酸、至少約 36 個胺基酸、至少約 42 個胺基酸、至少約

72 個胺基酸、至少約 144 個胺基酸或至少約 288 個胺基酸。

[0251] E7. 如 E1 至 E6 中任一項之 FIX 融合蛋白，其中該 XTEN 包含 AE42、AE72、AE864、AE576、AE288、AE144、AG864、AG576、AG288、AG144 或其任何組合。

[0252] E8. 如 E1 至 E7 中任一項之 FIX 融合蛋白，其中該 XTEN 包含與選自由以下組成之群之胺基酸至少約 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%一致之胺基酸序列：SEQ ID NO: 34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49、50、51、52、53 及其任何組合。

[0253] E9. 如 E7 或 E8 之 FIX 融合蛋白，其中該 XTEN 包含 AE72 或 AE144。

[0254] E10. 如 E1 至 E9 中任一項之 FIX 融合蛋白，其另外包含第二 XTEN。

[0255] E11. 如 E10 之 FIX 融合蛋白，其中該第二 XTEN 插入該 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 2 之胺基酸 103、SEQ ID NO: 2 之胺基酸 105、SEQ ID NO: 2 之胺基酸 142、SEQ ID NO: 2 之胺基酸 149、SEQ ID NO: 2 之胺基酸 162、SEQ ID NO: 2 之胺基酸 166、SEQ ID NO: 2 之胺基酸 174、SEQ ID NO: 2 之胺基酸 224、SEQ ID NO: 2 之胺基

酸 226、SEQ ID NO: 2 之胺基酸 228、SEQ ID NO: 2 之胺基酸 413 及其任何組合，或其中該第二 XTEN 與該 FIX 多肽之 C 末端融合或連接子與該 FIX 多肽之 C 末端融合。

[0256] E12. 如 E10 或 E11 之 FIX 融合蛋白，其中該 XTEN 及該第二 XTEN 分別插入該 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點及/或與該 FIX 多肽之 C 末端融合：

i. SEQ ID NO: 2 之胺基酸 105 及 SEQ ID NO: 2 之胺基酸 166；

ii. SEQ ID NO: 2 之胺基酸 105 及 SEQ ID NO: 2 之胺基酸 224；

iii. SEQ ID NO: 2 之胺基酸 105 及與該 C 末端融合；

iv. SEQ ID NO: 2 之胺基酸 166 及 SEQ ID NO: 2 之胺基酸 224；

v. SEQ ID NO: 2 之胺基酸 166 及與該 C 末端融合；及

vi. SEQ ID NO: 2 之胺基酸 224 及與該 C 末端融合。

[0257] E13. 如 E10 或 E11 之 FIX 融合蛋白，其中該 XTEN 插入該 FIX 多肽內對應於 SEQ ID NO: 2 之胺基酸 166 之插入位點，且其中該第二 XTEN 與該 FIX 多肽之 C 末端融合。

[0258] E14. 如 E10 至 E13 中任一項之 FIX 融合蛋

白，其中該第二 XTEN 包含至少約 6 個胺基酸、至少約 12 個胺基酸、至少約 36 個胺基酸、至少約 42 個胺基酸、至少約 72 個胺基酸、至少約 144 個胺基酸或至少約 288 個胺基酸。

[0259] E15. 如 E10 至 E14 中任一項之 FIX 融合蛋白，其中該第二 XTEN 係選自由以下組成之群：AE42、AE72、AE864、AE576、AE288、AE144、AG864、AG576、AG288、AG144 及其任何組合。

[0260] E16. 如 E15 之 FIX 融合蛋白，其中該第二 XTEN 為 AE72 或 AE144。

[0261] E17. 如 E10 至 E16 中任一項之 FIX 融合蛋白，其中該第二 XTEN 包含與選自由以下組成之群之胺基酸至少約 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%一致之胺基酸序列：SEQ ID NO: 34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49、50、51、52、53 及其任何組合。

[0262] E18. 如 E10 至 E17 中任一項之 FIX 融合蛋白，其另外包含第三、第四、第五或第六 XTEN。

[0263] E19. 一種 FIX 融合蛋白，其包含 FIX 多肽及包含 XTEN 之異源部分，其中該 XTEN 與該 FIX 多肽之 C 末端融合且包含長度超過 42 個胺基酸且短於 144 個胺基酸之胺基酸序列。

[0264] E20. 如 E19 之 FIX 融合蛋白，其中該 XTEN

包含長於 50、55、60、65 或 70 個胺基酸且短於 140、130、120、110、100、90 或 80 個胺基酸或其任何組合之胺基酸序列。

[0265] E21. 如 E20 之 FIX 融合蛋白，其中該 XTEN 為 72 個胺基酸長度。

[0266] E22. 如 E21 之 FIX 融合蛋白，其中該 XTEN 為 AE72。

[0267] E23. 如 E19 之 FIX 融合蛋白，其中該 XTEN 包含與 SEQ ID NO: 35 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%一致之胺基酸序列。

[0268] E24. 如 E1 至 E23 中任一項之 FIX 融合蛋白，其另外包含 Fc 結構域。

[0269] E25. 如 E24 之 FIX 融合蛋白，其中該 Fc 結構域與該 FIX 多肽或該 XTEN 融合。

[0270] E26. 如 E24 或 E25 之 FIX 融合蛋白，其包含第二 Fc 結構域。

[0271] E27. 如 E26 之 FIX 融合蛋白，其中該第二 Fc 結構域與該第一 Fc 結構域締合。

[0272] E28. 如 E26 或 E27 之 FIX 融合蛋白，其包含兩個多肽鏈，其中該第一多肽鏈包含與該 Fc 結構域融合之該 FIX 多肽，且該第二多肽鏈包含該第二 Fc 結構域，其中該第一 Fc 結構域與該第二 Fc 結構域藉由共價鍵締合。

[0273] E29. 如 E26 或 E27 之 FIX 融合蛋白，其為單一多肽鏈，該多肽鏈包含該 FIX 多肽、該 Fc 結構域、該第二 Fc 結構域及連接該 Fc 結構域與該第二 Fc 結構域之連接子。

[0274] E30. 如 E29 之 FIX 融合蛋白，其中該連接子另外包含一或多個細胞內加工位點。

[0275] E31. 如 E29 或 E30 之 FIX 融合蛋白，其中該連接子包含$(Gly_4Ser)_n$，其中 n 為選自 1 至 100 之整數。

[0276] E32. 如 E1 至 E31 之 FIX 融合蛋白，其包含與選自由不含信號肽及前肽序列之 SEQ ID NO: 54 至 SEQ ID NO: 153 組成之群之序列至少約 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%一致之胺基酸序列。

[0277] E33. 如 E1 至 E32 中任一項之 FIX 融合蛋白，其具有原生 FIX 至少約 10%、至少約 20%、至少約 30%、至少約 40%、至少約 50%、至少約 60%、至少約 70%、至少約 80%、至少約 90%或 100%的促凝血活性。

[0278] E34. 如 E33 之 FIX 融合蛋白，其中該促凝血活性係藉由發色基質分析、單極凝血分析或兩者量測。

[0279] E35. 如 E1 至 E34 中任一項之 FIX 融合蛋白，其中該 FIX 多肽為 R338L FIX 變異體。

[0280] E36. 如 E35 之 FIX 融合蛋白，其中該 R338L FIX 變異體包含與 SEQ ID NO: 2 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 100%一致之胺基酸序列。

[0281] E37. 一種分離之聚核苷酸，其包含編碼如 E1 至 E36 中任一項之 FIX 融合蛋白的序列。

[0282] E38. 一種表現載體，其包含如 E37 之聚核苷酸。

[0283] E39. 一種宿主細胞，其包含如 E37 之聚核苷酸或如 E38 之載體。

[0284] E40. 如 E39 之宿主細胞，其中該 FIX 融合蛋白係在活體內表現。

[0285] E41. 如 E39 之宿主細胞，其中該 FIX 融合蛋白係在活體外表現。

[0286] E42. 一種產生 FIX 融合蛋白之方法，其包含在使該 FIX 融合蛋白表現之條件下培養如 E39 之宿主細胞。

[0287] E43. 一種組合物，其包含如 E1 至 E36 中任一項之 FIX 融合蛋白、如 E37 之聚核苷酸、如 E38 之表現載體或如 E39 至 E41 中任一項之宿主細胞，及醫藥學上可接受之載劑。

[0288] E44. 一種預防、治療、改善或管理有需要患者之凝血性疾病或病狀之方法，其包括投與有效量的如 E1 至 E36 中任一項之 FIX 融合蛋白、如 E37 之聚核苷酸、如 E38 之表現載體、如 E39 至 E41 中任一項之宿主細胞或如 E43 之組合物。

[0289] E45. 如 E44 之方法，其中該投與包括向該患者皮下投與。

[0290] E46. 一種對受試者之凝血性疾病或病狀進行診斷或獲取圖像之方法，其包括使如 E1 至 E36 中任一項之 FIX 融合蛋白、如 E37 之聚核苷酸、如 E38 之表現載體或如 E39 至 E41 中任一項之宿主細胞與該受試者之樣品接觸。

[0291] E47. 一種延長 FIX 多肽之半衰期的方法，其包括將 XTEN 插入該 FIX 多肽內對應於選自由以下組成之群之胺基酸的插入位點：SEQ ID NO: 2 之胺基酸 103、SEQ ID NO: 2 之胺基酸 105、SEQ ID NO: 2 之胺基酸 142、SEQ ID NO: 2 之胺基酸 149、SEQ ID NO: 2 之胺基酸 162、SEQ ID NO: 2 之胺基酸 166、SEQ ID NO: 2 之胺基酸 174、SEQ ID NO: 2 之胺基酸 224、SEQ ID NO: 2 之胺基酸 226、SEQ ID NO: 2 之胺基酸 228、SEQ ID NO: 2 之胺基酸 413 及其任何組合，由此構築 FIX 融合蛋白，其中該 FIX 蛋白展現促凝血活性。

[0292] E48. 一種因子 IX (FIX)融合蛋白，其包含第一鏈及第二鏈，其中：

a. 該第一鏈包含：

i. FIX 多肽；

ii. 至少一個 XTEN，其中該至少一個 XTEN 插入該 FIX 多肽內對應於 SEQ ID NO: 2 之胺基酸 166 的插入位點，且其中該至少一個 XTEN 包含具有至少約 72 個胺基

酸之胺基酸序列；及

iii. 第一 Fc 結構域，其中該第一 Fc 結構域與該 FIX 多肽中該至少一個 XTEN 融合；且

b. 該第二鏈包含第二 Fc 結構域

其中該第一 Fc 結構域與該第二 Fc 結構域藉由共價鍵締合；且其中該 FIX 融合蛋白展現促凝血活性。

[0293] E49. 如 E48 之 FIX 融合蛋白，其中該至少一個 XTEN 包含與 SEQ ID NO: 35 之胺基酸序列至少約 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%一致之胺基酸序列。

[0294] E50. 如 E48 或 E49 之 FIX 融合蛋白，其中該 FIX 融合蛋白之第一鏈包含與 SEQ ID NO: 227 之胺基酸序列至少約 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%或至少約 99%一致之胺基酸序列；且其中該 FIX 融合蛋白之第二鏈包含與 SEQ ID NO: 228 之胺基酸序列至少約 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%或至少約 99%一致之胺基酸序列。

[0295] E51. 如 E48 至 E50 中任一項之 FIX 融合蛋白，其中 FIX 融合蛋白之第一鏈包含 SEQ ID NO: 227 之胺基酸序列；且其中該 FIX 融合蛋白之第二鏈包含 SEQ ID NO: 228 之胺基酸序列。

[0296] 前述實例及本申請案別處提及以下載體序

列。以下關鍵詞將有助於瞭解資訊：

關鍵詞：

信號肽(前肽)

前肽

具有或不具有蛋白質標籤之連接子

裂解位點

XTEN 及/或 Fc 之插入或融合

SEQ ID NO: 54 E0113_AE42; PNL118

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTE**GAPGSPAGSPTSTEEGTSESATPESGPGSEPAT**
SGSETPASSGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 55 N0089_AE42 pNL116

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNGAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASSIKNGRCEQFCKNSAD
NKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 56 A0103_AE42 pNL117

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC

ELDVTCNIKNGRCEQFCKNSA**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**D
NKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 57 P0129_AE42 pNL119

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPG**APGSPAGSPTSTEEGT**
SESATPESGPGSEPATSGSETPASSFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 58 K0142_AE42 pNL120

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSK**GAPG**
SPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASSLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 59 V0149_AE42 pNL121

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETV**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**FPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 60 E0162_AE42 pNL122

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA

ETVFPDVDYVNSTEAE**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**TILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 61 D0166_AE42 pNL123

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILD**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**NI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 62 S0174_AE42 pNL124

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQS**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGS**
ETPASSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 63 K0188_AE42 pNL125

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAK**GAPGSPAGSPTSTEEGTSESAT**
PESGPGSEPATSGSETPASSPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 64 V0202_AE42 pNL126

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKV**GAPGSPAG**
SPTSTEEGTSESATPESGPGSEPATSGSETPASSDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS

CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 65 E0224_AE42 pNL127

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVE**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**TGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 66 E0240_AE42 pNL128

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEE**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATS**
GSETPASSTEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 67 E0257_AE42 pNL129

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHH**GAPGSPAGSPTSTEEGT**
SESATPESGPGSEPATSGSETPASSNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 68 K0265_AE42 pNL130

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINK**GAPGSPAGS**
PTSTEEGTSESATPESGPGSEPATSGSETPASSYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 69 E0277_AE42 pNL131

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEGAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASSPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 70 D0292_AE42 pNL132

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADGAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASSKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 71 K0316_AE4 pNL133

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGAPGSPAGSPTSTEEGTSESAT
PESGPGSEPATSGSETPASSGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 72 K0341_AE42 pNL134

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKGAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASSFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 73 K0354_AE42 pNL135

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE

LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFH**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**EGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 74 K0392_AE42 pNL136

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMK**GAPGSPAGSP**
TSTEEGTSESATPESGPGSEPATSGSETPASSGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 75 R0403_AE42 pNL137

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
R**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**YVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 76 K0413_AE42 pNL138

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTK**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**LTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 77 CT_AE42 pNL140

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKLTGAGSPGAETA***LVPRSFLLRNPNDKYEPFWEDEES***GAGSPGAETA**GAPGSPA**
GSPTSTEEGTSESATPESGPGSEPATSGSETPASSGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 78 E0052_AE42 pNL141

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCE**GAPGSPAGSPTSTEEGTSESATPESGPGSE**
PATSGSETPASSSNPCLNGGSCKDDINSYECWCPFGFEGKNCELDVTCNIKNGRCEQFCKNSAD
NKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 79 G0059_AE42 pNL142

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNG**GAPGSPAGSPTSTEEGTSESATP**
ESGPGSEPATSGSETPASSGSCKDDINSYECWCPFGFEGKNCELDVTCNIKNGRCEQFCKNSAD
NKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 80 I0066_AE42 pNL143

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDI**GAPGSPAGSPTSTEEG**
TSESATPESGPGSEPATSGSETPASSNSYECWCPFGFEGKNCELDVTCNIKNGRCEQFCKNSAD
NKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 81 K0080_AE42 pNL144

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGK**GA**
PGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASSNCELDVTCNIKNGRCEQFCKNSAD
NKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 82 D0085_AE42 pNL145

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELD**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**VTCNIKNGRCEQFCKNSAD
NKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI

TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 83 CT_AE144 pNL164

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKLTGAGSPGAETA***LVPRSFLLRNPNDKYEPFWEDEES***GAGSPGAETA**GAPTSTE**
PSEGSAPGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGS
ETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPG
TSTEPSEGSAPGASSGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 84 CT_AE288 pNL165

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKLTGAGSPGAETA***LVPRSFLLRNPNDKYEPFWEDEES***GAGSPGAETA**GAPGTSE**
SATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSE
GSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEE
GSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEP
ATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSG
SETPGTSESATPESGPGTSTEPSEGSAPASSGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 85 CT_AE864 pNL166

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKLTGAGSPGAETA***LVPRSFLLRNPNDKYEPFWEDEES***GAGSPGAETA**GAPGSPA**
GSPTSTEEGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSE
GSAPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSESATPESGP
GTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGTSE
SATPESGPGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGTSTEPSEGSAPGTSTEPSE
GSAPGTSESATPESGPGTSESATPESGPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETP

GTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTST
EPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGSEPATSG
SETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSESATPESGP
GSPAGSPTSTEEGSPAGSPTSTEEGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGTSE
SATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSE
GSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEE
GSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEP
ATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSG
SETPGTSESATPESGPGTSTEPSEGSAPASSGAETAEQKLISEEDLSPATGHHHHHHHHH

SEQ ID NO: 86 K0142_AE72 pNL167

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKGAPS
PAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEP
SEGSAPGASSLTRAETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQV
VLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYN
AAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQ
YLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEE
CAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLISEEDLSPAT
GHHHHHHHHH

SEQ ID NO: 87 K0142_AE144 pNL168

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKGAPS
PAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEP
SEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTST
EEGTSTEPSEGSAPGASSLTRAETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAK
PGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIR
IIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHK
GRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLT
GIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLIS
EEDLSPATGHHHHHHHHH

SEQ ID NO: 88 K0142_AE288 pNL169

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKGAPG
TSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTE
PSEGSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTS
TEEGSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSESATPESGPGTSESATPESGPG
SEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPA
TSGSETPGTSESATPESGPGTSTEPSEGSAPASSLTRAETVFPDVDYVNSTEAETILDNITQST
QSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEH
NIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFL
KFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGD

SGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAET
GAGSPGAETAEQKLISEEDLSPATGHHHHHHHHH

SEQ ID NO: 89 V0149_AE72 pNL170

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSA
PGTSTEPSEGSAPGASSFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQV
VLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYN
AAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQ
YLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEE
CAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLISEEDLSPAT
GHHHHHHHHH

SEQ ID NO: 90 V0149_AE144 pNL171

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSA
PGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSP
AGSPTSTEEGTSTEPSEGSAPGASSFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAK
PGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIR
IIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHK
GRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLT
GIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLIS
EEDLSPATGHHHHHHHHH

SEQ ID NO: 91 V0149_AE288 pNL172

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVGAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPES
GPGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGS
PAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSESATPESGPGTSESA
TPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGS
APGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPASSFPDVDYVNSTEAETILDNITQST
QSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEH
NIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFL
KFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGD
SGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAET
GAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 92 E0162_AE72 pNL173

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAEGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPES
GPGTSTEPSEGSAPGTSTEPSEGSAPGASSTILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQV

VLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYN
AAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQ
YLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEE
CAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLISEEDLSPAT
GHHHHHHHH

SEQ ID NO: 93 E0162_AE144 pNL174

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAE**GAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPES**
GPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGT
STEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASSTILDNITQSTQSFNDFTRVVGGEDAK
PGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIR
IIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHK
GRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLT
GIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLIS
EEDLSPATGHHHHHHHH

SEQ ID NO: 94 E0162_AE288 pNL175

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAE**GAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGS**
ETPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPG
TSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSES
ATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEG
SAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPASSTILDNITQST
QSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEH
NIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFL
KFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGD
SGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAET
GAGSPGAETAEQKLISEEDLSPATGHHHHHHH

SEQ ID NO: 95 D0166_AE72 pNL176

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILD**GAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA**
TPESGPGTSTEPSEGSAPGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAKPGQFPWQV
VLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYN
AAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQ
YLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEE
CAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLISEEDLSPAT
GHHHHHHHH

SEQ ID NO: 96 D0166_AE144 pNL177

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC

ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA
TPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGS
APGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAK
PGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIR
IIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHK
GRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLT
GIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLIS
EEDLSPATGHHHHHHHH

SEQ ID NO: 97 D0166_AE288 pNL178

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDGAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPA
TSGSETPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGS
ETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPG
TSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTE
PSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPASSNITQST
QSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEH
NIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFL
KFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGD
SGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAET
GAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 98 S0174_AE72 pNL179

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSE
TPGTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGASSFNDFTRVVGGEDAKPGQFPWQV
VLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYN
AAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQ
YLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEE
CAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLISEEDLSPAT
GHHHHHHHH

SEQ ID NO: 99 S0174_AE144 pNL180

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSE
TPGTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGT
STEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASSFNDFTRVVGGEDAK
PGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIR
IIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHK
GRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLT

GIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLIS
EEDLSPATGHHHHHHHH

SEQ ID NO: 100 S0174_AE288 pNL181

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQS**GAPGTSESATPESGPGSEPATSGSETPGTSESATPE**
SGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESGPG
SEPATSGSETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGSAPGTSES
ATPESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTS
TEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPA
SSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEH
NIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFL
KFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGD
SGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAET
GAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 101 E0224_AE72 pNL182

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVE**GAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGP**
GTSTEPSEGSAPGTSTEPSEGSAPGASSTGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYN
AAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQ
YLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEE
CAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLISEEDLSPAT
GHHHHHHHH

SEQ ID NO: 102 E0224_AE144 pNL183

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVE**GAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGP**
GTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTST
EPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASSTGVKITVVAGEHNIEETEHTEQKRNVIR
IIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHK
GRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLT
GIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLIS
EEDLSPATGHHHHHHHH

SEQ ID NO: 103 E0224_AE288 pNL184

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVE**GAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSET**

PGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTS
ESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSESAT
PESGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEGSA
PGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPASSTGVKITVVAGEH
NIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFL
KFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGD
SGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAET
GAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 104 K0413_AE72 pNL185

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTS
TEPSEGSAPGTSTEPSEGSAPGASSLTGPEGPSKLTRAETGAGSPGAETAEQKLISEEDLSPAT
GHHHHHHHH

SEQ ID NO: 105 K0413_AE144 pNL186

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTS
TEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPS
EGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASSLTGPEGPSKLTRAETGAGSPGAETAEQKLIS
EEDLSPATGHHHHHHHH

SEQ ID NO: 106 K0413_AE288 pNL187

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKGAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGT
SESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA
TPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSESATPES
GPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEGSAPGT

STEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPASSLTGPEGPSKLTRAET
GAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 107 A0103_AE72 pNL188

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSA**GAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSES**
ATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGASSDNKVVCSCTEGYRLAENQKSCEPAVPFPC
GRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQV
VLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYN
AAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQ
YLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEE
CAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLISEEDLSPAT
GHHHHHHHH

SEQ ID NO: 108 A0103_AE144 pNL189

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSA**GAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSES**
ATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEG
SAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASSDNKVVCSCTEGYRLAENQKSC
EPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAK
PGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIR
IIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHK
GRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLT
GIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAETGAGSPGAETAEQKLIS
EEDLSPATGHHHHHHHH

SEQ ID NO: 109 A0103_AE288 pNL190

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSA**GAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEP**
ATSGSETPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSG
SETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGP
GTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTST
EPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPASSDNKVV
CSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNITQST
QSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEH
NILETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFL
KFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGD
SGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLTRAET
GAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 110 G0226_AE42 pNL195

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETG**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**VKITVV

AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 111 K0228_AE42 pNL196

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVK**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**ITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 112 T0230_AE42 pNL197

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKIT**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**VV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 113 N0105_AE42 pNL198

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADN**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPAS**
SKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 114 S0283_AE42 pNL199

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNS**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**YVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGPEGPSKLT
RAETGAGSPGAETAEQKLISEEDLSPATGHHHHHHHH

SEQ ID NO: 115 CT_AE72 pNL202

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKLTGAGSPGAETA*LVPRSFLLRNPNDKYEPFWEDEES*GAGSPGAETAGAPSPAG
SPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEPSEG
SAPGASSGAETAEQKLISEEDLSPATGHHHHHHHHH

SEQ ID NO: 116 C- 末端 -AE864 FIX-092

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLR
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKLTGPEGPS*KLTRAET*GSPGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSA
PGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGSE
PATSGSETPGSPAGSPTSTEEGTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSP
TSTEEGTSTEPSEGSAPGTSTEPSEGSAPGTSESATPESGPGTSTEPSEGSAPGTSESATPESG
PGSEPATSGSETPGTSTEPSEGSAPGTSTEPSEGSAPGTSESATPESGPGTSESATPESGPGSP
AGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEPS
EGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTE
EGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTS
ESATPESGPGTSTEPSEGSAPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGSPAGSP
TSTEEGTSESATPESGPGTSTEPSEGSAPGTSESATPESGPGSEPATSGSETPGTSESATPESG
PGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESGPGSE
PATSGSETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGSAPGTSESAT
PESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTE
EGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGSS
S

SEQ ID NO: 117 C- 末端 -AE144 pJH0131

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKLTGAGSPGAETA*LVPRSFLLRNPNDKYEPFWEDEES*GAGSPGAETAGAPSPAG
SPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEPSEG
SAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEEG
TSTEPSEGSAPGASS

SEQ ID NO: 118 N105-AE42 pJH44

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADN**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPAS**
SKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLT

SEQ ID NO: 119 D166-AE72 pJH46

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILD**GAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA**
TPESGPGTSTEPSEGSAPGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAKPGQFPWQV
VLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYN
AAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQ
YLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEE
CAMKGKYGIYTKVSRYVNWIKEKTKLT

SEQ ID NO: 120 D166-AE144 pJH47

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILD**GAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA**
TPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGS
APGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAK
PGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIR
IIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHK
GRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLT
GIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLT

SEQ ID NO: 121 C-末端-AE144 pJH50

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKLTGAGSPGAETA***LVPRSFLLRNPNDKYEPFWEDEES***GAGSPGAETA**GAPTSTE**
PSEGSAPGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGS
ETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPG
TSTEPSEGSAPGASS

SEQ ID NO: 122 C-末端-AE288 pJH51

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKLTGAGSPGAETA*LVPRSFLLRNPNDKYEPFWEDEES*GAGSPGAETAGAPGTSE
SATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSE
GSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEE
GSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEP
ATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSG
SETPGTSESATPESGPGTSTEPSEGSAPASS

SEQ ID NO: 123 C- 末端 -AE72 pJH52

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKLTGAGSPGAETA*LVPRSFLLRNPNDKYEPFWEDEES*GAGSPGAETAGAPTSES
ATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEG
SAPGASS

SEQ ID NO: 124 E224-AE42 pJH54

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVE**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**TGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLT

SEQ ID NO: 125 D166-AE42 pJH55

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILD**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**NI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKL

SEQ ID NO: 126 D166-AE42, C-末端 -AE72 pJH59

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC

ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDGAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASSNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAET
*ALVPRSFLLRNPNDKYEPFWEDEES*GAGSPGAETAGAPTSESATPESGPGSEPATSGSETPGTS
ESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGAS

SEQ ID NO: 127 D166-AE42, C-末端-AE144 pJH60

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDGAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASSNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAET
*ALVPRSFLLRNPNDKYEPFWEDEES*GAGSPGAETAGAPSPAGSPTSTEEGTSESATPESGPGSE
PATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPS
EGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASS

SEQ ID NO: 128 D166-AE42, C-末端-AE288 pJH61

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDGAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASSNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAET
*ALVPRSFLLRNPNDKYEPFWEDEES*GAGSPGAETAGAPGTSESATPESGPGSEPATSGSETPGT
SESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESA
TPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGS
APGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGS
PAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEP
SEGSAPASS

SEQ ID NO: 129 D166-AE72, C-末端-AE72 pJH62

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA
TPESGPGTSTEPSEGSAPGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAKPGQFPWQV
VLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYN
AAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQ
YLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEE

CAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAETA*LVPRSFLLRNPNDKYEPFWEDEES*GAG
SPGAETAGAPTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESAT
PESGPGTSTEPSEGSAPGASS

SEQ ID NO: 130 D166-AE72, C-末端-AE144 pJH63
MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA
TPESGPGTSTEPSEGSAPGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAKPGQFPWQV
VLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYN
AAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQ
YLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEE
CAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAETA*LVPRSFLLRNPNDKYEPFWEDEES*GAG
SPGAETAGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPS
EGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSA
PGSPAGSPTSTEEGTSTEPSEGSAPGASS

SEQ ID NO: 131 D166-AE72, C-末端-AE288 pJH64
MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA
TPESGPGTSTEPSEGSAPGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAKPGQFPWQV
VLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYN
AAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQ
YLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEE
CAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAETA*LVPRSFLLRNPNDKYEPFWEDEES*GAG
SPGAETAGAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESA
TPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPES
GPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSESATPESGPGT
SESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEGSAPGTSTEP
SEGSAPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPASS

SEQ ID NO: 132 D166-AE144, C-末端-AE72 pJH65
MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA
TPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGS
APGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAK
PGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIR
IIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHK
GRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLT
GIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAETA*LVPRSFLLRNPNDKYEPFW*
*EDEES*GAGSPGAETAGAPTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSET
PGTSESATPESGPGTSTEPSEGSAPGASS

SEQ ID NO: 133 D166-AE144, C-末端-AE144 pJH66

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA
TPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGS
APGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAK
PGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIR
IIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHK
GRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLT
GIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAETA*LVPRSFLLRNPNDKYEPFW*
*EDEES*GAGSPGAETAGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESG
PGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTS
TEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASS

SEQ ID NO: 134 D166-AE144, C-末端 -AE288 pJH67

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA
TPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGS
APGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAK
PGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIR
IIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHK
GRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLT
GIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAETA*LVPRSFLLRNPNDKYEPFW*
*EDEES*GAGSPGAETAGAPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSE
TPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGT
SESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSESA
TPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGSPAGSPTSTEEGTSTEPSEGS
APGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPASS

SEQ ID NO: 135 N105-AE42, D166-AE42 pJH68

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNGAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPAS
SKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDGA
PGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASSNITQSTQSFNDFTRVVGGEDAKPG
QFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRII
PHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGR
SALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGI
ISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLT

SEQ ID NO: 136 N105-AE42, D166-AE72 pJH69

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNGAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPAS
SKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDGA
PSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTST

EPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVT
AAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLN
SYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYN
NMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKE
KTKLT

SEQ ID NO: 137 N105-AE42, D166-AE144 pJH70

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADN**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPAS**
SKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDG**A**
PSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTST
EPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPT
STEEGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKLT

SEQ ID NO: 138 N105-AE42, C-末端-AE72 pJH71

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGN
LERECMEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGF
EGKNCELDVTCNIKNGRCEQFCKNSADN**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGS**
ETPASSKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAET
ILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGV
KITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIA
DKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHE
GGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGAGS
PGAETA*LVPRSFLLRNPNDKYEPFWEDEES*GAGSPGAETAGAP**TSESATPESGPGSEPATSGSE**
TPGTSESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGASS

SEQ ID NO: 139 N105-AE42, C-末端-AE144 pJH72

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADN**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPAS**
SKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAET
A*LVPRSFLLRNPNDKYEPFWEDEES*GAGSPGAETA**GAPSPAGSPTSTEEGTSESATPESGPGSE**
PATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPS
EGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASS

SEQ ID NO: 140 N105-AE42, C-末端-AE288 pJH73

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADN**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPAS**
SKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI

TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAET
*ALVPRSFLLRNPNDKYEPFWEDEES*GAGSPGAETA**GAPGTSESATPESGPGSEPATSGSETPGT**
SESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESA
TPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGS
APGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGS
PAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEP
SEGSAPASS

SEQ ID NO: 141 N105-AE42, E224-AE42 pJH74

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADN**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPAS**
SKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVE**GAPGSPAG**
SPTSTEEGTSESATPESGPGSEPATSGSETPASSTGVKITVVAGEHNIEETEHTEQKRNVIRII
PHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGR
SALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGI
ISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLT

SEQ ID NO: 142 D166-AE42, E224-AE42 pJH75

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILD**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**NI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVE**GAPGSPAG**
SPTSTEEGTSESATPESGPGSEPATSGSETPASSTGVKITVVAGEHNIEETEHTEQKRNVIRII
PHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGR
SALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGI
ISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLT

SEQ ID NO: 143 D166-AE72, E224-AE42 pJH76

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILD**GAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA**
TPESGPGTSTEPSEGSAPGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAKPGQFPWQV
VLNGKVDAFCGGSIVNEKWIVTAAHCVE**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGS**
ETPASSTGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLN
SYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYN
NMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKE
KTKLT

SEQ ID NO: 144 D166-AE144, E224-AE42 pJH77

MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILD**GAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA**

TPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGS
APGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAK
PGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVE**GAPGSPAGSPTSTEEGTSESATPESGPG**
SEPATSGSETPASSTGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLE
LDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLL
STKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVS
RYVNWIKEKTKLT

SEQ ID NO: 145 E224-AE42, C-末端-AE72 pJH78

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVE**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**TGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAET
*ALVPRSFLLRNPNDKYEPFWEDEES*GAGSPGAETAGAP**TSESATPESGPGSEPATSGSETPGTS**
ESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGASS

SEQ ID NO: 146 E224-AE42, C-末端-AE144 pJH79

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVE**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**TGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAET
*ALVPRSFLLRNPNDKYEPFWEDEES*GAGSPGAETA**GAPSPAGSPTSTEEGTSESATPESGPGSE**
PATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPS
EGSAPGTSTEPSEGSAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASS

SEQ ID NO: 147 E224-AE42, C-末端-AE288 pJH80

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVE**GAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASS**TGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTGAGSPGAET
*ALVPRSFLLRNPNDKYEPFWEDEES*GAGSPGAETA**GAPGTSESATPESGPGSEPATSGSETPGT**
SESATPESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESA
TPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEEGSPAGSPTSTEEGTSTEPSEGS
APGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPATSGSETPGS

PAGSPTSTEEGTSTEPSEGSAPGTSTEPSEGSAPGSEPATSGSETPGTSESATPESGPGTSTEP
SEGSAPASS

SEQ ID NO: 148 N105-AE42, C-末端-Fc pJH81

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNGAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPAS
SKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTDKTHTCPPC
PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK

SEQ ID NO: 149 E224-AE42, C-末端-Fc pJH82

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSI
VNEKWIVTAAHCVEGAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASSTGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTDKTHTCPPC
PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK

SEQ ID NO: 150 D166-AE42, C-末端-Fc pJH83

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDGAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPASSNI
TQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVV
AGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYT
NIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDS
CQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTDKTHTCPPC

PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK

SEQ ID NO: 151 D166-AE72, C-末端-Fc pJH84

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLEREC
MEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNC
ELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRA
ETVFPDVDYVNSTEAETILDGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESA
TPESGPGTSTEPSEGSAPGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGEDAKPGQFPWQV
VLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYN
AAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQ
YLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEE
CAMKGKYGIYTKVSRYVNWIKEKTKLTDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG
QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGG
GGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 152 D166-AE144, C-末端-Fc pJH85

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGN
LERECMEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGF
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KLTRAETVFPDVDYVNSTEAETILDGAPSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPG
TSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTEPSEGSAPGTSTE
PSEGSAPGTSTEPSEGSAPGSPAGSPTSTEEGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVG
GEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQK
RNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWG
RVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEG
TSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGKGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI
SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
ESNGQ

SEQ ID NO: 153 C-末端-Fc pJH56

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLERECMEEKCSFEEAREVFENTERTTEFWKQYVDGDQCESNPCLNGGSCKDDINSYECWCPFGFEGKNCELDVTCNIKNGRCEQFCKNSADNKVVCSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGEDAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAINKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLSTKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 226 C-末端-AE288 pSYN-FIX-102

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLERECMEEKCSFEEAREV
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CSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDNITQSTQSFNDFTRVVGGE
DAKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAA
INKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLS
TKFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTG
PEGP*SKLTRAETGAGSPGAETA*GTSESATPESGPGSEPATSGSETPGTSESATPESGPGSEPATSGSETPGTSESAT
PESGPGTSTEPSEGSAPGSPAGSPTSTEEGTSESATPESGPGSEPATSGSETPGTSESATPESGPGSPAGSPTSTEE
GSPAGSPTSTEEGTSTEPSEGSAPGTSESATPESGPGTSESATPESGPGTSESATPESGPGSEPATSGSETPGSEPA
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SEQ ID NO: 227 雙鏈 D166-AE72, C-末端-Fc pSYN-FIX-216

MQRVNMIMAESPGLITICLLGYLLSAECTVFLDHENANKILNRPKRYNSGKLEEFVQGNLERECMEEKCSFEEAREV
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CSCTEGYRLAENQKSCEPAVPFPCGRVSVSQTSKLTRAETVFPDVDYVNSTEAETILDGPSPGSPTSTEEGTSESAT
PESGPGSEPATSGSETPGTSESATPESGPGTSTEPSEGSAPGTSTEPSEGSAPGASSNITQSTQSFNDFTRVVGGED
AKPGQFPWQVVLNGKVDAFCGGSIVNEKWIVTAAHCVETGVKITVVAGEHNIEETEHTEQKRNVIRIIPHHNYNAAI
NKYNHDIALLELDEPLVLNSYVTPICIADKEYTNIFLKFGSGYVSGWGRVFHKGRSALVLQYLRVPLVDRATCLLST
KFTIYNNMFCAGFHEGGRDSCQGDSGGPHVTEVEGTSFLTGIISWGEECAMKGKYGIYTKVSRYVNWIKEKTKLTDK
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO: 228 雙鏈 D166-AE72, C-末端-Fc pSYN-FIX-216-Fc 鏈部分

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

序列表

<110> 美商百歐維拉提夫治療公司(BIOVERATIV THERAPEUTICS INC.)

<120> 因子IX融合蛋白以及其製備及使用方法

<150> 62/200,590
<151> 2015-08-03

<150> 62/281,993
<151> 2016-01-22

<160> 228

<170> PatentIn 3.5版

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Glu Cys Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe
            20                  25                  30

Glu Asn Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly
        35                  40                  45

Asp Gln Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp
    50                  55                  60

Asp Ile Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys
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65 70 75 80

Asn Cys Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu
85 90 95

Gln Phe Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr
100 105 110

Glu Gly Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val
115 120 125

Pro Phe Pro Cys Gly Arg Val Ser Val Ser Gln Thr Ser Lys Leu Thr
130 135 140

Arg Ala Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu
145 150 155 160

Ala Glu Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn
165 170 175

Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe
180 185 190

Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly
195 200 205

Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu
210 215 220

Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu
225 230 235 240

Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His

245 250 255

His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu
260 265 270

Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile
275 280 285

Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser
290 295 300

Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala
305 310 315 320

Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys
325 330 335

Leu Arg Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly
340 345 350

Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro
355 360 365

His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser
370 375 380

Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys
385 390 395 400

Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr
405 410 415

<210> 2

<211> 415
<212> PRT
<213> 人工序列

<220>
<223> Padua FIX多肽

<400> 2

Tyr Asn Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg
1 5 10 15

Glu Cys Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe
20 25 30

Glu Asn Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly
35 40 45

Asp Gln Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp
50 55 60

Asp Ile Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys
65 70 75 80

Asn Cys Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu
85 90 95

Gln Phe Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr
100 105 110

Glu Gly Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val
115 120 125

Pro Phe Pro Cys Gly Arg Val Ser Val Ser Gln Thr Ser Lys Leu Thr
130 135 140

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Arg Ala Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu
145                 150                 155                 160

Ala Glu Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn
                165                 170                 175

Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe
            180                 185                 190

Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly
        195                 200                 205

Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu
    210                 215                 220

Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu
225                 230                 235                 240

Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His
                245                 250                 255

His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu
            260                 265                 270

Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile
        275                 280                 285

Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser
    290                 295                 300

Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala
305                 310                 315                 320
```

Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys
325 330 335

Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly
340 345 350

Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro
355 360 365

His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser
370 375 380

Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys
385 390 395 400

Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr
405 410 415

<210> 3
<211> 46
<212> PRT
<213> 人類 FIX 信號肽及前肽

<400> 3

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg
35 40 45

<210> 4
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AD

<400> 4

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

<210> 5
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AD

<400> 5

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

<210> 6
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AD

<400> 6

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

<210> 7
<211> 12

<212> PRT
<213> 人工序列

<220>
<223> AD

<400> 7

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

<210> 8
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AE、AM

<400> 8

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

<210> 9
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AE、AM、AQ

<400> 9

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

<210> 10
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AE、AM、AQ

<400> 10

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

<210> 11
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AE、AM、AQ

<400> 11

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

<210> 12
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AF、AM

<400> 12

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

<210> 13
<211> 12
<212> PRT
<213> 人工序列

<220>

<223> AF、AM

<400> 13

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

<210> 14
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AF、AM

<400> 14

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

<210> 15
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AF、AM

<400> 15

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

<210> 16
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AG、AM

<400> 16

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

<210> 17
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AG、AM

<400> 17

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

<210> 18
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AG、AM

<400> 18

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

<210> 19
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AG、AM

<400> 19

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

<210> 20
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AQ

<400> 20

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

<210> 21
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AQ

<400> 21

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

<210> 22
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AQ

<400> 22

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

<210> 23
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AQ

<400> 23

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

<210> 24
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AQ

<400> 24

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

<210> 25
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> AQ

<400> 25

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

<210> 26
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> BC

<400> 26

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

<210> 27
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> BC

<400> 27

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

<210> 28
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> BC

<400> 28

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

<210> 29
<211> 12

<212> PRT
<213> 人工序列

<220>
<223> BC

<400> 29

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

<210> 30
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> BD

<400> 30

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

<210> 31
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> BD

<400> 31

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

<210> 32
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> BD

<400> 32

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

<210> 33
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> BD

<400> 33

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

<210> 34
<211> 42
<212> PRT
<213> 人工序列

<220>
<223> AE42

<400> 34

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

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

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

<210> 35
<211> 78
<212> PRT
<213> 人工序列

<220>
<223> AE72

<400> 35

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

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

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

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

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

<210> 36
<211> 144
<212> PRT
<213> 人工序列

<220>
<223> AE144

<400> 36

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

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

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

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

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

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

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

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

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

<210> 37
<211> 144
<212> PRT
<213> 人工序列

<220>
<223> AE144_2A

<400> 37

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

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

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

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

<210> 38
<211> 144
<212> PRT
<213> 人工序列

<220>
<223> AE144_3B

<400> 38

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> 39
<211> 144
<212> PRT
<213> 人工序列

<220>

<223> AE144_4A

<400> 39

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> 40
<211> 144
<212> PRT
<213> 人工序列

<220>
<223> AE144_5A

<400> 40

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> 41
<211> 144

<212> PRT
<213> 人工序列

<220>
<223> AE144_6B

<400> 41

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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
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<210> 42
<211> 144
<212> PRT
<213> 人工序列

<220>
<223> AG144

<400> 42

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

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

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

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

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

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

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

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

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

<210> 43
<211> 144
<212> PRT
<213> 人工序列

<220>
<223> AG144_A

<400> 43

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> 44
<211> 144
<212> PRT
<213> 人工序列

<220>
<223> AG144_B

<400> 44

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> 45
<211> 144
<212> PRT
<213> 人工序列

<220>
<223> AG144_C

<400> 45

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> 46
<211> 144
<212> PRT
<213> 人工序列

<220>
<223> AG144_F

<400> 46

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> 47
<211> 288
<212> PRT
<213> 人工序列

<220>
<223> AE288

<400> 47

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 48
<211> 288
<212> PRT
<213> 人工序列

<220>
<223> AE288_2

<400> 48

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> 49
<211> 288

<212> PRT
<213> 人工序列

<220>
<223> AG288

<400> 49

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

Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr
            20                  25                  30

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

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

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

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

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

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

Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser
    130                 135                 140
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Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser
145                 150                 155                 160

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

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

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

Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly
    210                 215                 220

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

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

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

Ala Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser
        275                 280                 285
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<210> 50
<211> 576
<212> PRT
<213> 人工序列

<220>
<223> AE576

<400> 50

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
305 310 315 320

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
325 330 335

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
340 345 350

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu
355 360 365

Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
370 375 380

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
385 390 395 400

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
405 410 415

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
420 425 430

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
435 440 445

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
450 455 460

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
465 470 475 480

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
485 490 495

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
500 505 510

Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
515 520 525

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala
530 535 540

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro
545 550 555 560

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
565 570 575

<210> 51
<211> 576
<212> PRT
<213> 人工序列

<220>
<223> AG576

<400> 51

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

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

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

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

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

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

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

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

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

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

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

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

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

Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly
210 215 220

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

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

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

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

Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser
    290                 295                 300

Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser
305                 310                 315                 320

Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser
                325                 330                 335

Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala Ser
            340                 345                 350

Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser
        355                 360                 365

Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser
    370                 375                 380

Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Thr Pro
385                 390                 395                 400

Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly
                405                 410                 415

Ala Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser
            420                 425                 430
```

Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Thr Pro
435 440 445

Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly
450 455 460

Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser
465 470 475 480

Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser
485 490 495

Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser
500 505 510

Ser Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser
515 520 525

Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser
530 535 540

Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser Pro Ser Ala Ser
545 550 555 560

Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser
565 570 575

<210> 52
<211> 864
<212> PRT
<213> 人工序列

<220>
<223> AE864

<400> 52

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
305 310 315 320

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
325 330 335

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
340 345 350

```
Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu
        355                 360                 365

Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
    370                 375                 380

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
385                 390                 395                 400

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
                405                 410                 415

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
            420                 425                 430

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
        435                 440                 445

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
    450                 455                 460

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
465                 470                 475                 480

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
                485                 490                 495

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
            500                 505                 510

Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
        515                 520                 525
```

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala
530 535 540

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro
545 550 555 560

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
565 570 575

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
580 585 590

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
595 600 605

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
610 615 620

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
625 630 635 640

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
645 650 655

Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
660 665 670

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu
675 680 685

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr
690 695 700

Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
705 710 715 720

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu
725 730 735

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro
740 745 750

Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
755 760 765

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro
770 775 780

Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr
785 790 795 800

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
805 810 815

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro
820 825 830

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
835 840 845

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
850 855 860

<210> 53
<211> 864

<212> PRT
<213> 人工序列

<220>
<223> AG864

<400> 53

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala Ser Pro
    290                 295                 300

Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
305                 310                 315                 320
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Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
325 330 335

Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Thr Pro Gly
340 345 350

Ser Gly Thr Ala Ser Ser Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
355 360 365

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
370 375 380

Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ser Ser Thr
385 390 395 400

Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala
405 410 415

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
420 425 430

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr
435 440 445

Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala
450 455 460

Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro
465 470 475 480

Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro
485 490 495

Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
500 505 510

Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro
515 520 525

Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro
530 535 540

Gly Thr Ser Ser Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser
545 550 555 560

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
565 570 575

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr
580 585 590

Pro Ser Gly Ala Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala
595 600 605

Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro
610 615 620

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr
625 630 635 640

Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala
645 650 655

Thr Gly Ser Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro
660 665 670

Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro
675 680 685

Gly Thr Ser Ser Thr Gly Ser Pro Gly Thr Pro Gly Ser Gly Thr Ala
690 695 700

Ser Ser Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro
705 710 715 720

Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro Gly Ser Ser Pro
725 730 735

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser
740 745 750

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
755 760 765

Gly Ser Ser Thr Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Pro
770 775 780

Ser Ala Ser Thr Gly Thr Gly Pro Gly Ala Ser Pro Gly Thr Ser Ser
785 790 795 800

Thr Gly Ser Pro Gly Ser Ser Pro Ser Ala Ser Thr Gly Thr Gly Pro
805 810 815

Gly Thr Pro Gly Ser Gly Thr Ala Ser Ser Ser Pro Gly Ser Ser Thr
820 825 830

Pro Ser Gly Ala Thr Gly Ser Pro Gly Ser Ser Thr Pro Ser Gly Ala
835 840 845

Thr Gly Ser Pro Gly Ala Ser Pro Gly Thr Ser Ser Thr Gly Ser Pro
850 855 860

<210> 54
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL118

<400> 54

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

```
Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

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

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

Ser Gly Ser Glu Thr Pro Ala Ser Ser Gly Tyr Arg Leu Ala Glu Asn
        195                 200                 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
    210                 215                 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300
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Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305 310 315 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 55
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL116

<400> 55

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Gly Ala Pro Gly Ser Pro Ala Gly Ser
130 135 140

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

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

Ser Ile Lys Asn Gly Arg Cys Glu Gln Phe Cys Lys Asn Ser Ala Asp
180 185 190

Asn Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
195 200 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
210 215 220

```
Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400
```

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 56
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL117

<400> 56

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
145 150 155 160

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

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

Asn Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
        195                 200                 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
    210                 215                 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335
```

```
Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
            500                 505                 510
```

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 57
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL119

<400> 57

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

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Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Gly
                165                 170                 175

Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu 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 Ala Ser Ser Phe Pro Cys Gly Arg Val Ser
    210                 215                 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255
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Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
260 265 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
275 280 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
290 295 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305 310 315 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 58
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL120

<400> 58

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

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

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

Glu Thr Pro Ala Ser Ser Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365
```

```
Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
            500                 505                 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
        515                 520                 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
    530                 535                 540
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His His His His His
545

<210> 59
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL121

<400> 59

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

```
Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

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

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

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

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285
```

```
Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460
```

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 60
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL122

<400> 60

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

```
Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

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

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

Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser Thr Ile Leu Asp Asn Ile
245 250 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
260 265 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
275 280 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
290 295 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305 310 315 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 61
<211> 549

<212> PRT
<213> 人工序列

<220>
<223> pNL123

<400> 61

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

```
Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
    210                 215                 220

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

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

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320
```

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 62
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL124

<400> 62

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Gly Ala Pro Gly
210 215 220

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

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

```
Glu Thr Pro Ala Ser Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430
```

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 63
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL125

<400> 63

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1               5                  10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175
```

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Gly Ala Pro Gly Ser Pro
225 230 235 240

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

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

Pro Ala Ser Ser Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
275 280 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
290 295 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305 310 315 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

```
Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
            500                 505                 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
        515                 520                 525
```

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 64
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL126

<400> 64

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Gly Ala Pro Gly Ser Pro Ala Gly
245 250 255

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

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

```
Ser Ser Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460
```

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 65
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL127

<400> 65

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

```
Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Gly Ala
            260                 265                 270

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

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

Gly Ser Glu Thr Pro Ala Ser Ser Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380
```

```
Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
            500                 505                 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
        515                 520                 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
    530                 535                 540

His His His His His
545
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<210> 66
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL128

<400> 66

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Gly Ala
275 280 285

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

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
305 310 315 320

Gly Ser Glu Thr Pro Ala Ser Ser Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 67
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL129

<400> 67

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

```
Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Gly
    290                 295                 300

Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr
305                 310                 315                 320

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr
                325                 330                 335

Ser Gly Ser Glu Thr Pro Ala Ser Ser Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415
```

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 68
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL130

<400> 68

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1               5                  10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175
```

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Gly Ala Pro Gly Ser Pro Ala Gly Ser
305                 310                 315                 320

Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
                325                 330                 335

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Ala Ser
            340                 345                 350
```

Ser Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 69
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL131

<400> 69

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

```
Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270
```

```
Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr
                325                 330                 335

Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
            340                 345                 350

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445
```

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 70
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL132

<400> 70

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
290 295 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu
340 345 350

Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu
355 360 365

Pro Ala Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser Lys Glu Tyr Thr
370 375 380

```
Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
            500                 505                 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
        515                 520                 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
    530                 535                 540

His His His His His
545
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<210> 71
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL133

<400> 71

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

```
Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300
```

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
340 345 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Ala Pro Gly Ser Pro
355 360 365

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr
370 375 380

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
385 390 395 400

Pro Ala Ser Ser Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 72
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL134

<400> 72

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
290 295 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
340 345 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
355 360 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
370 375 380

Ser Thr Lys Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr
385 390 395 400

Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
405 410 415

```
Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
            500                 505                 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
        515                 520                 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
    530                 535                 540

His His His His His
545
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<210> 73
<211> 549
<212> PRT
<213> 人工序列

<220>

<223> pNL135

<400> 73

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1               5                  10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160
```

```
Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
                325                 330                 335
```

```
Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
            340                 345                 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
    370                 375                 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385                 390                 395                 400

Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
                405                 410                 415

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
            420                 425                 430

Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
            500                 505                 510
```

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 74
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL136

<400> 74

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

```
Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
                325                 330                 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
            340                 345                 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
    370                 375                 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385                 390                 395                 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
                405                 410                 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
            420                 425                 430

Glu Glu Cys Ala Met Lys Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro
        435                 440                 445
```

Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
450 455 460

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His His
545

<210> 75
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL137

<400> 75

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

```
Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
                325                 330                 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
            340                 345                 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365
```

```
Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
    370                 375                 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385                 390                 395                 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
                405                 410                 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
            420                 425                 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
        435                 440                 445

Arg Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
    450                 455                 460

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
465                 470                 475                 480

Ala Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
            500                 505                 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
        515                 520                 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
    530                 535                 540
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His His His His His
545

<210> 76
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL138

<400> 76

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
290 295 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
340 345 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
355 360 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
370 375 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385 390 395 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
405 410 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
420 425 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
435 440 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Gly Ala Pro Gly Ser
450 455 460

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala
465 470 475 480

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
485 490 495

Thr Pro Ala Ser Ser Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 77
<211> 575
<212> PRT
<213> 人工序列

<220>
<223> pNL140

<400> 77

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

```
Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220
```

```
Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
                325                 330                 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
            340                 345                 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
    370                 375                 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385                 390                 395                 400
```

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
405 410 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
420 425 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
435 440 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly
450 455 460

Ser Pro Gly Ala Glu Thr Ala Leu Val Pro Arg Ser Phe Leu Leu Arg
465 470 475 480

Asn Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly
485 490 495

Ala Gly Ser Pro Gly Ala Glu Thr Ala Gly Ala Pro Gly Ser Pro Ala
500 505 510

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro
515 520 525

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
530 535 540

Ala Ser Ser Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser Glu Glu
545 550 555 560

Asp Leu Ser Pro Ala Thr Gly His His His His His His His His
565 570 575

<210> 78
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL141

<400> 78

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

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

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

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

Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile Asn Ser Tyr Glu Cys Trp
145 150 155 160

Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys Glu Leu Asp Val Thr Cys
165 170 175

Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe Cys Lys Asn Ser Ala Asp
180 185 190

Asn Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
195 200 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
210 215 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225 230 235 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
245 250 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
260 265 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
275 280 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
290 295 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305 310 315 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 79
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL142

<400> 79

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

```
Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ala Pro Gly Ser Pro Ala
            100                 105                 110

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

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

Ala Ser Ser Gly Ser Cys Lys Asp Asp Ile Asn Ser Tyr Glu Cys Trp
145                 150                 155                 160

Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys Glu Leu Asp Val Thr Cys
                165                 170                 175

Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe Cys Lys Asn Ser Ala Asp
            180                 185                 190

Asn Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
        195                 200                 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
    210                 215                 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240
```

```
Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415
```

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 80
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL143

<400> 80

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1               5                  10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

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

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

Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser Asn Ser Tyr Glu Cys Trp
145                 150                 155                 160

Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys Glu Leu Asp Val Thr Cys
                165                 170                 175
```

```
Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe Cys Lys Asn Ser Ala Asp
            180                 185                 190

Asn Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
        195                 200                 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
    210                 215                 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350
```

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 81
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL144

<400> 81

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

```
Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Gly Ala
        115                 120                 125

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

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

Gly Ser Glu Thr Pro Ala Ser Ser Asn Cys Glu Leu Asp Val Thr Cys
                165                 170                 175

Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe Cys Lys Asn Ser Ala Asp
            180                 185                 190

Asn Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
        195                 200                 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
    210                 215                 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270
```

```
Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445
```

```
Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
            500                 505                 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
        515                 520                 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
    530                 535                 540

His His His His His
545
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<210> 82
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL145

<400> 82

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1               5                   10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30
```

```
Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

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

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

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

Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe Cys Lys Asn Ser Ala Asp
            180                 185                 190

Asn Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
        195                 200                 205
```

```
Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
    210                 215                 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380
```

```
Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
            500                 505                 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
        515                 520                 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
    530                 535                 540

His His His His His
545
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<210> 83
<211> 683
<212> PRT
<213> 人工序列

<220>
<223> pNL164

<400> 83

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
290 295 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
340 345 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
355 360 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
370 375 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385 390 395 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
405 410 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
420 425 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
435 440 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly
450 455 460

Ser Pro Gly Ala Glu Thr Ala Leu Val Pro Arg Ser Phe Leu Leu Arg
465 470 475 480

Asn Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly
485 490 495

Ala Gly Ser Pro Gly Ala Glu Thr Ala Gly Ala Pro Thr Ser Thr Glu
500 505 510

Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
515 520 525

Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
530 535 540

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
545 550 555 560

Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
565 570 575

Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
580 585 590

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu
595 600 605

Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
610 615 620

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
625 630 635 640

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser Gly
645 650 655

Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro
660 665 670

Ala Thr Gly His His His His His His His His
675 680

<210> 84
<211> 827
<212> PRT
<213> 人工序列

<220>
<223> pNL165

<400> 84

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

```
His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
                325                 330                 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
            340                 345                 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
    370                 375                 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385                 390                 395                 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
                405                 410                 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
            420                 425                 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
        435                 440                 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly
    450                 455                 460
```

Ser Pro Gly Ala Glu Thr Ala Leu Val Pro Arg Ser Phe Leu Leu Arg
465 470 475 480

Asn Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly
485 490 495

Ala Gly Ser Pro Gly Ala Glu Thr Ala Gly Ala Pro Gly Thr Ser Glu
500 505 510

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
515 520 525

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
530 535 540

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu
545 550 555 560

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu
565 570 575

Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
580 585 590

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
595 600 605

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
610 615 620

Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
625 630 635 640

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr
645 650 655

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
660 665 670

Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
675 680 685

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
690 695 700

Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly
705 710 715 720

Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
725 730 735

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
740 745 750

Glu Pro Ser Glu Gly Ser Ala 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 Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala Ser Ser Gly
785 790 795 800

Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro
805 810 815

Ala Thr Gly His His His His His His His His
820 825

<210> 85
<211> 1403
<212> PRT
<213> 人工序列

<220>
<223> pNL166

<400> 85

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

```
His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
                325                 330                 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
            340                 345                 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
    370                 375                 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385                 390                 395                 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
                405                 410                 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
            420                 425                 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
        435                 440                 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly
    450                 455                 460
```

```
Ser Pro Gly Ala Glu Thr Ala Leu Val Pro Arg Ser Phe Leu Leu Arg
465                 470                 475                 480

Asn Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly
                485                 490                 495

Ala Gly Ser Pro Gly Ala Glu Thr Ala Gly Ala Pro Gly Ser Pro Ala
            500                 505                 510

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro
        515                 520                 525

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
    530                 535                 540

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr
545                 550                 555                 560

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu
                565                 570                 575

Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
            580                 585                 590

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro
        595                 600                 605

Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr
    610                 615                 620

Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
625                 630                 635                 640
```

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
645 650 655

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
660 665 670

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
675 680 685

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu
690 695 700

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu
705 710 715 720

Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
725 730 735

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Thr
740 745 750

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu
755 760 765

Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
770 775 780

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala
785 790 795 800

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro
805 810 815

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
820 825 830

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
835 840 845

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu
850 855 860

Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
865 870 875 880

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
885 890 895

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu
900 905 910

Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
915 920 925

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu
930 935 940

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
945 950 955 960

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
965 970 975

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu
980 985 990

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu
995 1000 1005

Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
1010 1015 1020

Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser
1025 1030 1035

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly
1040 1045 1050

Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro
1055 1060 1065

Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
1070 1075 1080

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
1085 1090 1095

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser
1100 1105 1110

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
1115 1120 1125

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
1130 1135 1140

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
1145 1150 1155

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser
1160 1165 1170

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
1175 1180 1185

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
1190 1195 1200

Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser
1205 1210 1215

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu
1220 1225 1230

Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
1235 1240 1245

Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
1250 1255 1260

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
1265 1270 1275

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala
1280 1285 1290

Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr
1295 1300 1305

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
1310 1315 1320

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
1325 1330 1335

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser
1340 1345 1350

Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu
1355 1360 1365

Gly Ser Ala Pro Ala Ser Ser Gly Ala Glu Thr Ala Glu Gln Lys
1370 1375 1380

Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
1385 1390 1395

His His His His His
1400

<210> 86
<211> 585
<212> PRT
<213> 人工序列

<220>
<223> pNL167

<400> 86

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

```
Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

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

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

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

Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile
275 280 285

Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg
290 295 300

Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val
305 310 315 320

Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn
325 330 335

Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys
340 345 350

Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr
355 360 365

Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn
370 375 380

Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp
385 390 395 400

Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp
405 410 415

Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser
420 425 430

Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln
435 440 445

Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr
450 455 460

Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly
465 470 475 480

Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu
485 490 495

Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu
500 505 510

Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr
515 520 525

Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro
530 535 540

Ser Lys Leu Thr Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu
545 550 555 560

Thr Ala Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr
565 570 575

Gly His His His His His His His His
580 585

<210> 87
<211> 657
<212> PRT
<213> 人工序列

<220>
<223> pNL168

<400> 87

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

```
Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

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

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

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

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

```
Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro
    290                 295                 300

Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr
305                 310                 315                 320

Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala
                325                 330                 335

Ser Ser Leu Thr Arg Ala Glu Thr Val Phe Pro Asp Val Asp Tyr Val
            340                 345                 350

Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr
        355                 360                 365

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
    370                 375                 380

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
385                 390                 395                 400

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
                405                 410                 415

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
            420                 425                 430

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
        435                 440                 445

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
    450                 455                 460
```

```
Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
465                 470                 475                 480

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
                485                 490                 495

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
            500                 505                 510

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
        515                 520                 525

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
    530                 535                 540

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
545                 550                 555                 560

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
                565                 570                 575

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
            580                 585                 590

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
        595                 600                 605

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
    610                 615                 620

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
625                 630                 635                 640
```

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
645 650 655

His

<210> 88
<211> 801
<212> PRT
<213> 人工序列

<220>
<223> pNL169

<400> 88

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

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

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

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

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

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

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

```
Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser
    290                 295                 300

Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
305                 310                 315                 320

Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
                325                 330                 335

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser
            340                 345                 350

Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
        355                 360                 365

Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
    370                 375                 380

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala
385                 390                 395                 400

Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
                405                 410                 415

Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
            420                 425                 430

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala
        435                 440                 445

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
    450                 455                 460
```

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala
465 470 475 480

Ser Ser Leu Thr Arg Ala Glu Thr Val Phe Pro Asp Val Asp Tyr Val
485 490 495

Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr
500 505 510

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
515 520 525

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
530 535 540

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
545 550 555 560

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
565 570 575

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
580 585 590

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
595 600 605

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
610 615 620

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
625 630 635 640

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
645 650 655

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
660 665 670

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
675 680 685

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
690 695 700

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
705 710 715 720

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
725 730 735

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
740 745 750

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
755 760 765

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
770 775 780

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
785 790 795 800

His

<210> 89
<211> 585
<212> PRT
<213> 人工序列

<220>
<223> pNL170

<400> 89

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

```
Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

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

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

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

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

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

Ser Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile
        275                 280                 285

Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg
    290                 295                 300
```

Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val
305 310 315 320

Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn
325 330 335

Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys
340 345 350

Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr
355 360 365

Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn
370 375 380

Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp
385 390 395 400

Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp
405 410 415

Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser
420 425 430

Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln
435 440 445

Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr
450 455 460

Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly
465 470 475 480

Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu
485 490 495

Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu
500 505 510

Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr
515 520 525

Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro
530 535 540

Ser Lys Leu Thr Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu
545 550 555 560

Thr Ala Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr
565 570 575

Gly His His His His His His His His
580 585

<210> 90
<211> 657
<212> PRT
<213> 人工序列

<220>
<223> pNL171

<400> 90

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

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

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

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

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

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

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

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

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro
305 310 315 320

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser
325 330 335

Glu Gly Ser Ala Pro Gly Ala Ser Ser Phe Pro Asp Val Asp Tyr Val
340 345 350

Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr
355 360 365

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
370 375 380

```
Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
385                 390                 395                 400

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
                405                 410                 415

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
            420                 425                 430

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
        435                 440                 445

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
    450                 455                 460

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
465                 470                 475                 480

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
                485                 490                 495

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
            500                 505                 510

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
        515                 520                 525

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
    530                 535                 540

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
545                 550                 555                 560
```

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
565 570 575

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
580 585 590

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
595 600 605

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
610 615 620

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
625 630 635 640

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
645 650 655

His

<210> 91
<211> 801
<212> PRT
<213> 人工序列

<220>
<223> pNL172

<400> 91

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

```
Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

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

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

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

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

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

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

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

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
305 310 315 320

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser
325 330 335

Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
340 345 350

Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr
355 360 365

```
Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala
    370                 375                 380

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
385                 390                 395                 400

Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser
                405                 410                 415

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
            420                 425                 430

Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
        435                 440                 445

Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
    450                 455                 460

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro
465                 470                 475                 480

Ser Glu Gly Ser Ala Pro Ala Ser Ser Phe Pro Asp Val Asp Tyr Val
                485                 490                 495

Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr
            500                 505                 510

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
        515                 520                 525

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
    530                 535                 540
```

```
Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
545                 550                 555                 560

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
                565                 570                 575

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
            580                 585                 590

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
        595                 600                 605

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
    610                 615                 620

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
625                 630                 635                 640

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
                645                 650                 655

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
            660                 665                 670

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
        675                 680                 685

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
    690                 695                 700

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
705                 710                 715                 720
```

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
725 730 735

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
740 745 750

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
755 760 765

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
770 775 780

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
785 790 795 800

His

<210> 92
<211> 585
<212> PRT
<213> 人工序列

<220>
<223> pNL173

<400> 92

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

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

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

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

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

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

Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg
    290                 295                 300

Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val
305                 310                 315                 320

Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn
                325                 330                 335

Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys
            340                 345                 350

Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr
        355                 360                 365

Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn
    370                 375                 380

Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp
385                 390                 395                 400
```

Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp
405 410 415

Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser
420 425 430

Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln
435 440 445

Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr
450 455 460

Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly
465 470 475 480

Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu
485 490 495

Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu
500 505 510

Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr
515 520 525

Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro
530 535 540

Ser Lys Leu Thr Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu
545 550 555 560

Thr Ala Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr
565 570 575

Gly His His His His His His His His
580 585

<210> 93
<211> 657
<212> PRT
<213> 人工序列

<220>
<223> pNL174

<400> 93

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

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

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

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

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

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

```
Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
    290                 295                 300

Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr
305                 310                 315                 320

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser
                325                 330                 335

Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
            340                 345                 350

Ala Pro Gly Ala Ser Ser Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr
        355                 360                 365

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
    370                 375                 380

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
385                 390                 395                 400

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
                405                 410                 415

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
            420                 425                 430

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
        435                 440                 445

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
    450                 455                 460
```

```
Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
465                 470                 475                 480

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
                485                 490                 495

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
            500                 505                 510

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
        515                 520                 525

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
    530                 535                 540

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
545                 550                 555                 560

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
                565                 570                 575

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
            580                 585                 590

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
        595                 600                 605

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
    610                 615                 620

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
625                 630                 635                 640
```

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
645 650 655

His

<210> 94
<211> 801
<212> PRT
<213> 人工序列

<220>
<223> pNL175

<400> 94

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

```
Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

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

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

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

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

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

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

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
305 310 315 320

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly
325 330 335

Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser
340 345 350

Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
355 360 365

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser
370 375 380

Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
385 390 395 400

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
405 410 415

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly
420 425 430

Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly
435 440 445

Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
450 455 460

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser
465 470 475 480

Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly
485 490 495

Ser Ala Pro Ala Ser Ser Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr
500 505 510

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
515 520 525

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
530 535 540

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
545 550 555 560

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
565 570 575

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
580 585 590

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
595 600 605

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
610 615 620

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
625 630 635 640

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
645 650 655

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
660 665 670

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
675 680 685

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
690 695 700

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
705 710 715 720

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
725 730 735

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
740 745 750

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
755 760 765

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
770 775 780

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
785 790 795 800

His

<210> 95
<211> 585
<212> PRT
<213> 人工序列

<220>
<223> pNL176

<400> 95

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

```
Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
    210                 215                 220

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

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

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

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

Ser Ser Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg
    290                 295                 300
```

Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val
305 310 315 320

Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn
325 330 335

Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys
340 345 350

Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr
355 360 365

Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn
370 375 380

Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp
385 390 395 400

Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp
405 410 415

Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser
420 425 430

Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln
435 440 445

Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr
450 455 460

Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly
465 470 475 480

```
Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu
                485                 490                 495

Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu
            500                 505                 510

Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr
        515                 520                 525

Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro
    530                 535                 540

Ser Lys Leu Thr Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu
545                 550                 555                 560

Thr Ala Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr
                565                 570                 575

Gly His His His His His His His His
            580                 585
```

<210> 96
<211> 657
<212> PRT
<213> 人工序列

<220>
<223> pNL177

<400> 96

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1               5                   10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30
```

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
210 215 220

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

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

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

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

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

Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
305 310 315 320

Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
325 330 335

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
340 345 350

Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser Asn Ile Thr Gln Ser Thr
355 360 365

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
370 375 380

```
Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
385                 390                 395                 400

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
                405                 410                 415

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
            420                 425                 430

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
        435                 440                 445

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
    450                 455                 460

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
465                 470                 475                 480

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
                485                 490                 495

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
            500                 505                 510

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
        515                 520                 525

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
    530                 535                 540

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
545                 550                 555                 560
```

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
565 570 575

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
580 585 590

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
595 600 605

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
610 615 620

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
625 630 635 640

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
645 650 655

His

<210> 97
<211> 801
<212> PRT
<213> 人工序列

<220>
<223> pNL178

<400> 97

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

```
Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
    210                 215                 220

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

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

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

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

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

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
305                 310                 315                 320

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
                325                 330                 335

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly
            340                 345                 350

Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly
        355                 360                 365
```

Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
370 375 380

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser
385 390 395 400

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
405 410 415

Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
420 425 430

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu
435 440 445

Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly
450 455 460

Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
465 470 475 480

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu
485 490 495

Pro Ser Glu Gly Ser Ala Pro Ala Ser Ser Asn Ile Thr Gln Ser Thr
500 505 510

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
515 520 525

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
530 535 540

```
Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
545                 550                 555                 560

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
                565                 570                 575

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
            580                 585                 590

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
        595                 600                 605

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
    610                 615                 620

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
625                 630                 635                 640

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
                645                 650                 655

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
            660                 665                 670

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
        675                 680                 685

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
    690                 695                 700

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
705                 710                 715                 720
```

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
725 730 735

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
740 745 750

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
755 760 765

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
770 775 780

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
785 790 795 800

His

<210> 98
<211> 585
<212> PRT
<213> 人工序列

<220>
<223> pNL179

<400> 98

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Gly Ala Pro Ser
210 215 220

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

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

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

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

Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser Phe Asn Asp Phe Thr Arg
290 295 300

Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val
305 310 315 320

Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn
325 330 335

Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys
340 345 350

Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr
355 360 365

Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn
370 375 380

Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp
385 390 395 400

Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp
405 410 415

Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser
420 425 430

Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln
435 440 445

Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr
450 455 460

Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly
465 470 475 480

Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu
485 490 495

Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu
500 505 510

Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr
515 520 525

Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro
530 535 540

Ser Lys Leu Thr Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu
545 550 555 560

Thr Ala Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr
565 570 575

Gly His His His His His His His His
580 585

<210> 99
<211> 657
<212> PRT
<213> 人工序列

<220>
<223> pNL180

<400> 99

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

```
Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Gly Ala Pro Ser
    210                 215                 220

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

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

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

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

```
Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
    290                 295                 300

Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr
305                 310                 315                 320

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro
                325                 330                 335

Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr
            340                 345                 350

Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala
        355                 360                 365

Ser Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
    370                 375                 380

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
385                 390                 395                 400

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
                405                 410                 415

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
            420                 425                 430

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
        435                 440                 445

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
    450                 455                 460
```

```
Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
465                 470                 475                 480

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
                485                 490                 495

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
            500                 505                 510

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
        515                 520                 525

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
    530                 535                 540

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
545                 550                 555                 560

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
                565                 570                 575

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
            580                 585                 590

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
        595                 600                 605

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
    610                 615                 620

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
625                 630                 635                 640
```

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
645 650 655

His

<210> 100
<211> 801
<212> PRT
<213> 人工序列

<220>
<223> pNL181

<400> 100

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

```
Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Gly Ala Pro Gly
    210                 215                 220

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

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

Ser Gly 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 Gly Ser Pro Ala Gly Ser Pro Thr Ser
290 295 300

Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
305 310 315 320

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser
325 330 335

Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
340 345 350

Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
355 360 365

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser
370 375 380

Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
385 390 395 400

Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
405 410 415

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala
420 425 430

Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
435 440 445

Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
450 455 460

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala
465 470 475 480

Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
485 490 495

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala
500 505 510

Ser Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
515 520 525

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
530 535 540

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
545 550 555 560

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
565 570 575

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
580 585 590

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
595 600 605

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
610 615 620

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
625 630 635 640

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
645 650 655

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
660 665 670

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
675 680 685

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
690 695 700

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
705 710 715 720

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
725 730 735

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
740 745 750

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
755 760 765

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
770 775 780

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
785 790 795 800

His

<210> 101
<211> 585
<212> PRT
<213> 人工序列

<220>
<223> pNL182

<400> 101

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Gly Ala
260 265 270

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

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

```
Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
305                 310                 315                 320

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
                325                 330                 335

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser Thr Gly Val Lys
            340                 345                 350

Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr
        355                 360                 365

Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn
    370                 375                 380

Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp
385                 390                 395                 400

Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp
                405                 410                 415

Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser
            420                 425                 430

Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln
        435                 440                 445

Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr
    450                 455                 460

Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly
465                 470                 475                 480
```

Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu
485 490 495

Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu
500 505 510

Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr
515 520 525

Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro
530 535 540

Ser Lys Leu Thr Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu
545 550 555 560

Thr Ala Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr
565 570 575

Gly His His His His His His His His
580 585

<210> 102
<211> 657
<212> PRT
<213> 人工序列

<220>
<223> pNL183

<400> 102

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

```
Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205
```

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Gly Ala
260 265 270

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

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

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
305 310 315 320

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
325 330 335

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu
340 345 350

Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
355 360 365

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
370 375 380

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
385 390 395 400

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
405 410 415

Gly Ala Ser Ser Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
420 425 430

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
435 440 445

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
450 455 460

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
465 470 475 480

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
485 490 495

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
500 505 510

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
515 520 525

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
530 535 540

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
545 550 555 560

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
565 570 575

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
580 585 590

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
595 600 605

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
610 615 620

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
625 630 635 640

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
645 650 655

His

<210> 103
<211> 801
<212> PRT
<213> 人工序列

<220>
<223> pNL184

<400> 103

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

```
Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Gly Ala
            260                 265                 270

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

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

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
305                 310                 315                 320

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
                325                 330                 335

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro
            340                 345                 350

Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
        355                 360                 365
```

```
Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
    370                 375                 380

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro
385                 390                 395                 400

Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu
                405                 410                 415

Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser
            420                 425                 430

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr
        435                 440                 445

Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
    450                 455                 460

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu
465                 470                 475                 480

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro
            485                 490                 495

Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
            500                 505                 510

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu
        515                 520                 525

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr
    530                 535                 540
```

```
Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
545                 550                 555                 560

Pro Ala Ser Ser Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
                565                 570                 575

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
            580                 585                 590

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
        595                 600                 605

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
    610                 615                 620

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
625                 630                 635                 640

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
                645                 650                 655

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
            660                 665                 670

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
        675                 680                 685

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
    690                 695                 700

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
705                 710                 715                 720
```

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
725 730 735

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
740 745 750

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
755 760 765

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
770 775 780

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
785 790 795 800

His

<210> 104
<211> 585
<212> PRT
<213> 人工序列

<220>
<223> pNL185

<400> 104

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
290 295 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
340 345 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
355 360 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
370 375 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385 390 395 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
405 410 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
420 425 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
435 440 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Gly Ala Pro Ser Pro
450 455 460

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr
465 470 475 480

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
485 490 495

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
500 505 510

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser
515 520 525

Glu Gly Ser Ala Pro Gly Ala Ser Ser Leu Thr Gly Pro Glu Gly Pro
530 535 540

Ser Lys Leu Thr Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu
545 550 555 560

Thr Ala Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr
565 570 575

Gly His His His His His His His His
580 585

<210> 105
<211> 657
<212> PRT
<213> 人工序列

<220>
<223> pNL186

<400> 105

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

```
Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285
```

```
His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
                325                 330                 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
            340                 345                 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
    370                 375                 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385                 390                 395                 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
                405                 410                 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
            420                 425                 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
        435                 440                 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Gly Ala Pro Ser Pro
    450                 455                 460
```

```
Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr
465                 470                 475                 480

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
                485                 490                 495

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
            500                 505                 510

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser
        515                 520                 525

Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
    530                 535                 540

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser
545                 550                 555                 560

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser
                565                 570                 575

Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu
            580                 585                 590

Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser
        595                 600                 605

Ser Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
    610                 615                 620

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
625                 630                 635                 640
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Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
645 650 655

His

<210> 106
<211> 801
<212> PRT
<213> 人工序列

<220>
<223> pNL187

<400> 106

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

```
His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
                325                 330                 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
            340                 345                 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
    370                 375                 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385                 390                 395                 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
                405                 410                 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
            420                 425                 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
        435                 440                 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Gly Ala Pro Gly Thr
    450                 455                 460
```

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr
465 470 475 480

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
485 490 495

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
500 505 510

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro
515 520 525

Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr
530 535 540

Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
545 550 555 560

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala
565 570 575

Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr
580 585 590

Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr
595 600 605

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala
610 615 620

Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
625 630 635 640

Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
645 650 655

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr
660 665 670

Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr
675 680 685

Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr
690 695 700

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr
705 710 715 720

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
725 730 735

Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala Ser
740 745 750

Ser Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
755 760 765

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
770 775 780

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
785 790 795 800

His

<210> 107
<211> 585
<212> PRT
<213> 人工序列

<220>
<223> pNL188

<400> 107

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser
145 150 155 160

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

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

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

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

Ala Ser Ser Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg
225 230 235 240

Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys
245 250 255

Gly Arg Val Ser Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr
260 265 270

Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile
275 280 285

Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg
290 295 300

```
Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val
305                 310                 315                 320

Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn
                325                 330                 335

Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys
            340                 345                 350

Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr
        355                 360                 365

Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn
    370                 375                 380

Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp
385                 390                 395                 400

Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp
                405                 410                 415

Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser
            420                 425                 430

Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln
        435                 440                 445

Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr
    450                 455                 460

Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly
465                 470                 475                 480
```

Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu
485 490 495

Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu
500 505 510

Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr
515 520 525

Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro
530 535 540

Ser Lys Leu Thr Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu
545 550 555 560

Thr Ala Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr
565 570 575

Gly His His His His His His His His
580 585

<210> 108
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<223> pNL189

<400> 108

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser
145 150 155 160

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

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

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

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

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

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

Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser Asp Asn Lys Val Val
    290                 295                 300

Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys
305                 310                 315                 320

Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser Val Ser Gln Thr
                325                 330                 335

Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp Val Asp Tyr Val
            340                 345                 350

Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr
        355                 360                 365

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
    370                 375                 380
```

```
Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
385                 390                 395                 400

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
                405                 410                 415

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
            420                 425                 430

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
        435                 440                 445

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
    450                 455                 460

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
465                 470                 475                 480

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
                485                 490                 495

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
            500                 505                 510

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
        515                 520                 525

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
    530                 535                 540

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
545                 550                 555                 560
```

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
565 570 575

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
580 585 590

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
595 600 605

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
610 615 620

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
625 630 635 640

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
645 650 655

His

<210> 109
<211> 801
<212> PRT
<213> 人工序列

<220>
<223> pNL190

<400> 109

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Gly Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
145 150 155 160

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

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

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

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

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

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

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

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

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu
    290                 295                 300

Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
305                 310                 315                 320

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu
                325                 330                 335

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
            340                 345                 350

Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
        355                 360                 365
```

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr
370 375 380

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu
385 390 395 400

Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
405 410 415

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr
420 425 430

Glu Pro Ser Glu Gly Ser Ala Pro Ala Ser Ser Asp Asn Lys Val Val
435 440 445

Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys
450 455 460

Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser Val Ser Gln Thr
465 470 475 480

Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp Val Asp Tyr Val
485 490 495

Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr
500 505 510

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
515 520 525

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
530 535 540

```
Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
545                 550                 555                 560

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
                565                 570                 575

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
            580                 585                 590

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
        595                 600                 605

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
    610                 615                 620

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
625                 630                 635                 640

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
                645                 650                 655

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
            660                 665                 670

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
        675                 680                 685

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
    690                 695                 700

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
705                 710                 715                 720
```

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
725 730 735

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
740 745 750

Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr
755 760 765

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser
770 775 780

Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His His
785 790 795 800

His

<210> 110
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL195

<400> 110

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

```
Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

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

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

Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400
```

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 111
<211> 549

<212> PRT
<213> 人工序列

<220>
<223> pNL196

<400> 111

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

```
Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

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

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

Pro Ala Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser Ile Thr Val Val
305                 310                 315                 320
```

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

<210> 112
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL197

<400> 112

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

```
Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255
```

```
Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

Val Lys Ile Thr Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
        275                 280                 285

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

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430
```

```
Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
            500                 505                 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
        515                 520                 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
    530                 535                 540

His His His His His
545
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<210> 113
<211> 549
<212> PRT
<213> 人工序列

<220>
<223> pNL198

<400> 113

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1               5                  10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Gly Ala Pro Gly Ser Pro Ala Gly Ser
145                 150                 155                 160

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

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

Ser Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
        195                 200                 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
    210                 215                 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350
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Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
            500                 505                 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
        515                 520                 525
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Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

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His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Gly Ala Pro Gly Ser Pro Ala
                325                 330                 335

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro
            340                 345                 350

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
        355                 360                 365

Ala Ser Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460
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Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu Gly Pro Ser Lys Leu Thr
500 505 510

Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Glu Gln
515 520 525

Lys Leu Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His
530 535 540

His His His His His
545

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
290 295 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
340 345 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
355 360 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
370 375 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385 390 395 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
405 410 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
420 425 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
435 440 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly
450 455 460

Ser Pro Gly Ala Glu Thr Ala Leu Val Pro Arg Ser Phe Leu Leu Arg
465 470 475 480

Asn Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly
485 490 495

Ala Gly Ser Pro Gly Ala Glu Thr Ala Gly Ala Pro Ser Pro Ala Gly
500 505 510

Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu
515 520 525

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
530 535 540

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu
545 550 555 560

Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly
565 570 575

Ser Ala Pro Gly Ala Ser Ser Gly Ala Glu Thr Ala Glu Gln Lys Leu
580 585 590

Ile Ser Glu Glu Asp Leu Ser Pro Ala Thr Gly His His His His His
595 600 605

His His His
610

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
290 295 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
340 345 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
355 360 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Arg
370 375 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385 390 395 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
405 410 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
420 425 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
435 440 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu
450 455 460

Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr Gly Ser Pro Gly Ser Pro
465 470 475 480

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr
485 490 495

Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
500 505 510

Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser
515 520 525

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser
530 535 540

Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
545 550 555 560

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu
565 570 575

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro
580 585 590

Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
595 600 605

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser
610 615 620

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro
625 630 635 640

Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
645 650 655

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser
660 665 670

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser
675 680 685

Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
690 695 700

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
705 710 715 720

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser
725 730 735

Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
740 745 750

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro
755 760 765

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr
770 775 780

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
785 790 795 800

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
805 810 815

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser
820 825 830

Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
835 840 845

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser
850 855 860

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser
865 870 875 880

Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu
885 890 895

Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser
900 905 910

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
915 920 925

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
930 935 940

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
945 950 955 960

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser
965 970 975

Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
980 985 990

Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro
995 1000 1005

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser
1010 1015 1020

Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu
1025 1030 1035

Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
1040 1045 1050

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu
1055 1060 1065

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala
1070 1075 1080

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
1085 1090 1095

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
1100 1105 1110

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro
1115 1120 1125

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala
1130 1135 1140

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
1145 1150 1155

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
1160 1165 1170

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro
1175 1180 1185

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
1190 1195 1200

Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
1205 1210 1215

Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
1220 1225 1230

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu
1235 1240 1245

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr
1250 1255 1260

Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
1265 1270 1275

Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
1280 1285 1290

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu
1295 1300 1305

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala
1310 1315 1320

Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly
1325 1330 1335

Ser Ala Pro Gly Ser Ser Ser
1340 1345

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Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

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Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240
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Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
290 295 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
340 345 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
355 360 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
370 375 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385 390 395 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
405 410 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
420 425 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
435 440 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly
450 455 460

Ser Pro Gly Ala Glu Thr Ala Leu Val Pro Arg Ser Phe Leu Leu Arg
465 470 475 480

Asn Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly
485 490 495

Ala Gly Ser Pro Gly Ala Glu Thr Ala Gly Ala Pro Ser Pro Ala Gly
500 505 510

Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu
515 520 525

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly
530 535 540

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu
545 550 555 560

Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly
565 570 575

Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly
580 585 590

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu
595 600 605

Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly
610 615 620

Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
625 630 635 640

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser
645 650 655

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<400> 118

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Gly Ala Pro Gly Ser Pro Ala Gly Ser
145 150 155 160

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

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

Ser Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
195 200 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
210 215 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225 230 235 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
245 250 255

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Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430
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Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr
500

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<400> 119

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
210 215 220

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

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

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

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

Ser Ser Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg
290 295 300

Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val
305 310 315 320

Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn
325 330 335

Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys
340 345 350

Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr
355 360 365

Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn
370 375 380

Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp
385 390 395 400

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Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp
                405                 410                 415

Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser
            420                 425                 430

Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln
        435                 440                 445

Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr
    450                 455                 460

Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly
465                 470                 475                 480

Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu
                485                 490                 495

Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu
            500                 505                 510

Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr
        515                 520                 525

Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr
    530                 535
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<213> 人工序列

<220>
<223> pJH47

<400> 120

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
210 215 220

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

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

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

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

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

Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
305 310 315 320

Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
325 330 335

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
340 345 350

Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser Asn Ile Thr Gln Ser Thr
355 360 365

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
370 375 380

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
385 390 395 400

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
405 410 415

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
420 425 430

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
435 440 445

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
450 455 460

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
465 470 475 480

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
485 490 495

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
500 505 510

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
515 520 525

```
Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
    530                 535                 540

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
545                 550                 555                 560

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
                565                 570                 575

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
            580                 585                 590

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
        595                 600                 605

Lys Leu Thr
    610
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<210> 121
<211> 655
<212> PRT
<213> 人工序列

<220>
<223> pJH50

<400> 121

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1               5                   10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30
```

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
260 265 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
290 295 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
340 345 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
355 360 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
370 375 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385 390 395 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
405 410 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
420 425 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
435 440 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly
450 455 460

Ser Pro Gly Ala Glu Thr Ala Leu Val Pro Arg Ser Phe Leu Leu Arg
465 470 475 480

Asn Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly
485 490 495

Ala Gly Ser Pro Gly Ala Glu Thr Ala Gly Ala Pro Thr Ser Thr Glu
500 505 510

Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu
515 520 525

Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
530 535 540

Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala
545 550 555 560

Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
565 570 575

Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly
580 585 590

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu
595 600 605

Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
610 615 620

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
625 630 635 640

Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser
645 650 655

<210> 122
<211> 799
<212> PRT
<213> 人工序列

<220>
<223> pJH51

<400> 122

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

```
Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
                325                 330                 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
            340                 345                 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
    370                 375                 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385                 390                 395                 400
```

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
405 410 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
420 425 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
435 440 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly
450 455 460

Ser Pro Gly Ala Glu Thr Ala Leu Val Pro Arg Ser Phe Leu Leu Arg
465 470 475 480

Asn Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly
485 490 495

Ala Gly Ser Pro Gly Ala Glu Thr Ala Gly Ala Pro Gly Thr Ser Glu
500 505 510

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
515 520 525

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
530 535 540

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu
545 550 555 560

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu
565 570 575

Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
580 585 590

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
595 600 605

Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro
610 615 620

Glu Ser Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
625 630 635 640

Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr
645 650 655

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro
660 665 670

Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
675 680 685

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro
690 695 700

Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly
705 710 715 720

Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu
725 730 735

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
740 745 750

Glu Pro Ser Glu Gly Ser Ala 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 Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala Ser Ser
785 790 795

<210> 123
<211> 583
<212> PRT
<213> 人工序列

<220>
<223> pJH52

<400> 123

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

```
Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
                325                 330                 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
            340                 345                 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
    370                 375                 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385                 390                 395                 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
                405                 410                 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
            420                 425                 430
```

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
435 440 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly
450 455 460

Ser Pro Gly Ala Glu Thr Ala Leu Val Pro Arg Ser Phe Leu Leu Arg
465 470 475 480

Asn Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly
485 490 495

Ala Gly Ser Pro Gly Ala Glu Thr Ala Gly Ala Pro Thr Ser Glu Ser
500 505 510

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
515 520 525

Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
530 535 540

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser
545 550 555 560

Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly
565 570 575

Ser Ala Pro Gly Ala Ser Ser
580

<210> 124
<211> 503
<212> PRT
<213> 人工序列

<220>
<223> pJH54

<400> 124

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Gly Ala
260 265 270

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

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

Gly Ser Glu Thr Pro Ala Ser Ser Thr Gly Val Lys Ile Thr Val Val
305 310 315 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr
500

<210> 125
<211> 503
<212> PRT
<213> 人工序列

<220>
<223> pJH55

<400> 125

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

```
Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
    210                 215                 220

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

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

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300
```

```
Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480
```

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr
500

<210> 126
<211> 625
<212> PRT
<213> 人工序列

<220>
<223> pJH59

<400> 126

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
210 215 220

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

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

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
260 265 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
275 280 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
290 295 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305 310 315 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr
500 505 510

Ala Leu Val Pro Arg Ser Phe Leu Leu Arg Asn Pro Asn Asp Lys Tyr
515 520 525

Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly Ala Gly Ser Pro Gly Ala
530 535 540

Glu Thr Ala Gly Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
545 550 555 560

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
565 570 575

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
580 585 590

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
595 600 605

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser
610 615 620

Ser
625

<210> 127
<211> 697
<212> PRT
<213> 人工序列

<220>
<223> pJH60

<400> 127

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

```
Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
    210                 215                 220

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

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

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300
```

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305 310 315 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

```
Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr
            500                 505                 510

Ala Leu Val Pro Arg Ser Phe Leu Leu Arg Asn Pro Asn Asp Lys Tyr
        515                 520                 525

Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly Ala Gly Ser Pro Gly Ala
    530                 535                 540

Glu Thr Ala Gly Ala Pro Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
545                 550                 555                 560

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
                565                 570                 575

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr
            580                 585                 590

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
        595                 600                 605

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro
    610                 615                 620

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser
625                 630                 635                 640

Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
                645                 650                 655
```

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
660 665 670

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser
675 680 685

Glu Gly Ser Ala Pro Gly Ala Ser Ser
690 695

<210> 128
<211> 841
<212> PRT
<213> 人工序列

<220>
<223> pJH61

<400> 128

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

```
Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
    210                 215                 220

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

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

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270
```

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
275 280 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
290 295 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305 310 315 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

```
Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr
            500                 505                 510

Ala Leu Val Pro Arg Ser Phe Leu Leu Arg Asn Pro Asn Asp Lys Tyr
        515                 520                 525

Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly Ala Gly Ser Pro Gly Ala
    530                 535                 540

Glu Thr Ala Gly Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
545                 550                 555                 560

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
                565                 570                 575

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr
            580                 585                 590

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
        595                 600                 605

Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
    610                 615                 620
```

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala
625 630 635 640

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
645 650 655

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
660 665 670

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser
675 680 685

Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
690 695 700

Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr
705 710 715 720

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala
725 730 735

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
740 745 750

Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser
755 760 765

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
770 775 780

Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
785 790 795 800

```
Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
               805                 810                 815

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro
           820                 825                 830

Ser Glu Gly Ser Ala Pro Ala Ser Ser
       835                 840
```

<210> 129
<211> 661
<212> PRT
<213> 人工序列

<220>
<223> pJH62

<400> 129

```
Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1               5                  10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
           20                  25                  30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
       35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
   50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80
```

```
Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
    210                 215                 220

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

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

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

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

Ser Ser Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg
290 295 300

Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val
305 310 315 320

Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn
325 330 335

Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys
340 345 350

Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr
355 360 365

Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn
370 375 380

Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp
385 390 395 400

Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp
405 410 415

Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser
420 425 430

Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln
435 440 445

Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr
450 455 460

Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly
465 470 475 480

Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu
485 490 495

Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu
500 505 510

Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr
515 520 525

Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly Ser Pro
530 535 540

Gly Ala Glu Thr Ala Leu Val Pro Arg Ser Phe Leu Leu Arg Asn Pro
545 550 555 560

Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly Ala Gly
565 570 575

Ser Pro Gly Ala Glu Thr Ala Gly Ala Pro Thr Ser Glu Ser Ala Thr
580 585 590

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
595 600 605

```
Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu
    610                 615                 620

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr
625                 630                 635                 640

Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
                645                 650                 655

Pro Gly Ala Ser Ser
            660
```

<210> 130
<211> 733
<212> PRT
<213> 人工序列

<220>
<223> pJH63

<400> 130

```
Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1               5                   10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80
```

```
Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
    210                 215                 220

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

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

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

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

Ser Ser Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg
    290                 295                 300

Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val
305                 310                 315                 320

Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn
                325                 330                 335

Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys
            340                 345                 350

Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr
        355                 360                 365

Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn
    370                 375                 380

Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp
385                 390                 395                 400

Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp
                405                 410                 415

Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser
            420                 425                 430
```

Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln
435 440 445

Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr
450 455 460

Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly
465 470 475 480

Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu
485 490 495

Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu
500 505 510

Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr
515 520 525

Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly Ser Pro
530 535 540

Gly Ala Glu Thr Ala Leu Val Pro Arg Ser Phe Leu Leu Arg Asn Pro
545 550 555 560

Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly Ala Gly
565 570 575

Ser Pro Gly Ala Glu Thr Ala Gly Ala Pro Thr Ser Thr Glu Pro Ser
580 585 590

Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
595 600 605

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
610 615 620

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
625 630 635 640

Gly Ser Glu Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
645 650 655

Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser
660 665 670

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser
675 680 685

Glu Gly Ser Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
690 695 700

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
705 710 715 720

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser
725 730

<210> 131
<211> 877
<212> PRT
<213> 人工序列

<220>
<223> pJH64

<400> 131

```
Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1               5                  10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175
```

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
    210                 215                 220

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

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

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

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

Ser Ser Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg
    290                 295                 300

Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val
305                 310                 315                 320

Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn
                325                 330                 335

Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys
            340                 345                 350
```

Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr
355 360 365

Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn
370 375 380

Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp
385 390 395 400

Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp
405 410 415

Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser
420 425 430

Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln
435 440 445

Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr
450 455 460

Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly
465 470 475 480

Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu
485 490 495

Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu
500 505 510

Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr
515 520 525

```
Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly Ser Pro
    530                 535                 540

Gly Ala Glu Thr Ala Leu Val Pro Arg Ser Phe Leu Leu Arg Asn Pro
545                 550                 555                 560

Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly Ala Gly
                565                 570                 575

Ser Pro Gly Ala Glu Thr Ala Gly Ala Pro Gly Thr Ser Glu Ser Ala
            580                 585                 590

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
        595                 600                 605

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
    610                 615                 620

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala
625                 630                 635                 640

Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
                645                 650                 655

Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr
            660                 665                 670

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr
        675                 680                 685

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
    690                 695                 700
```

Gly Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser
705 710 715 720

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
725 730 735

Ser Glu Gly Ser Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
740 745 750

Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly 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 Ser Glu Pro Ala Thr Ser Gly Ser Glu
785 790 795 800

Thr Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr
805 810 815

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro
820 825 830

Ser Glu Gly Ser Ala 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 Thr
850 855 860

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Ala Ser Ser
865 870 875

<210> 132
<211> 733
<212> PRT
<213> 人工序列

<220>
<223> pJH65

<400> 132

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

```
Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
    210                 215                 220

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

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

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

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

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

Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
305                 310                 315                 320
```

Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
325 330 335

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
340 345 350

Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser Asn Ile Thr Gln Ser Thr
355 360 365

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
370 375 380

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
385 390 395 400

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
405 410 415

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
420 425 430

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
435 440 445

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
450 455 460

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
465 470 475 480

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
485 490 495

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
500 505 510

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
515 520 525

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
530 535 540

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
545 550 555 560

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
565 570 575

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
580 585 590

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
595 600 605

Lys Leu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Leu Val Pro
610 615 620

Arg Ser Phe Leu Leu Arg Asn Pro Asn Asp Lys Tyr Glu Pro Phe Trp
625 630 635 640

Glu Asp Glu Glu Ser Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Gly
645 650 655

Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu
660 665 670

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr
675 680 685

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
690 695 700

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
705 710 715 720

Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser
725 730

<210> 133
<211> 805
<212> PRT
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<220>
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<400> 133

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
210 215 220

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

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

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

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

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

Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
305                 310                 315                 320

Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
                325                 330                 335

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
            340                 345                 350

Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser Asn Ile Thr Gln Ser Thr
        355                 360                 365

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
    370                 375                 380

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
385                 390                 395                 400

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
                405                 410                 415
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His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
420 425 430

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
435 440 445

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
450 455 460

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
465 470 475 480

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
485 490 495

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
500 505 510

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
515 520 525

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
530 535 540

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
545 550 555 560

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
565 570 575

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
580 585 590

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
595 600 605

Lys Leu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Leu Val Pro
610 615 620

Arg Ser Phe Leu Leu Arg Asn Pro Asn Asp Lys Tyr Glu Pro Phe Trp
625 630 635 640

Glu Asp Glu Glu Ser Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Gly
645 650 655

Ala Pro Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser
660 665 670

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr
675 680 685

Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
690 695 700

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Glu
705 710 715 720

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala Gly Ser Pro
725 730 735

Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
740 745 750

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Glu
755 760 765

Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr
770 775 780

Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
785 790 795 800

Pro Gly Ala Ser Ser
805

<210> 134
<211> 949
<212> PRT
<213> 人工序列

<220>
<223> pJH67

<400> 134

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

```
Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
    210                 215                 220

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

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

Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
            260                 265                 270
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Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr
        275                 280                 285

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

Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
305                 310                 315                 320

Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
                325                 330                 335

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
            340                 345                 350

Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser Asn Ile Thr Gln Ser Thr
        355                 360                 365

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
    370                 375                 380

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
385                 390                 395                 400

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
                405                 410                 415

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
            420                 425                 430

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
        435                 440                 445
```

```
Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
    450                 455                 460

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
465                 470                 475                 480

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
                485                 490                 495

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
            500                 505                 510

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
        515                 520                 525

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
    530                 535                 540

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
545                 550                 555                 560

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
                565                 570                 575

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
            580                 585                 590

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
        595                 600                 605

Lys Leu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Leu Val Pro
    610                 615                 620
```

Arg Ser Phe Leu Leu Arg Asn Pro Asn Asp Lys Tyr Glu Pro Phe Trp
625 630 635 640

Glu Asp Glu Glu Ser Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Gly
645 650 655

Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
660 665 670

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala
675 680 685

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
690 695 700

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr
705 710 715 720

Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser
725 730 735

Pro Thr Ser Thr Glu Glu 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 Pro Ala Gly Ser
770 775 780

Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr Ser Thr
785 790 795 800

Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr
805 810 815

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala
820 825 830

Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
835 840 845

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser
850 855 860

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro 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 Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
900 905 910

Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala
915 920 925

Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
930 935 940

Ala Pro Ala Ser Ser
945

<210> 135
<211> 545

<212> PRT
<213> 人工序列

<220>
<223> pJH68

<400> 135

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Gly Ala Pro Gly Ser Pro Ala Gly Ser
145 150 155 160

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

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

Ser Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
195 200 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
210 215 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225 230 235 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Gly Ala
245 250 255

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

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

Gly Ser Glu Thr Pro Ala Ser Ser Asn Ile Thr Gln Ser Thr Gln Ser
290 295 300

Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly
305 310 315 320

Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys
325 330 335

Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys
340 345 350

Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile
355 360 365

Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile
370 375 380

Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile
385 390 395 400

Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr
405 410 415

Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe
420 425 430

Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg
435 440 445

Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala
450 455 460

Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys
465 470 475 480

Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly
485 490 495

Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile
500 505 510

Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr
515 520 525

Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu
530 535 540

Thr
545

<210> 136
<211> 581
<212> PRT
<213> 人工序列

<220>
<223> pJH69

<400> 136

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

```
Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Gly Ala Pro Gly Ser Pro Ala Gly Ser
145                 150                 155                 160

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

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

Ser Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
        195                 200                 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
    210                 215                 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Gly Ala
                245                 250                 255
```

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

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

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

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
305 310 315 320

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser Asn Ile Thr Gln
325 330 335

Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp
340 345 350

Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val
355 360 365

Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr
370 375 380

Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly
385 390 395 400

Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val
405 410 415

Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr
420 425 430

Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn
435 440 445

Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile
450 455 460

Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe
465 470 475 480

His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu
485 490 495

Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn
500 505 510

Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln
515 520 525

Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe
530 535 540

Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys
545 550 555 560

Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu
565 570 575

Lys Thr Lys Leu Thr
580

<210> 137
<211> 653

<212> PRT
<213> 人工序列

<220>
<223> pJH70

<400> 137

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Gly Ala Pro Gly Ser Pro Ala Gly Ser
145 150 155 160

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

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

Ser Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
195 200 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
210 215 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225 230 235 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Gly Ala
245 250 255

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

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

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

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
305 310 315 320

Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu
325 330 335

Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
340 345 350

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr
355 360 365

Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr
370 375 380

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
385 390 395 400

Gly Ala Ser Ser Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
405 410 415

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
420 425 430

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
435 440 445

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
450 455 460

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
465 470 475 480

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
485 490 495

```
Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
            500                 505                 510

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
        515                 520                 525

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

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
545                 550                 555                 560

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
                565                 570                 575

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
            580                 585                 590

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
        595                 600                 605

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
    610                 615                 620

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
625                 630                 635                 640

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr
                645                 650
```

<210> 138
<211> 625
<212> PRT
<213> 人工序列

<220>
<223> pJH71

<400> 138

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Gly Ala Pro Gly Ser Pro Ala Gly Ser
145 150 155 160

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

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

Ser Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
        195                 200                 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
    210                 215                 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335
```

```
Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr
            500                 505                 510
```

Ala Leu Val Pro Arg Ser Phe Leu Leu Arg Asn Pro Asn Asp Lys Tyr
515 520 525

Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly Ala Gly Ser Pro Gly Ala
530 535 540

Glu Thr Ala Gly Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
545 550 555 560

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
565 570 575

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
580 585 590

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
595 600 605

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser
610 615 620

Ser
625

<210> 139
<211> 697
<212> PRT
<213> 人工序列

<220>
<223> pJH72

<400> 139

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1               5                  10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Gly Ala Pro Gly Ser Pro Ala Gly Ser
145                 150                 155                 160

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

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

Ser Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
        195                 200                 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
    210                 215                 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350
```

```
Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr
            500                 505                 510

Ala Leu Val Pro Arg Ser Phe Leu Leu Arg Asn Pro Asn Asp Lys Tyr
        515                 520                 525
```

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Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly Ala Gly Ser Pro Gly Ala
    530                 535                 540

Glu Thr Ala Gly Ala Pro Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
545                 550                 555                 560

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
                565                 570                 575

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr
            580                 585                 590

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
        595                 600                 605

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro
    610                 615                 620

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser
625                 630                 635                 640

Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
                645                 650                 655

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
            660                 665                 670

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser
        675                 680                 685

Glu Gly Ser Ala Pro Gly Ala Ser Ser
    690                 695
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<210> 140
<211> 841
<212> PRT
<213> 人工序列

<220>
<223> pJH73

<400> 140

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Gly Ala Pro Gly Ser Pro Ala Gly Ser
145 150 155 160

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

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

Ser Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
195 200 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
210 215 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225 230 235 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
245 250 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
260 265 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
275 280 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
290 295 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305 310 315 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr
500 505 510

Ala Leu Val Pro Arg Ser Phe Leu Leu Arg Asn Pro Asn Asp Lys Tyr
515 520 525

Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly Ala Gly Ser Pro Gly Ala
530 535 540

Glu Thr Ala Gly Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
545 550 555 560

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
565 570 575

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr
580 585 590

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
595 600 605

Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
610 615 620

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala
625 630 635 640

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
645 650 655

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
660 665 670

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser
675 680 685

Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
690 695 700

Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr
705 710 715 720

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala
725 730 735

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
740 745 750

Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser
755 760 765

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
770 775 780

Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
785 790 795 800

Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
805 810 815

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro
820 825 830

Ser Glu Gly Ser Ala Pro Ala Ser Ser
835 840

<210> 141
<211> 545
<212> PRT
<213> 人工序列

<220>
<223> pJH74

<400> 141

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

```
Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Gly Ala Pro Gly Ser Pro Ala Gly Ser
145                 150                 155                 160

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

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

Ser Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
        195                 200                 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
    210                 215                 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225                 230                 235                 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
                245                 250                 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
            260                 265                 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
        275                 280                 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
    290                 295                 300
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Val Thr Ala Ala His Cys Val Glu Gly Ala Pro Gly Ser Pro Ala Gly
305                 310                 315                 320

Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu
                325                 330                 335

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Ala
            340                 345                 350

Ser Ser Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile
        355                 360                 365

Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile
    370                 375                 380

Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile
385                 390                 395                 400

Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr
                405                 410                 415

Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe
            420                 425                 430

Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg
        435                 440                 445

Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala
    450                 455                 460

Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys
465                 470                 475                 480
```

Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly
485 490 495

Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile
500 505 510

Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr
515 520 525

Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu
530 535 540

Thr
545

<210> 142
<211> 545
<212> PRT
<213> 人工序列

<220>
<223> pJH75

<400> 142

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
210 215 220

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

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

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
260 265 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
275 280 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
290 295 300

Val Thr Ala Ala His Cys Val Glu Gly Ala Pro Gly Ser Pro Ala Gly
305 310 315 320

Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu
325 330 335

Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Ala
340 345 350

Ser Ser Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile
355 360 365

Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile
370 375 380

Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile
385 390 395 400

Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr
405 410 415

Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe
420 425 430

Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg
435 440 445

Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala
450 455 460

Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys
465 470 475 480

Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly
485 490 495

Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile
500 505 510

Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr
515 520 525

Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu
530 535 540

Thr
545

<210> 143
<211> 581
<212> PRT
<213> 人工序列

<220>

<223> pJH76

<400> 143

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1               5                  10                  15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160
```

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
210 215 220

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

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

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

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

Ser Ser Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg
290 295 300

Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val
305 310 315 320

Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn
325 330 335

```
Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Gly Ala Pro Gly
            340                 345                 350

Ser Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser
        355                 360                 365

Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser
    370                 375                 380

Glu Thr Pro Ala Ser Ser Thr Gly Val Lys Ile Thr Val Val Ala Gly
385                 390                 395                 400

Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val
                405                 410                 415

Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr
            420                 425                 430

Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn
        435                 440                 445

Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile
    450                 455                 460

Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe
465                 470                 475                 480

His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu
                485                 490                 495

Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn
            500                 505                 510
```

Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln
515 520 525

Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe
530 535 540

Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys
545 550 555 560

Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu
565 570 575

Lys Thr Lys Leu Thr
580

<210> 144
<211> 653
<212> PRT
<213> 人工序列

<220>
<223> pJH77

<400> 144

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
210 215 220

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

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

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

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

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

Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
305 310 315 320

Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
325 330 335

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
340 345 350

Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser Asn Ile Thr Gln Ser Thr
355 360 365

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
370 375 380

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
385 390 395 400

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
405 410 415

```
His Cys Val Glu Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
            420                 425                 430

Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly
        435                 440                 445

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Ala Ser Ser Thr Gly
    450                 455                 460

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
465                 470                 475                 480

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
                485                 490                 495

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
            500                 505                 510

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
        515                 520                 525

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

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
545                 550                 555                 560

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
                565                 570                 575

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
            580                 585                 590
```

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
595 600 605

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
610 615 620

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
625 630 635 640

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr
645 650

<210> 145
<211> 625
<212> PRT
<213> 人工序列

<220>
<223> pJH78

<400> 145

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

```
Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Gly Ala
            260                 265                 270

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

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

Gly Ser Glu Thr Pro Ala Ser Ser Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415
```

```
Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
            420                 425                 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
        435                 440                 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
    450                 455                 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465                 470                 475                 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
                485                 490                 495

Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr
            500                 505                 510

Ala Leu Val Pro Arg Ser Phe Leu Leu Arg Asn Pro Asn Asp Lys Tyr
        515                 520                 525

Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly Ala Gly Ser Pro Gly Ala
    530                 535                 540

Glu Thr Ala Gly Ala Pro Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
545                 550                 555                 560

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
                565                 570                 575

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser
            580                 585                 590
```

Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly
595 600 605

Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ala Ser
610 615 620

Ser
625

<210> 146
<211> 697
<212> PRT
<213> 人工序列

<220>
<223> pJH79

<400> 146

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225 230 235 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
245 250 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Gly Ala
260 265 270

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

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

Gly Ser Glu Thr Pro Ala Ser Ser Thr Gly Val Lys Ile Thr Val Val
305 310 315 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr
500 505 510

Ala Leu Val Pro Arg Ser Phe Leu Leu Arg Asn Pro Asn Asp Lys Tyr
515 520 525

Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly Ala Gly Ser Pro Gly Ala
530 535 540

Glu Thr Ala Gly Ala Pro Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
545 550 555 560

Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser
565 570 575

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr
580 585 590

Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr
595 600 605

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro
610 615 620

Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser
625 630 635 640

Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala
645 650 655

Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser
660 665 670

Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser
675 680 685

Glu Gly Ser Ala Pro Gly Ala Ser Ser
690 695

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Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
210 215 220

```
Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Gly Ala
            260                 265                 270

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

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

Gly Ser Glu Thr Pro Ala Ser Ser Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400
```

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Gly Ala Gly Ser Pro Gly Ala Glu Thr
500 505 510

Ala Leu Val Pro Arg Ser Phe Leu Leu Arg Asn Pro Asn Asp Lys Tyr
515 520 525

Glu Pro Phe Trp Glu Asp Glu Glu Ser Gly Ala Gly Ser Pro Gly Ala
530 535 540

Glu Thr Ala Gly Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
545 550 555 560

Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
565 570 575

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr
580 585 590

Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser
595 600 605

Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
610 615 620

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala
625 630 635 640

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
645 650 655

Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser
660 665 670

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser
675 680 685

Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
690 695 700

Ala Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr
705 710 715 720

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala
725 730 735

Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu
740 745 750

Thr Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser
755 760 765

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
770 775 780

Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
785 790 795 800

Ala Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr
805 810 815

Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro
820 825 830

Ser Glu Gly Ser Ala Pro Ala Ser Ser
835 840

<210> 148
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<400> 148

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Gly Ala Pro Gly Ser Pro Ala Gly Ser
145 150 155 160

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

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

Ser Lys Val Val Cys Ser Cys Thr Glu Gly Tyr Arg Leu Ala Glu Asn
195 200 205

Gln Lys Ser Cys Glu Pro Ala Val Pro Phe Pro Cys Gly Arg Val Ser
210 215 220

Val Ser Gln Thr Ser Lys Leu Thr Arg Ala Glu Thr Val Phe Pro Asp
225 230 235 240

Val Asp Tyr Val Asn Ser Thr Glu Ala Glu Thr Ile Leu Asp Asn Ile
245 250 255

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
260 265 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
275 280 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
290 295 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305 310 315 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Asp Lys Thr His Thr Cys Pro Pro Cys
500 505 510

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
515 520 525

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
530 535 540

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
545 550 555 560

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
565 570 575

```
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            580                 585                 590

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        595                 600                 605

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    610                 615                 620

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
625                 630                 635                 640

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                645                 650                 655

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            660                 665                 670

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        675                 680                 685

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    690                 695                 700

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
705                 710                 715                 720

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys
            740                 745                 750
```

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
755 760 765

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
770 775 780

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
785 790 795 800

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
805 810 815

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
820 825 830

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
835 840 845

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
850 855 860

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
865 870 875 880

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
885 890 895

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

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
915 920 925

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
930 935 940

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
945 950 955 960

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
965 970 975

Lys

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<400> 149

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

```
Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240
```

```
Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Gly Ala
            260                 265                 270

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

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

Gly Ser Glu Thr Pro Ala Ser Ser Thr Gly Val Lys Ile Thr Val Val
305                 310                 315                 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
                325                 330                 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
            340                 345                 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
        355                 360                 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
    370                 375                 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385                 390                 395                 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
                405                 410                 415
```

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Asp Lys Thr His Thr Cys Pro Pro Cys
500 505 510

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
515 520 525

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
530 535 540

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
545 550 555 560

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
565 570 575

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
580 585 590

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        595                 600                 605

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    610                 615                 620

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
625                 630                 635                 640

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                645                 650                 655

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            660                 665                 670

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        675                 680                 685

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    690                 695                 700

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
705                 710                 715                 720

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys
            740                 745                 750

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
        755                 760                 765
```

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
770 775 780

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
785 790 795 800

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
805 810 815

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
820 825 830

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
835 840 845

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
850 855 860

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
865 870 875 880

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
885 890 895

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

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
915 920 925

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
930 935 940

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
945 950 955 960

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
965 970 975

Lys

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<400> 150

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Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
130 135 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145 150 155 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
165 170 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
195 200 205

Thr Ile Leu Asp Gly Ala Pro Gly Ser Pro Ala Gly Ser Pro Thr Ser
210 215 220

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

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

Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly
260 265 270

Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly
275 280 285

Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile
290 295 300

Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val
305 310 315 320

Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg
325 330 335

Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn
340 345 350

Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val
355 360 365

Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr
370 375 380

Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg
385 390 395 400

Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val
405 410 415

Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile
420 425 430

Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser
435 440 445

Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr
450 455 460

Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys
465 470 475 480

Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile
485 490 495

Lys Glu Lys Thr Lys Leu Thr Asp Lys Thr His Thr Cys Pro Pro Cys
500 505 510

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
515 520 525

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
530 535 540

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
545 550 555 560

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
565 570 575

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
580 585 590

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
595 600 605

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
610 615 620

```
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
625                 630                 635                 640

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                645                 650                 655

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            660                 665                 670

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        675                 680                 685

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    690                 695                 700

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
705                 710                 715                 720

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys
            740                 745                 750

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
        755                 760                 765

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    770                 775                 780

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
785                 790                 795                 800
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Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
805 810 815

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
820 825 830

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
835 840 845

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
850 855 860

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
865 870 875 880

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
885 890 895

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

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
915 920 925

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
930 935 940

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
945 950 955 960

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
965 970 975

Lys

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<400> 151

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

```
Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
    210                 215                 220

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

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

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

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

```
Ser Ser Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg
    290                 295                 300

Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val
305                 310                 315                 320

Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn
                325                 330                 335

Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys
            340                 345                 350

Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr
        355                 360                 365

Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn
    370                 375                 380

Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp
385                 390                 395                 400

Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp
                405                 410                 415

Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser
            420                 425                 430

Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln
        435                 440                 445

Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr
    450                 455                 460
```

```
Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly
465                 470                 475                 480

Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu
                485                 490                 495

Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu
            500                 505                 510

Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr
        515                 520                 525

Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Asp Lys Thr His Thr
    530                 535                 540

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
545                 550                 555                 560

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                565                 570                 575

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            580                 585                 590

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        595                 600                 605

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    610                 615                 620

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
625                 630                 635                 640
```

```
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                645                 650                 655

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            660                 665                 670

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        675                 680                 685

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    690                 695                 700

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
705                 710                 715                 720

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                725                 730                 735

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            740                 745                 750

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly
        755                 760                 765

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    770                 775                 780

Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
785                 790                 795                 800

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                805                 810                 815
```

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
820 825 830

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
835 840 845

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
850 855 860

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
865 870 875 880

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
885 890 895

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
900 905 910

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
915 920 925

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
930 935 940

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
945 950 955 960

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
965 970 975

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
980 985 990

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
995 1000 1005

Leu Ser Pro Gly Lys
1010

<210> 152
<211> 1085
<212> PRT
<213> 人工序列

<220>
<223> pJH85

<400> 152

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

```
Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Ala Pro Ser Pro Ala Gly Ser Pro Thr Ser Thr
    210                 215                 220

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

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

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

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

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

Ser Glu Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser
305 310 315 320

Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser
325 330 335

Pro Ala Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro
340 345 350

Ser Glu Gly Ser Ala Pro Gly Ala Ser Ser Asn Ile Thr Gln Ser Thr
355 360 365

Gln Ser Phe Asn Asp Phe Thr Arg Val Val Gly Gly Glu Asp Ala Lys
370 375 380

Pro Gly Gln Phe Pro Trp Gln Val Val Leu Asn Gly Lys Val Asp Ala
385 390 395 400

Phe Cys Gly Gly Ser Ile Val Asn Glu Lys Trp Ile Val Thr Ala Ala
405 410 415

His Cys Val Glu Thr Gly Val Lys Ile Thr Val Val Ala Gly Glu His
420 425 430

Asn Ile Glu Glu Thr Glu His Thr Glu Gln Lys Arg Asn Val Ile Arg
435 440 445

Ile Ile Pro His His Asn Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His
450 455 460

Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr
465 470 475 480

Val Thr Pro Ile Cys Ile Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu
485 490 495

Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp Gly Arg Val Phe His Lys
500 505 510

Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu Arg Val Pro Leu Val Asp
515 520 525

Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met
530 535 540

Phe Cys Ala Gly Phe His Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp
545 550 555 560

Ser Gly Gly Pro His Val Thr Glu Val Glu Gly Thr Ser Phe Leu Thr
565 570 575

Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly
580 585 590

Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr
595 600 605

Lys Leu Thr Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
610 615 620

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
625 630 635 640

```
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
                645                 650                 655

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
            660                 665                 670

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
        675                 680                 685

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
    690                 695                 700

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
705                 710                 715                 720

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
                725                 730                 735

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
            740                 745                 750

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
        755                 760                 765

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
    770                 775                 780

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
785                 790                 795                 800

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
                805                 810                 815
```

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
820 825 830

Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
835 840 845

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys
850 855 860

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
865 870 875 880

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
885 890 895

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
900 905 910

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
915 920 925

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
930 935 940

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
945 950 955 960

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
965 970 975

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
980 985 990

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
995 1000 1005

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
1010 1015 1020

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
1025 1030 1035

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
1040 1045 1050

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
1055 1060 1065

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
1070 1075 1080

Gly Lys
1085

<210> 153
<211> 935
<212> PRT
<213> 人工序列

<220>
<223> pJH56

<400> 153

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

```
Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
            20                  25                  30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
        35                  40                  45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
    50                  55                  60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65                  70                  75                  80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
                85                  90                  95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

```
Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
        275                 280                 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
    290                 295                 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305                 310                 315                 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
                325                 330                 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
            340                 345                 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
        355                 360                 365
```

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
370 375 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385 390 395 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
405 410 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
420 425 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
435 440 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Asp Lys Thr
450 455 460

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
465 470 475 480

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
485 490 495

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
500 505 510

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
515 520 525

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
530 535 540

```
Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
545                 550                 555                 560

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                565                 570                 575

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            580                 585                 590

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
        595                 600                 605

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    610                 615                 620

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
625                 630                 635                 640

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

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            660                 665                 670

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        675                 680                 685

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    690                 695                 700

Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
705                 710                 715                 720
```

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
725 730 735

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
740 745 750

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
755 760 765

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
770 775 780

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
785 790 795 800

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
805 810 815

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
820 825 830

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
835 840 845

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
850 855 860

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
865 870 875 880

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
885 890 895

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
900 905 910

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
915 920 925

Leu Ser Leu Ser Pro Gly Lys
930 935

<210> 154
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> PAS肽

<400> 154

Ala Ser Pro Ala Ala Pro Ala Pro Ala Ser Pro Ala Ala Pro Ala Pro
1 5 10 15

Ser Ala Pro Ala
20

<210> 155
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> PAS肽

<400> 155

Ala Ala Pro Ala Ser Pro Ala Pro Ala Ala Pro Ser Ala Pro Ala Pro
1 5 10 15

Ala Ala Pro Ser
20

<210> 156
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> PAS肽

<400> 156

Ala Pro Ser Ser Pro Ser Pro Ser Ala Pro Ser Ser Pro Ser Pro Ala
1 5 10 15

Ser Pro Ser Ser
20

<210> 157
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> PAS肽

<400> 157

Ala Pro Ser Ser Pro Ser Pro Ser Ala Pro Ser Ser Pro Ser Pro Ala
1 5 10 15

Ser Pro Ser

<210> 158
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> PAS 肽

<400> 158

Ser Ser Pro Ser Ala Pro Ser Pro Ser Ser Pro Ala Ser Pro Ser Pro
1 5 10 15

Ser Ser Pro Ala
20

<210> 159
<211> 24
<212> PRT
<213> 人工序列

<220>
<223> PAS 肽

<400> 159

Ala Ala Ser Pro Ala Ala Pro Ser Ala Pro Pro Ala Ala Ala Ser Pro
1 5 10 15

Ala Ala Pro Ser Ala Pro Pro Ala
20

<210> 160
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> PAS 肽

<400> 160

Ala Ser Ala Ala Ala Pro Ala Ala Ala Ser Ala Ala Ala Ser Ala Pro
1 5 10 15

Ser Ala Ala Ala
20

<210> 161
<211> 4
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 161

Gly Gly Gly Ser
1

<210> 162
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 162

Gly Gly Gly Ser Gly Gly Gly Ser
1 5

<210> 163
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 白蛋白結合肽核心序列

<400> 163

Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp
1 5 10

<210> 164
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> CTP肽

<400> 164

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

Leu Pro Ser Pro Ser Arg Leu Pro Gly Pro Ser Asp Thr Pro Ile Leu
20 25 30

<210> 165
<211> 28
<212> PRT
<213> 人工序列

<220>
<223> CTP肽

<400> 165

Ser Ser Ser Ser Lys Ala Pro Pro Pro Ser Leu Pro Ser Pro Ser Arg
1 5 10 15

Leu Pro Gly Pro Ser Asp Thr Pro Ile Leu Pro Gln
20 25

<210> 166
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> FXIa 裂解位點

<400> 166

Thr Gln Ser Phe Asn Asp Phe Thr Arg
1 5

<210> 167
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> FXIa 裂解位點

<400> 167

Ser Val Ser Gln Thr Ser Lys Leu Thr Arg
1 5 10

<210> 168
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 凝血酶裂解位點

<400> 168

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

<210> 169
<211> 7
<212> PRT
<213> 人工序列

<220>

<223> 凝血酶裂解位點

<400> 169

Thr Thr Lys Ile Lys Pro Arg
1 5

<210> 170
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 凝血酶裂解位點

<400> 170

Leu Val Pro Arg Gly
1 5

<210> 171
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 凝血酶裂解位點

<400> 171

Ala Leu Arg Pro Arg
1 5

<210> 172
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 172

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10

<210> 173
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 173

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10 15

<210> 174
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 174

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Ser
20

<210> 175
<211> 24
<212> PRT
<213> 人工序列

<220>

<223> Gly-Ser 肽連接子

<400> 175

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Ser
20

<210> 176
<211> 28
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 176

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
20 25

<210> 177
<211> 32
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 177

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
20 25 30

<210> 178
<211> 36
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 178

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
20 25 30

Gly Gly Gly Ser
35

<210> 179
<211> 40
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 179

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
20 25 30

Gly Gly Gly Ser Gly Gly Gly Ser
35 40

<210> 180
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 180

Ser Gly Gly Gly Ser
1 5

<210> 181
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 181

Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5

<210> 182
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 182

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10

<210> 183
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 183

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
1 5 10 15

Ser

<210> 184
<211> 21
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 184

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
1 5 10 15

Ser Gly Gly Gly Ser
20

<210> 185
<211> 25
<212> PRT
<213> 人工序列

<220>

<223> Gly-Ser 肽連接子

<400> 185

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
1 5 10 15

Ser Gly Gly Gly Ser Gly Gly Gly Ser
20 25

<210> 186
<211> 29
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 186

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
1 5 10 15

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
20 25

<210> 187
<211> 33
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 187

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
1 5 10 15

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
20 25 30

Ser

<210> 188
<211> 37
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 188

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
1 5 10 15

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
20 25 30

Ser Gly Gly Gly Ser
35

<210> 189
<211> 41
<212> PRT
<213> 人工序列

<220>
<223> Gly-Ser 肽連接子

<400> 189

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
1 5 10 15

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
20 25 30

Ser Gly Gly Gly Ser Gly Gly Gly Ser
35 40

<210> 190
<211> 6
<212> PRT
<213> 人工序列

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<400> 190

Ser Phe Leu Leu Arg Asn
1 5

<210> 191
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<400> 191

Pro Asn Asp Lys
1

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<400> 192

Pro Asn Asp Lys Tyr
1 5

<210> 193
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<400> 193

Pro Asn Asp Lys Tyr Glu
1 5

<210> 194
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<220>
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<400> 194

Pro Asn Asp Lys Tyr Glu Pro
1 5

<210> 195
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<220>
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<400> 195

Pro Asn Asp Lys Tyr Glu Pro Phe
1 5

<210> 196
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<220>
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<400> 196

Pro Asn Asp Lys Tyr Glu Pro Phe Trp
1 5

<210> 197
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<213> 人工序列

<220>
<223> PAR1 連接子基元

<400> 197

Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu
1 5 10

<210> 198
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<220>
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<400> 198

Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp
1 5 10

<210> 199
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<400> 199

Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu
1 5 10

<210> 200
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<213> 人工序列

<220>
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<400> 200

Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu
1 5 10

<210> 201
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> PAR1 連接子基元

<400> 201

Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Ser
1 5 10

<210> 202
<211> 72
<212> PRT
<213> 人工序列

<220>
<223> XTEN_AE72_2A_1

<400> 202

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

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

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

<210> 203
<211> 72
<212> PRT
<213> 人工序列

<220>
<223> XTEN_AE72_2A_2

<400> 203

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 Thr Glu Pro Ser Glu Gly
20 25 30

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

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

Ala Thr Pro Glu Ser Gly Pro Gly
65 70

<210> 204
<211> 72
<212> PRT
<213> 人工序列

<220>
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<400> 204

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
65 70

<210> 205
<211> 72
<212> PRT
<213> 人工序列

<220>
<223> XTEN_AE72_3B_2

<400> 205

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

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

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

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

Pro Ser Glu Gly Ser Ala Pro Gly
65 70

<210> 206
<211> 72
<212> PRT
<213> 人工序列

<220>
<223> XTEN_AE72_4A_2

<400> 206

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

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

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

<210> 207
<211> 72
<212> PRT
<213> 人工序列

<220>
<223> XTEN_AE72_5A_2

<400> 207

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

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

Ser Pro Thr Ser Thr Glu Glu Gly
65 70

<210> 208
<211> 72
<212> PRT
<213> 人工序列

<220>
<223> XTEN_AE72_6B_1

<400> 208

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
65 70

<210> 209
<211> 72
<212> PRT
<213> 人工序列

<220>
<223> XTEN_AE72_6B_2

<400> 209

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

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

Ser Ala 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
65 70

<210> 210
<211> 72
<212> PRT
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<220>
<223> XTEN_AE72_1A_1

<400> 210

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 Thr Ser Thr Glu Pro Ser Glu Gly
20 25 30

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

<210> 211
<211> 72
<212> PRT
<213> 人工序列

<220>
<223> XTEN_AE72_1A_2

<400> 211

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 Ser Glu Pro Ala Thr Ser Gly Ser
20 25 30

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

<210> 212
<211> 144
<212> PRT
<213> 人工序列

<220>
<223> XTEN_AE144_1A

<400> 212

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 Thr Ser Thr Glu Pro Ser Glu Gly
20 25 30

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

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

Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro 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> 213
<211> 150
<212> PRT
<213> 人工序列

<220>

<223> AE150

<400> 213

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

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

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

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

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

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

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

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

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

Ser Ala Pro Ala Ser Ser
145                 150
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<210> 214
<211> 150
<212> PRT
<213> 人工序列

<220>
<223> AG150

<400> 214

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

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

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

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

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

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

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

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

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

Gly Ser Pro Ala Ser Ser
145 150

<210> 215
<211> 294
<212> PRT
<213> 人工序列

<220>
<223> AE294

<400> 215

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ser Ala Pro Ala Ser Ser
290

<210> 216
<211> 294
<212> PRT
<213> 人工序列

<220>
<223> AG294

<400> 216

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thr Gly Ser Ala Ser Ser
290

<210> 217
<211> 36
<212> PRT
<213> 人工序列

<220>
<223> AE36

<400> 217

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
35

<210> 218
<211> 78
<212> PRT
<213> 人工序列

<220>
<223> AE78

<400> 218

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

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

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

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

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

<210> 219
<211> 46
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 219

Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr Gly Ala Gly
1 5 10 15

Ser Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser Glu Glu Asp
20 25 30

Leu Ser Pro Ala Thr Gly His His His His His His His His
35 40 45

<210> 220
<211> 25
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 220

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Leu Val Pro Arg Gly Ala
1 5 10 15

Gly Ser Pro Gly Ala Glu Thr Ala Gly
20 25

<210> 221
<211> 44
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 221

Gly Ala Gly Ser Pro Gly Ala Glu Thr Ala Leu Val Pro Arg Ser Phe
1 5 10 15

Leu Leu Arg Asn Pro Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu
20 25 30

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

<210> 222
<211> 23
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 222

Gly Pro Glu Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr Gly Ala Gly
1 5 10 15

Ser Pro Gly Ala Glu Thr Ala
20

<210> 223
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 223

Gly Gly Gly Gly Ala Leu Arg Pro Arg Val Val Gly Gly Ala Gly Ser
1 5 10 15

Pro Gly Ala Glu Thr Ala
20

<210> 224
<211> 40
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 224

Gly Gly Gly Gly Thr Leu Asp Pro Arg Ser Phe Leu Leu Arg Asn Pro
1 5 10 15

Asn Asp Lys Tyr Glu Pro Phe Trp Glu Asp Glu Glu Lys Gly Gly Ala
20 25 30

Gly Ser Pro Gly Ala Glu Thr Ala
35 40

<210> 225
<211> 11

<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 225

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

<210> 226
<211> 798
<212> PRT
<213> 人工序列

<220>
<223> pSYN-FIX-102

<400> 226

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

```
Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
            100                 105                 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
        115                 120                 125

Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe
    210                 215                 220

Thr Arg Val Val Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp
225                 230                 235                 240

Gln Val Val Leu Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile
                245                 250                 255

Val Asn Glu Lys Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly
            260                 265                 270
```

Val Lys Ile Thr Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu
275 280 285

His Thr Glu Gln Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn
290 295 300

Tyr Asn Ala Ala Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu
305 310 315 320

Leu Asp Glu Pro Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile
325 330 335

Ala Asp Lys Glu Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr
340 345 350

Val Ser Gly Trp Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val
355 360 365

Leu Gln Tyr Leu Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu
370 375 380

Ser Thr Lys Phe Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His
385 390 395 400

Glu Gly Gly Arg Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val
405 410 415

Thr Glu Val Glu Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly
420 425 430

Glu Glu Cys Ala Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser
435 440 445

Arg Tyr Val Asn Trp Ile Lys Glu Lys Thr Lys Leu Thr Gly Pro Glu
450 455 460

Gly Pro Ser Lys Leu Thr Arg Ala Glu Thr Gly Ala Gly Ser Pro Gly
465 470 475 480

Ala Glu Thr Ala Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
485 490 495

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu
500 505 510

Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly
515 520 525

Ser Glu Thr Pro Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro
530 535 540

Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro Gly Ser Pro Ala
545 550 555 560

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Glu Ser Ala Thr Pro
565 570 575

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
580 585 590

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Ser Pro Ala
595 600 605

Gly Ser Pro Thr Ser Thr Glu Glu Gly Ser Pro Ala Gly Ser Pro Thr
610 615 620

Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
625 630 635 640

Gly Thr Ser Glu Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu
645 650 655

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Glu Ser Ala Thr Pro
660 665 670

Glu Ser Gly Pro Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro
675 680 685

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Ser Pro Ala
690 695 700

Gly Ser Pro Thr Ser Thr Glu Glu Gly Thr Ser Thr Glu Pro Ser Glu
705 710 715 720

Gly Ser Ala Pro Gly Thr Ser Thr Glu Pro Ser Glu Gly Ser Ala Pro
725 730 735

Gly Ser Glu Pro Ala Thr Ser Gly Ser Glu Thr Pro Gly Thr Ser Glu
740 745 750

Ser Ala Thr Pro Glu Ser Gly Pro Gly Thr Ser Thr Glu Pro Ser Glu
755 760 765

Gly Ser Ala Pro Gly Ala Glu Thr Ala Glu Gln Lys Leu Ile Ser Glu
770 775 780

Glu Asp Leu Ser Pro Ala Thr Gly His His His His His His
785 790 795

<210> 227
<211> 763
<212> PRT
<213> 人工序列

<220>
<223> pSYN-FIX-216

<400> 227

Met Gln Arg Val Asn Met Ile Met Ala Glu Ser Pro Gly Leu Ile Thr
1 5 10 15

Ile Cys Leu Leu Gly Tyr Leu Leu Ser Ala Glu Cys Thr Val Phe Leu
20 25 30

Asp His Glu Asn Ala Asn Lys Ile Leu Asn Arg Pro Lys Arg Tyr Asn
35 40 45

Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg Glu Cys
50 55 60

Met Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe Glu Asn
65 70 75 80

Thr Glu Arg Thr Thr Glu Phe Trp Lys Gln Tyr Val Asp Gly Asp Gln
85 90 95

Cys Glu Ser Asn Pro Cys Leu Asn Gly Gly Ser Cys Lys Asp Asp Ile
100 105 110

Asn Ser Tyr Glu Cys Trp Cys Pro Phe Gly Phe Glu Gly Lys Asn Cys
115 120 125

```
Glu Leu Asp Val Thr Cys Asn Ile Lys Asn Gly Arg Cys Glu Gln Phe
    130                 135                 140

Cys Lys Asn Ser Ala Asp Asn Lys Val Val Cys Ser Cys Thr Glu Gly
145                 150                 155                 160

Tyr Arg Leu Ala Glu Asn Gln Lys Ser Cys Glu Pro Ala Val Pro Phe
                165                 170                 175

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

Glu Thr Val Phe Pro Asp Val Asp Tyr Val Asn Ser Thr Glu Ala Glu
        195                 200                 205

Thr Ile Leu Asp Gly Pro Ser Pro Gly Ser Pro Thr Ser Thr Glu Glu
    210                 215                 220

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

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

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

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

Asn Ile Thr Gln Ser Thr Gln Ser Phe Asn Asp Phe Thr Arg Val Val
    290                 295                 300
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Gly Gly Glu Asp Ala Lys Pro Gly Gln Phe Pro Trp Gln Val Val Leu
305 310 315 320

Asn Gly Lys Val Asp Ala Phe Cys Gly Gly Ser Ile Val Asn Glu Lys
325 330 335

Trp Ile Val Thr Ala Ala His Cys Val Glu Thr Gly Val Lys Ile Thr
340 345 350

Val Val Ala Gly Glu His Asn Ile Glu Glu Thr Glu His Thr Glu Gln
355 360 365

Lys Arg Asn Val Ile Arg Ile Ile Pro His His Asn Tyr Asn Ala Ala
370 375 380

Ile Asn Lys Tyr Asn His Asp Ile Ala Leu Leu Glu Leu Asp Glu Pro
385 390 395 400

Leu Val Leu Asn Ser Tyr Val Thr Pro Ile Cys Ile Ala Asp Lys Glu
405 410 415

Tyr Thr Asn Ile Phe Leu Lys Phe Gly Ser Gly Tyr Val Ser Gly Trp
420 425 430

Gly Arg Val Phe His Lys Gly Arg Ser Ala Leu Val Leu Gln Tyr Leu
435 440 445

Arg Val Pro Leu Val Asp Arg Ala Thr Cys Leu Leu Ser Thr Lys Phe
450 455 460

Thr Ile Tyr Asn Asn Met Phe Cys Ala Gly Phe His Glu Gly Gly Arg
465 470 475 480

```
Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Val Thr Glu Val Glu
                485                 490                 495

Gly Thr Ser Phe Leu Thr Gly Ile Ile Ser Trp Gly Glu Glu Cys Ala
            500                 505                 510

Met Lys Gly Lys Tyr Gly Ile Tyr Thr Lys Val Ser Arg Tyr Val Asn
        515                 520                 525

Trp Ile Lys Glu Lys Thr Lys Leu Thr Asp Lys Thr His Thr Cys Pro
    530                 535                 540

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
545                 550                 555                 560

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
                565                 570                 575

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
            580                 585                 590

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
        595                 600                 605

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
    610                 615                 620

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
625                 630                 635                 640

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
                645                 650                 655
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Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
660 665 670

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
675 680 685

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
690 695 700

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

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
725 730 735

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
740 745 750

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
755 760

<210> 228
<211> 226
<212> PRT
<213> 人工序列

<220>
<223> pSYN-FIX-216-Fc

<400> 228

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

專利申請案第 105124637 號
ROC Patent Appln. No. 105124637
修正部分無劃線之申請專利範圍中文本－附件(二)
Amended Claims in Chinese－Encl.(II)
(民國 110 年 3 月 25 日送呈)
(Submitted on March 25, 2021)

2021 年 3 月 25 日修正

申請專利範圍

1. 一種因子 IX (FIX)融合蛋白，其包含 FIX 多肽及插入該 FIX 多肽內的 XTEN，其中該 FIX 融合蛋白包含 SEQ ID NO: 2 之 FIX 多肽胺基酸序列，其具有該 XTEN 插入在選自由以下組成之群組的插入位點：SEQ ID NO: 2 之胺基酸 149、SEQ ID NO: 2 之胺基酸 162、SEQ ID NO: 2 之胺基酸 166 及 SEQ ID NO: 2 之胺基酸 174，其中該 XTEN 為約 42 個胺基酸至約 288 個胺基酸長度，且其中該 FIX 融合蛋白展現促凝血活性。

2. 如申請專利範圍第 1 項之 FIX 融合蛋白，其中當與缺乏該 XTEN 插入之 R338L FIX (Padua)變異體多肽相較，該 FIX 融合蛋白能夠展現大於至少 1.5 倍的活體內半衰期。

3. 如申請專利範圍第 1 項之 FIX 融合蛋白，其中該插入位點為 SEQ ID NO: 2 之胺基酸 166。

4. 如申請專利範圍第 1 項之 FIX 融合蛋白，其中該 XTEN 包含約 72 個胺基酸。

5. 如申請專利範圍第 1 項之 FIX 融合蛋白，其中該 XTEN 包含約 144 個胺基酸或約 288 個胺基酸。

6. 如申請專利範圍第 1 項之 FIX 融合蛋白，其另外包含第一 Fc 結構域，其具有 SEQ ID NO: 228 之胺基酸序列。

7. 如申請專利範圍第 6 項之 FIX 融合蛋白，其另外包含第二 Fc 結構域，其具有 SEQ ID NO: 228 之胺基酸序

列。

8. 如申請專利範圍第 7 項之 FIX 融合蛋白，其包含兩條多肽鏈，其中：

a. 該第一多肽鏈包含該第一 Fc 結構域，該第一 Fc 結構域融合至含有該 XTEN 之該 FIX 多肽的 N 末端或 C 末端，且

b. 該第二多肽鏈包含該第二 Fc 結構域，其中該第一 Fc 結構域與該第二 Fc 結構域藉由共價鍵締合，其中該共價鍵為二硫鍵。

9. 如申請專利範圍第 8 項之 FIX 融合蛋白，其中該第一 Fc 結構域與該第二 Fc 結構域藉由兩個二硫鍵締合。

10. 如申請專利範圍第 1 項之 FIX 融合蛋白，其中該 FIX 融合蛋白包含 SEQ ID NO: 227 之胺基酸序列。

11. 如申請專利範圍第 1 項之 FIX 融合蛋白，其中該 FIX 融合蛋白包含 SEQ ID NO: 227 之胺基酸序列，且無信號肽及無前肽(胺基酸 1-46)。

12. 一種因子 IX (FIX)融合蛋白，其包含第一多肽鏈及第二多肽鏈，其中：

a. 該第一多肽鏈包含：

i. FIX 多肽及插入該 FIX 多肽內的 XTEN，其中該 FIX 融合蛋白包含 SEQ ID NO: 2 之 FIX 多肽胺基酸序列，其具有該 XTEN 插入在 SEQ ID NO: 2 之胺基酸 166，且其中該 XTEN 包含具有約 76 個胺基酸之胺基酸序列；及

ii. 第一 Fc 結構域，其具有 SEQ ID NO: 228 之胺基酸序列，其中該第一 Fc 結構域融合至含有該 XTEN 之該 FIX 多肽的 C 末端；且

b. 該第二多肽鏈包含具有 SEQ ID NO: 228 之胺基酸序列的第二 Fc 結構域，

其中該第一 Fc 結構域與該第二 Fc 結構域藉由共價鍵締合；

其中該共價鍵為二硫鍵；且其中該 FIX 融合蛋白展現促凝血活性。

13. 如申請專利範圍第 12 項之 FIX 融合蛋白，其中該第一 Fc 結構域與該第二 Fc 結構域以兩個二硫鍵締合。

14. 如申請專利範圍第 12 項之 FIX 融合蛋白，其中該第一多肽鏈包含 SEQ ID NO: 227 之胺基酸序列，且其中該第二多肽鏈包含 SEQ ID NO: 228 之胺基酸序列。

15. 如申請專利範圍第 14 項之 FIX 融合蛋白，其中該第一多肽鏈包含 SEQ ID NO: 227 之胺基酸序列，且無信號肽及無前肽(胺基酸 1-46)，及其中該第二多肽鏈包含 SEQ ID NO: 228 之胺基酸序列。

16. 一種經分離之聚核苷酸，其包含編碼如申請專利範圍第 1-15 項任一項之 FIX 融合蛋白的序列。

17. 一種表現載體，其包含如申請專利範圍第 16 項之聚核苷酸。

18. 一種宿主細胞，其包含如申請專利範圍第 17 項之表現載體。

19. 一種有效量之如申請專利範圍第 1-15 項任一項之 FIX 融合蛋白於製造用於降低人類受試者中出血事件頻率之藥物的用途，其中該受試者具有 B 型血友病。

20. 一種有效量之如申請專利範圍第 1-15 項任一項之 FIX 融合蛋白於製造用於人類受試者中出血預防性治療之藥物的用途，其中該受試者具有 B 型血友病。

21. 一種有效量之如申請專利範圍第 1-15 項任一項之 FIX 融合蛋白於製造用於人類受試者中出血需要性(on-demand)治療之藥物的用途，其中該受試者具有 B 型血友病。

圖式

圖1-有關AE42插入及C末端融合之活性篩選
條件培養基中之FIX活性
(%基礎構築體，發色分析)
0
10
20
30
40
50
60
70
80
90
GLA
H
EGF1
EGF2
連接子
AP
催化結構域
R338L
C末端
E G I K D N A N E P K V E D S K V E G K T E H K E S D K K K H K R K
52 59 66 80 85 89 103 105 113 129 142 149 162 166 174 188 202 224 226 228 230 240 257 265 277 283 292 316 341 354 392 403 413 415

圖2-有關XTEN插入位點及長度之活性篩選

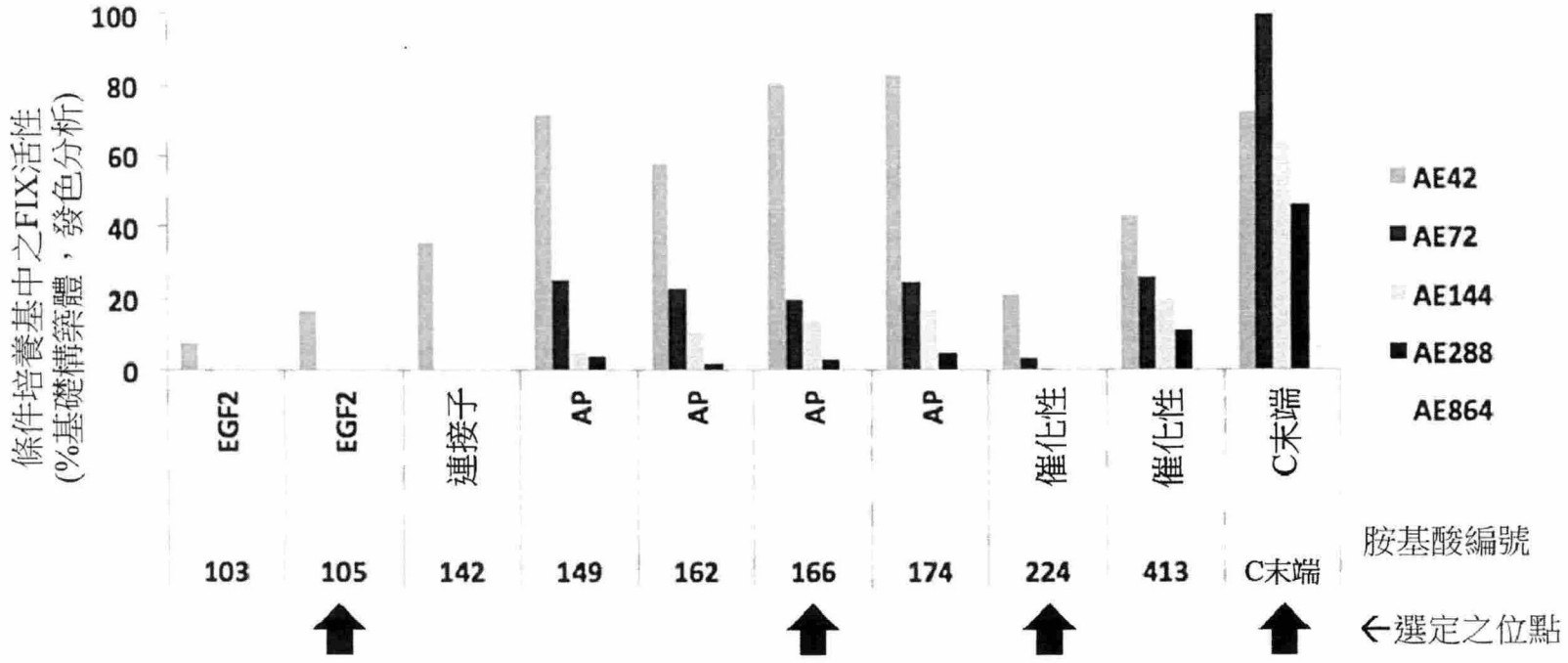


圖3-FIX中關於組合文庫選擇之四個位點

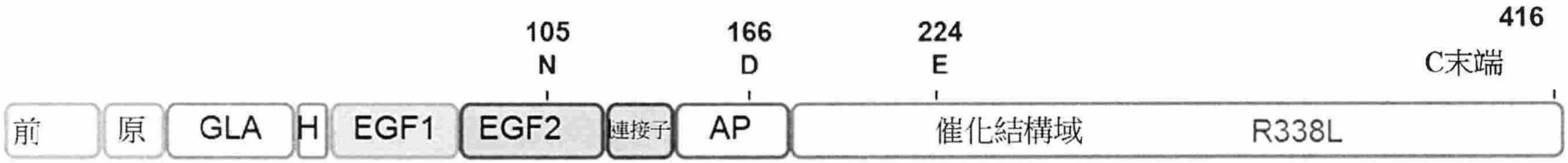


圖 3A

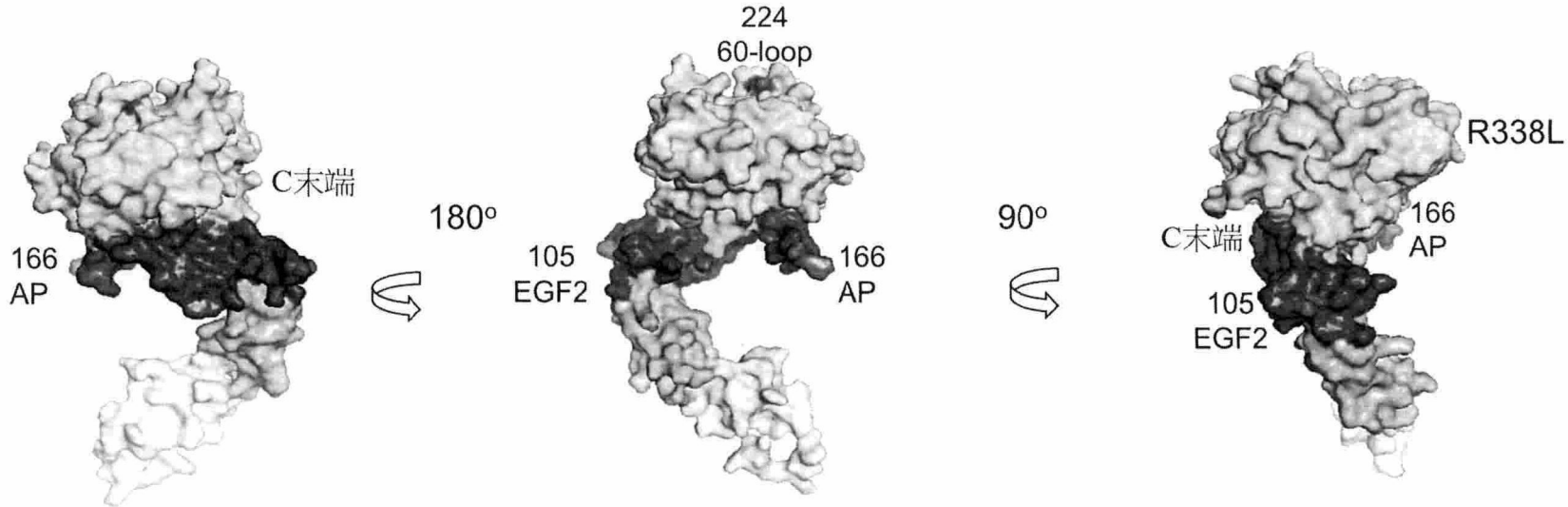
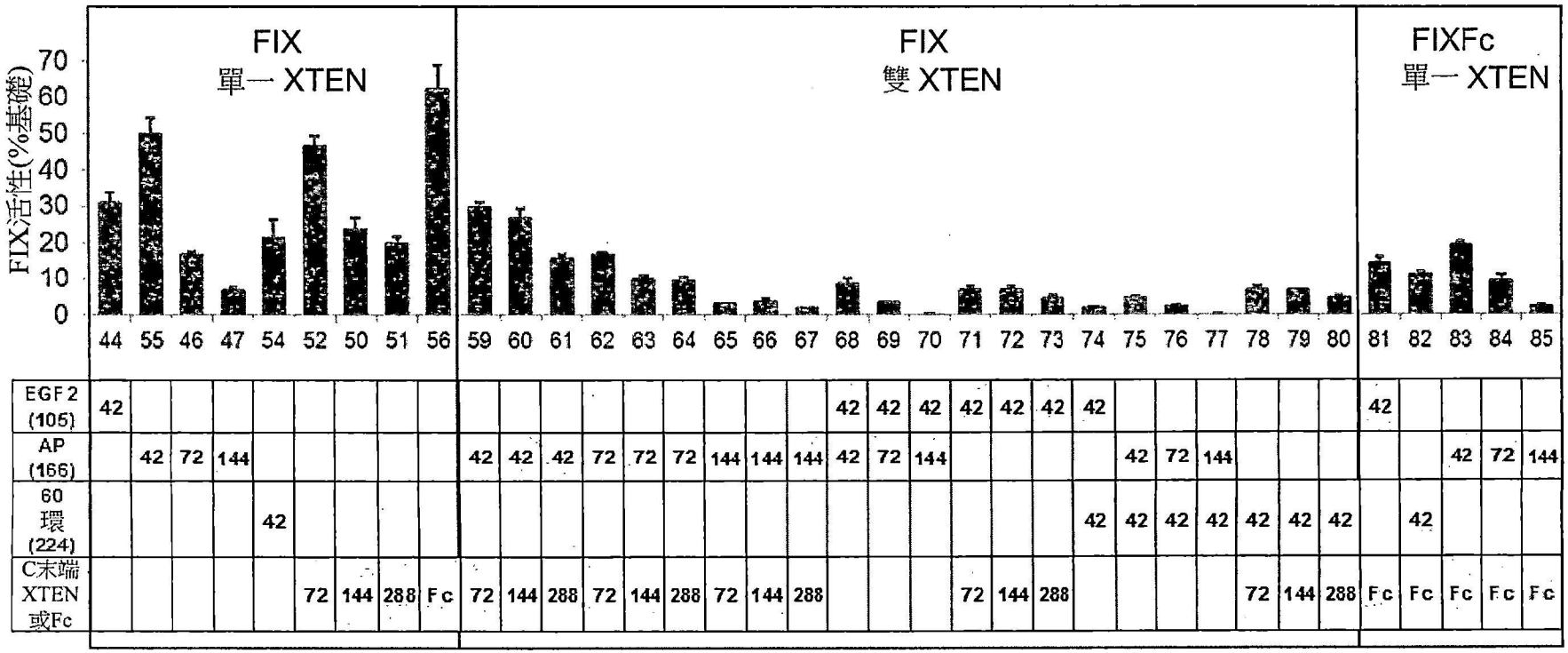


圖 3B

圖4-具有可偵測活性之三組FIX-XTEN



HemB小鼠
FIX-CT.288
FIX-CT.864
FIXFc
FIX
~30%
FIX活性(%劑量)
天數
圖 5A
FIX-AP.144
FIXFc
FIX-AP.72
FIX-AP.42
FIX
~50%
FIX活性(%劑量)
天數
圖 5B
回收率(%)
FIX-CT.288
FIX-CT.864
FIX-AP.144
FIXFc
FIX-AP.42
FIX-AP.72
FIX
0.1
0.5
AUC/D
(h/kg/mL)
MRT (h)
圖 5C
圖 5

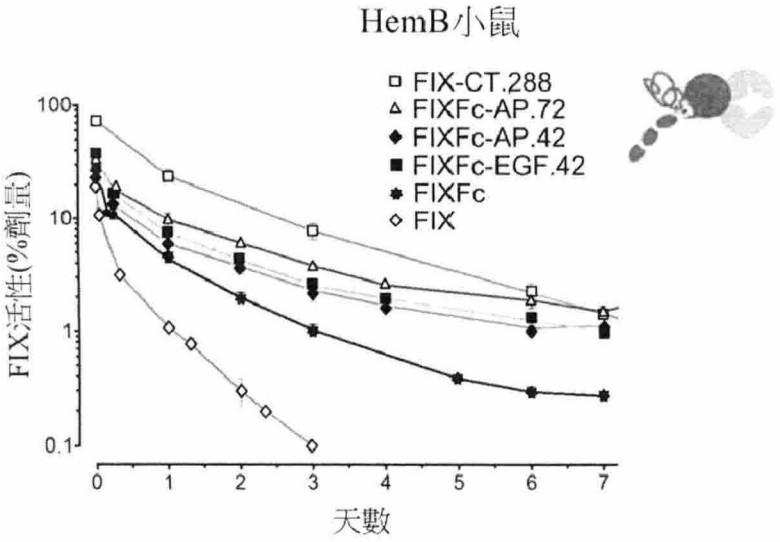

HemB小鼠
FIX-CT.288
FIXFc-AP.72
FIXFc-AP.42
FIXFc-EGF.42
FIXFc
FIX
FIX活性(%劑量)
100
10
1
0.1
0
1
2
3
4
5
6
7
天數

圖 6A

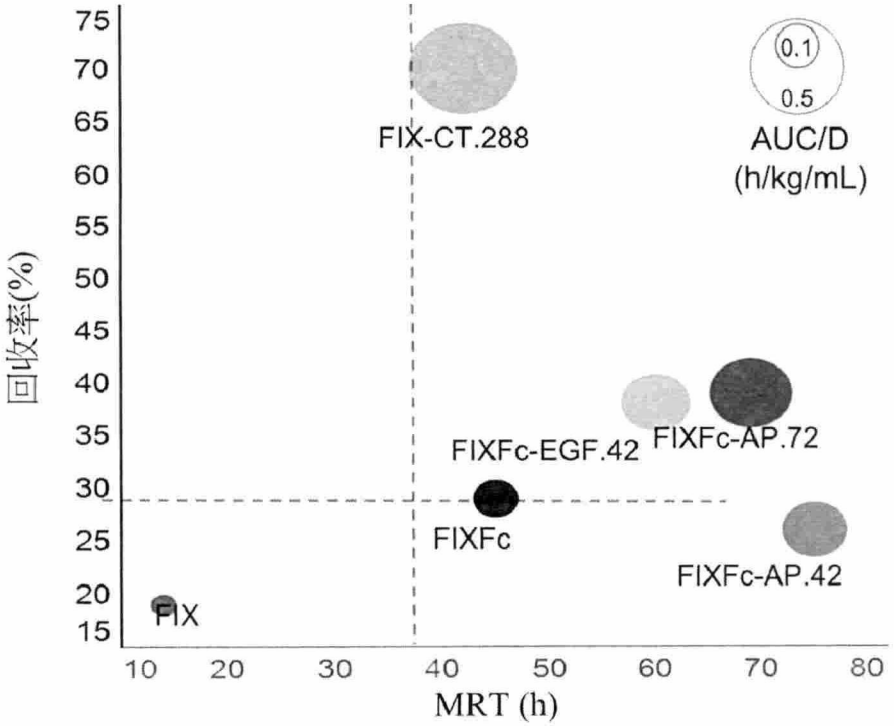

回收率(%)
75
70
65
60
55
50
45
40
35
30
25
20
15
10
20
30
40
50
60
70
80
MRT (h)
FIX-CT.288
0.1
0.5
AUC/D
(h/kg/mL)
FIXFc-EGF.42
FIXFc-AP.72
FIXFc
FIXFc-AP.42
FIX

圖 6B

圖 6

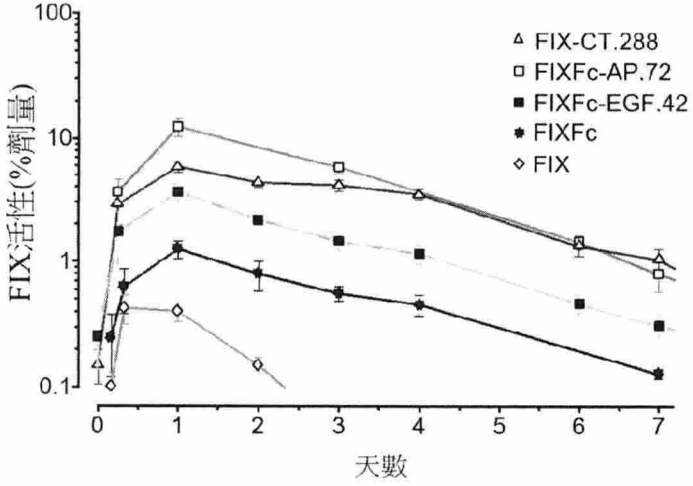

FIX-CT.288
FIXFc-AP.72
FIXFc-EGF.42
FIXFc
FIX
FIX活性(%劑量)
100
10
1
0.1
0
1
2
3
4
5
6
7
天數

圖 7A

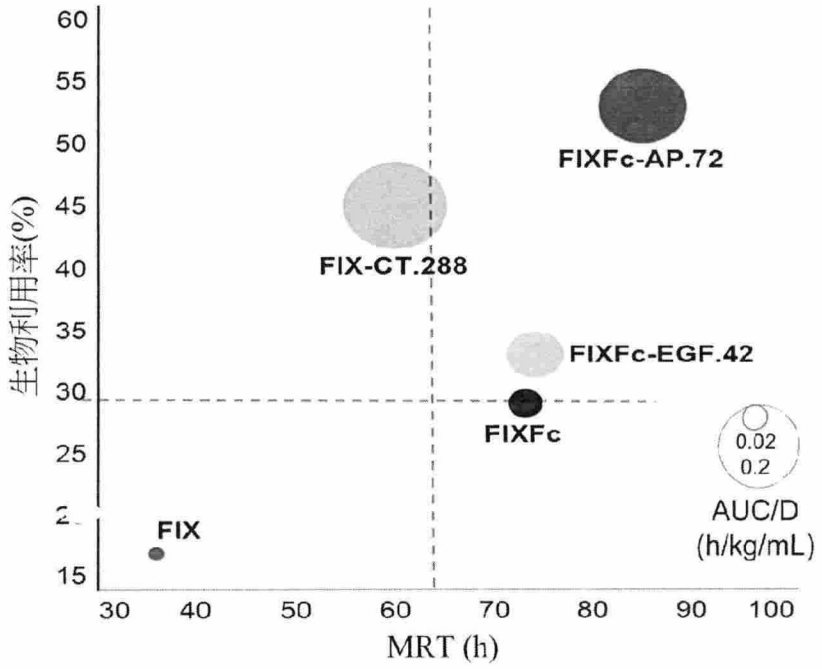

60
55
50
45
40
35
30
25
15
生物利用率(%)
FIXFc-AP.72
FIX-CT.288
FIXFc-EGF.42
FIXFc
FIX
0.02
0.2
AUC/D
(h/kg/mL)
30
40
50
60
70
80
90
100
MRT (h)

圖 7B

圖 7

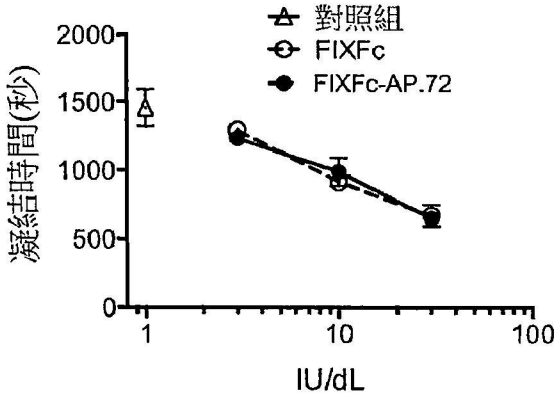


圖 8A

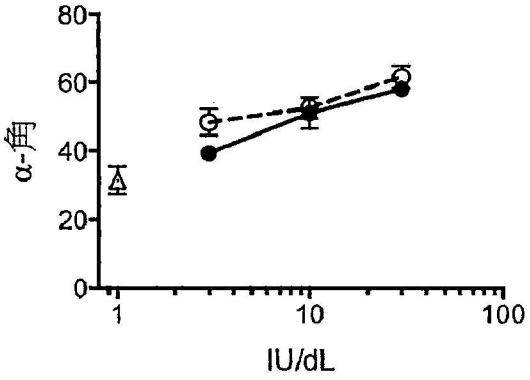


圖 8B

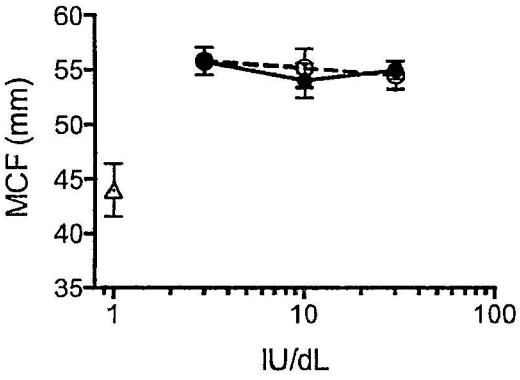


圖 8C

圖 8

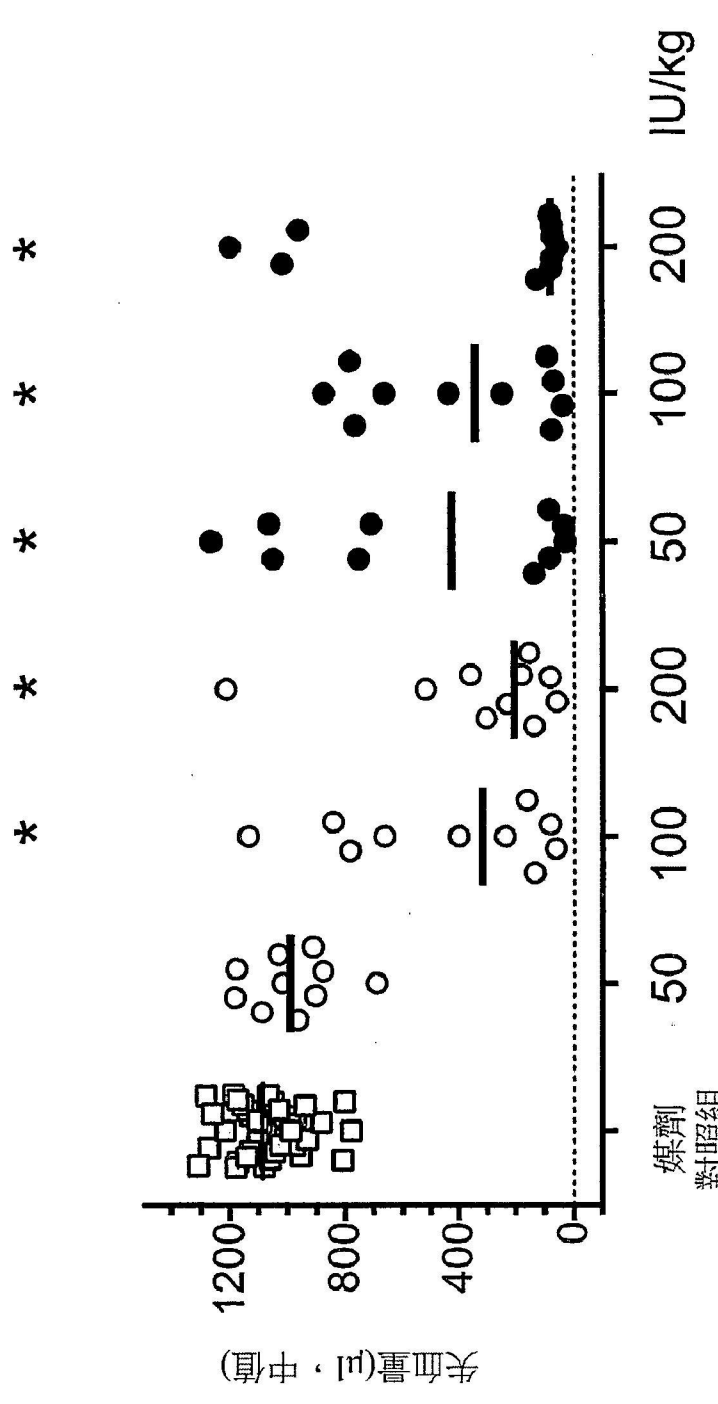

失血量(μl，中值)
1200
800
400
0
媒劑
對照組
50
100
200
50
100
200
IU/kg
rFIXFc
rFIXFc-AP.72
*
*
*
*
*

圖 9

* $p < 0.0001$

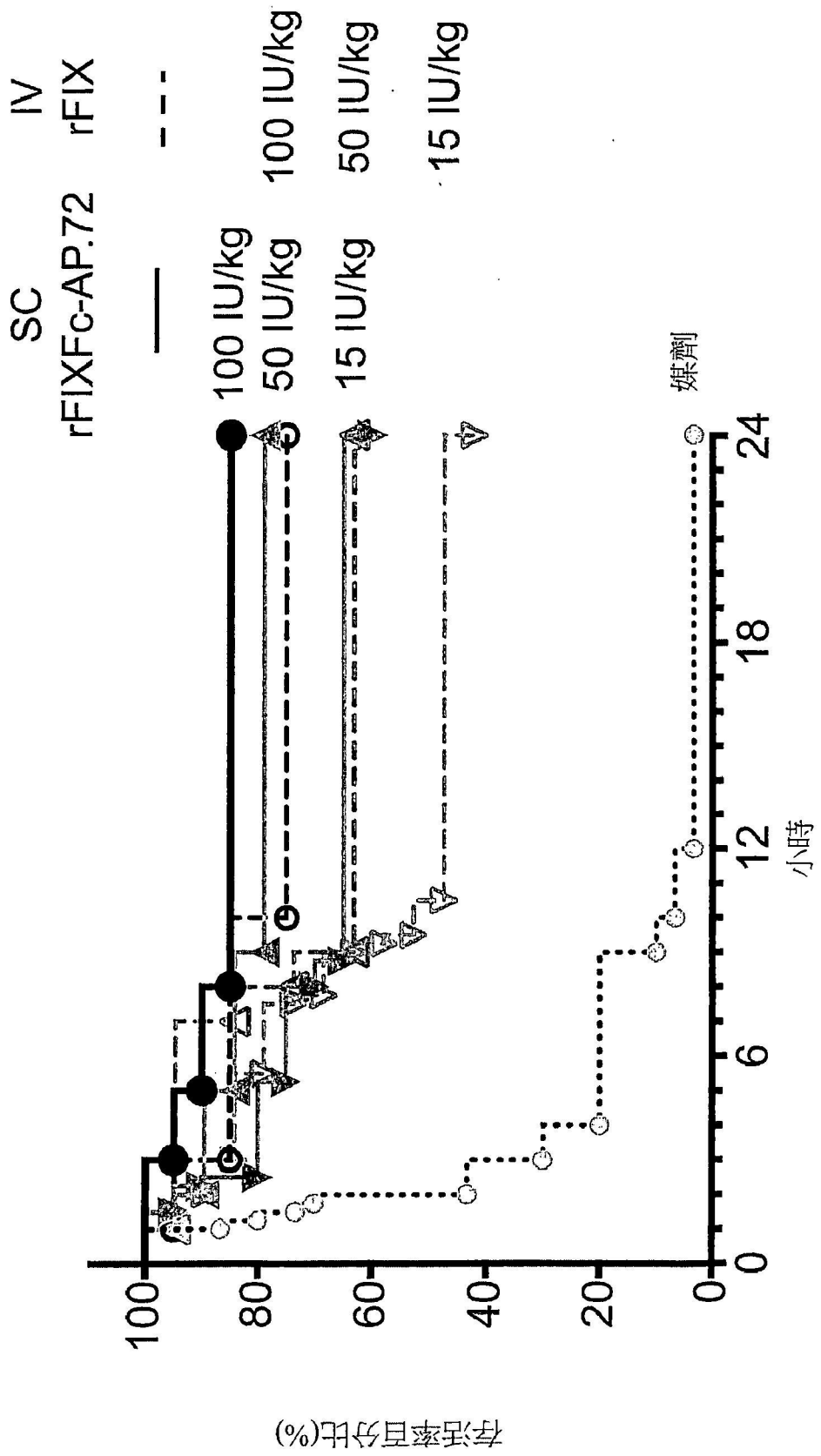

SC
rFIXFc-AP.72
IV
rFIX
100 IU/kg
50 IU/kg
15 IU/kg
100 IU/kg
50 IU/kg
15 IU/kg
媒劑
存活率百分比(%)
小時
0
20
40
60
80
100
0
6
12
18
24

圖 10

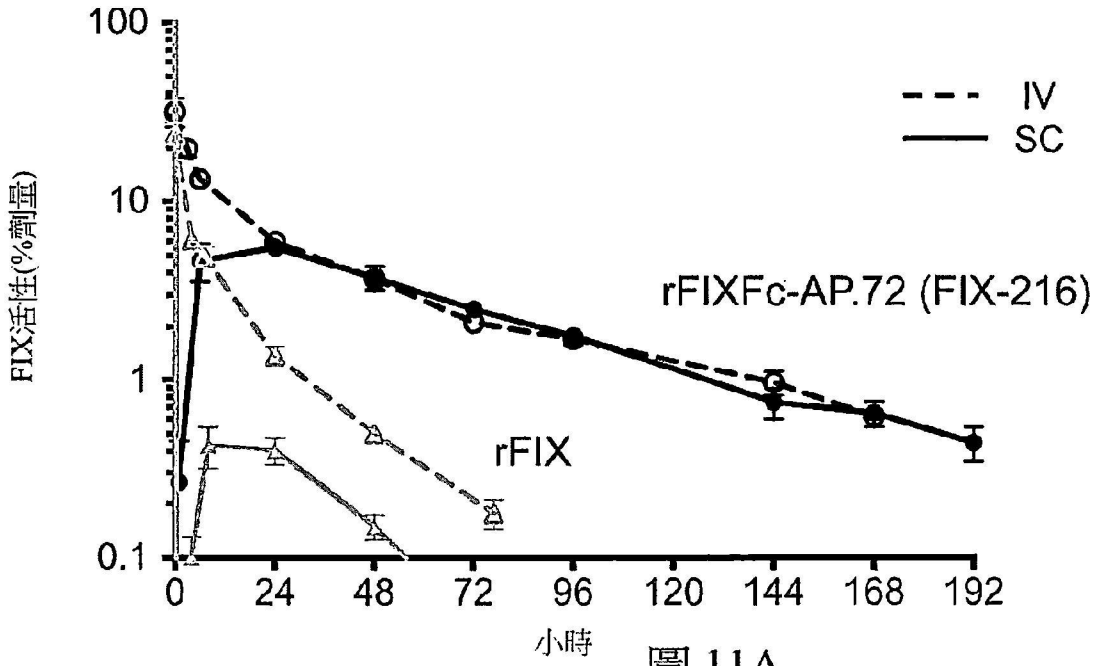
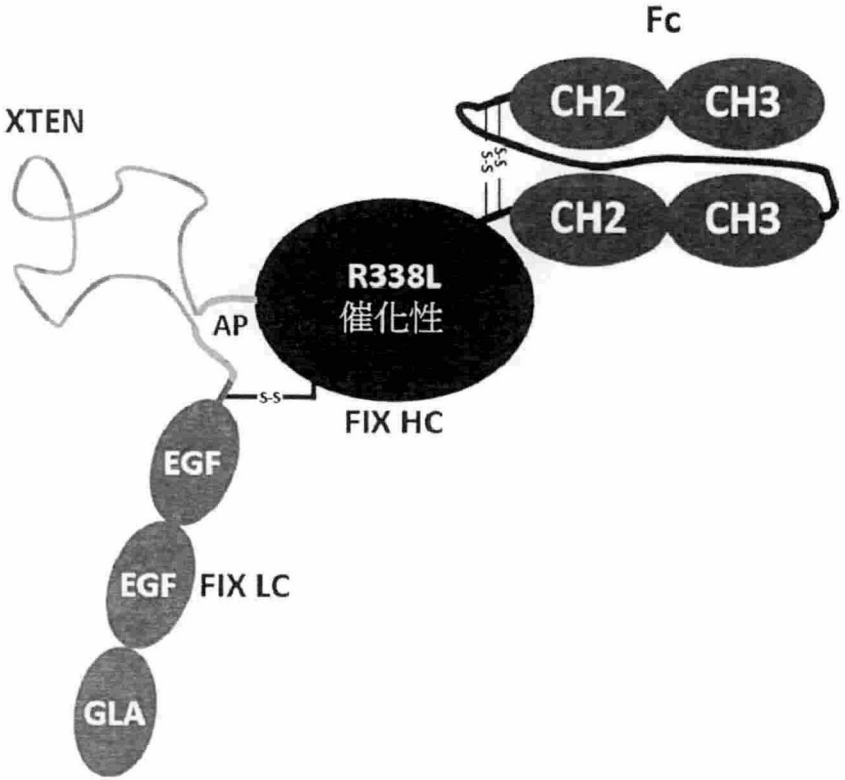


圖 11A

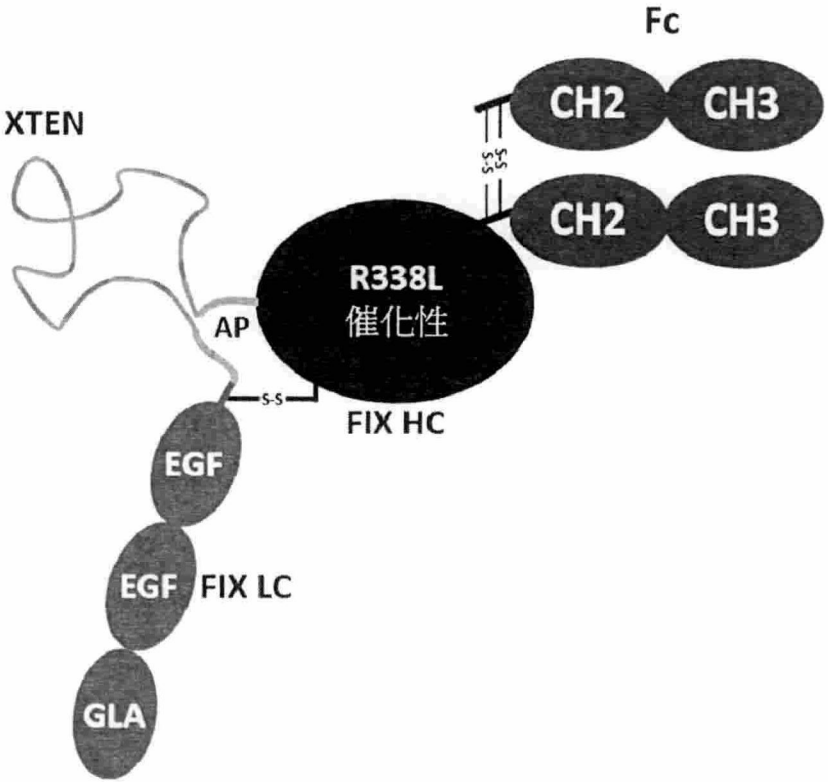
	靜脈內					皮下				
	I.R. (%)	$t_{1/2}$ (h)	MRT (h)	AUC/D (h*kg/mL)	Cl (mL/h/kg)	F (%)	$t_{1/2}$ (h)	MRT (h)	AUC/D (h*kg/mL)	Cl (mL/h/kg)
rFIX	21	17	17	0.043	23.2	14	21	38	0.006	175
rFIXFc-AP.72	32	51	53	0.165	6.0	70	48	72	0.116	8.6

圖 11B



rFIXFc-AP.72
(單一Fc鏈)

圖 12A



rFIXFc-AP.72
(雙Fc鏈)

圖 12B

FIX構築體名稱	SEQ ID NO	說明	質體名稱
rFIX-CT.72	123	R338L，C末端 AE72	pJH52
rFIX-CT.144	121	R338L，C末端 AE144	pJH50
rFIX-CT-288	226	R338L，C末端 AE288標籤	FIX-102
rFIX-CT.288	122	R338L，C末端 AE288	pJH51
rFIX-CT.864	116	R338L，C末端 AE864	FIX-92
rFIX-AP.72	119	R338L, D166-AE72	pJH46
rFIX-AP.144	120	R338L, D166-AE144	pJH47
rFIXFc-EGF.42	148	R338L, N105-AE42，C末端 -Fc	pJH81
rFIXFc-AP.42	150	R338L, D166-AE42，C末端 Fc	pJH83
rFIXFc-AP.72	151	R338L, D166-AE72，C末端 Fc	pJH84
rFIXFc-AP.72 (雙鏈Fc)	227 & 228	R338L, D166-AE72，C末端 Fc (雙鏈Fc)	FIX-216

圖 13