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(56)參考文獻：

WO 2007031559A2

Jais R. Bjelke et al., "A loop of coagulation factor VIIa influencing macromolecular substrate specificity", FEBS Letters 581 (2007) 71-76.

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(54)名稱

經修飾的因子ＶＩＩ多肽和其用途

FACTOR VII POLYPEPTIDES THAT ARE MODIFIED AND USES THEREOF

(57)摘要

本發明提供經修飾的因子 VII 多肽和其用途。該等經修飾的 FVII 多肽包括因子 VIIa 及因子 VII 之其他形式。所提供之經修飾的 FVII 多肽中，有具有經改變之活性(典型地經改變之促凝血活性，包括促凝血活性增強之彼等 FVII 多肽)者。因此，該等經修飾的多肽為治療劑。

Modified factor VII polypeptides and uses thereof are provided. Such modified FVII polypeptides include Factor VIIa and other forms of Factor VII. Among modified FVII polypeptides provided are those that have altered activities, typically altered procoagulant activity, including increased procoagulant activities. Hence, such modified polypeptides are therapeutics.

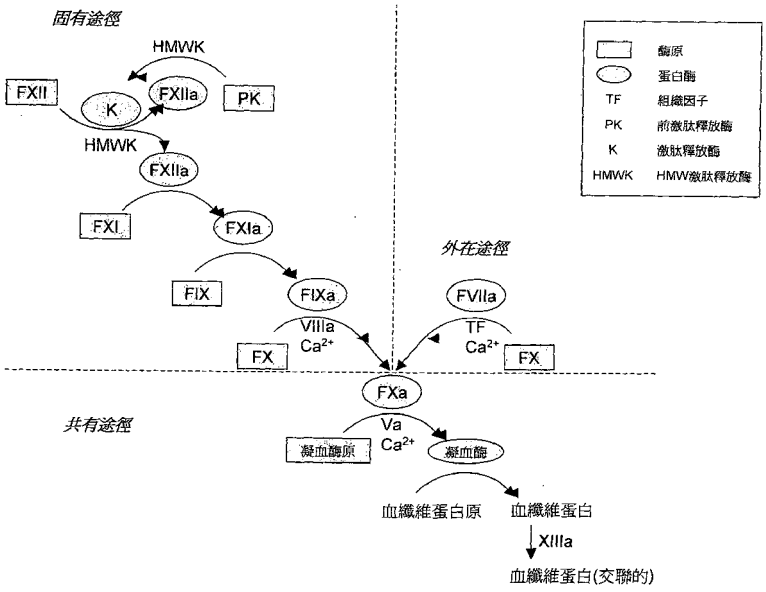
固有途徑
HMWK
FXII
K
FXIIa
PK
HMWK
FXIIa
FXI
FXIa
FIX
FIXa
VIIIa
Ca2+
FX
外在途徑
FVIIa
TF
Ca2+
FX
FXa
共有途徑
Va
Ca2+
凝血酶原
凝血酶
血纖維蛋白原
血纖維蛋白
XIIIa
血纖維蛋白(交聯的)
酶原
蛋白酶
TF 組織因子
PK 前激肽釋放酶
K 激肽釋放酶
HMWK HMW激肽釋放酶

圖1.凝血級聯

六、發明說明：

相關申請案

本發明主張 2008 年 4 月 11 日申請之 Edwin Madison 及 Christopher Thanos 之標題為「FACTOR VII POLYPEPTIDES THAT ARE MODIFIED AND USES THEREOF」的美國臨時申請案第 61/124,021 號之優先權。

以上所引用申請案之標的係以引用的方式全部併入本文中。

【發明所屬之技術領域】

本發明提供經修飾之治療性蛋白質。詳言之，提供經修飾之因子 VII 多肽，其包括因子 VIIa 及因子 VII 之其他形式，及其用途。

【先前技術】

止血為引起出血停止之複雜生理過程。血小板、血漿蛋白質及血管與內皮細胞為此過程的三種組份，其各自在組織損傷後不久出現之事件中起重要作用且在正常情況下引起凝塊之迅速形成。此事件之最重要部分為凝血級聯，亦即其中某些血漿蛋白質（或凝血因子）在「級聯」中由另一預先活化凝血因子依次活化，引起凝血酶快速產生之一系列蛋白水解事件。接著，在此級聯中產生之大量凝血酶起作用以將血纖維蛋白原裂解為形成凝塊所需之血纖蛋白肽。

凝血因子以無活性單鏈酶原形式循環，且藉由在一或多個位置裂解活化以產生雙鏈活化形式之蛋白質。因子 VII（FVII）-一種維生素 K 依賴性血漿蛋白質-最初在血液中以酶原形式循環。FVII 酶原係藉由在單一位點 Arg^{152}-Ile^{153} 經蛋白水解裂解而活化，產生由單個雙硫鍵連接之雙鏈蛋白酶（FVIIa）。FVIIa 結合其輔因子、組織因子（TF）以形成其中 FVIIa 可有效地將因子 X（FX）活化為 FXa，藉此起始引起血纖蛋白形成及止血的一系列事件之複合物。

雖然在大多數情況下得以實現正常止血，但該過程之缺陷會導致其中凝塊形成所消耗時間延長之出血病症。該等病症可為先天性或後天性的。舉例而言，A 型及 B 型血友病為遺傳性疾病，其特徵在於分別缺乏因子 VIII（FVIII）及因子 IX（FIX）。替代療法為對 A 型及 B 型血友病之傳統治療法，且包括靜脈內投予自人類血漿製備或以重組蛋白質形式製備之 FVIII 或 FIX。然而，在多數情況下，患者發展針對所輸注蛋白質之抗體（亦稱為抑制子），其降低或抵消治療功效。重組 FVIIa（Novoseven®）已經批准用於治療具有針對 FVIII 或 FIX 之抑制子的 A 型或 B 型血友病患者，且其亦用以終止出血事件或預防與外傷及/或手術相關的出血。重組 FVIIa 亦已經批准用於治療患有先天性 FVII 缺乏之患者，且其日益用於標示適應症外之用途，諸如治療非血友病患者之與其他先天性或後天性出血病症、外傷及手術相關的出血。

重組 FVIIa 促進凝塊形成之用途凸顯其日益增長的作

為治療劑之重要性。FVIIa 療法留下顯著未滿足之醫學需要。舉例而言，基於臨床試驗資料，需要經 6 小時或更長時間段平均給予 3 劑 FVIIa 來控制血友病患者之急性出血事件。需要 FVIIa 之更有效變異體來降低此等要求。因此，在本文之目標中，一目標為提供經修飾之 FVII 多肽，其經設計以具有改良之治療特性。

【發明內容】

本文提供經修飾之因子 VII（FVII）多肽。詳言之，本文提供展現促凝血活性的經修飾 FVII 多肽。與未經修飾之 FVII 多肽相比，FVII 多肽之一級序列經修飾，且其可包括胺基酸插入、缺失及置換。本文中提供之經修飾之 FVII 多肽包括展現以下各特徵之 FVII 多肽：對諸如抗凝血酶 III（AT-III）之抑制子及組織因子途徑抑制子（tissue factor pathway inhibitor，TFPI）具有增加之抗性者，對 Zn^{2+}之抑制作用具有增加之抗性者，在 TF 存在及/或不存在之情況下具有增加之催化活性者，具有改良之藥物動力學特性（諸如增加之半衰期）者，對血小板表面具有增加之結合及/或親和力者，對血清白蛋白具有增加之結合及/或親和力者，及對血小板整合素 $\alpha_{IIb}\beta_3$ 具有增加之結合及/或親和力者。經修飾之 FVII 多肽可含有本文中提供之修飾的任何組合，藉此與未經修飾之 FVII 多肽相比，多肽之一或多種活性或特性得以改變。典型地，經修飾之 FVII 多肽保留促凝血活性。本文亦提供編碼/表現經修飾之 FVII 多肽的核酸分

子、載體及細胞。本文亦提供醫藥組成物、製品、套組及治療方法。FVII 多肽包括具有影響其他活性及/或特性之修飾的對偶基因及物種變異體及多肽及其他變異體。亦包括包含本文所提供之修飾的 FVII 多肽之活性片段。例示性 FVII 多肽為包括 SEQ ID NO:3 中所闡明之胺基酸序列者以及與其具有 60%、65%、70%、75%、80%、85%、88%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或更高之序列一致性的變異體。

本文提供在 FVII 多肽中在具有 SEQ ID NO:3 中所闡明之胺基酸序列的 FVII 多肽之位置 Q286 或在 FVII 多肽之對應殘基中含有修飾的經修飾之因子 VII（FVII）多肽。該修飾可為胺基酸置換、胺基酸插入或缺失或其組合。在修飾為胺基酸置換之情況下，置換可藉由以下胺基酸實現：鹼性胺基酸（例如 Arg（R）、Lys（K）及 His（H））；或選自以下者之胺基酸：Arg（R）、Lys（K）、His（H）、Tyr（Y）、Gly（G）、Phe（F）、Met（M）、Ile（I）、Leu（L）、Val（V）、Pro（P）、Glu（E）、Trp（W）、Asp（D）及 Cys（C）。該等胺基酸置換之實例包括 Q286R、Q286K、Q286H、Q286Y、Q286G、Q286F、Q286M、Q286I、Q286L、Q286V、Q286P、Q286E、Q286W、Q286D 及 Q286C。可在含有 SEQ ID NO: 1-3 之任一者中所闡明的序列之未經修飾之 FVII 多肽或其對偶基因或物種變異體或與 SEQ ID NO: 1-3 之任一者之 FVII 具有至少 60%序列一致性之變異體，或包含 SEQ ID NO: 1-3 之任一者中所闡明的胺基酸序

列之FVII多肽或其對偶基因或物種變異體或與SEQ ID NO: 1-3之任一者之FVII具有至少60%序列一致性之變異體之活性片段中進行該等修飾。舉例而言，經修飾之FVII多肽可為在對應於FVII多肽之位置Q286的位置含有置換之活性片段。

本文提供經修飾之因子VII多肽，其在對應於包含SEQ ID NO:3中所闡明的胺基酸序列之FVII多肽的位置286之位置或在FVII多肽之對應殘基中含有為胺基酸置換之修飾。該修飾為藉由鹼性胺基酸在位置286之置換，其產生與在位置286不具有修飾的FVII多肽相比，展現增加之凝血活性的經修飾之FVII多肽。可用作置換胺基酸之鹼性胺基酸可選自Arg(R)、Lys(K)及His(H)。在一實例中，經修飾之FVII中之修飾為以Arg(R)置換Gln(Q)。本文亦提供經修飾之FVII多肽，其為在對應於FVII多肽之位置286的位置含有置換之活性片段。

在一些實例中，經修飾之FVII多肽在FVII多肽之另外的位置亦含有一或多個其他修飾。其他修飾可為胺基酸置換、插入或缺失。舉例而言，其他修飾可為在對應於選自以下者的位置之胺基酸置換：A51、S52、P54、S60、Q66、Y68、K109、S119、A122、G124、T130、E132、V158、K161、A175、D196、K197、K199、R202、H216、S222、G237、T239、H257、Q286、L287、R290、A292、A294、E296、M298、L305、S314、G318、P321、K337、K341、Q366、H373、F374、E394、P395及R396。該等修飾之實例包括

D196K、D196R、D196A、D196Y、D196F、D196W、D196L、D196I、K197Y、K197A、K197E、K197D、K197L、K197M、K197I、K197V、K197F、K197W、K199A、K199D、K199E、G237W、G237T、G237I、G237V、T239A、R290A、R290E、R290D、R290N、R290Q、R290K、R290M、R290V、K341E、K341R、K341Q、K341N、K341M、K341D、G237T238 插入 A、G237T238 插入 S、G237T238 插入 V、G237T238 插入 AS、G237T238 插入 SA、D196K197 插入 K、D196K197 插入 R、D196K197 插入 Y、D196K197 插入 W、D196K197 插入 A、D196K197 插入 M、K197I198 插入 E、K197I198 插入 Y、K197I198 插入 A、K197I198 插入 S、T239S、T239N、T239Q、T239V、T239L、T239H、T239I、L287T、M298Q、P321K、P321E、P321Y、P321S、Q366D、Q366E、Q366N、Q366T、Q366S、Q366V、Q366I、Q366L、Q366M、H373D、H373E、H373S、H373L、H373I、H373F、H373A、K161S、K161A、K161V、H216S、H216A、H216K、H216R、S222A、S222K、S222V、S222N、S222E、S222D、H257A、H257S、Gla 交換 FIX、Gla 交換 FX、Gla 交換蛋白質 C、Gla 交換蛋白質 S、Gla 交換凝血酶、S52A、S60A、E394N、P395A、R396S、R202S、A292N、A294S、G318N、A175S、K109N、A122N、G124S、A51N、T130N、E132S、S52N、P54S、S119N、L121S、T128N、P129A、Q66N、Y68S、S103S111 缺失插入 QRLMEDICLPRWGCLWEDDF、H115S126 缺失插入 QRLMEDICLPRWGCLWEDDF、T128P134 缺失插入

QRLMEDICLPRWGCLWEDDF、S103S111 缺失插入 IEDICLPRWGCLWE、H115S126 缺失插入 IEDICLPRWGCLWE、T128P134 缺失插入 IEDICLPRWGCLWE、S103S111 缺失插入 DICLPRWGCLWED、H115S126 缺失插入 DICLPRWGCLWED、T128P134 缺失插入 DICLPRWGCLWED、P406 插入 IEDICLPRWGCLW、P406 插入 GGGSIEDICLPRWGCLW、P406 插入 DICLPRWGCLWED、P406 插入 GGGSDICLPRWGCLWED、S103S111 缺失插入 SFGRGDIRNV、H115S126 缺失插入 SFGRGDIRNV、T127P134 缺失插入 SFGRGDIRNV、P406 插入 CSFGRGDIRNVC、P406 插入 GGGSCSFGRGDIRNVC、V158T、V158D、L287T、M298K 及 M298Q。

此等組合修飾之實例包括 Q286R/Gla 交換 FIX、Q286R/H257A、Q286R/S222A、Q286R/S222A/H257A、Q286R/S222A/Gla 交換 FIX、Q286R/H257A/Gla 交換 FIX、Q286R/S222A/H257A/Gla 交換 FIX、Q286R/M298Q、Q286R/M298Q/K341Q、Q286R/M298Q/K199E、Q286R/M298Q/Gla 交換 FIX、Q286R/Q366V、Q286R/A292N/A294S/Q366V、A175S/Q286R/Q366V、S222A/Q286R/Q366V、H257S/Q286R、H257S/Q286R/Q366V、S222A/H257A/Q286R/Q366V、Q286R/H373A、S222A/H257A/Q286R/M298Q、Q286R/K341D、Q286R/Q366D、Q286R/Q366N、

Q286R/M298Q/Q366D、Q286R/M298Q/Q366N、Q286R/H373F 及 Q286R/M298Q/H373F。

本文提供經修飾之 FVII 多肽，其在 FVII 多肽、其對偶基因或物種變異體或其活性片段中含有兩個或更多個修飾。該等多肽之至少一個修飾係在對應於具有 SEQ ID NO:3 中所闡明之胺基酸序列的 FVII 多肽之位置 Q286 的位置或在 FVII 多肽之對應殘基中，其限制條件為與未經修飾之 FVII 多肽相比，位置 Q286 之修飾未引入新糖苷化位點。該等修飾可為胺基酸置換、插入或缺失。舉例而言，位置 Q286 之修飾可為藉由選自以下者之胺基酸置換：Arg（R）、Lys（K）、His（H）、Tyr（Y）、Gly（G）、Phe（F）、Met（M）、Ile（I）、Leu（L）、Val（V）、Pro（P）、Glu（E）、Trp（W）、Asp（D）及 Cys（C）。在一些實例中，修飾為 Q286R。該一或多種其他修飾可選自 D196K、D196R、D196A、D196Y、D196F、D196W、D196L、D196I、K197Y、K197A、K197E、K197D、K197L、K197M、K197I、K197V、K197F、K197W、K199A、K199D、K199E、G237W、G237T、G237I、G237V、T239A、R290A、R290E、R290D、R290N、R290Q、R290K、R290M、R290V、K341E、K341R、K341Q、K341N、K341M、K341D、G237T238 插入 A、G237T238 插入 S、G237T238 插入 V、G237T238 插入 AS、G237T238 插入 SA、D196K197 插入 K、D196K197 插入 R、D196K197 插入 Y、D196K197 插入 W、D196K197 插入 A、D196K197 插入 M、K197I198 插入 E、K197I198 插入 Y、K197I198 插

入 A、K197I198 插入 S、T239S、T239N、T239Q、T239V、T239L、T239H、T239I、L287T、P321K、P321E、P321Y、P321S、Q366D、Q366E、Q366N、Q366T、Q366S、Q366V、Q366I、Q366L、Q366M、H373D、H373E、H373S、H373F、H373A、K161S、K161A、K161V、H216S、H216A、H216K、H216R、S222A、S222K、S222V、S222N、S222E、S222D、H257A、H257S、Gla 交換 FIX、Gla 交換 FX、Gla 交換蛋白質 C、Gla 交換蛋白質 S、Gla 交換凝血酶、S52A、S60A、E394N、P395A、R396S、R202S、A292N、A294S、G318N、A175S、K109N、A122N、G124S、A51N、T130N、E132S、S52N、P54S、S119N、L121S、T128N、P129A、Q66N、Y68S、S103S111 缺失插入 QRLMEDICLPRWGCLWEDDF、H115S126 缺失插入 QRLMEDICLPRWGCLWEDDF、T128P134 缺失插入 QRLMEDICLPRWGCLWEDDF、S103S111 缺失插入 IEDICLPRWGCLWE、H115S126 缺失插入 IEDICLPRWGCLWE、T128P134 缺失插入 IEDICLPRWGCLWE、S103S111 缺失插入 DICLPRWGCLWED、H115S126 缺失插入 DICLPRWGCLWED、T128P134 缺失插入 DICLPRWGCLWED、P406 插入 IEDICLPRWGCLW、P406 插入 GGGSIEDICLPRWGCLW、P406 插入 DICLPRWGCLWED、P406 插入 GGGSDICLPRWGCLWED、S103S111 缺失插入 SFGRGDIRNV、H115S126 缺失插入 SFGRGDIRNV、T127P134 缺失插入 SFGRGDIRNV、P406

插入 CSFGRGDIRNVC、P406 插入 GGGSCSFGRGDIRNVC、V158T、V158D、L287T、M298K 及 M298Q。

本文中提供的在 FVII 多肽中含有兩個或更多個修飾之經修飾之 FVII 多肽的實例包括（但不限於）Q286R/Gla 交換 FIX、Q286R/H257A、Q286R/S222A、Q286R/S222A/H257、Q286R/S222A/Gla 交換 FIX、Q286R/H257A/Gla 交換 FIX、Q286R/S222A/H257A/Gla 交換 FIX、Q286R/M298Q、Q286R/M298Q/K341Q、Q286R/M298Q/K199E、Q286R/M298Q/Gla 交換 FIX、Q286R/Q366V、Q286R/A292N/A294S/Q366V、A175S/Q286R/Q366V、S222A/Q286R/Q366V、H257S/Q286R、H257S/Q286R/Q366V、S222A/H257A/Q286R/Q366V、Q286R/H373A、S222A/H257A/Q286R/M298Q、V158D/E296V/M298Q、{Gla 交換 FIX/E40L}/Q286R/M298Q、{Gla 交換 FIX/K43I}/Q286R/M298Q、{Gla 交換 FIX/Q44S}/Q286R/M298Q、{Gla 交換 FIX/M19K}/Q286R/M298Q、{Gla 交換 FIX/M19K/E40L/K43I/Q44S}/Q286R/M298Q、T128N/P129A/Q286R、T128N/P129A/Q286R/M298Q、T128N/P129A/Q286R/H373F、V158D/Q286R/E296V/M298Q、Gla 交換 FIX/T128N/P129A/S222A/Q286R、Gla 交換 FIX/T128N/P129A/Q286R/M298Q、

T128N/P129A/S222A/H257A/Q286R/M298Q、T128N/P129A/Q286R/M298Q/H373F、S52A/S60A/Q286R、Gla 交換 FIX/S52A/S60A/S222A/Q286R、S52A/S60A/Q286R/M298Q、Gla 交換 FIX/S52A/S60A/Q286R/M298Q、S52A/S60A/S222A/H257A/Q286R/M298Q、S52A/S60A/Q286R/H373F/、S52A/S60A/Q286R/M298Q/H373F、T239V/Q286R、Gla 交換 FIX/S222A/T239V/Q286R、T239V/Q286R/M298Q、S222A/T239V/H257A/Q286R/M298Q、Gla 交換 FIX/T239V/Q286R/M298Q、T239V/Q286R/H373F、T239V/Q286R/M298Q/H373F、T239I/Q286R、Gla 交換 FIX/S222A/T239I/Q286R、T239I/Q286R/M298Q、S222A/T239I/H257A/Q286R/M298Q、Gla 交換 FIX/T239I/Q286R/M298Q、T239I/Q286R/H373F、T239I/Q286R/M298Q/H373F、Gla 交換 FIX/S222A/Q286R/H373F、Gla 交換 FIX/S222A/Q286R/M298Q、Gla 交換 FIX/S222A/Q286R/M298Q/H373F、V158D/Q286R/E296V/M298Q/H373F、H257A/Q286R/M298Q、H257S/Q286R/M298Q、Gla 交換 FIX/S222A/H257S/Q286R/、S222A/H257S/Q286R/M298Q、H257S/Q286R/M298Q/H373F、S222A/Q286R/M298Q/H373F、S222A/Q286R/M298Q、

T128N/P129A/A175S/Q286R、A122N/G124S/A175S/Q286R、Gla 交換 FIX/T128N/P129A/A175S/S222A/Q286R、Gla 交換 FIX/A122N/G124S/A175S/S222A/Q286R、T128N/P129A/A175S/Q286R/M298Q、A122N/G124S/A175S/Q286R/M298Q、T128N/P129A/A175S/S222A/H257A/Q286R/M298Q、A122N/G124S/A175S/S222A/H257A/Q286R/M298Q、T128N/P129A/A175S/Q286R/M298Q/H373F、A122N/G124S/A175S/Q286R/M298Q/H373F、{Gla 交換 FIX/K43I}/T128N/P129A/Q286R/M298Q、T128N/P129A/Q286R/M298Q/Q366N、{Gla 交換 FIX/K43I}/Q286R/M298Q/Q366N、{Gla 交換 FIX/K43I}/T128N/P129A/Q286R/M298Q/Q366N、V158D/Q286R/E296V/M298Q、T128N/P129A/Q286R/M298Q/Q366N/H373F、T239V/Q286R/M298Q/Q366N、T239I/Q286R/M298Q/Q366N、T128N/P129A/T239V/Q286R/M298Q、T128N/P129A/S222A/T239V/H257A/Q286R/M298Q、T128N/P129A/T239V/Q286R/M298Q/H373F 及 T128N/P129A/T239I/Q286R/M298Q。

本文提供經修飾之 FVII 多肽，其在對應於具有 SEQ ID NO:3 中所闡明的胺基酸序列之 FVII 多肽的 P54、Q66、

L121、A122、P129 或 E132 之位置或在 FVII 多肽之對應殘基中含有修飾。例示性修飾包括 P54S、Q66N、L121S、A122N、P129A 及 E132S。在一些實例中，在對應於 P54、Q66、L121、A122、P129 或 E132 之位置含有修飾的經修飾之 FVII 多肽亦含有一或多個其他修飾，包括在 FVII 多肽之另外的位置之胺基酸置換、插入或缺失。該等修飾包括 P54S、S52N、Y58S、S119N、T128N、T130N、G241S、E394N、P395A、R396S、G318N、G124S、A175S、E394N 及 P395A。因此，本文中提供之 FVII 多肽的組合修飾之實例為 S119N/L121S、T128N/P129A、A122N/G124S、A122N/G124S/A175S、A122N/G124S/E394N/P395A/R396S、A122N/G124S/E394N/P395A/R396S/G318N、A122N/G124S/E394N/P395A/R396S、S52N/P54S/A122N/G124S/E394N/P395A/R396S、S52N/P54S、S119N/L121S/A175S、T128N/P129A/A175S、T130N/E132S、Q66N/Y68S、T128N/P129A/V158D/E296V/M298Q、T128N/P129A/S222A、T128N/P129A/A175S/Q366V、A122N/G124S/A175S/Q366V、T128N/P129A/A175S/S222A、A122N/G124S/A175S/S222A、T128N/P129A/M298Q 及 T128N/P129A/M298Q/H373F。

本文亦提供經修飾之 FVII 多肽，其在具有 SEQ ID NO:3 中所闡明的胺基酸序列之 FVII 多肽中或在 FVII 多肽之對應殘基中含有對應於 T239S、T239Q、T239V、T239L、T239H、

T239I、P321K、P321E、P321Y、P321S、Q366D、Q366N、Q366V、Q366I、Q366L、Q366M、H373D、H373E、H373S、H373F、H373A、K161S、K161V、H216S、H216K、H216R、S222A、S222K、S222V、S222D、S222N、S222E 或 H257S 之修飾。另外，該等經修飾之 FVII 多肽亦可在另外的位置含有一或多個其他修飾，該另外的位置諸如胺基酸位置 A51、S52、P54、S60、Q66、Y68、K109、S119、A122、G124、T130、E132、V158、K161、A175、D196、K197、K199、R202、H216、S222、G237、T239、H257、Q286、L287、R290 A292、A294、E296、M298、L305、S314、G318、P321、K337、K341、Q366、H373、F374、E394、P395 及 R396。該等位置之例示性修飾包括 Q286N、Q286E、Q286D、Q286S、Q286T、Q286R、Q286K、Q286A、Q286V、Q286M、Q286L、Q286Y、D196K、D196R、D196A、D196Y、D196F、D196W、D196L、D196I、K197Y、K197A、K197E、K197D、K197L、K197M、K197I、K197V、K197F、K197W、K199A、K199D、K199E、G237W、G237T、G237I、G237V、T239A、R290A、R290E、R290D、R290N、R290Q、R290K、R290M、R290V、K341E、K341R、K341Q、K341N、K341M、K341D、G237T238 插入 A、G237T238 插入 S、G237T238 插入 V、G237T238 插入 AS、G237T238 插入 SA、D196K197 插入 K、D196K197 插入 R、D196K197 插入 Y、D196K197 插入 W、D196K197 插入 A、D196K197 插入 M、K197I198 插入 E、K197I198 插入 Y、K197I198 插入 A、K197I198 插入 S、

T239S、T239N、T239Q、T239V、T239L、T239H、T239I、L287T、P321K、P321E、P321Y、P321S、Q366D、Q366E、Q366N、Q366T、Q366S、Q366V、Q366I、Q366L、Q366M、H373D、H373E、H373S、H373F、H373A、K161S、K161A、K161V、H216S、H216A、H216K、H216R、S222A、S222K、S222V、S222N、S222E、S222D、H257A、H257S、Gla 交換 FIX、Gla 交換 FX、Gla 交換蛋白質 C、Gla 交換蛋白質 S、Gla 交換凝血酶、S52A、S60A、E394N、P395A、R396S、R202S、A292N、A294S、G318N、A175S、K109N、A122N、G124S、A51N、T130N、E132S、S52N、P54S、S119N、L121S、T128N、P129A、Q66N、Y68S、S103S111 缺失插入 QRLMEDICLPRWGCLWEDDF、H115S126 缺失插入 QRLMEDICLPRWGCLWEDDF、T128P134 缺失插入 QRLMEDICLPRWGCLWEDDF、S103S111 缺失插入 IEDICLPRWGCLWE、H115S126 缺失插入 IEDICLPRWGCLWE、T128P134 缺失插入 IEDICLPRWGCLWE、S103S111 缺失插入 DICLPRWGCLWED、H115S126 缺失插入 DICLPRWGCLWED、T128P134 缺失插入 DICLPRWGCLWED、P406 插入 IEDICLPRWGCLW、P406 插入 GGGSIEDICLPRWGCLW、P406 插入 DICLPRWGCLWED、P406 插入 GGGSDICLPRWGCLWED、S103S111 缺失插入 SFGRGDIRNV、H115S126 缺失插入 SFGRGDIRNV、T127P134 缺失插入 SFGRGDIRNV、P406

插入 CSFGRGDIRNVC、P406 插入 GGGSCSFGRGDIRNVC、V158T、V158D、L287T、M298K 及 M298Q。所得組合修飾可包括 Q366D/H373E、Q366V/H373V、Q366V/H373L、Q366V/H373I、S222K/H257A、H216A/S222A、S222S/Gla 交換 FIX、S222A/H257A/Gla 交換 FIX、S222A/M298Q、S222A/H257A/M298Q、S222A/A292N/A294S/Q366V、A175S/S222A/Q366V、S222A/Q366V、H257S/Q366V、S222A/H373A、M298Q/H373F、S52A/S60A/S222A、S222A/T239V、V158D/T239V/E296V/M298Q、S222A/T239I、V158D/E296V/M298Q/H373F、M298Q/Q366N/H373F、T239V/M298Q/H373F、T239I/M298Q/H373F 及 Gla 交換 FIX/Q366V。

本文提供經修飾之 FVII 多肽，其在 FVII 多肽、其對偶基因及物種變異體或其活性片段中含有兩個或更多個修飾，其中該兩個或更多個胺基酸修飾係選自對應於 H216A、H257A、E394N、P395A、R396S、K109N、A292N、A175S、H257A 及 Gla 交換 FIX 之胺基酸修飾。舉例而言，本文中提供之經修飾之 FVII 多肽包括彼等具有選自 H216A/H257A、E394N/P395A/R396S 及 K109N/A175S 之修飾者。另外，亦可包括對應於 M298Q 或 A294S 之修飾。因此，本文中亦提供經修飾之 FVII 多肽，其含有選自 H257A/M298Q 及 K109N/A292N/A294S 之修飾。

在一些實例中，本文中提供之經修飾之 FVII 多肽含有血清白蛋白結合序列，諸如 SEQ ID NO: 103-109 之任一者

中闡明之胺基酸序列，或其足以實現血清白蛋白結合之部分。與未經修飾之 FVII 多肽相比，該等經修飾之 FVII 多肽可對血清白蛋白結合展現增加之親和力或結合。舉例而言，含有血清白蛋白結合序列的經修飾之 FVII 多肽對血清白蛋白結合可展現至少約為或為 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、100%、200%、300%、400%、500%或更高之親和力或結合增加。血清白蛋白結合序列可置換未經修飾之 FVII 多肽的胺基酸殘基之連續序列。含有血清白蛋白結合序列的經修飾之 FVII 多肽可含有選自以下者之修飾：S103S111 缺失插入 QRLMEDICLPRWGCLWEDDF、H115S126 缺失插入 QRLMEDICLPRWGCLWEDDF、T128P134 缺失插入 QRLMEDICLPRWGCLWEDDF、S103S111 缺失插入 IEDICLPRWGCLWE、H115S126 缺失插入 IEDICLPRWGCLWE、T128P134 缺失插入 IEDICLPRWGCLWE、S103S111 缺失插入 DICLPRWGCLWED、H115S126 缺失插入 DICLPRWGCLWED、T128P134 缺失插入 DICLPRWGCLWED、P406 插入 IEDICLPRWGCLW、P406 插入 GGGSIEDICLPRWGCLW、P406 插入 DICLPRWGCLWED 及 P406 插入 GGGSDICLPRWGCLWED。

本文中提供經修飾之 FVII 多肽，其含有血小板整合素 $\alpha_{IIb}\beta_3$ 結合序列。與未經修飾之 FVII 多肽相比，該等經修

飾之 FVII 多肽可對血小板整合素 $\alpha_{IIb}\beta_3$ 展現增加之親和力或結合。舉例而言，與未經修飾之 FVII 多肽相比，含有血小板整合素 $\alpha_{IIb}\beta_3$ 結合序列的經修飾之 FVII 多肽對血小板整合素 $\alpha_{IIb}\beta_3$ 結合可展現至少約為或為 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、100%、200%、300%、400%、500%或更高之親和力或結合增加。血清白蛋白結合序列之實例包括 SEQ ID NO: 110-112 之任一者中闡明的彼等胺基酸序列，或其足以實現血小板整合素 $\alpha_{IIb}\beta_3$ 結合之部分，其可置換未經修飾之 FVII 多肽的胺基酸殘基之連續序列。經修飾之 FVII 多肽含有選自以下者之修飾：S103S111 缺失插入 SFGRGDIRNV、H115S126 缺失插入 SFGRGDIRNV、T127P134 缺失插入 SFGRGDIRNV、P406 插入 CSFGRGDIRNVC 及 P406 插入 GGGSCSFGRGDIRNVC。

含有血清白蛋白或血小板整合素 $\alpha_{IIb}\beta_3$ 結合序列的經修飾之 FVII 多肽亦可在 FVII 多肽之另外的位置含有一或多個其他修飾，諸如在對應於位置 G237V 之位置的胺基酸置換。因此，本文亦提供經修飾之 FVII 多肽，其含有選自以下者之修飾：S103S111 缺失插入 IEDICLPRWGCLWE/G237V、S103S111 缺失插入 DICLPRWGCLWED/G237V、H115S126 缺失插入 QRLMEDICLPRWGCLWEDDF/G237V、H115S126 缺失插入 IEDICLPRWGCLWE/G237V、H115S126 缺失插入

DICLPRWGCLWED/G237V、T128P134 缺失插入 QRLMEDICLPRWGCLWEDDF/G237V、T128P134 缺失插入 IEDICLPRWGCLWE/G237V、S103S111 缺失插入 QRLMEDICLPRWGCLWEDDF/G237V and T128P134 缺失插入 DICLPRWGCLWED/G237V。

在一些實例中，本文中提供之經修飾之 FVII 多肽含有 2、3、4、5、6、7 或更多個修飾。在其他實例中，本文中提供之經修飾之 FVII 多肽含有異源 Gla 域或其足以實現磷脂結合之部分。與未經修飾之 FVII 多肽相比，該等多肽可對磷脂展現增加之親和力或結合，諸如對磷脂展現至少約為或為 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、100%、200%、300%、400%、500%或更高之親和力或結合增加。異源 Gla 域可選自因子 IX（FIX）、因子 X（FX）、凝血酶原、蛋白質 C、蛋白質 S、骨鈣蛋白（osteocalcin）、基質 Gla 蛋白質、生長抑止特異性蛋白 6（Growth-arrest-specific protein 6，Gas6）及蛋白質 Z 之 Gla 域，且在一些實例中可具有 SEQ ID NO: 83-91、93 及 94 之任一者中所闡明之胺基酸序列或其足以實現磷脂結合之部分。可移除且以異源 Gla 域或其足以實現磷脂結合之部分置換可包括具有 SEQ ID NO:3 中所闡明之胺基酸序列的 FVII 多肽之胺基酸 1-45 的原生 FVII Gla 域或 FVII 多肽之對應殘基之全部或連續部分。

與未經修飾之 FVII 多肽相比，本文中提供之經修飾之

FVII 多肽可展現增加之對抗凝血酶 III 的抗性。該經修飾之 FVII 多肽可具有至少約或具有 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、100%、200%、300%、400%、500%或更高的對抗凝血酶 III 的抗性。與未經修飾之 FVII 多肽相比，本文中提供之經修飾之 FVII 多肽亦可展現增加之催化或凝血活性，諸如比未經修飾之 FVII 多肽的催化或凝血活性增加至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、100%、200%、300%、400%、500%或更高。另外，與未經修飾之 FVII 多肽相比，本文中提供之經修飾之 FVII 多肽可展現增加之對 TFPI 的抗性。與未經修飾之 FVII 多肽相比，該等經修飾之 FVII 多肽可具有至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、100%、200%、300%、400%、500%或更高的對 TFPI 的抗性。與未經修飾之 FVII 多肽相比，本文中提供之經修飾之 FVII 多肽亦可展現增加之對 Zn^{2+}抑制作用的抗性。舉例而言，與未經修飾之 FVII 多肽相比，經修飾之 FVII 多肽可具有至少約或具有 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、100%、200%、

300%、400%、500%或更高的對 Zn^{2+}抑制作用的抗性。

在一些實例中，與未經修飾之 FVII 多肽相比，本文中提供之經修飾之 FVII 多肽含有引入及/或消除一或多個糖苷化位點之一或多個修飾。舉例而言，可引入或消除 1、2、3、4、5、6 或更多個糖苷化位點。可引入或消除之糖苷化位點包括 N-糖苷化位點及 O-糖苷化位點。本文中提供之經修飾之 FVII 多肽可含有一或多個其他胺基酸修飾，其提高對抗凝血酶 III 的抗性、提高對磷脂之結合及/或親和力、提高對組織因子之親和力、提高固有活性、提高 TF 依賴性活性、提高凝血活性、改變多肽之構形以改變酶原性、藉由使高活性與較低活性 FVIIa 構形之間的平衡移動偏向高活性構形來提高催化或凝血活性、提高對蛋白酶的抗性、減少糖苷化、增加糖苷化、降低免疫原性、提高穩定性及/或促進化學基團連接。在一些實例中，經改變之酶原性賦予更高酶原樣形狀或更低酶原樣形狀。

本文中提供之經修飾之 FVII 多肽可含有一或多個選自以下修飾之其他胺基酸修飾：S279C/V302C、L280C/N301C、V210C/V302C、S282C/V299C、位置 4 之酪胺酸插入、F4S、F4T、P10Q、P10E、P10D、P10N、Q21N、R28F、R28E、I30C、I30D、I30E、K32D、K32Q、K32E、K32G、K32H、K32T、K32C、K32A、K32S、D33C、D33F、D33E、D33K、A34C、A34E、A34D、A34I、A34L、A34M、A34V、A34F、A34W、A34Y、R36D、R36E、T37C、T37D、T37E、K38C、K38E、K38T、K38D、K38L、K38G、K38A、

K38S、K38N、K38H、L39E、L39Q、L39H、W41N、W41C、W41E、W41D、I42R、I42N、I42S、I42A、I42Q、I42N、I42S、I42A、I42Q、I42K、S43Q、S43N、Y44K、Y44C、Y44D、Y44E、S45C、S45D、S45E、D46C、A51N、S53N、G58N、G59S、G59T、K62E、K62R、K62D、K62N、K62Q、K62T、L65Q、L65S、L65N、F71D、F71Y、F71E、F71Q、F71N、P74S、P74A、A75E、A75D、E77A、E82Q、E82N、E82S、E82T T83K、N95S、N95T、G97S、G97T、Y101N、D104N、T106N、K109N、E116D、G117N、G124N、S126N、T128N、L141C、L141D、L141E、E142D、E142C、K143C、K143D、K143E、R144E、R144C、R144D、N145Y、N145G、N145F、N145M、N145S、N145I、N145L、N145T、N145V、N145P、N145K、N145H、N145Q、N145E、N145R、N145W、N145D、N145C、K157V、K157L、K157I、K157M、K157F、K157W、K157P、K157G、K157S、K157T、K157C、K157Y、K157N、K157E、K157R、K157H、K157D、K157Q、V158L、V158I、V158M、V158F、V158W、V158P、V158G、V158S、V158T、V158C、V158Y、V158N、V158E、V158R、V158K、V158H、V158D、V158Q、A175S、A175T、G179N、I186S、I186T、V188N、R202S、R202T、I205S、I205T、D212N、E220N、I230N、P231N、P236N、G237N、Q250C、V253N、E265N、T267N、E270N、A274M、A274L、A274K、A274R、A274D、A274V、A274I、A274F、A274W、A274P、A274G、A274T、A274C、A274Y、A274N、A274E、A274H、A274S、A274Q、

F275H、R277N、F278S、F278A、F278N、F278Q、F278G、L280N、L288K、L288C、L288D、D289C、D289K、L288E、R290C、R290G、R290A、R290S、R290T、R290K、R290D、R290E、G291E、G291D、G291C、G291N、G291K、A292C、A292K、A292D、A292E、T293K、E296V、E296L、E296I、E296M、E296F、E296W、E296P、E296G、E296S、E296T、E296C、E296Y、E296N、E296K、E296R、E296H、E296D、E296Q、M298Q、M298V、M298L、M298I、M298F、M298W、M298P、M298G、M298S、M298T、M298C、M298Y、M298N、M298K、M298R、M298H、M298E、M298D、P303S、P303ST、R304Y、R304F、R304L、R304M、R304G、R304T、R304A、R304S、R304N、L305V、L305Y、L305I、L305F、L305A、L305M、L305W、L305P、L305G、L305S、L305T、L305C、L305N、L305E、L305K、L305R、L305H、L305D、L305Q、M306D、M306N、D309S、D309T、Q312N、Q313K、Q313D、Q313E、S314A、S314V、S314I、S314M、S314F、S314W、S314P、S314G、S314L、S314T、S314C、S314Y、S314N、S314E、S314K、S314R、S314H、S314D、S314Q、R315K、R315G、R315A、R315S、R315T、R315Q、R315C、R315D、R315E、K316D、K316C、K316E、V317C、V317K、V317D、V317E、G318N、N322Y、N322G、N322F、N322M、N322S、N322I、N322L、N322T、N322V、N322P、N322K、N322H、N322Q、N322E、N322R、N322W、N322C、G331N、Y332S、Y332A、Y332N、Y332Q、Y332G、D334G、D334E、D334A、

D334V、D334I、D334M、D334F、D334W、D334P、D334L、D334T、D334C、D334Y、D334N、D334K、D334R、D334H、D334S、D334Q、S336G、S336E、S336A、S336V、S336I、S336M、S336F、S336W、S336P、S336L、S336T、S336C、S336Y、S336N、S336K、S336R、S336H、S336D、S336Q、K337L、K337V、K337I、K337M、K337F、K337W、K337P、K337G、K337S、K337T、K337C、K337Y、K337N、K337E、K337R、K337H、K337D、K337Q、K341E、K341Q、K341G、K341T、K341A、K341S、G342N、H348N、R353N、Y357N、I361N、F374P、F374A、F374V、F374I、F374L、F374M、F374W、F374G、F374S、F374T、F374C、F374Y、F374N、F374E、F374K、F374R、F374H、F374D、F374Q、V376N、R379N、L390C、L390K、L390D、L390E、M391D、M391C、M391K、M391N、M391E、R392C、R392D、R392E、S393D、S393C、S393K、S393E、E394K、P395K、E394C、P395D、P395C、P395E、R396K、R396C、R396D、R396E、P397D、P397K、P397C、P397E、G398K、G398C、G398D、G398E、V399C、V399D、V399K、V399E、L400K、L401K、L401C、L401D、L401E、R402D、R402C、R402K、R402E、A403K、A403C、A403D、A403E、P404E、P404D、P404C、P404K、F405K、P406C、K32N/A34S、K32N/A34T、F31N/D33S、F31N/D33T、I30N/K32S、I30N/K32T、A34N/R36S、A34N/R36T、K38N/F40S、K38N/F40T、T37N/L39S、T37N/L39T、R36N/K38S、R36N/K38T、L39N/W41S、

L39N/W41T、F40N/I42S、F40N/I42T、I42N/Y44S、I42N/Y44T、Y44N/D46S、Y44N/D46T、D46N/D48S、D46N/D48T、G47N/Q49S、G47N/Q49T、K143N/N145S、K143N/N145T、E142N/R144S、E142N/R144T、L141N/K143S、L141N/K143T、I140N/E142S/、I140N/E142T、R144N/A146S、R144N/A146T、A146N/K148S、A146N/K148T、S147N/P149S/、S147N/P149T、R290N/A292S、R290N/A292T、D289N/G291S、D289N/G291T、L288N/R290S、L288N/R290T、L287N/D289S、L287N/D289T、A292N/A294S、A292N/A294T、T293N/L295S、T293N/L295T、R315N/V317S、R315N/V317T、S314N/K316S、S314N/K316T、Q313N/R315S、Q313N/R315T、K316N/G318S、K316N/G318T、V317N/D319S、V317N/D319T、K341N/D343S、K341N/D343T、S339N/K341S、S339N/K341T、D343N/G345S、D343N/G345T、R392N/E394S、R392N/E394T、L390N/R392S、L390N/R392T、K389N/M391S、K389N/M391T、S393N/P395S、S393N/P395T、E394N/R396S、E394N/R396T、P395N/P397S、P395N/P397T、R396N/G398S、R396N/G398T、P397N/V399S、P397N/V399T、G398N/L400S、G398N/L400T、V399N/L401S、V399N/L401T、L400N/R402S、L400N/R402T、L401N/A403S、

L401N/A403T、R402N/P404S、R402N/P404T、A403N/F405S、A403N/F405T、P404N/P406S 及 P404N/P406T。在一些實例中，經修飾之 FVII 多肽亦含有位置 300-322、305-322、300-312 或 305-312 之經來自胰蛋白酶、凝血酶或 FX 的對應胺基酸之取代，或位置 310-329、311-322 或 233-329 之經來自胰蛋白酶的對應胺基酸之取代。

本文中提供之經修飾之 FVII 多肽的實例為彼等具有 SEQ ID NO: 113-273 之任一者中所闡明的胺基酸序列者。在一些實例中，在為 SEQ ID NO:3 中所闡明的多肽之對偶基因或物種變異體的未經修飾之 FVII 多肽中進行修飾。排除胺基酸修飾，對偶基因或物種或其他變異體可與 SEQ ID NO: 3 中闡明之多肽具有 40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、或 99% 序列一致性。本文中提供之經修飾之 FVII 多肽可為人類多肽、非人類多肽及/或成熟多肽。在一些實例中，僅修飾一級序列。在其他實例中，亦包括化學修飾或轉譯後修飾。舉例而言，經修飾之 FVII 多肽可經糖苷化、羧基化、羥基化、硫酸化、磷酸化、白蛋白化或與聚乙二醇（PEG）部分接合。

本文中提供之經修飾之 FVII 多肽可為單鏈多肽、雙鏈多肽及/或具有活性或經活化。可藉由自體活化來蛋白水解裂解、藉由因子 IX（FIXa）裂解、藉由因子 X（FXa）裂解、藉由因子 XII（FXIIa）裂解或藉由凝血酶裂解來實現活化。

本文中提供之經修飾之 FVII 多肽可保留未經修飾之 FVII 多肽的一或多種活性。舉例而言，經修飾之 FVII 多肽可含有胺基酸位置 1、2、3、4、5、6、7、8、9、10、20、30、40、50 或 60 之修飾，只要多肽保留未經修飾之 FVII 多肽的至少一種 FVII 活性即可。該等經修飾之 FVII 多肽可保留未經修飾之 FVII 多肽之活性的至少約 1%、2%、3%、4%、5%、10%、20%、30%、40%、50%、60%、70%、80%、90%、95%、96%、97%、98%、99%、100%、200%、300%、400%、500%或更高。在一些實例中，一或多種活性係選自組織因子（TF）結合、因子 X（FX）活化、因子 IX（FIX）活化、磷脂結合及凝血活性。另外，與未經修飾之 FVII 多肽相比，所保留之活性可增強或降低。在一些實例中，與未經修飾之 FVII 多肽相比凝血活性增強，諸如未經修飾之 FVII 多肽之凝血活性的至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、100%、200%、300%、400%、500%或更高。可活體外、試管內或活體內量測活性。

本文提供含有編碼本文中提供之經修飾之 FVII 多肽的核苷酸序列的核酸分子。亦提供含有該等核酸分子之載體，包括原核載體、病毒載體或真核載體，諸如哺乳動物載體。病毒載體可選自腺病毒、腺相關病毒、逆轉錄病毒、疱疹病毒、慢病毒、痘病毒及細胞巨大病毒。本文中提供含有此等載體之細胞，包括真核細胞，諸如哺乳動物細胞。

例示性哺乳動物細胞為幼小倉鼠腎臟細胞（BHK-21）或 293 細胞或 CHO 細胞。在一些實例中，該等細胞表現經修飾之 FVII 多肽。因此，本文中亦提供由該等細胞產生的經修飾之 FVII 多肽。

本文中提供在醫藥學上可接受之媒劑中含有治療有效濃度或量之本文中提供的任何經修飾之 FVII 多肽、核酸分子、載體或細胞的醫藥組成物。在一些實例中，醫藥組成物經調配用於局部（local）、全身性或局部性（topical）投藥，諸如經口、經鼻、肺部、頰內、經皮、皮下、十二指腸內、腸內、非經腸、靜脈內或肌肉內投藥。醫藥組成物亦可經調配用於控釋及/或單劑投藥。

本文中提供藉由投予本文中提供之醫藥組成物來治療個體之方法，其中該個體患有藉由投予 FVII 或促凝血劑，諸如藉由投予活性 FVII（FVIIa）治療之疾病或病狀。在一些實例中，以醫藥組成物治療改善或緩與疾病或病狀相關的症狀。在其他實例中，本文中提供之方法亦包括監測個體之與藉由投予 FVII 或促凝血劑治療之疾病或病狀相關的症狀變化。待使用本文中提供之方法治療之疾病或病狀可選自凝血病症、血液學病症、出血性病症、血友病（諸如 A 型血友病或 B 型血友病或 C 型血友病、先天性或後天性血友病）、因子 VII 缺乏及出血病症，包括歸因於手術（諸如心臟手術、血管成形術、肺部手術、腹部手術、脊椎手術、腦部手術、血管手術、牙科手術或器官移植手術）或外傷之出血併發症。在一些實例中，出血表現為急性關節積血、

慢性血友病性關節病、血腫、血尿、中樞神經系統出血、胃腸出血、或大腦出血。在其他實例中，出血歸因於拔牙。移植手術可選自骨髓、心臟、肺、胰腺及肝臟之移植。

在一些實例中，本文中提供之方法可用於治療具有因子 VIII 或因子 IX 之自體抗體的個體。本文中提供之方法亦可包括投予一或多種其他凝血因子，諸如血漿純化或重組凝血因子、促凝血劑，諸如維生素 K、維生素 K 衍生物及蛋白質 C 抑制劑、血漿、血小板、紅血球及皮質類固醇、或療法。

本文中提供含有包裝材料及含於該包裝材料內之本文中提供之醫藥組成物的製品。在一些實例中，醫藥組成物中之經修飾之 FVII 多肽有效治療 FVII 介導的疾病或病症，且包裝材料包括指示使用該經修飾之 FVII 多肽來治療 FVII 介導之疾病或病症的標籤。本文中亦提供套組，其包含本文所述之醫藥組成物，用於投予該組成物之裝置及視情況投藥用法說明書。

【實施方式】

大綱

A. 定義

B. 止血概述

1. 血小板黏附及聚集

2. 凝血級聯

a. 起始

b. 擴增

c. 增長

3. 凝血調節

C. 因子 VII（FVII）

1. FVII 結構及組建

2. 轉譯後修飾

3. FVII 加工

4. FVII 活化

5. FVII 功能

a. 組織因子依賴性 FVIIa 活性

b. 組織因子獨立性 FVIIa 活性

6. FVII 作爲生物醫藥

D. 經修飾之 FVII 多肽

1. 增強之催化活性

a. 增強催化活性之例示性修飾

b. Q286R

2. 增強之對 AT-III 之抗性

實現增強之對 AT-III 之抗性的例示性修飾

3. 增強之對 Zn^{2+}抑制的抗性

增強對 Zn^{2+}抑制的抗性之例示性修飾

4. 改變之糖苷化

改變糖苷化之例示性修飾

5. 增強之與血清白蛋白及/或血小板整合素 $\alpha_{IIb}\beta_3$ 的結合

a. 具有血清白蛋白結合序列之例示性 FVII 多肽

b. 具有血小板整合素 $\alpha_{IIb}\beta_3$ 結合序列之例示性 FVII 多肽

6. 藉由引入異源 Gla 域加以修飾

7. 組合及其他修飾

a. 增強對 TFPI 之抗性的修飾

b. 增強固有活性之修飾

c. 增強對蛋白酶之抗性的修飾

d. 增強對磷脂之親和力的修飾

e. 改變糖苷化之修飾

f. 促進化學基團連接之修飾

g. 例示性組合突變

E. FVII 多肽之製備

1. 載體及細胞

2. 表現系統

a. 原核表現

b. 酵母菌

c. 昆蟲及昆蟲細胞

d. 哺乳動物細胞

e. 植物

2. 純化

3. 融合蛋白

4. 多肽修飾

5. 核苷酸序列

F. 評估經修飾之 FVII 多肽活性

1. 試管內檢定

a. 轉譯後修飾

b. 蛋白水解活性

c. 凝血活性

d. 結合其他蛋白質及/或受其他蛋白質抑制

e. 磷脂結合

2. 非人類動物模型

3. 臨床檢定

G. 調配物及投藥

1. 調配物

a. 劑量

b. 劑型

2. 投予經修飾之 FVII 多肽

3. 投予編碼經修飾之 FVII 多肽的核酸（基因療法）

H. 治療用途

1. 先天性出血病症

a. 血友病

b. FVII 缺乏

c. 其他

2. 後天性出血病症

a. 化學療法-後天性血小板減少症

b. 其他凝血病

c. 移植-後天性出血

d. 抗凝血療法-誘導出血

e. 後天性血友病

3. 外傷及手術出血

I. 組合療法

J. 製品及套組

K. 實施例

A. 定義

除非另作定義，否則文中所用之所有技術及科學術語具有如本發明所屬之技術中的一般技術者通常所瞭解相同之含義。除非另外說明，否則本文之全部揭示內容通篇提及之所有專利、專利申請案、公開申請案及公開案、Genbank序列、資料庫、網站及其他公開材料係以引用的方式全部併入本文中。在本文中之術語存在複數種定義之情況下，以此部分中之彼等定義為主。若引用 URL 或其他此類識別符或位址，則應瞭解該等識別符可改變，且尤其有關因特網之資訊可出現或消失，但藉由檢索因特網可發現等效資訊。其引用證明該資訊之可用性及公開傳播性。

如本文中所用，凝血途徑或凝血級聯係指引起不溶性血纖維蛋白凝塊形成之一系列活化事件。在凝血級聯或途徑中，絲胺酸蛋白酶之無活性蛋白質（亦稱為酶原）藉由裂解一或多個肽鍵轉化成活性蛋白酶，其接著充當級聯中下一個酶原分子之活化蛋白酶。在級聯之最終蛋白水解步

驟中，血纖維蛋白原藉由凝血酶蛋白水解裂解為血纖蛋白，其接著在損傷部位交聯以形成凝塊。

如本文中所用，「止血（hemostasis）」係指使器官或身體部分中之出血或血流停止。術語止血可涵蓋血管損傷後血液凝結以防止失血至隨後組織修復後血凝塊溶解之整個過程。

如本文中所用，「凝結（clotting）」或「凝血（coagulation）」係指不溶性血纖維蛋白凝塊之形成，或血液之凝血因子在凝血級聯中交互作用，最終引起不溶性血纖維蛋白凝塊形成的過程。

如本文中所用，「蛋白酶（protease）」為催化共價肽鍵水解之酶。此等命名包括酶原形式及其經活化之單鏈、雙鏈及多鏈形式。為清晰起見，對蛋白酶之提及係指所有形式。蛋白酶包括（例如）絲胺酸蛋白酶、半胱胺酸蛋白酶、天冬胺酸蛋白酶、蘇胺酸及金屬蛋白酶，此取決於其活性位點之催化活性及裂解目標受質的肽鍵之機制。

如本文中所用，絲胺酸蛋白酶或絲胺酸肽鍵內切酶係指一類肽酶，其特徵在於酶之活性位點中存在絲胺酸殘基。絲胺酸蛋白酶在體內參與多種功能，包括血液凝結及發炎，以及在原核生物及真核生物中充當消化酶。絲胺酸蛋白酶裂解之機制係基於絲胺酸對目標肽鍵之親核攻擊。與天冬胺酸或金屬締合之半胱胺酸、蘇胺酸或水分子亦可起此作用。絲胺酸、組胺酸及天冬胺酸之經對準側鏈形成大多數絲胺酸蛋白酶所共有之催化三合體。絲胺酸蛋白酶

之活性位點形狀為多肽受質結合之裂口。

如本文中所用，因子 VII（FVII、F7；亦稱為因子 7、凝血因子 VII、血清因子 VII、血清凝血酶原轉變加速因子、SPCA、轉變素原及依他凝血素 α（eptacog alpha））係指為凝血級聯之部分的絲胺酸蛋白酶。FVII 包括一個 Gla 域、兩個 EGF 域（EGF-1 及 EGF-2）及一個在絲胺酸蛋白酶之肽酶 S1 家族的所有成員（諸如胰凝乳蛋白酶）中高度保守之絲胺酸蛋白酶域（或肽酶 S1 域）。具有信號肽及前肽之例示性前驅體 FVII 的序列闡明於 SEQ ID NO: 1 中。一例示性成熟 FVII 多肽闡明於 SEQ ID NO:3 中。FVII 以單鏈酶原、酶原樣雙鏈多肽及充分活化雙鏈形式存在。與輔因子組織因子結合後發生充分活化，該充分活化在構形自酶原樣形式改變後發生。亦可在組織因子不存在之情況下引入引起構形變化之突變。

因此，對 FVII 之提及包括其單鏈及雙鏈形式，包括酶原樣及充分活化之雙鏈形式。

對 FVII 多肽之提及亦包括單鏈或雙鏈形式之前驅體多肽及成熟 FVII 多肽，具有活性之其截斷形式，且包括對偶基因變異體及物種變異體、由剪接變異體編碼之變異體及其他變異體，包括與 SEQ ID NO: 1 中闡明之前驅體多肽或其成熟形式具有至少 40%、45%、50%、55%、65%、70%、75%、80%、85%、90%、95%、96%、97%、98%、99%或更高的序列一致性之多肽。包括經修飾之 FVII 多肽，諸如 SEQ ID NO: 113 及 273 之多肽及其變異體。亦包括彼等保留 FVII

之至少一種活性者，諸如 FVII 之 TF 結合、因子 X 結合、磷脂結合及/或凝血活性。藉由保留活性，活性可改變，諸如與野生型 FVII 相比降低或增強，只要所保留活性之量足以產生可偵測作用。FVII 多肽包括（但不限於）組織特異性同功異型物及其對偶基因變異體、藉由轉譯核酸製備之合成分子、藉由化學合成產生之蛋白質（諸如包括經由重組性方法連接較短多肽之合成）、自人類及非人類組織及細胞分離之蛋白質、嵌合 FVII 多肽及其經修飾形式。FVII 多肽亦包括 FVII 之具有足夠長度或包括適當區域以保留全長成熟多肽的至少一種活性（必要時，在活化後）的片段或部分。FVII 多肽亦包括彼等含有化學或轉譯後修飾者及彼等不含化學或轉譯後修飾者。該等修飾包括（但不限於）聚乙二醇化、白蛋白化、糖苷化、法尼基化、羧基化、羥基化、磷酸化及其他在此項技術中已知之多肽修飾。

例示性 FVII 多肽為哺乳動物、包括人類來源之 FVII 多肽。人類來源之 FVII 的例示性胺基酸序列闡明於 SEQ ID NO: 1、2 及 3 中。該人類 FVII 多肽之例示性變異體包括 SEQ ID NO: 18-74 中所闡明之前驅體多肽的任一者。FVII 多肽亦包括非人類來源之任一者，該非人類來源包括（但不限於）鼠、犬、貓、野兔、禽、牛、羊、豬、馬、魚、蛙及其他靈長類因子 VII 多肽。非人類來源之例示性 FVII 多肽包括例如母牛（家牛（*Bos taurus*），SEQ ID NO:4）、小鼠（家鼷鼠（*Mus musculus*），SEQ ID NO:5）、侏儒黑猩猩（*Pan paniscus*，SEQ ID NO:6）、黑猩猩（*Pan*

troglodytes，SEQ ID NO:7）、兔（穴兔（*Oryctolagus cuniculus*），SEQ ID NO:8）、大鼠（挪威大鼠（*Rattus norvegicus*），SEQ ID NO: 9）、恆河猴（恆河獼猴（*Macaca mulatta*），SEQ ID NO:10）、豬（*Sus scrofa*，SEQ ID NO:11）、犬（家犬（*Canis familiaris*），SEQ ID NO:12）、斑馬魚（*Brachydanio rerio*，SEQ ID NO:13）、日本河豚（河豚（*Fugu rubripes*），SEQ ID NO:14）、雞（*Gallus gallus*，SEQ ID NO:15）、紅毛猩猩（*Pongo pygmaeus*，SEQ ID NO: 16）及大猩猩（*Gorilla gorilla*，SEQ ID NO:17）。

熟習此項技術者認識到當與 SEQ ID NO: 1 中所闡明之同功異型物 a 前驅體 FVII 多肽（其為含有信號肽及前肽序列之同功異型物 a 因子 VII 多肽）相比時，成熟因子 VII 多肽（SEQ ID NO: 3）之參考位置之不同之處在於 60 個胺基酸殘基。因此，SEQ ID NO: 3 之第一個胺基酸殘基「對應於」SEQ ID NO: 1 之第六十一個（第 61 個）胺基酸殘基。熟習此項技術者亦認識到當與 SEQ ID NO: 2 中所闡明之前驅體 FVII 多肽（其為含有信號肽及前肽序列之同功異型物 b 因子 VII 多肽）相比時，成熟因子 VII 多肽（SEQ ID NO: 3）之參考位置之不同之處在於 38 個胺基酸殘基。因此，SEQ ID NO: 3 之第一個胺基酸殘基「對應於」SEQ ID NO:2 之第三十九個（第 39 個）胺基酸殘基。

如本文中所用，對應殘基係指經對準之位置處存在之殘基。藉由熟習此項技術者已知之任何方法使相關或變異體多肽對準。該等方法通常使匹配最大化，且包括諸如使

用人工比對及藉由使用許多可用比對程式（例如 BLASTP）之方法及熟習此項技術者已知之其他方法。藉由將多肽之序列對準，熟習此項技術者可使用保守及一致胺基酸殘基作為指導來鑑別對應殘基。舉例而言，藉由將因子 VII 多肽之序列對準，熟習此項技術者可使用保守及一致胺基酸殘基作為指導來鑑別對應殘基。舉例而言，SEQ ID NO:3（成熟因子 VII）之胺基酸位置 1（A1）的丙胺酸對應於 SEQ ID NO:1 的胺基酸位置 61（A61）之丙胺酸及 SEQ ID NO:2 之胺基酸位置 39（A39）的丙胺酸。在其他情況下，可鑑別對應區域。舉例而言，Gla 域對應於 SEQ ID NO:3 之胺基酸位置 A1 至 F45，對應於 SEQ ID NO:1 之胺基酸位置 A61 至 S105 且對應於 SEQ ID NO:2 之胺基酸位置 A39 至 S83。熟習此項技術者亦可採用保守胺基酸殘基作為指導來發現人類與非人類序列之間及其中的對應胺基酸殘基。舉例而言，SEQ ID NO:3（人類）之胺基酸殘基 S43 及 E163 對應於 SEQ ID NO: 4（牛）之 S83 及 E203。使位置對應亦可基於結構比對，例如藉由使用蛋白質結構之電腦模擬比對。在其他情況下，可鑑別對應區域。

如本文中所用，「前區域（proregion）」、「前肽（propeptide）」或「前序列（pro sequence）」係指裂解產生成熟蛋白質之區域或區段。其可包括起作用以藉由掩蔽催化機構且因此防止催化中間物形成（亦即藉由空間上阻塞受質結合位點）來抑制蛋白水解活性之區段。前區域為位於成熟生物活性多肽之胺基末端之胺基酸序列且可少至

數個胺基酸或可為多域結構。

如本文中所用，「成熟因子 VII（mature factor VII）」係指缺乏信號序列及前肽序列的 FVII 多肽。典型地，信號序列經由內質網（ER）-高爾基體途徑靶向用於分泌之蛋白質，且在轉譯期間在插入 ER 後經裂解。前肽序列典型地在蛋白質之轉譯後修飾中起作用且在蛋白質自細胞分泌前裂解。因此，成熟 FVII 多肽典型地為分泌型蛋白質。在一實例中，成熟人類 FVII 多肽闡明於 SEQ ID NO:3 中。SEQ ID NO:3 中闡明之胺基酸序列與 SEQ ID NOS:1 及 2 中所闡明的前驅體多肽之胺基酸序列不同之處在於 SEQ ID NO:3 缺乏對應於 SEQ ID NOS:1 及 2 之胺基酸殘基 1-20 的信號序列；且亦缺乏對應於 SEQ ID NO:1 之胺基酸殘基 21-60 及 SEQ ID NO:2 之胺基酸殘基 21-38 的前肽序列。對成熟 FVII 多肽之提及涵蓋單鏈酶原形式及雙鏈形式。

如本文中所用，關於 FVII 之「野生型（wild-type）」或「原生（native）」係指藉由在自然界中包括人類及其他動物之生物體中存在的原生或天然存在之 FVII 基因（包括對偶基因變異體）編碼的 FVII 多肽。在未提及物種情況下，對野生型因子 VII 之提及意欲涵蓋野生型因子 VII 之任何物種。野生型 FVII 多肽包括所編碼之前驅體多肽、其片段及其經加工形式，諸如缺乏信號肽之成熟形式以及任何轉譯前或轉譯後加工或修飾形式。原生 FVII 多肽亦包括彼等經轉譯後修飾者，包括（但不限於）藉由糖苷化、羧基化及羥基化修飾。原生 FVII 多肽亦包括單鏈及雙鏈形式。舉例

而言，人類表現原生 FVII。例示性野生型人類 FVII 之胺基酸序列經闡明於 SEQ ID NO: 1、2、3 中及經闡明於 SEQ ID NO: 44-100 中之對偶基因變異體及其成熟形式。其他動物產生原生 FVII，包括（但不限於）母牛（家牛，SEQ ID NO:4）、小鼠（家鼷鼠，SEQ ID NO:5）、侏儒黑猩猩（SEQ ID NO:6）、黑猩猩（SEQ ID NO:7）、兔（穴兔，SEQ ID NO:8）、大鼠（挪威大鼠，SEQ ID NO: 9）、恆河猴（恆河獼猴，SEQ ID NO:10）、豬（SEQ ID NO:11）、犬（家犬，SEQ ID NO:12）、斑馬魚（SEQ ID NO:13）、日本河豚（河豚，SEQ ID NO:14）、雞（SEQ ID NO:15）、紅毛猩猩（SEQ ID NO: 16）及大猩猩（SEQ ID NO:17）。

如本文中所用，物種變異體係指多肽在包括諸如小鼠及人類之不同哺乳動物物種的不同物種間的變異體。

如本文中所用，對偶基因變異體係指蛋白質在相同物種之成員間的變異。

如本文中所用，剪接變異體係指藉由不同加工產生一種以上類型的 mRNA 之基因組 DNA 之初級轉錄物產生的變異體。

如本文中所用，酶原係指藉由蛋白水解裂解（包括成熟裂解，諸如活化裂解）及/或與其他蛋白質及/或輔因子形成複合物而活化之蛋白酶。酶原為蛋白水解酶之無活性前驅體。與活性形式相比，該等前驅體通常較大，儘管不必較大。關於絲胺酸蛋白酶，藉由包括催化及自體催化裂解的特異性裂解或藉由結合產生活性酶之活化輔因子將酶原

轉化成活性酶。舉例而言，酶原通常以單鏈形式存在。酶原通常無活性且可藉由在一或多個蛋白水解位點催化或自體催化裂解以產生諸如雙鏈之多鏈多肽來轉化成成熟活性多肽。因此，酶原為在活化劑的作用下轉化成蛋白水解酶之無酶促活性蛋白質。裂解可藉由自體活化實現。許多凝血蛋白質為酶原；其無活性，但在血管損傷後凝血系統起始後得以裂解且活化。關於 FVII，FVII 多肽在血漿中以酶原形式存在，直至藉由諸如經活化因子 IX（FIXa）、經活化因子 X（FXa）、經活化因子 XII（FXIIa）、凝血酶之蛋白酶裂解，或藉由自體活化裂解，以產生酶原樣雙鏈形式，其接著需要其他構形變化以實現充分活性。

如本文中所用，「酶原樣（zymogen-like）」蛋白質或多肽係指已藉由蛋白水解裂解活化，但仍展現與酶原相關的特性之蛋白質，該等特性諸如低或無活性，或與蛋白質之酶原形式的構形相似之構形。舉例而言，當未與組織因子結合時，FVII 之雙鏈經活化形式為酶原樣蛋白質；其保留類似於未裂解 FVII 酶原之構形且因此展現極低活性。與組織因子結合後，FVII 之雙鏈經活化形式經歷構形變化且獲得其作為凝血因子之充分活性。

如本文中所用，活化序列係指酶原中為活化裂解或成熟裂解以形成活性蛋白酶所需的位點之胺基酸序列。可自體催化或藉由活化搭配物催化活化序列之裂解。

如本文中所用，活化裂解為一種類型之成熟裂解，其誘導產生充分酶促活性所需的構形變化。此為例如絲胺酸

蛋白酶之典型活化途徑，其中裂解產生與諸如胰凝乳蛋白酶之 Asp194 的蛋白酶之保守區域交互作用的新 N 末端，以誘導活性所需之構形變化。活化可引起多鏈形式之蛋白酶產生。在一些情況下，單鏈形式之蛋白酶可展現蛋白水解活性。

如本文中所用，「經活化之因子 VII（activated Factor VII）」或「FVIIa」係指 FVII 多肽之任何雙鏈形式。雙鏈形式典型地由蛋白水解裂解產生，但其可合成產生。因此，經活化之因子 VII 包括具有低凝血活性之酶原樣雙鏈形式，與組織因子結合後產生之充分活化之形式（約 1000 倍更大活性），及以充分活化之雙鏈形式存在或經歷構形變化為充分活化之形式的突變形式。舉例而言，單鏈形式之 FVII 多肽（參見例如 SEQ ID NO:3）在成熟 FVII 多肽之胺基酸殘基 R152 及 I153 之間經蛋白水解裂解。藉由雙硫鍵（在 SEQ ID NO:3 之 FVII 的胺基酸殘基 C135 與 C262 之間）結合在一起的裂解產物 FVII 重鏈及 FVII 輕鏈形成雙鏈經活化 FVII 酶。舉例而言，可藉由經活化因子 IX（FIXa）、經活化因子 X（FXa）、經活化因子 XII（FXIIa）、凝血酶或藉由自體活化進行蛋白水解裂解。

如本文中所用，FVII 多肽之「特性」係指物理或結構特性，諸如三維結構、pI、半衰期、構形及其他此類物理特徵。

如本文中所用，FVII 多肽之「活性」係指因子 VII 多肽所展現的任何活性。可試管內及/或活體內測試該等活

性，且其包括（但不限於）凝血或凝血劑活性、促凝血活性、實現因子 X（FX）活化或因子 IX（FIX）活化之蛋白水解或催化活性；抗原性（與抗 FVII 抗體結合或與多肽競爭結合抗 FVII 抗體之能力）；結合組織因子、因子 X 或因子 IX 之能力；及/或結合磷脂之能力。可使用公認檢定，例如藉由量測試管內或活體內凝血來試管內或活體內評估活性。該等檢定之結果指示多肽展現可與活體內多肽之活性相關聯之活性，其中活體內活性可稱為生物活性。熟習此項技術者已知測定 FVII 之經修飾形式的功能性或活性的檢定。評估 FVII 多肽之活性的例示性檢定包括評估凝血活性之促凝血酶原激酶時間（PT）檢定或經活化部分凝血酶原激酶時間（aPTT）檢定，或諸如以下實施例中所述評估催化或蛋白水解活性之使用合成受質之發色檢定。

如本文中所用，「展現至少一種活性」或「保留至少一種活性」係指與相同形式且在相同條件下的未經修飾之 FVII 多肽相比，由經修飾之 FVII 多肽展現之活性。舉例而言，在相同實驗條件下，將雙鏈形式的經修飾之 FVII 多肽與雙鏈形式的未經修飾之 FVII 多肽相比較，其中兩個多肽之間的唯一差異為在研究中之修飾。在另一實例中，在相同實驗條件下將單鏈形式的經修飾之 FVII 多肽與單鏈形式的未經修飾之 FVII 多肽相比較，其中兩個多肽之間的唯一差異為在研究中之修飾。典型地，保留或展現相同形式的未經修飾之 FVII 多肽之至少一種活性的經修飾之 FVII 多肽保留足夠量之活性，以使得當活體內投予時，該經修飾之

FVII 多肽在治療上有效作為促凝血治療劑。通常，對於保留作為促凝血劑之治療功效的經修飾之 FVII 多肽而言，所保留活性之量為或約為顯示作為促凝血劑之治療功效的相同形式之未經修飾 FVII 多肽之活性的 0.5%、1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、11%、12%、13%、14%、15%、16%、17%、18%、19%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。必要時，可憑經驗確定保持作為促凝血劑之治療功效所需的活性之量。典型地，保留活性之 0.5%至 20%、0.5%至 10%、0.5%至 5%足以保留作為活體內促凝血劑之治療功效。

應瞭解，經修飾之 FVII 多肽所展現或保留的活性可為任何活性，包括（但不限於）凝血或凝血劑活性、促凝血活性；諸如實現因子 X（FX）活化或因子 IX（FIX）活化的蛋白水解或催化活性；抗原性（與抗 FVII 抗體結合或與多肽競爭結合抗 FVII 抗體的能力）；結合組織因子、因子 X 或因子 IX 之能力；及/或結合磷脂之能力。在一些情況下，經修飾之 FVII 多肽可保留與未經修飾之 FVII 多肽相比增強的活性。在一些情況下，經修飾之 FVII 多肽可保留與未經修飾之 FVII 多肽相比降低的活性。經修飾之 FVII 多肽的活性可為未經修飾之多肽的活性之任何百分比量（其中兩種多肽呈相同形式），包括（但不限於）與不含所討論修飾之多肽相比，活性之 1%，2%、3%、4%、5%、10%、20%、30%、40%、50%、60%、70%、80%、90%、95%、96%、97%、

98%、99%、100%、200%、300%、400%、500%或更高的活性。舉例而言，與相同形式的未經修飾之 FVII 多肽相比，經修飾之 FVII 多肽可展現增強或降低之活性。舉例而言，其可保留未經修飾 FVII 多肽之活性的至少約或活性的 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、95%、96%、97%、98%或至少 99%。在其他具體實例中，活性之改變為比未經修飾之 FVII 大至少約 2 倍、3 倍、4 倍、5 倍、6 倍、7 倍、8 倍、9 倍、10 倍、20 倍、30 倍、40 倍、50 倍、60 倍、70 倍、80 倍、90 倍、100 倍、200 倍、300 倍、400 倍、500 倍、600 倍、700、800 倍、900 倍、1000 倍或 1000 倍以上。待保留之特定量與多肽之預定用途有關且可憑經驗確定。可例如使用諸如彼等本文或以下實施例中所述之試管內或活體內檢定量測活性。

如本文中所用，「凝血活性（coagulation activity）」或「凝血劑活性（coagulant activity）」或「促凝血活性（pro-coagulant activity）」係指多肽實現凝血之能力。熟習此項技術者已知評估凝血活性之檢定，且其包括促凝血酶原激酶時間（PT）檢定或經活化部分凝血酶原激酶時間（aPTT）檢定。

如本文中所用，關於 FVII 之「催化活性」或「蛋白水解活性」係指 FVII 蛋白質催化受質蛋白水解裂解之能力且可互換使用。在此項技術中已知評估該等活性之檢定。舉例而言，可使用諸如 Spectrozyme FVIIa

（CH3SO2-D-CHA-But-Arg-pNA）之發色受質來量測 FVII 之蛋白水解活性，其中藉由吸光率監測受質之裂解且藉由線性回歸測定受質水解之速率。

如本文中所用，關於 FVII 之「固有活性」係指在組織因子不存在之情況下，FVII 蛋白質之催化、蛋白水解及/或凝血活性。

如本文中所用，域（典型地三個或更多個，通常 5 或 7 個或更多個胺基酸之序列）係指諸如蛋白質或編碼核酸的分子之一部分，其在結構及/或功能上不同於分子之其他部分且可鑑別。舉例而言，域包括多肽鏈中可在由一或多個結構基元構成之蛋白質內形成獨立摺疊結構及/或根據諸如蛋白水解活性之功能活性識別的彼等部分。蛋白質可具有一個或更多個不同域。舉例而言，可藉由其中的序列與相關家族成員之同源性，諸如與界定蛋白酶域或 gla 域的基元之同源性，來鑑別、界定或區別域。在另一實例中，可藉由功能，諸如藉由蛋白水解活性或與生物分子交互作用的能力（諸如 DNA 結合、配位體結合及二聚化）來區別域。域可獨立地展現生物學功能或活性，以使得該獨立或與另一分子融合之域可執行諸如蛋白水解活性或配位體結合之活性。域可為胺基酸之線性序列或胺基酸之非線性序列。許多多肽含有複數個域。該等域已知且可藉由熟習此項技術者鑑別。出於在本文中例示之目的，提供定義，但應瞭解其充分處於此項技術內以便藉由名稱識別特定域。若需要，則可採用適當軟體來鑑別域。

如本文中所用，蛋白酶域為蛋白酶之催化活性部分。對蛋白酶之蛋白酶域的提及包括該等蛋白質中任一者之單鏈、雙鏈及多鏈形式。蛋白質之蛋白酶域含有彼蛋白質之蛋白水解活性所需的全部必要特性，諸如催化中心。參考FVII，蛋白酶域與胰凝乳蛋白酶/胰蛋白酶家族蛋白酶域共有同源性及結構特徵，包括催化三合體。舉例而言，在SEQ ID NO:3中所闡明之成熟FVII多肽中，蛋白酶域對應於胺基酸位置153至392。

如本文中所用，γ-羧基麩胺酸（Gla）域係指例如維生素K依賴性蛋白質的蛋白質之部分，其藉由維生素K依賴性羧基化以形成Gla，含有對麩胺酸殘基，通常大多數但非所有麩胺酸殘基之轉譯後修飾。Gla域負責鈣離子之高親和力結合及與帶負電磷脂之結合。典型地，Gla域起始於成熟形式之維生素K依賴性蛋白質的N末端，且終止於保守芳族殘基。在成熟FVII多肽中，Gla域對應於SEQ ID NO:3中所闡明的例示性多肽之胺基酸位置1至45。Gla域已熟知且可在特定多肽中鑑別出其基因座。各種維生素K依賴性蛋白質之Gla域共有序列、結構及功能同源性，包括N末端疏水性殘基叢集為介導與細胞表面膜上的帶負電磷脂之交互作用的疏水性補丁。例示性其他含Gla之多肽包括（但不限於）FIX、FX、凝血酶原、蛋白質C、蛋白質S、骨鈣蛋白、基質Gla蛋白質、生長抑止特異性蛋白6（Gas6）及蛋白質Z。此等及其他例示性蛋白質之Gla域經闡明於SEQ ID NO: 83-94之任一者中。

如本文中所用，關於 Gla 域之「原生」或「內源性」係指與具有 Gla 域之多肽的全部或一部分相關的天然存在 Gla 域。出於本文之目的，原生 Gla 域係與 FVII 多肽相關。舉例而言，SEQ ID NO:92 中所闡明的 FVII 之原生 Gla 域對應於 SEQ ID NO:3 中所闡明的胺基酸序列之胺基酸 1-45。

如本文中所用，異源 Gla 域係指不為 FVII Gla 域的來自相同或不同物種之多肽的 Gla 域。例示性異源 Gla 域為含 Gla 之多肽的 Gla 域，該等多肽包括（但不限於）FIX、FX、凝血酶原、蛋白質 C、蛋白質 S、骨鈣蛋白、基質 Gla 蛋白質、生長抑止特異性蛋白 6（Gas6）及蛋白質 Z。此等及其他例示性蛋白質之 Gla 域經闡明於 SEQ ID NO: 83-91、93 及 94 之任一者中。

如本文中所用，Gla 域之連續部分係指至少兩個或更多個相鄰胺基酸，典型地構成 Gla 域之 2、3、4、5、6、8、10、15、20、30、40 或更多個至多達全部胺基酸。

如本文中所用，「實現磷脂結合之 Gla 域的足夠部分」包括域之至少一個胺基酸，典型地 2、3、4、5、6、8、10、15 或更多個胺基酸，但少於構成域之全部胺基酸，只要含有該部分之多肽展現磷脂結合即可。

如本文中所用，關於 Gla 域之「置換」或「Gla 域交換」係指使用重組、合成或其他方法使蛋白質之內源性 Gla 域經另一蛋白質之 Gla 域置換的過程。在「Gla 域交換」之上下文中，「Gla 域」為來自足以保留磷脂結合活性之 Gla 域及相鄰區域的任意選擇之胺基酸。典型地，Gla 域交換將包括

以另一蛋白質之 40 與 50 個之間的胺基酸置換內源性蛋白質之 40 與 50 個之間的胺基酸，但可包括較少或較多胺基酸。

如本文中所用，上皮生長因子（EGF）域（EGF-1 或 EGF-2）係指與上皮生長因子（EGF）序列之 30 至 40 個胺基酸的特定部分共有序列同源性之蛋白質的部分。EGF 域包括已展示（在 EGF 中）與雙硫鍵有關的六個半胱胺酸殘基。EGF 域之主要結構為雙鏈 β 摺疊，後接一環，再後為 C 末端短雙鏈摺疊。FVII 含有兩個 EGF 域：EGF-1 及 EGF-2。此等域分別對應於 SEQ ID NO:3 中所闡明的成熟 FVII 多肽之胺基酸位置 46-82 及 87-128。

如本文中所用，「未經修飾之多肽」或「未經修飾之 FVII」及其語法變化形式係指經選擇用於如本文所提供之修飾的起始多肽。起始多肽可為天然存在野生型形式之多肽。另外，起始多肽可經改變或突變，以使得其與原生野生型同功異型物不同，但相對於本文中產生之經後續修飾之多肽，在本文中仍然稱作起始未經修飾之多肽。因此，可選擇已經修飾以與未經修飾之參考蛋白質相比具有特定活性或特性之所需增強或降低的在此項技術中已知之現有蛋白質，且將其用作起始未經修飾之多肽。舉例而言，已藉由一或多種單一胺基酸改變自原生形式修飾且具有增強或降低之所需特性（諸如改變糖苷化之胺基酸殘基變化）之蛋白質可為供進一步修飾相同或不同特性之目標蛋白質，在本文中稱作未經修飾。在此項技術中已知的例示性

經修飾之 FVII 多肽包括例如美國專利第 5580560 號、第 6017882 號、第 6693075 號、第 6762286 號及第 6806063 號，美國專利公開案第 20030100506 號及第 20040220106 號及國際專利公開案第 WO1988010295 號、第 WO200183725 號、第 WO2003093465 號、第 WO200338162 號、第 WO2004083361 號、第 WO2004108763 號、第 WO2004029090 號、第 WO2004029091 號、第 WO2004111242 號及第 WO2005123916 號所述之任何 FVII 多肽。

如本文中所用，「經修飾之因子 VII 多肽（modified factor VII polypeptides）」及「經修飾之因子 VII（modified factor VII）」係指與未經修飾之因子 VII 多肽相比，具有一或多個胺基酸差異的 FVII 多肽。該一或多種胺基酸差異可為胺基酸突變，諸如一或多個胺基酸置換（取代）、插入或缺失，或其可為整個域之插入或缺失及其任何組合。典型地，與未經修飾之 FVII 多肽相比，經修飾之 FVII 多肽在一級序列中具有一或多個修飾。舉例而言，與未經修飾之 FVII 多肽相比，本文中提供的經修飾之 FVII 多肽可具有 1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、30、40、50 或更多個胺基酸差異。涵蓋任何修飾，只要所得多肽展現至少一種與原生 FVII 多肽相關的 FVII 活性即可，該活性諸如催化活性、蛋白水解活性、結合 TF 之能力或結合經活化之血小板的能力。

如本文中所用，「凝血抑制子（inhibitor of coagulation）」係指起作用以抑制或防止凝血或凝塊形成的

蛋白質或分子。可活體內或試管內觀察抑制或防止凝血，且其可使用在此項技術中已知之包括（但不限於）促凝血酶原激酶時間（PT）檢定或活化部分凝血酶原激酶時間（aPTT）檢定之任何方法檢定。

如本文中所用，組織因子途徑抑制子（TFPI，亦稱為TFPI-1)為與FVIIa之活性受抑制的四級TF/FVIIa/TFPI/FXa抑制性複合物之形成有關的Kunitz型抑制子。替代性剪接後TFPI表現為兩種不同前驅體形式TFPIα（SEQ ID NO:75）及TFPIβ（SEQ IDNO:77）前驅體，其在分泌期間裂解以分別產生276個胺基酸（SEQ IDNO:76）及223個胺基酸（SEQ IDNO:78）之成熟蛋白質。TFPI含有3個Kunitz域，其中Kunitz-1域負責對FVIIa之結合及抑制。

如本文中所用，TFPI-2（亦稱為胎盤蛋白質5（PP5）及基質相關絲胺酸蛋白酶抑制子（MSPI））係指TFPI之同源物。213個胺基酸之成熟TFPI-2蛋白質（SEQ ID NO:79）含有三個Kunitz型域，其與TFPI-1 Kunitz型域1、2及3分別展現43%、35%及53%一級序列一致性。TFPI-2在調節胞外基質消化及重塑中起作用，且並不認為其為凝血途徑之重要因子。

如本文中所用，抗凝血酶III（AT-III）為絲胺酸蛋白酶抑制子（serpin）。AT-III經合成為含有464個胺基酸殘基之前驅體蛋白質（SEQ ID NO:95），其在分泌期間裂解以釋放432個胺基酸之成熟抗凝血酶（SEQ ID NO:96）。

如本文中所用，輔因子係指與其他特定蛋白質或分子

結合以形成活性複合物之蛋白質或分子。在一些實例中，最佳蛋白水解活性要求與輔因子結合。舉例而言，組織因子（TF）為 FVIIa 之輔因子。FVIIa 與 TF 之結合誘導引起 FVIIa 對其受質 FX 及 FIX 之蛋白水解活性增強的構形變化，

如本文中所用，組織因子（TF）係指 263 個胺基酸之跨膜醣蛋白（SEQ ID NO:97），其充當 FVIIa 之輔因子。其由平滑肌細胞及纖維母細胞組成性表現，且當組織損傷後此等細胞接觸血流時幫助藉由結合 FVII 及 FVIIa 起始凝血。

如本文中所用，經活化之血小板係指已藉由結合諸如膠原、凝血烷 A2、ADP 及凝血酶之分子觸發以經歷最終促進凝血的各種形態學、表型及功能變化之血小板。舉例而言，經活化之血小板形狀變化為具有凸出指狀物之更加無晶型形式。經活化之血小板亦經歷細胞膜「翻轉」，以使得磷脂醯絲胺酸及通常存在於細胞膜之內部小葉中之其他帶負電磷脂移位至外部血漿取向表面。經活化血小板之此等膜提供實現許多凝血級聯反應之表面。經活化之血小板亦分泌含有諸如 vWF、FV、凝血酶、ADP 及凝血烷 A2 之促凝血因子之囊泡且彼此黏附以形成藉由血纖蛋白穩定以變成凝塊之血小板栓塞。

如本文中所用，對經活化血小板之結合及/或親和力增強及其任何語法變化形式係指與參考多肽或蛋白質相比較，多肽或蛋白質（例如 FVII 多肽）結合經活化血小板之表面的能力增強。舉例而言，經修飾之 FVII 多肽結合經活

化血小板之能力可大於未經修飾之FVII多肽結合經活化血小板之能力。與未經修飾之多肽之結合及/或親和力相比，多肽對經活化血小板之結合及/或親和力可增加至少約1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。在此項技術中已知測定多肽對經活化血小板之結合及/或親和力的檢定。經由FVII多肽之Gla域中的胺基酸與經活化血小板上帶負電磷脂（諸如磷脂醯絲胺酸）之交互作用介導FVII多肽與經活化血小板之結合。因而，檢定諸如FVII多肽之多肽與經活化血小板之結合的方法使用含有諸如磷脂醯絲胺酸的磷脂之膜及微脂粒。舉例而言，藉由可藉由光散射技術量測的多肽結合磷脂微脂粒之能力反映多肽結合經活化血小板之能力。

如本文中所用，對磷脂結合及/或親和力增強及其任何語法變化形式係指與參考多肽或蛋白質相比較，多肽或蛋白質結合磷脂的能力增強。磷脂可包括任何磷脂，但尤其包括磷脂醯絲胺酸。與未經修飾之多肽之結合及/或親和力相比，多肽對磷脂之結合及/或親和力可增加至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。在此項技術中已知測定多肽與磷脂之親和力及/或結合的檢定。舉例而言，可藉由與入射光成90°之相對光散射測定FVII多肽與磷脂微脂粒之結合。量測僅磷脂微脂粒及磷脂微脂粒與FVII之光散射強度以測定解離

常數。亦可使用諸如於 BIAcore 生物傳感器儀器上之表面電漿共振來量測 FVII 多肽對磷脂膜之親和力。

如本文中所用，對抑制子之抗性增強或「對 AT-III 之抗性增強」或「對 TFPI 之抗性增強」係指與諸如未經修飾之 FVII 多肽的參考多肽相比，多肽對諸如 AT-III 或 TFPI 的抑制子之抑制作用的敏感性的任何量之降低。可藉由評估經修飾之 FVII 多肽與抑制子之結合來檢定對諸如 AT-III 之抑制子之抗性增強。亦可藉由在 AT-III 存在下量測 FVII 多肽之固有活性或凝血活性來檢定對諸如 AT-III 之抑制子的抗性增強。在此項技術中已知測定多肽與抑制子之結合的檢定。對於諸如 AT-III 之共價抑制子，可量測抑制之二級速率常數。對於諸如 TFPI 之非共價抑制子，可量測 k_i。另外，亦可使用諸如於 BIAcore 生物傳感器儀器上之表面電漿共振來量測 FVII 多肽與 AT-III 或其他抑制子之結合。然而，對於諸如 AT-III 之共價抑制子，使用 BIAcore 僅可量測結合速率。在此項技術中亦已知測定例如 AT-III 對 FVII 凝血活性或固有活性之抑制作用的檢定。舉例而言，可量測在 AT-III 存在或不存在之情況下經修飾之 FVII 多肽裂解其受質 FX 的能力，且測定 AT-III 抑制反應之程度。可將此與在 AT-III 存在或不存在情況下未經修飾之 FVII 多肽裂解其受質 FX 之能力相比較。與未經修飾之多肽相比，展現對抑制子的抗性增強之經修飾多肽展現對抑制子之作用的抗性增加 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、91%、92%、

93%、94%、95%、96%、97%、98%、99%、100%、200%、300%、400%、500%或更高。

如本文中所用，「對 Zn^{2+}抑制之抗性增強」、「對 Zn^{2+}之抑制作用的抗性增強」或「對 Zn^{2+}之抗性增強」係指與諸如未經修飾之 FVII 多肽的參考多肽相比，多肽對 Zn^{2+}之抑制作用之敏感性之任何量的降低。諸如實施例 11 所述，可藉由例如在 Zn^{2+}存在下量測 FVII 多肽之固有活性或凝血活性來檢定對 Zn^{2+}之抗性增強。對 Zn2+之抑制作用的抗性增強可為與 Zn^{2+}之結合降低的結果。可藉由量測每個分子 FVIIa 所結合 Zn^{2+}之量，或藉由量測 Zn^{2+}結合 FVIIa 之親和力或藉由量測鋅抑制 FVIIa 活性之 IC_{50}值來檢定與 Zn^{2+}的結合降低。與未經修飾之多肽相比，展現對 Zn^{2+}的抑制作用之抗性增強之經修飾之多肽展現例如對 Zn^{2+}之作用的抗性增加 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、100%、200%、300%、400%、500%或更高。

如本文中所用，血清白蛋白結合序列係指可實現與血清白蛋白之結合的胺基酸殘基之序列。因此，當插入 FVII 多肽中時，血清白蛋白結合序列可增強對 FVII 多肽之血清白蛋白親和力或結合。因此，含有血清白蛋白結合序列的經修飾之 FVII 多肽之能力對血清白蛋白可展現增強之結合及/或親和力。與未經修飾之多肽的結合及/或親和力相比，對血清白蛋白展現增強之結合及/或親和力的經修飾之多肽

展現例如 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、100%、200%、300%、400%、500%或更高之增加。典型地，血清白蛋白結合序列含有至少 10 個或更多個胺基酸，典型地 10、11、12、13、14、15、20、30、40 個或更多個胺基酸。例示性血清白蛋白結合序列為彼等闡明於 SEQ ID NO: 103-109 中者。

如本文中所用，血小板整合素 $\alpha_{IIb}\beta_3$ 結合序列係指可實現與血小板整合素 $\alpha_{IIb}\beta_3$ 之結合的胺基酸殘基之序列。因此，當插入 FVII 多肽中時，血小板整合素 $\alpha_{IIb}\beta_3$ 結合序列可增強 FVII 多肽結合血小板整合素 $\alpha_{IIb}\beta_3$ 且因此包括經活化血小板之血小板的能力。因此，含有血小板整合素 $\alpha_{IIb}\beta_3$ 結合序列的經修飾之 FVII 多肽之能力可展現對血小板整合素 $\alpha_{IIb}\beta_3$ 及/或血小板之結合及/或親和力增強。與未經修飾之多肽的結合及/或親和力相比，展現對血小板整合素 $\alpha_{IIb}\beta_3$ 的結合及/或親和力增強之經修飾之多肽展現例如 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、100%、200%、300%、400%、500%或更高之增加。典型地，血小板整合素 αIIbβ3 結合序列含有至少 5 個或更多個胺基酸，典型地 5、6、7、8、9、10、11、12、13、14、15、20、30、40 個或更多個胺基酸。例示性血小板整合素 αIIbβ3 結合序列為彼等闡明於 SEQ ID NO: 110-112 中者。

如本文中所用，糖苷化位點係指多肽中碳水化合物部分可連接之胺基位置。典型地，糖苷化蛋白質含有一或多個諸如天冬醯胺或絲胺酸之胺基酸殘基用於連接碳水化合物部分。

如本文中所用，原生糖苷化位點係指野生型多肽中碳水化合物部分連接之胺基位置。FVII 中存在四個原生糖苷化位點：對應於 SEQ ID NO:3 中所闡明之成熟 FVII 多肽中的胺基酸位置的兩個處於 N145 及 N322 之 N-糖苷化位點，及兩個處於 S52 及 S60 之 O-糖苷化位點。

如本文中所用，非原生糖苷化位點係指經修飾之多肽中之野生型多肽中不存在之碳水化合物部分連接的胺基位置。可藉由胺基酸置換將非原生糖苷化位點引入 FVII 多肽中。舉例而言，可藉由以絲胺酸或蘇胺酸胺基酸置換原生殘基產生 O-糖苷化位點。舉例而言，可藉由建立 Xaa 不為脯胺酸之基元 Asn-Xaa-Ser/Thr/Cys 產生 N-糖苷化位點。藉由胺基酸修飾產生此一致序列可包括（例如）以天冬醯胺對原生胺基酸殘基進行單一胺基酸置換，以絲胺酸、蘇胺酸或半胱胺酸對原生胺基酸殘基進行單一胺基酸置換，或雙重胺基酸置換，其包括以天冬醯胺對原生殘基進行第一胺基酸置換及以絲胺酸、蘇胺酸或半胱胺酸對原生殘基進行第二胺基酸置換。

如本文中所用，「生物活性（biological activity）」係指化合物之活體內活性或在活體內投予化合物、組成物或其他混合物後產生之生理學反應。因此，生物活性涵蓋該

等化合物、組成物及混合物之治療作用及醫藥活性。可在經設計以測試或使用該等活性之試管內系統中觀察生物活性。因此，出於本文之目的，FVII 多肽之生物活性涵蓋凝血活性。

如本文中所用，術語「評估」及其語法變化形式意欲包括在獲得多肽之活性的絕對值以及獲得指數、比率、百分比、直觀或其他指示活性程度之值的意義上的定量及定性測定。可直接或間接評估。舉例而言，可藉由直接量測產物來直接量測或可藉由測定所裂解受質之所得活性來間接量測，偵測多肽對受質之裂解。

如本文中所用，「胰凝乳蛋白酶編號」係指 SEQ ID NO:80 的成熟胰凝乳蛋白酶多肽之胺基酸編號。可將另一蛋白酶之蛋白酶域（諸如因子 VII 之蛋白酶域）與胰凝乳蛋白酶進行比對。在該情況下，對相應於胰凝乳蛋白酶之胺基酸的因子 VII 之胺基酸給予胰凝乳蛋白酶胺基酸之編號。可藉由熟習此項技術者使用人工比對，或藉由使用許多可用比對程式（例如 BLASTP），進行該比對來確定對應位置。對應位置亦可基於結構比對，例如藉由使用蛋白質結構之電腦模擬比對。多肽之胺基酸對應於所揭示序列中之胺基酸的敘述係指使用諸如 GAP 演算法之標準比對演算法比對該多肽與所揭示序列以最大化一致性或同源性（其中對準保守胺基酸）後鑑別之胺基酸。表 1 提供闡明於 SEQ ID NO:3 中之 FVII 多肽的胺基酸位置 1 至 406 之對應胰凝乳蛋白酶編號。相對於 SEQ ID NO:3 中所闡明之序列的胺基酸

位置呈普通字體形式，且彼等位置之胺基酸殘基呈粗體形式，且對應胰凝乳蛋白酶編號呈斜體形式。舉例而言，比對成熟因子 VII（SEQ ID NO:3）與成熟胰凝乳蛋白酶（SEQ ID NO:80）後，對因子 VII 中胺基酸位置 153 之異白胺酸（I）給予胰凝乳蛋白酶編號 I16。後續胺基酸據此編號。在一實例中，基於胰凝乳蛋白酶編號，成熟因子 VII（SEQ ID NO:3）之胺基酸位置 210 之麩胺酸（E）對應於胺基酸位置 E70。若某殘基存在於蛋白酶中，但並不存在於胰凝乳蛋白酶中，則給予該胺基酸殘基字母符號。舉例而言，與胰凝乳蛋白酶相比，為具有基於胰凝乳蛋白酶編號之胺基酸 60 的環之部分，但插入因子 VII 序列中的胰凝乳蛋白酶中之殘基稱為例如 K60a、I60b、K60c 或 N60d。藉由相對於成熟因子 VII 序列（SEQ ID NO:3）進行編號，此等殘基分別對應於 K197、I198、K199 及 N200。

表 1. 因子 VII 之胰凝乳蛋白酶編號

153	154	155	156	157	158	159	160	161	162	163	164	165	166	167
I	**V**	**G**	**G**	**K**	**V**	**C**	**P**	**K**	**G**	**E**	**C**	**P**	**W**	**Q**
16	*17*	*18*	*19*	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*	*28*	*29*	*30*
168	169	170	171	172	173	174	175	176	177	178	179	180	181	182
V	**L**	**L**	**L**	**V**	**N**	**G**	**A**	**Q**	**L**	**C**	**G**	**G**	**T**	**L**
31	*32*	*33*	*34*	*35*	*37*	*38*	*39*	*40*	*41*	*42*	*43*	*44*	*45*	*46*
183	184	185	186	187	188	189	190	191	192	193	194	195	196	197
I	**N**	**T**	**I**	**W**	**V**	**V**	**S**	**A**	**A**	**H**	**C**	**F**	**D**	**K**
47	*48*	*49*	*50*	*51*	*52*	*53*	*54*	*55*	*56*	*57*	*58*	*59*	*60*	*60A*
198	199	200	201	202	203	204	205	206	207	208	209	210	211	212
I	**K**	**N**	**W**	**R**	**N**	**L**	**I**	**A**	**V**	**L**	**G**	**E**	**H**	**D**
60B	*60C*	*60D*	*61*	*62*	*63*	*64*	*65*	*66*	*67*	*68*	*69*	*70*	*71*	*72*
213	214	215	216	217	218	219	220	221	222	223	224	225	226	227
L	**S**	**E**	**H**	**D**	**G**	**D**	**E**	**Q**	**S**	**R**	**R**	**V**	**A**	**Q**
73	*74*	*75*	*76*	*77*	*78*	*79*	*80*	*81*	*82*	*83*	*84*	*85*	*86*	*87*
228	229	230	231	232	233	234	235	236	237	238	239	240	241	242
V	**I**	**I**	**P**	**S**	**T**	**Y**	**V**	**P**	**G**	**T**	**T**	**N**	**H**	**D**
88	*89*	*90*	*91*	*92*	*93*	*94*	*95*	*96*	*97*	*98*	*99*	*100*	*101*	*102*
243	244	245	246	247	248	249	250	251	252	253	254	255	256	257
I	**A**	**L**	**L**	**R**	**L**	**H**	**Q**	**P**	**V**	**V**	**L**	**T**	**D**	**H**
103	*104*	*105*	*106*	*107*	*108*	*109*	*110*	*111*	*112*	*113*	*114*	*115*	*116*	*117*
258	259	260	261	262	263	264	265	266	267	268	269	270	271	272

V	V	P	L	C	L	P	E	R	T	F	S	E	R	T
118	*119*	*120*	*121*	*122*	*123*	*124*	*125*	*126*	*127*	*128*	*129*	*129A*	*129B*	*129C*
273	274	275	276	277	278	279	280	281	282	283	284	285	286	287
L	A	F	V	R	F	S	L	V	S	G	W	G	Q	L
129D	*129E*	*129F*	*129G*	*134*	*135*	*136*	*137*	*138*	*139*	*140*	*141*	*142*	*143*	*144*
288	289	290	291	292	293	294	295	296	297	298	299	300	301	302
L	D	R	G	A	T	A	L	E	L	M	V	L	N	V
145	*146*	*147*	*149*	*150*	*151*	*152*	*153*	*154*	*155*	*156*	*157*	*158*	*159*	*160*
303	304	305	306	307	308	309	310	311	312	313	314	315	316	317
P	R	L	M	T	Q	D	C	L	Q	Q	S	R	K	V
161	*162*	*163*	*164*	*165*	*166*	*167*	*168*	*169*	*170*	*170A*	*170B*	*170C*	*170D*	*170E*
318	319	320	321	322	323	324	325	326	327	328	329	330	331	332
G	D	S	P	N	I	T	E	Y	M	F	C	A	G	Y
170F	*170G*	*170H*	*170I*	*175*	*176*	*177*	*178*	*179*	*180*	*181*	*182*	*183*	*184A*	*184*
333	334	335	336	337	338	339	340	341	342	343	344	345	346	347
S	D	G	S	K	D	S	C	K	G	D	S	G	G	P
185	*186*	*187*	*188A*	*188*	*189*	*190*	*191*	*192*	*193*	*194*	*195*	*196*	*197*	*198*
348	349	350	351	352	353	354	355	356	357	358	359	360	361	362
H	A	T	H	Y	R	G	T	W	Y	L	T	G	I	V
199	*200*	*201*	*202*	*203*	*204*	*205*	*206*	*207*	*208*	*209*	*210*	*211*	*212*	*213*
363	364	365	366	367	368	369	370	371	372	373	374	375	376	377
S	W	G	Q	G	C	A	T	V	G	H	F	G	V	Y
214	*215*	*216*	*217*	*219*	*220*	*221A*	*221*	*222*	*223*	*224*	*225*	*226*	*227*	*228*
378	379	380	381	382	383	384	385	386	387	388	389	390	391	392
T	R	V	S	Q	Y	I	E	W	L	Q	K	L	M	R
229	*230*	*231*	*232*	*233*	*234*	*235*	*236*	*237*	*238*	*239*	*240*	*241*	*242*	*243*
393	394	395	396	397	398	399	400	401	402	403	404	405	406	
S	E	P	R	P	G	V	L	L	R	A	P	F	P	
244	*245*	*246*	*247*	*248*	*249*	*250*	*251*	*252*	*253*	*254*	*255*	*256*	*257*	

如本文中所用，核酸包括 DNA、RNA 及其類似物，包括肽核酸（PNA）及其混合物。核酸可為單鏈或雙鏈的。當提及視情況經諸如可偵測標記（諸如螢光或放射性標記）標記之探針或引子時，涵蓋單鏈分子。對於探測或引發文庫而言，該等分子典型地具有使得其目標在統計學上獨特的長度或具有低複本數（小於 5、通常小於 3）。通常，探針或引子含有與所關注之基因互補或一致的至少 14、16 或 30 個連續核苷酸序列。探針及引子可為 10、20、30、50、100 或更多個核酸長。

如本文中所用，肽係指長度為 2 至 40 個胺基酸之多肽。

如本文中所用，根據已知 3 字母或單字母縮寫（表 2）

鑑別本文中提供之各種胺基酸序列中存在的胺基酸。以在此項技術中通常使用之標準單字母命名將各種核酸片段中存在之核苷酸命名。

如本文中所用，「胺基酸（amino acid）」為含有胺基及羧酸基團之有機化合物。多肽含有兩個或更多個胺基酸。出於本文之目的，胺基酸包括二十種天然存在胺基酸、非天然胺基酸及胺基酸類似物（亦即，α碳具有側鏈的胺基酸）。

與 J. Biol. Chem., 243: 3552-3559 (1969)所述且採用 37 C.F.R.§§1.821-1.822 之標準多肽命名法相一致，將胺基酸殘基的縮寫展示於表 2 中：

表 2-對應表

符號		
1-字母	3-字母	胺基酸
Y	Tyr	酪胺酸
G	Gly	甘胺酸
F	Phe	苯丙胺酸
M	Met	甲硫胺酸
A	Ala	丙胺酸
S	Ser	絲胺酸
I	Ile	異白胺酸
L	Leu	白胺酸
T	Thr	蘇胺酸
V	Val	纈胺酸
P	Pro	脯胺酸
K	Lys	離胺酸
H	His	組胺酸
Q	Gln	麩胺醯胺
E	Glu	麩胺酸
Z	Glx	Glu 及/或 Gln
W	Trp	色胺酸
R	Arg	精胺酸
D	Asp	天冬胺酸
N	Asn	天冬醯胺
B	Asx	Asn 及/或 Asp
C	Cys	半胱胺酸
X	Xaa	未知或其他

應注意，本文中由式表示之全部胺基酸殘基序列具有在胺基末端至羧基末端之習知方向上的由左至右取向。另外，短語「胺基酸殘基（amino acid residue）」經廣泛定義包括列入對應表（表 2）中的胺基酸及經修飾及不常見胺基酸，諸如彼等在 37 C.F.R.§§1.821-1.822 中提及且以引用的方式併入本文中之胺基酸。此外，應注意到胺基酸殘基序列開始或結束處的破折號指示與一或多個胺基酸殘基之另一序列、諸如 NH_2 之胺基端基或諸如 COOH 之羧基端基所成的肽鍵。

如本文中所用，「疏水性胺基酸」包括使用 Eisenberg 疏水性共識量表經確定為疏水性的胺基酸中之任一者。例示性疏水性胺基酸為天然存在疏水性胺基酸，諸如異白胺酸、苯丙胺酸、纈胺酸、白胺酸、色胺酸、甲硫胺酸、丙胺酸、甘胺酸、半胱胺酸及酪胺酸（Eisenberg 等人, (1982) Faraday Symp. Chem. Soc. 17:109-120）。亦包括非天然存在疏水性胺基酸。

如本文中所用，「酸性胺基酸」包括天然存在胺基酸天冬胺酸及麩胺酸殘基。亦包括非天然存在酸性胺基酸。

如本文中所用，「天然存在胺基酸」係指多肽中存在之 20 種 L-胺基酸。

如本文中所用，「非天然胺基酸」係指含有胺基及羧酸基團之不為表 2 中所列的天然存在胺基酸中之一者的有機化合物。因此，非天然存在胺基酸包括（例如）除 20 種

天然存在胺基酸以外的胺基酸或胺基酸類似物，且包括（但不限於）胺基酸之 D-異立體異構體。熟習此項技術者已知例示性非天然胺基酸且其可包括於經修飾之因子 VII 多肽中。

如本文中所用，DNA 構築體為含有以在自然界中不存在之方式組合及並置的 DNA 區段之單鏈或雙鏈、線性或環狀 DNA 分子。DNA 構築體作為人類操縱之結果存在，且包括純系及受操縱分子之其他複本。

如本文中所用，DNA 區段為具有指定屬性的較大 DNA 分子之一部分。舉例而言，編碼指定多肽之 DNA 區段為諸如質體或質體片段的較長 DNA 分子之一部分，當由 5’ 至 3’ 方向閱讀時，其編碼指定多肽之胺基酸序列。

如本文中所用，術語聚核苷酸意謂由 5’ 至 3’ 端閱讀之脫氧核糖核苷酸或核糖核苷酸鹼基之單鏈或雙鏈聚合物。聚核苷酸包括 RNA 及 DNA，且可自天然來源分離、由天然及合成分子之組合試管內合成或製備。本文中以核苷酸（縮寫為「nt」）或鹼基對（縮寫為「bp」）方式提供聚核苷酸分子之長度。將術語核苷酸用於上下文允許之單鏈及雙鏈分子。當將該術語應用於雙鏈分子時，使用其表示全長且應理解為等效於術語鹼基對。熟習此項技術者將認識到雙鏈聚核苷酸之兩個鏈長度可稍微不同，且其末端可交錯；因此雙鏈聚核苷酸分子內之全部核苷酸不能配對。通常，該等未配對末端長度將不超過 20 個核苷酸。

如本文中所用，「一級序列（primary sequence）」係

指多肽中胺基酸殘基之序列。

如本文中所用，兩個蛋白質或核酸之間的「相似性」係指蛋白質之胺基酸序列或核酸之核苷酸序列之間的相關性。相似性可基於殘基序列及其中含有的殘基的一致性及/或同源性程度。熟習此項技術者已知用於評估蛋白質或核酸之間的相似度之方法。舉例而言，在一種評估序列相似性之方法中，將兩個胺基酸或核苷酸序列以產生序列之間的最大一致性程度的方式對準。「一致性（Identity）」係指胺基酸或核苷酸序列無變化的程度。胺基酸序列且在某種程度上核苷酸序列之比對亦可考慮胺基酸（或核苷酸）之保守性差異及/或頻繁取代。保守性差異為彼等保存所涉及殘基之物理-化學特性之差異。比對可為全局（序列之整個長度且包括所有殘基之所比較序列的比對）或局部（比對僅包括最相似區域的序列之一部分）比對。

如本文中所用，術語「同源性」及「一致性」可互換使用，但蛋白質之同源性可包括保守性胺基酸變化。通常，為鑑別對應位置，將胺基酸序列對準以便獲得最高等級匹配(參見例如：Computational Molecular Biology, Lesk, A.M.編, Oxford University Press, New York, 1988；Biocomputing: Informatics and Genome Projects, Smith, D.W.編, Academic Press, New York, 1993；Computer Analysis of Sequence Data, Part I, Griffin, A.M.及 Griffin, H.G.編, Humana Press, New Jersey, 1994；Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987；及 Sequence Analysis

Primer, Gribskov, M.及 Devereux, J.編, M Stockton Press, New York, 1991；Carillo 等人 (1988) *SIAM J Applied Math* 48:1073）。

如本文所用，「序列一致性」係指在測試與參考多肽或聚核苷酸之間的比較中一致胺基酸（或核苷酸鹼基）之數目。同源多肽係指一致或同源胺基酸殘基之預定數目。同源性包括保守性胺基酸取代以及一致殘基。可藉由連同由各供應商建立之預設間隙罰分一起使用之標準比對演算法程式確定序列一致性。同源核酸分子係指一致或同源核苷酸之預定數目。同源性包括並未改變所編碼胺基酸（亦即「沉默取代」）之取代以及一致殘基。實質上同源核酸分子典型地在中嚴格度或高嚴格度下始終沿核酸之長度或沿所關注全長核酸分子之至少約 70%、80%或 90%雜交。亦涵蓋含有簡并密碼子替代雜交核酸分子中之密碼子之核酸分子。（為測定蛋白質之同源性，可將保守性胺基酸以及一致胺基酸對準；在此情況下，一致性百分比及同源性百分比不同）。可使用諸如「FAST A」程式之已知電腦算法，使用例如如 Pearson 等人 *Proc. Natl. Acad. Sci. USA* 85: 2444 (1988)之預設參數確定任何兩個核酸分子是否具有至少 80%、85%、90%、95%、96%、97%、98%或 99%「一致」之核苷酸序列（或任何兩個多肽具有胺基酸序列）（其他程式包括 GCG 程式包（Devereux, J.等人, *Nucleic Acids Research* 12(I): 387 (1984)））、BLASTP、BLASTN、FASTA（Atschul, S.F.等人, *J. Molec. Biol.* 215:403 (1990)；Guide

to Huge Computers, Martin J. Bishop 編, Academic Press, San Diego (1994)；及 Carillo 等人 *SIAM J Applied Math* 48: 1073 (1988)))。舉例而言，可使用美國國家生物技術資訊中心（National Center for Biotechnology Information）資料庫之 BLAST 函數測定一致性。其他市售或公開可用程式包括 DNAStar「MegAlign」程式（Madison, WI）及威斯康辛大學遺傳計算集團（University of Wisconsin Genetics Computer Group，UWG）「Gap」程式（Madison WI）。舉例而言，可藉由使用如由 Smith 及 Waterman（*Adv. Appl. Math.* 2: 482 (1981)）修訂之 GAP 電腦程式（例如，Needleman 等人 *J. Mol. Biol.* 48: 443 (1970)）比較序列資訊來測定蛋白質及/或核酸分子之同源性或一致性百分比。簡言之，GAP 程式將相似性定義為類似的所對準符號（亦即核苷酸或胺基酸）之數目除以兩個序列中之較短者之符號的總數。GAP 程式之預設參數可包括：（1）一元比較矩陣（含有對於一致性而言為 1 且對於非一致性而言為 0 之值），及如 Schwartz 及 Dayhoff 編, Atlas of Protein Sequence and Structure, National Biomedical Research Foundation,第 353-358 頁(1979)所述 Gribskov 等人 Nucl. Acids Res. 14：6745 (1986)之權重比較矩陣；（2）對於各間隙罰分 3.0 及對於各間隙中之各符號另外罰分 0.10；及（3）末端間隙無罰分。

因此，如本文中所用，術語「一致性」表示在測試與參考多肽或聚核苷酸之間的比較。在一非限制性實例中，

「至少 90%一致」係指相對於參考多肽 90 至 100%之一致性百分比。90%或更高程度之一致性指示以下事實：假定出於例證目的，則比較 100 個胺基酸之測試與參考聚核苷酸長度，測試多肽中的至多 10%（亦即 100 中之 10 個）之胺基酸與參考多肽之胺基酸不同。可在測試與參考聚核苷酸之間進行類似比較。該等差異可表示為在胺基酸序列之整個長度上隨機分布之點突變，或其可叢集在不同長度之一或多個位置中至高達最大容許，例如 10/100 胺基酸差異（約 90%一致性）。差異定義為核酸或胺基酸取代、插入或缺失。在高於約 85-90%之同源性或一致性程度上，結果應獨立於程式及間隙參數集；通常不依賴於軟體，可易於評估該等高程度之一致性。如本文中所用，亦應瞭解術語「實質上一致」或「相似」隨如熟習相關技術者所瞭解之情形而變化，但熟習相關技術者可評估此「實質上一致」或「相似」。

如本文中所用，經對準之序列係指使用同源性（相似性及/或一致性）來對準核苷酸或胺基酸序列中之對應位置。典型地，對準因 50%或更高的一致性而相關之兩個或更多個序列。序列之對準組係指在對應位置對準之 2 個或更多個序列，且可包括對準與基因組 DNA 序列對準的來源於 RNA 之序列（諸如 EST 及其他 cDNA）。

如本文中所用，「特異性雜交」係指藉由互補鹼基配對使核酸分子（例如寡核苷酸）黏接為目標核酸分子。熟習此項技術者熟悉影響特異性雜交之試管內及活體內參數，諸如特定分子之長度及組成。與試管內雜交尤其相關

之參數進一步包括黏接及洗滌溫度、緩衝液組成及鹽濃度。用於在高嚴格度下移除非特異性結合之核酸分子的例示性洗滌條件為 0.1×SSPE、0.1% SDS、65℃，且在中嚴格度下之例示性洗滌條件為 0.2×SSPE、0.1% SDS、50℃。在此項技術中已知等效嚴格度條件。熟習此項技術者可易於調節此等參數以實現核酸分子與適合於特定應用的目標核酸分子之特異性雜交。

如本文中所用，經分離或純化之多肽或蛋白質或其生物活性部分實質上不含來自蛋白質所來源的組織之細胞的細胞物質或其他污染蛋白質，或當化學合成時實質上不含化學前驅體或其他化學品。若製劑似乎不含如藉由熟習此項技術者用以評估該純度之諸如薄層層析（TLC）、凝膠電泳及高效液相層析（HPLC）的標準分析方法測定之易偵測雜質，則可確定其實質上不含雜質，或足夠純，以使得進一步純化將無法可偵測地改變物質之物理及化學特性，諸如蛋白水解及生物活性。熟習此項技術者已知用於純化化合物以產生實質上化學純化合物之方法。然而，實質上化學純化合物可為立體異構體之混合物。在該等情況下，進一步純化可增加化合物之比活性。

術語實質上不含細胞物質包括使蛋白質與分離或重組產生其的細胞之細胞組份分離的蛋白質之製備。在一具體實例中，術語實質上不含細胞物質包括製備具有小於約 30%（乾重）之非蛋白酶蛋白質（本文中亦稱作污染蛋白質）、通常小於約 20%之非蛋白酶蛋白質或 10%之非蛋白酶蛋白

質或小於約 5%之非蛋白酶蛋白質的蛋白酶蛋白質。當重組產生蛋白酶蛋白質或其活性部分時，其亦實質上不含培養基，亦即培養基占蛋白酶蛋白質製劑之體積的小於、約或等於 20%、10%或 5%。

如本文中所用，術語實質上不含化學前驅體或其他化學品包括使蛋白質與蛋白質合成中所涉及的化學前驅體或其他化學品分離的蛋白酶蛋白質之製備。該術語包括製備具有小於約 30%（乾重）、20%、10%、5%或 5%以下之化學前驅體或非蛋白酶化學品或組份的蛋白酶蛋白質。

如本文中所用，藉由使用重組 DNA 方法來由重組方法產生係指使用熟知分子生物學方法來表現藉由所選殖 DNA 編碼之蛋白質。

如本文中所用，載體（或質體）係指用以將異源核酸引入細胞以供其表現或複製的獨立元件。載體典型地保持游離，但可經設計以實現基因或其部分整合於基因組之染色體中。亦涵蓋為人工染色體之載體，諸如細菌人工染色體、酵母菌人工染色體及哺乳動物人工染色體。熟習此項技術者熟知該等載體的選擇及使用。

如本文中所用，表現係指使核酸轉錄為 mRNA 且轉譯成肽、多肽或蛋白質之過程。若核酸係來源於基因組 DNA，則在選擇適當真核宿主細胞或生物體之情況下表現可包括加工，諸如 mRNA 之剪接。

如本文中所用，表現載體包括能夠表現與諸如啟動子區域之能夠實現 DNA 片段之表現的調節序列操作性連接的

該等 DNA 之載體。該等額外區段可包括啟動子及終止子序列，且視情況可包括一或多個複製起點、一或多個可選擇標誌、強化子、聚腺嘌呤信號及其類似物。表現載體通常來源於質體或病毒 DNA，或可含有此兩種元件。因此，表現載體係指重組 DNA 或 RNA 構築體，諸如質體、噬菌體、重組病毒或在引入適當宿主細胞後使所選殖 DNA 表現的其他載體。適當表現載體為熟習此項技術者所熟知，且包括彼等在真核細胞及/或原核細胞中可複製者，及彼等保持游離型者或彼等整合於宿主細胞基因組中者。

如本文中所用，載體亦包括「病毒載體」。病毒載體為與外源基因操作性連接以將外源基因轉移（作為媒介或穿梭）於細胞中之工程化病毒。

如本文中所用，腺病毒係指引起人類結膜炎及上呼吸道感染之一組含有 DNA 之病毒中的任一者。

如本文中所用，裸 DNA 係指不含組蛋白之 DNA，其可用於疫苗及基因療法。裸 DNA 為在稱為轉型或轉染之基因轉移過程中由細胞傳遞至細胞的遺傳物質。在轉型或轉染中，藉由受體細胞採集之經純化或裸 DNA 將為受體細胞提供新特徵或表型。

如本文中所用，當提及 DNA 區段時可操作連接或操作性連接意謂區段經排列以便其一致起作用以供實現預定目的，例如轉錄在啟動子中起始且經由編碼區段進行至終止子。

如本文中所用，調節蛋白質之活性或基因或核酸之表

現的藥劑降低或增強或以其他方式改變蛋白質之活性，或以某些方式上調或下調或以其他方式改變核酸在細胞中之表現。

如本文中所用，「嵌合蛋白（chimeric protein）」或「融合蛋白（fusion protein）」係指與不同多肽操作性連接之多肽。本文中提供之嵌合或融合蛋白可包括一或多個 FVII 多肽或其部分，及用於轉錄/轉譯控制信號、信號序列、用於定位之標籤、用於純化之標籤、免疫球蛋白 G 之域的部分及/或靶向劑之任一或多者之一或多種其他多肽。嵌合 FVII 多肽亦包括彼等使其多肽之內源性域或區域與另一多肽交換者。此等嵌合或融合蛋白包括彼等藉由重組方式產生為融合蛋白者，彼等藉由化學方法產生者（諸如藉由化學偶聯，經由例如偶聯至硫氫基），及彼等藉由任何其他方法產生者，藉此至少一種多肽（亦即 FVII）或其部分直接或經由連接子間接連接至另一多肽。

如本文中所用，當提及融合蛋白時操作性連接係指彼此同框融合之蛋白酶多肽及非蛋白酶多肽。非蛋白酶多肽可融合至蛋白酶多肽之 N 末端或 C 末端。

如本文中所用，靶向劑為諸如蛋白質或其有效部分之任何部分，其提供與細胞表面分子之特異性結合，該細胞表面受體在某些情況下可內化所結合接合物或其部分。靶向劑亦可為促進或利於接合物之親和力分離或純化；接合物與表面之連接；或接合物或含有接合物之複合物之偵測者。

如本文中所用，分子之衍生物或類似物係指來源於分子之部分或分子之經修飾型式。

如本文中所用，「疾病或病症」係指由包括（但不限於）感染、後天性病狀、遺傳病狀之病因或病狀產生且特徵在於可鑑別症狀的生物體之病理學病狀。本文中所關注之疾病及病症為彼等涉及凝血者（包括彼等藉由凝血蛋白質所介導者）及彼等凝血蛋白質在病原學或病變中起作用者。疾病及病症亦包括彼等由缺乏蛋白質所引起者（諸如在血友病中），且本文尤其關注由於凝血蛋白質缺乏或缺陷而未發生凝血之彼等病症。

如本文中所用，「促凝血劑（procoagulant）」係指促進凝血之任何物質。

如本文中所用，「抗凝血劑（anticoagulant）」係指抑制凝血之任何物質。

如本文中所用，「血友病（hemophilia）」係指由血凝因子缺乏所引起的出血病症。血友病可為例如凝結因子之不存在、表現降低或功能降低的結果。最常見類型之血友病為 A 型血友病，其由因子 VIII 缺乏導致。第二最常見類型之血友病為 B 型血友病，其由因子 IX 缺乏導致。亦稱為 FXI 缺乏之 C 型血友病為輕度且較不常見之血友病形式。

如本文中所用，「先天性血友病（congenital hemophilia）」係指血友病之遺傳類型。先天性血友病由凝結因子之產生不存在、降低或無功能的凝結因子基因之突變、缺失、插入或其他修飾導致。舉例而言，諸如因子 VIII

及因子 IX 的凝結因子基因之遺傳突變分別引起先天性血友病 A 型及 B 型血友病。

如本文中所用，「後天性血友病（acquired hemophilia）」係指在成年期因使 FVIII 失活之自體抗體之產生而發展的一種類型之血友病。

如本文中所用，「出血病症」係指個體具有降低之控制出血能力的病狀。出血病症可為遺傳性或後天性的，且可由例如凝血途徑缺陷或缺乏、血小板活性缺陷或缺乏或血管缺陷導致。

如本文中所用，「後天出血病症」係指由諸如肝臟疾病、維生素 K 缺乏或下丙酮香豆素鈉（coumadin）（華法林（warfarin））或其他抗凝結劑療法之病狀所導致的凝結缺乏所導致的出血病症。

如本文中所用，「治療」患有疾病或病狀之個體意謂對個體投予本文中提供之多肽、組成物或其他產物。

如本文中所用，治療劑、治療方案、輻射防護劑或化療劑意謂包括疫苗之熟習此項技術者已知的習知藥物及藥物療法。在此項技術中熟知放射治療劑。

如本文中所用，治療意謂使病狀、病症或疾病之症狀得以改善或以其他方式有利地改變之任何方式。因此，治療涵蓋預防、治療及/或治癒。治療亦涵蓋本文中之組成物的任何醫藥用途。治療亦涵蓋本文中提供之經修飾之 FVII 及組成物的任何醫藥用途。

如本文中所用，藉由治療（諸如藉由投予醫藥組成物

或其他治療劑）來使特定疾病或病症之症狀改善係指可歸於或與投予該組成物或治療劑相關的症狀之任何減輕，無論為永久性或暫時性、持續性或短暫的。

如本文中所用，預防係指使發展疾病或病狀之風險得以降低之方法。預防包括使發展疾病或病狀之風險降低，及/或預防症狀惡化或疾病進行或症狀惡化或疾病進行之風險降低。

如本文中所用，用於治療特定疾病的化合物或組成物之有效量為足以改善或以某些方式減少與疾病相關的症狀之量。該量可作為單一劑量投予，或可根據其有效之方案投予。該量可治癒疾病，但通常經投予以改善疾病之症狀。典型地，需要重複投藥來實現症狀之所需改善。

如本文中所用，「治療有效量」或「治療有效劑量」係指含有至少足以產生治療作用的含有化合物之藥劑、化合物、物質或組成物。有效量為預防、治癒、改善、抑制或部分抑制疾病或病症之症狀所必需的治療劑之量。

如本文中所用，待治療之「患者」或「個體」包括人類及/或非人類動物，包括哺乳動物。哺乳動物包括靈長類動物，諸如人類、黑猩猩、大猩猩及猴；馴養動物，諸如犬、馬、貓、豬、山羊、牛；及齧齒動物，諸如小鼠、大鼠、倉鼠及沙鼠。

如本文中所用，組合係指兩項之間或更多項之間的任何關聯。關聯可為空間關聯或指出於共同目的使用兩種或兩種以上項目。

如本文中所用，組成物係指兩種或兩種以上產物或化合物（例如，藥劑、調制劑、調節劑等）之任何混合物。其可為溶液、懸浮液、液體、粉末、糊劑、水性或非水性調配物或其任何組合。

如本文中所用，「製品」為經製造且銷售之產品。如本申請案中通篇所用，該術語意欲涵蓋含於封裝製品中的經修飾之蛋白酶多肽及核酸。

如本文中所用，流體係指可流動之任何組成物。因此，流體涵蓋呈半固體、糊劑、溶液、水性混合物、凝膠、洗劑、乳膏劑之形式的組成物及其他此類組成物。

如本文中所用，「套組」係指封裝組合，其視情況包括用於使用組合之元件來實施方法之試劑及其他產品及/或組份。舉例而言，提供含有本文中提供之經修飾之蛋白酶多肽或核酸分子及用於包括（但不限於）投藥、診斷及評估生物活性或特性之目的之另一項的套組。套組視情況包括使用說明書。

如本文中所用，抗體包括諸如 Fab 片段之抗體片段，其包含輕鏈及重鏈可變區。

如本文中所用，受體係指對特定配位體具有親和力之分子。受體可為天然存在或合成分子。受體在此項技術中亦可稱為抗配位體。

如本文中所用，動物包括任何動物，諸如（但不限於）靈長類動物，包括人類、大猩猩及猴；齧齒動物，諸如小鼠及大鼠；禽類，諸如雞；反芻動物，諸如山羊、牛、鹿、

綿羊；羊類，諸如豬及其他動物。非人類動物排除人類作為預期動物。本文中提供之蛋白酶來自任何來源、動物、植物、原核生物及真菌。

如本文中所用，基因療法包括將諸如 DNA 之異源核酸轉移至患有尋求該療法之病症或病狀的哺乳動物、尤其人類之某些細胞、目標細胞中。諸如直接或在載體或其他傳遞媒介中以使得諸如 DNA 之異源核酸得以表現且藉此產生所編碼治療產物的方式將諸如 DNA 之核酸引入所選目標細胞中。或者，諸如 DNA 之異源核酸可以某些方式介導編碼治療產物的 DNA 之表現，或其可編碼諸如肽或 RNA 之以某些方式直接或間接介導治療產物之表現的產物。亦可使用遺傳療法來傳遞編碼替代缺陷基因或補充由哺乳動物或其所引入之細胞產生的基因產物之基因產物之核酸。所引入核酸可編碼治療化合物，諸如蛋白酶或經修飾之蛋白酶，其通常並不在哺乳動物宿主中產生或並不以治療有效量或在治療有效時間產生。可在引入於患病宿主之細胞中之前修飾諸如 DNA 之編碼治療產物的異源核酸以增強或以其他方式改變其產物或表現。遺傳療法亦可包括傳遞抑制子或阻遏蛋白或基因表現之其他調節劑。

如本文中所用，異源核酸為通常並不由表現其之細胞活體內產生或由該細胞產生，但處於不同基因座或經不同地表現，或藉由影響轉錄、轉譯或其他可調節生化過程介導或編碼改變諸如 DNA 之內源性核酸表現的介體之核酸。異源核酸對於其所引入之細胞而言通常並非內源性的，而

自另一細胞獲得或合成製備。異源核酸可為內源性的，但為由不同基因座所表現或表現改變之核酸。通常，儘管不必，該核酸編碼通常並不由細胞產生或以表現其之細胞中相同的方式產生之 RNA 及蛋白質。諸如 DNA 之異源核酸亦可稱為外來核酸，諸如 DNA。因此，異源核酸或外來核酸包括不以確切取向或位置作為存在於基因組中之對應核酸分子（諸如 DNA）存在之核酸分子。其亦可指來自另一生物體或物種（亦即外源）之核酸分子。

本文中藉由異源核酸涵蓋諸如 DNA 之熟習此項技術者將認識到或認為對表現核酸之細胞為異源或外來的任何核酸；異源核酸包括亦內源性表現之外源添加之核酸。異源核酸之實例包括（但不限於）編碼諸如賦予抗藥性的蛋白質之可追蹤標誌蛋白質之核酸、編碼諸如抗癌劑、酶及激素的治療有效物質之核酸，及諸如 DNA 之編碼其他類型之諸如抗體的蛋白質之核酸。引入異源核酸之細胞的表面上可分泌或表現由異源核酸編碼之抗體。

如本文中所用，基因療法之治療有效產物為由異源核酸、典型地 DNA 編碼之產物，在將核酸引入宿主後，表現改善或消除遺傳或後天性疾病之症狀、表現或治癒疾病的產物。亦包括生物活性核酸分子，諸如 RNAi 及反義核酸。

如本文中所用，敘述多肽「基本上由所述胺基酸序列組成」意謂僅存在全長多肽的所述部分或其片段。多肽可視情況且通常將包括來自另一來源之額外胺基酸或可插入另一多肽中。

如本文中所用，除非上下文另外明確規定，否則單數形式「一」及「該」包括複數個指示物。因此，舉例而言，對包含「細胞外域」之化合物的提及包括具有一或複數個胞外域之化合物。

如本文中所用，範圍及量可表示為「約」特定值或範圍。約亦包括精確量。因此「約 5 個鹼基」意謂「約 5 個鹼基」以及「5 個鹼基」。

如本文中所用，「可選」或「視情況」意謂隨後描述之事件或情形發生或不發生，且該描述包括該事件或情形發生之情況以及其不發生之情況。舉例而言，視情況經取代之基團意謂該基團未經取代或經取代。

如本文中所用，除非另外指明，否則任何保護性基團、胺基酸及其他化合物之縮寫係與其常見用法、公認縮寫或 IUPAC-IUB 生物化學命名委員會（IUPAC-IUB Commission on Biochemical Nomenclature（（參見 (1972) Biochem. 11:1726）一致。

B. 止血概述

本文提供經修飾之因子 VII（FVII）多肽。該等 FVII 多肽經設計以具有增強之凝血活性。據此，此等多肽具有多種用途及應用，例如作為用於調節止血及其他相關生物過程之治療劑。為瞭解本文中提供之修飾及該等經修飾之 FVII 分子的用途，對止血系統及凝血級聯系統之瞭解為有利的。以下論述在論述因子 VII 及其修飾之前提供該背景。

止血為阻止由血管結構損傷導致的出血之生理機制。

正常止血取決於細胞組份及可溶性血漿蛋白，且涉及最終引起血凝塊形成之一系列信號傳輸事件。血管發生損傷及內皮細胞損壞後迅速起始凝血。在凝血之第一階段中，血小板活化以在損傷部位形成止血栓塞。接著為涉及在蛋白水解級聯中起作用，使得形成強化血小板栓塞之血纖蛋白束的血漿凝血因子之第二階段止血。

血管損傷後，流至直接損傷區域之血流受血管收縮限制，允許血小板黏附於內皮下結締組織上之新近暴露的纖絲狀膠原。此黏附依賴於溫韋伯氏因子（Von Willebrand factor，vWF），其在 3 秒內與損傷之內皮結合，藉此促進血小板黏附及聚集。所聚集血小板之活化引起包括 ADP、ATP、凝血烷及血清素之多種因子的分泌。亦釋放黏附分子、血纖維蛋白原、vWF、血小板反應蛋白及纖連蛋白。該分泌促進血小板之額外黏附及聚集，增加之血小板活化及血管收縮，及陰離子型磷脂在充當用於裝配凝血酶複合物的平台之血小板表面上之暴露。血小板改變形狀，引起偽足形成，其進一步促進其他血小板聚集，產生疏鬆血小板栓塞。

同時起始肽酶之凝結級聯（凝血級聯）。凝血級聯涉及包括蛋白水解裂解之一系列活化事件。在該級聯中，絲胺酸蛋白酶之無活性蛋白質（亦稱為酶原）藉由裂解一或多個肽鍵而轉化成活性蛋白酶，其接著充當級聯中下一個酶原分子之活化蛋白酶，最終藉由交聯血纖蛋白引起凝塊形成。舉例而言，該級聯產生諸如凝血酶（來自凝血酶原

裂解）之經活化分子，其進一步活化血小板且亦由裂解血纖維蛋白原產生血纖蛋白。接著，血纖蛋白在血小板栓塞周圍形成交聯聚合物以穩定凝塊。損傷修復後，由主要組份為纖維蛋白溶酶原及組織型纖維蛋白溶酶原活化因子（tPA）之纖溶系統消化血纖蛋白。此等蛋白質均併入聚合血纖蛋白中，其中其交互作用以產生纖維蛋白溶酶，其接著對血纖蛋白起作用以溶解預成型凝塊。凝塊形成期間，凝血因子抑制子亦在血液中循環以預防損傷部位以外凝塊形成。

自損傷至凝塊形成及後續纖維蛋白溶解之系統的交相互作用經描述如下。

1. 血小板黏附及聚集

在正常情況下，主動阻遏血液凝結。血管內皮支持血管擴張、抑制血小板黏附及活化、抑止凝血、增強血纖蛋白裂解且在性質上具消炎作用。血管內皮細胞分泌諸如氧化亞氮（NO）及前列腺環素（prostacylin）之分子，其抑制血小板聚集且使血管擴張。此等分子之釋放活化可溶性鳥苷酸環化酶(sGC)及 cGMP 依賴性蛋白質激酶 I(cGKI)，且提高環磷酸鳥苷（cGMP）含量，此引起血管壁中平滑肌之鬆弛。此外，內皮細胞表現諸如 CD39 之細胞表面 ADP 酶，其藉由將自血小板釋放之 ADP 轉化成腺嘌呤核苷酸血小板抑制子來控制血小板活化及聚集。內皮亦在纖維蛋白溶解級聯中在對酶之調節中起重要作用。內皮細胞經由表現纖維蛋白溶酶原（膜聯蛋白 II（annexin II））及尿激酶

之受體，以及分泌組織型及尿激酶纖維蛋白溶酶原活化因子（其全部促進凝塊清除），直接促進纖維蛋白溶酶之產生。在最後一層促血栓調節中，內皮細胞藉由產生提高對凝血酶及其他凝血因子之抗凝血酶 III 抑制的動力學之硫酸乙醯肝素在抑制凝血級聯中起活躍作用。

然而，在急性血管外傷情況下，血管收縮機制起主要作用且內皮在性質上變得促血栓、促凝血及促發炎。藉由減少內皮細胞擴張劑：腺苷、NO 及前列環素；及 ADP、血清素及凝血烷對血管平滑肌細胞之引發其收縮（Becker, Heindl 等人, 2000）的直接作用實現此點。對引起止血血栓形成之內皮細胞功能變化的主要觸發為血液與胞外基質（ECM）組份之間內皮細胞障壁之損失（Ruggeri (2002) Nat Med 8:1227-1234）。循環血小板識別且區分內皮細胞病變之區域，且黏附於所暴露內皮下層。其與各種成血栓受質及局部產生或釋放之促效劑的交互作用引起血小板活化。此過程經描述為具有兩個階段：1）黏附：初始限定於表面；及 2）聚集：血小板-血小板黏著（Savage 等人 (2001) Curr Opin Hematol 8:270-276）。

當循環血小板經由與細胞表面上之膠原結合蛋白交互作用且經由與亦存在於內皮上的 vWF 交互作用，結合於暴露膠原時起始血小板黏附。vWF 蛋白為由內皮在兩個方向分泌至基底外側及分泌至血流中之可變尺寸之多聚結構。vWF 亦結合因子 VIII，此在因子 VIII 之穩定化及其在循環中之存活中重要。

當 vWF 經由其 A1 域與 GPIb（血小板醣蛋白受體複合物 GPIb-IX-V 之部分）結合時實現血小板黏附及後續活化。藉由使得剪切應力增加引起 vWF 對 GPIb 之親和力相應地增加之剪切力，來調節 vWF 與 GPIb 之間的交互作用。亦已知在白血球上作為 VLA-2 之整合素 $\alpha 1\beta 2$ 為血小板上之主要膠原受體，且經由此受體之接合產生促進血小板活化之細胞內信號。經由 $\alpha 1\beta 2$ 結合促進較低親和力膠原受體 GPVI 之接合。此為免疫球蛋白超家族之部分且為產生對於血小板活化而言最有效細胞內信號之受體。血小板活化引起二磷酸腺苷（ADP）釋放，其轉化成凝血烷 A2。

血小板活化亦引起亦稱為血小板整合素 $\alpha_{IIb}\beta_3$ 之血小板醣蛋白 IIb-IIIa(GP IIb-IIIa)受體之表面表現。GP IIb-IIIa 受體允許血小板藉助於經由此等受體連接血小板之血纖維蛋白原分子彼此黏著（亦即聚集）。此使得在損傷部位形成血小板栓塞，以幫助防止進一步失血，而損壞之血管組織釋放起始凝血級聯及穩定血纖蛋白網圍繞血小板栓塞形成之因子。

2. 凝血級聯

凝血途徑為血漿中之各酶以酶原或無活性形式存在之蛋白水解途徑。調節酶原之裂解以自前驅體分子釋放活性形式。諸如醣蛋白 FVIII 及 FV 的經活化蛋白酶之輔因子亦在級聯反應中活化且在凝塊形成中起作用。該途徑充當控制活化過程之一系列正及負反饋環路，其中最終目標為產生凝血酶，其可隨後將可溶性血纖維蛋白原轉化成血纖蛋

白以形成凝塊。典型地對凝血中之該等因子給予羅馬數字編號，其中以附加小寫「a」指示經活化形式。下表 3 闡明該等因子之例示性列表，包括其常用名及其在凝血級聯中之作用。通常，此等蛋白質經由固有、外在或共有凝血途徑中之一或多者參與凝血（參見圖 1）。如下所述，此等途徑互相關聯，且咸信凝血經由為凝血之初始引發引子的因子 VII（FVII）活化之基於細胞的模式發生。

表 3

凝血因子

因子	常用名	途徑	特徵
I	血纖維蛋白原	兩者	-
II	凝血酶原	兩者	含有 N 末端 Gla 域
III	組織因子	外在	-
IV	鈣	兩者	-
V	促凝血球蛋白原、不穩定因子、加速球蛋白	兩者	蛋白輔因子
VI (Va)	促凝血球蛋白	-	（引子 V 之冗餘）
VII	前轉化素、血清凝血酶原轉變加速因子（SPCA）輔凝血酶原激酶	外在	具有 Gla 域之內肽酶
VIII	抗血友病因子 A 抗血友病球蛋白（AHG）	固有	蛋白輔因子
IX	克雷斯馬斯因子（Christmas factor）、抗血友病因子 B、血漿凝血酶原激酶組分（PTC）	固有	具有 Gla 域之內肽酶
X	司徒因子（Stuart prower factor）	兩者	具有 Gla 域之內肽酶
XI	血漿凝血酶原激酶前體（PTA）	固有	內肽酶
XII	哈格曼因子（Hageman factor）	固有	內肽酶
XIII	促麩胺醯胺轉移酶、血纖蛋白穩定因子（FSF）、纖維蛋白酶	兩者	轉肽酶

*表由 M.W.King (2006)之 med.unibs.it/~marchesi/blood.html 改編而來

歷史上，凝血酶之產生已分成三個途徑，亦即固有途徑（表明該途徑之所有組份為血漿所固有）；及外在途徑（表明該途徑之一或多個組份並非血漿所固有），其提供

產生活化因子 X（FXa）之替代途徑；及最終共有途徑，其引起凝血酶形成（圖 1）。此等途徑共同參與相互關聯且相互依賴之過程以實現凝血。發展出描述此等途徑的凝血之細胞基模型（圖 2）（Hoffman 等人 (2001) Thromb Haemost 85:958-965）。在此模型中，「外在」及「固有」途徑分別為在不同細胞表面、承載組織因子（TF）之細胞及血小板上之作用。凝血過程分成不同階段，亦即起始、擴增及增長，在此期間外在及固有途徑在各階段起作用以產生將足夠量之血纖維蛋白原轉化成血纖蛋白以供凝塊形成所需的大量突然增加之凝血酶。

a. 起始

將 FVII 視為負責起始凝血級聯之凝血因子，該起始依賴於其與 TF 之交互作用。TF 為由諸如平滑肌細胞、纖維母細胞、單核細胞、淋巴細胞、粒細胞、血小板及內皮細胞之多種細胞表現之跨膜醣蛋白。當諸如受促發炎細胞激素刺激時，骨髓細胞及內皮細胞僅表現 TF。然而，平滑肌細胞及纖維母細胞組成性表現 TF。據此，組織損傷後，此等細胞在與血流接觸後，藉由 TF 與血漿中之因子 VII 或 FVIIa 結合迅速起始凝血級聯。

如以下所述，血液中之大多數 FVII 呈酶原形式，其中約 1%之少量以 FVIIa 形式存在。然而，在 TF 結合不存在之情況下，甚至 FVIIa 具有酶原樣特徵且不顯示顯著活性，直至其與 TF 複合。因此，為達到充分活性，血漿 FVII 需要藉由蛋白水解裂解活化及經由與 TF 交互作用另外發生構

形變化。已展示包括因子 IXa、Xa、XIIa 及凝血酶之多種蛋白酶能夠試管內裂解 FVII，其在 TF 存在下加速之過程。在 TF 存在下，FVIIa 本身亦可活化 FVII，此為稱為自體活化之過程。血液中之少量 FVIIa 可能歸因於受 FXa 及/或 FIXa 活化（Wildgoose 等人 (1992) Blood 80:25-28 及 Butenas 等人 (1996) Biochemistry 35:1904-1910）。因此，TF/FVIIa 複合物可藉由 FVIIa 與 TF 直接結合或藉由 FVII 與 TF 結合，且隨後 FVII 受諸如 FXa、FIXa、FXIIa 或 FVIIa 本身之血漿蛋白酶後續活化為 FVIIa 來形成。TF/FVIIa 複合物保持錨定於承載 TF 之細胞，在此處其在稱為凝血之「外在途徑」中將少量 FX 活化為 FXa。

TF/FVIIa 複合物亦將少量 FIX 裂解為 FIXa。FXa 與其輔因子 FVa 相締合以亦在承載 TF 之細胞上形成複合物，該複合物隨後可將凝血酶原轉化為凝血酶。然而，所產生之少量凝血酶不足以支持完全凝結所需之血纖蛋白形成。另外，任何活性 FXa 及 FIXa 在循環中受抗凝血酶 III(AT-III) 及其他絲胺酸蛋白酶抑制子抑制，此在下文更詳細論述。此現象通常將防止循環中之凝塊形成。然而，在損傷存在下，對血管結構之損害引起血小板聚集及在此部位凝血酶形成之活化，藉此允許凝血信號擴增。

b. 擴增

當凝血酶與血小板結合且活化血小板時，發生擴增。經活化血小板自其 α 顆粒釋放 FV，其藉由凝血酶活化為 FVa。凝血酶亦自血小板膜上之 FVIII/vWF 複合物釋放且活

化 FVIII 且將 FXI 裂解為 FXIa。此等反應產生表面上具有 FVa、FVIIIa 及 FIXa 之經活化血小板，其為增長階段凝血酶產生之大量突然增加做必要準備。

c. 增長

凝血增長發生在損傷部位大量血小板之表面上。如上所述，經活化血小板在其表面上具有 FXIa、FVIIIa 及 FVa。外在途徑便在此處實現。FXIa 將 FIX 活化為 FIXa，其可隨後與 FVIIIa 結合。除藉由承載 TF 之細胞上的 TF/FVIIa 複合物裂解 FIX 產生之少量 FIXa 之外，此過程亦產生大量 FXIa/FVIIIa 複合物，其接著可將大量 FX 活化為 FXa。FXa 分子結合 FVa 以產生將凝血酶原活化為凝血酶之凝血酶原酶複合物。凝血酶在正反饋環路中起作用以活化甚至更多血小板且再次起始擴增階段所述之過程。

極快地出現足夠數目之具有適當複合物的經活化血小板以產生凝血酶之突然增加，凝血酶足夠大量以自血纖維蛋白原產生足夠量之血纖蛋白以便形成止血血纖蛋白凝塊。血纖維蛋白原為可溶於血漿中之二聚體，其當藉由凝血酶裂解時釋放纖維蛋白肽 A 及纖維蛋白肽 B。纖維蛋白肽 B 接著藉由凝血酶裂解，且由此第二蛋白水解裂解形成之纖維蛋白單體自發地形成不溶性凝膠。經聚合纖維蛋白藉由非共價及靜電力結合在一起，且由藉由凝血酶裂解 FXIII 所產生的轉醯胺酶因子 XIIIa（FXIIIa）穩定。凝血酶亦活化 TAFI，其藉由減少凝塊表面之纖維蛋白溶酶產生而抑制纖維蛋白溶解。另外，凝血酶本身被併入凝塊結構中

以便進一步穩定化。此等不溶性纖維蛋白聚集體（凝塊）與聚集之血小板（血栓）一起阻斷受損血管且防止進一步出血。

3. 凝血調節

凝血期間，藉由組成性且刺激性過程調節級聯以抑制進一步凝塊形成。存在多個需要該等調節機制之原因。首先，需要調節來限制纖維蛋白凝塊形成造成之組織之局部缺血。其次，調節藉由使凝塊形成僅侷限於組織損傷部位來防止普遍血栓形成。

調節由數種抑制性分子之陽離子實現。舉例而言，抗凝血酶 III（AT-III）及組織因子途徑抑制子（TFPI）組成性起作用以抑制凝血級聯中之因子。AT-III 抑制凝血酶、FIXa 及 FXa，而 TFPI 抑制 FXa 及 FVIIa/TF 複合物。經由血小板活化刺激之另一因子蛋白質 C 藉由使 FVa 及 FVIIIa 發生蛋白水解裂解及失活來調節凝血。蛋白質 S 增強蛋白質 C 之活性。另外，促進凝血抑制之另一因子為整合膜蛋白凝血調節蛋白（thrombomodulin），其由血管內皮細胞產生且充當凝血酶之受體。凝血酶與凝血調節蛋白之結合抑制凝血酶促凝血活性且亦促進蛋白質 C 活化。

纖維蛋白溶解，亦即纖維蛋白凝塊之分解亦提供調節凝血之機制。凝塊中之交聯纖維蛋白多聚體由絲胺酸蛋白酶纖維蛋白溶酶分解成可溶性多肽。纖維蛋白溶酶可自其無活性前驅體纖維蛋白溶酶原產生且以兩種方式募集至纖維蛋白凝塊部位：藉由與纖維蛋白凝塊表面上之組織纖維

蛋白溶酶原活化因子（tPA）交互作用，及藉由與細胞表面上之尿激酶纖維蛋白溶酶原活化因子（uPA）交互作用。第一種機制似乎為負責血管內之凝塊溶解的主要機制。儘管能夠介導凝塊溶解，但第二種機制可在組織重塑、細胞遷移及發炎中起重要作用。

凝塊溶解亦以兩種方式調節。首先，有效纖維蛋白溶酶活化及纖維蛋白溶解僅發生在在凝塊表面或細胞膜上形成之複合物中，而在血液中之游離之蛋白質為低效催化劑且迅速失活。其次，纖維蛋白溶酶原活化因子及纖維蛋白溶酶由諸如作用於纖維蛋白溶酶原活化因子之第 1 型纖維蛋白溶酶原活化因子抑制子（PAI-1）及 PAI-2，及使纖維蛋白溶酶失活之α2-抗纖維蛋白溶酶及α2-巨球蛋白之分子失活。在正常情況下，血管損傷後凝血與纖維蛋白溶解之間的及時平衡引起凝塊之有效形成及清除，而同時防止不當血栓形成或出血事件。

將例示性凝血因子、輔因子及調節蛋白及其活性之總結闡明於下表 4 中。

表 4

凝血因子酶原及輔因子

因子名稱	活性
絲胺酸蛋白酶之酶原	
因子 XII	結合血管壁損傷部位之暴露膠原，由高 MW 激肽原（kininogen）及激肽釋放酶（kallikrein）活化
因子 XI	由因子 XIIa 活化
因子 IX	由因子 XIa + Ca^{2+}活化
因子 VII	由凝血酶、因子 X、因子 IXa 或因子 XIIa + Ca^{2+}活化，或自體活化
因子 X	在血小板表面上由 tenase 複合物（FIXa/FVIIIa）活化； 亦由因子 VIIa +組織因子+ Ca^{2+}或因子 VIIa + Ca^{2+}活化
因子 II	由凝血酶原酶複合物（FXa/FVa）在血小板表面上活化
輔因子	
因子 VIII	由凝血酶活化；因子 VIIIa 在因子 X 之活化中充當因子 IXa 之輔因子
因子 V	由凝血酶活化；因子 Va 在凝血酶原之活化中充當因子 Xa 之輔因子
因子 III（組織因子）	充當因子 VIIa 之輔因子
血纖維蛋白原	
因子 I（血纖維蛋白原）	由凝血酶裂解以形成纖維蛋白
轉麩胺醯胺酶	
因子 XIII	由凝血酶 + Ca^{2+}活化；促進纖維蛋白之共價交聯
調節及其他蛋白質	
溫韋伯氏因子（vWF）	充當 GPIb-V-IX 複合物與膠原之間的橋
蛋白質 C	由與凝血調節蛋白結合之凝血酶活化；Ca 降解因子 VIIIa 及 Va
蛋白質 S	充當蛋白質 C 之輔因子
凝血調節蛋白	內皮細胞表面蛋白；結合活化蛋白質 C 之凝血酶
抗凝血酶 III	凝血抑制子，主要為凝血酶及因子 Xa，以及因子 IXa、XIa 及 XIIa，及與 TF 複合之因子 VIIa 的抑制子
組織因子途徑抑制子（TFPI）	結合 FXa 且隨後與 TF/FVIIa 形成抑制 TF/FVIIa 活性之四級結構

*表由 M.W.King (2006) med.unibs.it/~marchesi/blood.html改適而來

C. 因子 VII（FVII）

因子 VII 為在包括哺乳動物之動物中作為單鏈酶原在

肝臟中合成且分泌於血流中之維生素 K 依賴性絲胺酸蛋白酶醣蛋白。如上所述，FVII 為負責起始引起凝血酶產生及纖維蛋白沈積的蛋白水解事件之級聯的凝血蛋白酶。其為外在途徑之部分，儘管其活性之下游作用亦極大地影響固有途徑。凝塊形成中之此整體作用已在 FVII 作為用於臨床抗凝血劑及止血療法之目標方面吸引顯著關注。舉例而言，已發展出重組經活化 FVII（rFVIIa）作為用於血友病個體及患有其他出血病狀之個體的止血劑。本文提供經修飾之 FVII 多肽，其經設計以在活化後具有增強之凝血活性，且其可充當治療服從因子 VII 療法的疾病及病狀之經改良治療劑。

1. FVII 結構及組建

人類 FVII 基因（F7）位於染色體 13 之 13q34，且為 12.8 kb 長，具有 9 個外顯子。FVII 基因與編碼諸如凝血酶原、因子 IX、因子 X 及蛋白質 C 之其他維生素 K 依賴性蛋白之基因共有顯著結構相似性。FVII 之 mRNA 經歷替代性剪接，以產生兩種轉錄產物：變異體 1（Genbank 寄存編號 NM_000131，闡明於 SEQ ID NO: 81 中）及變異體 2（Genbank 寄存編號 NM_019616，闡明於 SEQ ID NO: 82 中）。與由轉錄產物變異體 1 編碼的 466 個胺基酸之前驅體多肽（FVII 同功異型物 a 前驅體；SEQ ID NO:1）相比，為肝臟中之更豐富形式的轉錄產物變異體 2 不包括外顯子 1b，且因此編碼 444 個胺基酸之較短前驅體多肽（FVII 同功異型物 b 前驅體；SEQ ID NO:2）。FVII 同功異型物 b 前驅體多肽中不

存在之胺基酸對應於 FVII 同功異型物 a 前驅體之胺基酸位置 22 至 43。此等胺基酸為前肽序列之部分，產生截斷 FVII 同功異型物 b 前肽。前驅體多肽由以下區段及域組成：疏水性信號肽（SEQ ID NO: 1 及 2 之 aa 1-20）、前肽（SEQ ID NO: 1 之 aa 21-60 及 SEQ ID NO: 2 之 aa 21-38）、Gla 域（SEQ ID NO:2 之 aa 39-83 及 SEQ ID NO: 1 之 aa 61-105）、B 型上皮生長因子域（EGF 樣 1，SEQ ID NO: 2 之 aa 84-120 及 SEQ ID NO: 1 之 aa 106-142）、A 型上皮生長因子域（EGF 樣 2，SEQ ID NO: 2 之 aa 125-166；及 SEQ ID NO: 1 之 aa 147-188）及絲胺酸蛋白酶域（SEQ ID NO: 2 之 aa 191-430 及 SEQ ID NO: 1 之 aa 213-452）。

406 個胺基酸之成熟形式之 FVII 多肽（SEQ ID NO: 3）缺乏信號肽及前肽序列，且與其所來源之同功異型物前驅體無關在長度及序列上一致。在成熟形式之 FVII 多肽中，上述域的對應胺基酸位置如下：Gla 域（SEQ ID NO: 3 之 aa 1-45）、EGF 樣 1（SEQ ID NO: 3 之 aa 46-82）、EGF 樣 2（SEQ ID NO: 3 之 aa 87-128）及絲胺酸蛋白酶域（SEQ ID NO: 3 之 aa 153-392）。

FVII 之 Gla 域為膜結合基元，其在鈣離子存在下與包括磷脂醯絲胺酸之磷脂膜交互作用。Gla 域亦在結合 FVIIa 輔因子組織因子（TF）中起作用。與 TF 複合情況下，FVIIa 之 Gla 域負載有 7 個 Ca^{2+} 離子，使 3 個疏水性側鏈在細胞膜方向上突出以便與細胞表面上的磷脂交互作用，且與 TF 之 C 末端域明顯接觸。Gla 域在諸如凝血酶原、凝血因子

VII、IX及X、蛋白質C、S及Z之維生素K依賴性蛋白質之間保守。此等蛋白質需要維生素K用於轉譯後合成γ-羧基麩胺酸，其為在此等蛋白質之N末端Gla域中叢集之胺基酸。域中存在之所有麩胺酸殘基為潛在羧基化位點且因此其中許多經羧基化修飾。

除Gla域之外，成熟FVII蛋白亦含有兩個EGF樣域。第一EGF樣域（EGF樣1或EGF1）為鈣結合EGF域，其中6個保守核心半胱胺酸形成三個雙硫橋。FVII之EGF1域僅結合一個Ca^{2+}離子，但其親和力顯著高於Gla域所觀察到之親和力（Banner等人 (1996) Nature 380:41-46）。此所結合之Ca^{2+}離子促進FVII之EGF1域與TF之間的強交互作用（Osterlund等人 (2000) Eur J Biochem 267:6204-6211）。第二EGF樣域（EGF樣2或EGF2）不為鈣結合域，但亦形成3個雙硫橋。類似於FVII中之其他域，EGF2域與TF交互作用。其亦經雙硫鍵與蛋白酶域結合在一起，其與蛋白酶域共有大接觸界面。

最後，FVII之絲胺酸蛋白酶域為負責FVIIa之蛋白水解活性的域。FVII在其催化域中之胺基酸序列顯示與諸如胰蛋白酶及胰凝乳蛋白酶之其他絲胺酸蛋白酶之高序列一致性及三級結構相似性（Jin等人 (2001) J Mol Biol, 307: 1503-1517）。舉例而言，此等絲胺酸蛋白酶共有基於胰凝乳蛋白酶編號之共同催化三合體H57、D102、S195。然而，不同於其他的絲胺酸蛋白酶，FVIIa之裂解不足以完成酶原向充分活性酶之轉化。相反，如下所述，FVIIa係藉由與細

胞表面受體 TF 結合而經別構活化其催化功能，細胞表面受體 TF 誘導 FVIIa 蛋白酶域構形變化，使其自酶原樣無活性狀態轉換為催化活性酶。FVIIa 的輔因子結合位點與活性位點之間的螺旋環區域（亦即胺基酸殘基位置 305-321，對應於基於胰凝乳蛋白酶編號之殘基 163-170i）對於 FVIIa 之別構性及酶原性重要（Persson 等人 (2004) Biochem J., 379: 497-503）。此區域包含短 α 螺旋（胺基酸殘基位置 307 至 312），接著為環。螺旋之 N 末端部分形成蛋白酶域與 TF 之間的界面之部分，且含有對於蛋白水解功能及與 TF 之最佳結合而言重要的許多殘基。僅 FVIIa 與複合 TF 之 FVIIa 的晶體結構之比較指示當 FVIIa 結合 TF 時 α 螺旋經歷顯著構形變化。僅 FVIIa 之 α 螺旋似乎扭曲、縮短且取向不同。此影響鄰近環結構，使其移動遠離活性位點。相反，當與 TF 複合時 FVIIa 之 α 螺旋得以穩定，且相鄰環更接近活性位點定位。經由涉及至少 FVII 之胺基酸位置 306（根據胰凝乳蛋白酶編號，胺基酸殘基 Met^{164}）的甲硫胺酸之機制實現此穩定化（Pike 等人 (1999) PNAS 8925-8930）。

2. 轉譯後修飾

藉由插入內質網（ER）以起始跨膜移位的疏水性信號肽，使 FVII 前驅體多肽（因子 VII 基因之任一同功異型物）靶向細胞分泌途徑。在蛋白質移位穿過 ER 膜之時，ER 腔內的信號肽酶裂解 20 個胺基酸之信號肽，此後多肽經歷進一步轉譯後修飾，包括 N-糖苷化與 O-糖苷化、N 末端麩胺酸之維生素 K 依賴性羧基化為 γ-羧基麩胺酸，及天冬胺酸

羥基化為β-羥基天冬胺酸。

前肽提供識別FVII前肽中之10個殘基之兩性α螺旋的維生素K依賴性羧化酶之結合位點。結合後，羧化酶γ羧基化FVII多肽之Gla域內之10個麩胺酸之殘基，在相對於SEQ ID NO: 2中所闡明之FVII前驅體胺基酸序列之位置E66、E67、E74、E76、E79、E80、E85、E86、E89及E95產生γ-羧基麩胺醯基殘基。此等位置對應於SEQ ID NO: 3中所闡明的成熟FVII多肽之位置E6、E7、E14、E19、E20、E25、E26、E29及E35。對於最佳活性而言，FVII分子需要鈣，其結合多肽且促進FVIIa與TF及脂質結合所需之構形變化。經γ羧基化之Gla域以可變親和力結合7個Ca^{2+}離子，此誘導使得Gla域能夠與TF之C末端域、以及血小板膜上之磷脂醯絲胺酸或其他帶負電磷脂交互作用之構形變化。

藉由將Glc_3Man_9(GlcNAc)轉移至FVII多肽中對應於成熟蛋白質(SEQ ID NO:3)之胺基酸殘基145及322的位置處的兩個天冬醯胺殘基進行N-連接型糖苷化。O-連接型糖苷化在成熟多肽之胺基酸殘基52及60處進行，且羥基化為β-羥基天冬胺酸在位置63之天冬胺酸殘基處進行。此等O-糖苷化絲胺酸殘基及β-羥基化天冬胺酸殘基處於FVII之EGF-1域中。此等修飾係在ER中實現且在將多肽最終加工為其成熟形式之前進行高爾基體(Golgi)複合。

3. FVII加工

經修飾之前FVII多肽經由高爾基體腔運輸至反-高爾

基體隔室，在此處該前肽在自細胞分泌蛋白質之前不久由前肽酶裂解。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）之簡稱）為定位於高爾基體膜之內肽酶，其裂解許多蛋白質之序列基元 Arg-[任何殘基]-(Lys 或 Arg)-Arg 的羧基端側。此等前肽酶裂解維生素 K 依賴性醣蛋白，諸如前因子 IX 及前 vWF 多肽(Himmelspach 等人 (2000) Thromb Research 97; 51-67)，藉此自成熟蛋白質釋放前肽。使適當 PACE/弗林蛋白酶識別位點包含於重組因子 VII 前驅體中促進重組多肽之正確加工及分泌(Margaritas 等人 (2004) Clin Invest 113(7): 1025-1031)。PACE/弗林蛋白酶或另一枯草菌素樣（subtilising-like）前肽酶可能負責使前 FVII 蛋白水解加工為 FVII。其可識別且結合 SEQ ID NO: 1 中所闡明的序列之胺基酸位置 35-38 及 SEQ ID NO: 2 中所闡明的序列之位置 57-60 之-Arg-Arg-Arg-Arg-一致基元，藉此裂解前肽且釋放成熟蛋白質以便分泌。

4. FVII 活化

血液中之大多數 FVII 呈未經活化單鏈酶原之形式，儘管少量 FVII 以雙鏈活化形式存在。Arg^{152}-Ile^{153} 鍵（相對於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之位置）蛋白水解裂解後發生 FVII 活化，產生含有由雙硫橋連接至 254 個胺基酸之重鏈(約 30 kDa)的 152 個胺基酸之輕鏈(約 20 kDa)的雙鏈多肽。FVIIa 之輕鏈含有 Gla 域及 EGF 樣域，而重鏈含有分子之催化或絲胺酸蛋白酶部分。藉由 FIXa、FXa、

FXIIa、凝血酶裂解，或藉由內源性 FVIIa 以自體催化方式介導單鏈 FVII 轉化為雙鏈 FVIIa（Butenas 等人 (1996) Biochem 35:1904-1910；Nakagaki 等人 (1991) Biochem 30:10819-10824）。循環中存在之微量 FVIIa 可能由 FXa 及 FIXa 之作用產生。

如以上所討論，對於充分活性而言，FVII 自其酶原形式裂解為 FVIIa 並不足夠。FVIIa 需要與 TF 締合以實現充分活性（Higashi 等人 (1996) J Biol Chem 271:26569-26574）。由於此需求，將酶原樣特徵僅歸於 FVIIa，其顯示酶原摺疊及形狀且展現相對低的活性。不存在與 TF 的締合的情況下，FVIIa 之此酶原樣特徵使其相對而言對抗凝血酶 III（AT-III）及通常主要作用於活性形式而非酶原形式之絲胺酸蛋白酶的其他絲胺酸蛋白酶抑制子具有抗性。另外，TF/FVIIa 活性之主要抑制子 TFPI 亦不有效地與「無活性」未複合形式之 FVIIa 結合。

與 TF 複合後，FVIIa 經歷允許分子之充分活性的構形變化。所有 FVII 域均參與與 TF 之交互作用，但所發生之構形變化係侷限於 FVIIa 之蛋白酶域。舉例而言，FVIIa 與 TF 之別構交互作用後發生之構形變化包括產生結合外在結合位點的經擴展大分子受質。此經擴展結合位點極大地增強因子 X 的 FVII 介導之蛋白水解活化。

當 FVIIa 與細胞表面表現之 TF 交互作用時，FVIIa 之活性進一步增強（亦即，上千倍）。此係由於含有諸如磷脂醯絲胺酸的帶負電磷脂的磷脂膜為諸如 FIX 及 FX 之經由

Gla 域結合的其他維生素 K 依賴性凝血因子之交互作用的位點。因此，此等維生素 K 依賴性蛋白質在細胞表面之局部濃度高，藉此促進其與 TF/FVIIa 複合物的交互作用。

5. FVII 功能

儘管 FVIIa 在藉由 TF 別構活化後，展現增強之活性，但證據表明存在 FVIIa 單獨可起始凝血之機制。因此，FVII 可以 TF 依賴性及 TF 獨立性方式起作用。此後者途徑在正常止血中可起甚小作用，儘管當在出血病症及其治療之環境中對其加以考慮時，其顯著性可增加。

a. 組織因子依賴性 FVIIa 活性

循環 FVII 結合細胞表面 TF，且如上所述由 FIXa、FXa、凝血酶或以自體催化方式由內源性 FVIIa 活化。或者，極少量之循環 FVIIa 可直接結合 TF。接著，TF/FVIIa 複合物結合小部分血漿 FX，且 FVIIa 催化域裂解 FX 以產生 FXa。因此，當 FXa 複合 FVa 且將凝血酶原活化為凝血酶時，在承載 TF 的細胞之表面上經由外在途徑形成凝血酶（圖 3）。FIX 亦由 TF/FVIIa 複合物活化，提供與在經活化血小板之表面上作用的固有途徑之聯繫。以上所述凝血級聯中之正反饋系統提供產生大量凝血酶之方式，該凝血酶將血纖維蛋白原裂解為纖維蛋白以形成凝塊。

b. 組織因子獨立性 FVIIa 活性

除用於將 FX 活化為 FXa 的 TF 依賴性機制之外，證據表明在 TF 不存在情況下，FVIIa 亦可活化 FX。經活化血小板將磷脂醯絲胺酸及其他帶負電磷脂移位至外部血漿取向

表面（Hemker 等人 (1983) Blood Cells 9:303-317）。此等移位提供 FVIIa 可結合之替代「受體」，雖然親和力相對低，比 FVIIa 與 TF 之結合親和力小 1000 倍（Monroe 等人 (1997) Br J Haematol 99:542-7）。經由 Gla 域中之殘基介導此交互作用（Harvey 等人 (2003) 278:8363-8369）。FVIIa 可隨後在經活化血小板表面上將 FX 轉化為 FXa 且將 FIX 轉化為 FIXa（Hoffman 等人 (1998) Blood Coagul Fibrinolysis 9:S61-S65）。FXa 保持與血小板表面結合，在此處其可與 FVa 結合且自凝血酶原產生足夠凝血酶，而新形成之 FIXa 與 FVIIIa 組裝以催化更多 FX 活化為 FXa（圖 3）。可隨後藉由如上所述之正反饋及增長機制在 TF 不存在情況下實現止血。然而，顯然儘管 FVIIIa 可促進經活化血小板上之凝血過程，但其存在並不為以 TF 獨立性機制產生凝血酶所需（圖 3）。因此，在 FVIII 不存在情況下，諸如在血友病患者中，有證據表明 FVIIa 可經由此二級機制起始及/或擴增凝血酶產生，且實現凝塊形成。

6. FVII 作為生物醫藥

FVII 起作用以起始凝血。重組 FVIIa（NovoSeven®；rFVIIa）經批准用於在患有 A 型或 B 型血友病（具有因子 VIII 或因子 IX 之抑制子）的患者及患有先天性因子 VII 缺乏的患者之手術或侵襲性程序中治療出血事件或預防出血。Novoseven®為使用幼小倉鼠腎臟（BHK）細胞在哺乳動物表現系統中產生的因子 VIIa 之遺傳工程化製劑。該藥劑之結構及功能幾乎等同於來源於血漿之因子 VIIa（Ratko

等人 (2004), P & T, 29: 712-720）。

已展示投予重組 FVIIa（rFVIIa）促進患有血友病之患者的血液凝結，且已發現以 FVIIa 之劑量治療在人類個體中安全且耐受性良好。典型地，已在產生因子 VIII 或因子 IX 之抑制子（亦即同種抗體）的患者中使用 rFVIIa。rFVIIa 作為凝血劑之用途已擴展至治療其他出血病症，例如格蘭士文氏血小板功能不足（Glanzmann' s thrombasthenia）；與廣泛性出血相關的其他事件，諸如外傷或手術之結果，該外傷或手術包括（但不限於）肝臟移植、前列腺手術及出血外傷；新生兒凝血病，嚴重肝病；骨髓移植、血小板減少症及血小板功能異常；緊急逆轉口服抗凝血劑；先天性缺乏因子 V、VII、X 及 XI；及具有溫韋伯氏因子之抑制子的溫韋伯氏病（von Willebrand）。

需要高劑量之 rFVII 來實現治療作用。投予 rFVII 所需的劑量及給藥方案視臨床適應症而不同。舉例而言，用於患有具有同種抗體的 A 型血友病或 B 型血友病之患者之出血事件的 rFVII 之典型劑量為藉由靜脈內（IV）注射投予 90 μg/kg。由於 rFVII 具有 2 小時之半衰期，因此需要重複給藥。可每 2 小時給予額外給藥，直至實現止血。可視病狀之嚴重程度而改變劑量範圍。舉例而言，35-120 μg/kg 範圍內之劑量為有效的。劑量及給藥方案亦可隨其他適應症而改變。舉例而言，可在手術前不久向經歷手術之 A 型血友病或 B 型血友病患者投予 90 μg/kg 之初始劑量，而手術期間及手術後每 2 小時重複給藥。視手術及出血事件

之嚴重程度而定，可每 2 至 6 個小時繼續快速 IV 輸液，直至實現痊癒。在先天性 FVII 缺乏患者中，典型地每 4-6 小時以 15-30 μg/kg 投予 rFVII，以防止手術或其他侵襲性程序中之出血，直至實現止血。

rFVIIa 起始止血之作用的機制說明高劑量要求。血友病患者具有正常凝血起始階段，其中 TF/FVIIa 複合物將 FX 活化為 FXa 且在承載 TF 之細胞的位點引起凝血酶產生。然而，由於血友病患者缺乏 FVIII（A 型血友病）或 FIX（B 型血友病），此後凝血過程中斷，且因此不能在經活化血小板之表面上形成 FVIIIa/FIXa 複合物，其通常在先前所述之擴增及增長階段中用來將大量 FX 活化為 FXa。由於諸如 TFPI 及 AT-III 的抑制子之存在，藉由 TF/FVIIa 裂解後承載 TF 之細胞上產生的 FXa 在細胞表面之間無法易於擴散。因此，經活化血小板之表面上不發生大規模凝血酶產生且不形成凝塊。

有證據表明可使用藉由 rFVIIa 使 FXa 在經活化血小板上 TF 依賴性及/或 TF 獨立性產生實現高劑量 rFVIIa 之止血作用（圖 3）。可以內源性 FVIIa 及 rFVIIa 使 TF 分子飽和來使 TF 依賴性凝血酶產生極快達到最大。在一些情況下，高劑量 rFVIIa 可結合經活化血小板且將 FX 轉化為 FXa。表面結合之 FXa 活化 FVa 以產生足夠凝血酶以供止血。由於 rFVII 以低親和力結合血小板表面，因此凝血酶產生可要求較高劑量之 rFVII。經活化血小板上 FXa 之活化確保 rFVIIa 介導之止血侷限於損傷部位。

實現 rFVII 之劑量降低的方法可提高其作為藥物之效用及效率。本文提供經修飾之 FVII 多肽。在 TF 存在及/或不存在之情況下，此等經修飾之 FVII 多肽展現增強之 AT-III 抗性及增強之催化活性。本文中提供之經修飾之 FVII 多肽亦可展現增強之 TFPI 抗性，增強之對 Zn^{2+} 之抑制作用的抗性，改良之藥物動力學特性，諸如增加之血清半衰期、對經活化血小板增強之結合及/或親和力、對血清白蛋白增強之結合及/或親和力及/或對血小板整合素 $\alpha_{IIb}\beta_3$ 增強之結合及/或親和力。此等經修飾之 FVII 多肽可展現增強之凝血活性。本文中提供之 FVII 多肽可用於治療以用使得 FXa 產生且凝血酶產生之 TF 依賴性及/或 TF 獨立性機制起始止血。

D. 經修飾之 FVII 多肽

本文提供經修飾之 FVII 多肽。與未經如此修飾之 FVII 多肽相比，FVII 多肽展現一或多種活性或特性改變。可由修飾改變之活性或特性包括（但不限於）凝血或凝血劑活性；促凝血活性；諸如實現因子 X(FX)活化或因子 IX(FIX)活化的蛋白水解或催化活性；抗原性（與抗 FVII 抗體結合或與多肽競爭結合抗 FVII 抗體的能力）；結合組織因子、因子 X 或因子 IX 之能力；結合磷脂之能力；半衰期；三維結構；pI；及/或構形。典型地，經修飾之 FVII 多肽展現促凝血活性。本文提供經修飾之 FVII 多肽，其自單鏈酶原形式活化後展現增強之凝血活性。該等經修飾之 FVII 多肽可用於治療出血病症或事件，諸如血友病或損傷，其中 FVII

多肽可起作用以促進凝血。該等經修飾之 FVII 多肽包括對諸如抗凝血酶 III（AT-III）及組織因子途徑抑制子（TFPI）之抑制子具有增強之抗性者，對 Zn^{2+}之抑制作用具有增強之抗性者，在 TF 存在及/或不存在之情況下具有增強之催化活性者，具有改良之藥物動力學特性（諸如增加之半衰期）者，對血小板表面具有增加之結合及/或親和力者，對血清白蛋白具有增強之結合及/或親和力者，及對血小板整合素 $\alpha_{IIb}\beta_3$ 具有增強之結合及/或親和力者。詳言之，該等經修飾之 FVII 多肽可用於疾病或病狀以提供凝血活性，而同時繞過對 FVIIIa 及 FIXa 之要求。在一實例中，本文中提供之經修飾之 FVII 多肽可用於具有 FVIIIa 及 FIXa 之自體抗體的血友病患者。因此，本文中提供之經修飾之 FVII 多肽提供包括在血清中保持足夠濃度之活性 FVII 以供止血所需的所投予 FVII 的量降低之優勢。此可產生（例如）實現可比生物作用所必需的較低劑量及/或劑量頻率，較高個體舒適度及接受性及次級效應減弱。

可對任何形式的 FVII 多肽進行 FVII 多肽之修飾，該形式包括對偶基因及物種變異體、剪接變異體、在此項技術中已知之變異體或雜交或嵌合 FVII 分子。舉例而言，可對 SEQ ID NO: 1 或 2 中所闡明之前驅體 FVII 多肽、SEQ ID NO: 3 中所闡明之成熟 FVII 多肽，或與 SEQ ID NO: 1-3 中所闡明之任一 FVII 多肽具有 40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%或 99%序列一致性的任何物種、對偶基因或經修飾變異體及其活性

片段，進行本文提供之修飾。FVII 之對偶基因變異體包括（但不限於）具有 SEQ ID NO: 18-74 之任一者中所闡明的胺基酸序列之彼等前驅體多肽中的任一者。用於本文之修飾的例示性物種變異體包括（但不限於）人類及非人類多肽，包括來自母牛、小鼠、侏儒黑猩猩、黑猩猩、兔、大鼠、恆河猴、豬、犬、斑馬魚、河豚、雞、猩猩及大猩猩 FVII 多肽之 FVII 多肽，其序列分別闡明於 SEQ ID NO: 4-17 中。可對亦含有其他修飾的 FVII 多肽進行 FVII 多肽之修飾，該等其他修飾諸如彼等在此項技術中所述者，包括對多肽的一級序列之修飾及對非一級序列之修飾。

FVII 多肽之修飾亦包括對為不同 FVII 多肽以及基於已知多肽之序列重組製備或合成或藉由在此項技術中已知之其他方法構築的合成 FVII 多肽之雜交體的多肽之修飾。舉例而言，基於 FVII 與諸如因子 IX（FIX）或因子 X（FX）的其他凝血因子家族成員之比對，易於鑑別出家族成員之間的同源域。可構築使用相應家族成員之胺基酸序列將 FVII 胺基酸序列中之一或多個胺基酸或整個域置換的 FVII 多肽之嵌合變異體。另外，嵌合 FVII 多肽包括使用不同物種之胺基酸序列將人類 FVII 胺基酸序列中的一或多個胺基酸或整個域置換者（參見例如 Williamson 等人 (2005) J Thromb Haemost 3:1250-6）。在本文中，該等嵌合蛋白可用作起始未經修飾之 FVII 多肽。

本文提供之起始未經修飾之參考多肽的修飾包括胺基酸置換或取代、胺基酸添加或缺失或其任何組合。舉例而

言，經修飾之 FVII 多肽包括彼等具有 1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、30、40、50 或更多個經修飾之位置者。本文亦提供與起始參考 FVII 多肽相比，具有兩個或更多個修飾的經修飾之 FVII 多肽。經修飾之 FVII 多肽包括彼等具有 2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、30、40、50 或更多個經修飾之位置者。可將本文中提供之任何修飾與熟習此項技術者已知之任何其他修飾組合，只要所得經修飾之 FVII 多肽在呈雙鏈形式時展現增強之凝血活性。典型地，經修飾之 FVII 多肽展現增強之促凝血活性。可由修飾改變之活性或特性包括（但不限於）凝血或凝血劑活性；促凝血活性；實現因子 X（FX）活化或因子 IX（FIX）活化的蛋白水解或催化活性；抗原性（與抗 FVII 抗體結合或與多肽競爭結合抗 FVII 抗體的能力）；結合組織因子、組織因子抑制子（TFPI）、抗凝血酶 III、因子 X 或因子 IX 之能力；結合磷脂、血清白蛋白或血小板整合素 $\alpha_{IIb}\beta_3$ 之能力；血清半衰期；三維結構；pI；及/或構形。本文提供之經修飾之 FVII 多肽包括具有增強之抗凝血酶 III（AT-III）抗性、在 TF 存在及/或不存在之情況下增強之催化活性、增強之組織因子途徑抑制子（TFPI）抗性、增強之對 Zn^{2+} 抑制作用之抗性、改良之藥物動力學特性（諸如增加之血清半衰期）、增強之固有活性、改變之糖苷化、對血清白蛋白增強之親和力及/或結合、對血小板整合素 $\alpha_{IIb}\beta_3$ 增強之親和力及/或結合，及/或對活化血小板增強之

親和力及/或結合者。

在一些實例中，修飾可影響 FVII 多肽之兩種或兩種以上特性或活性。舉例而言，與未經修飾之 FVII 多肽相比，修飾可使經修飾之 FVII 多肽的 AT-III 抗性增強及催化活性增強。可檢定本文中提供之經修飾之 FVII 多肽的各特性及活性，以鑑別修飾作用之範圍。該等檢定在此項技術中已知且在下文描述。本文中提供之經修飾之 FVII 多肽亦包括由細胞機構另外修飾的 FVII 多肽且包括例如糖苷化、γ-羧基化及β-羥基化多肽。

進行本文中提供之對 FVII 多肽的修飾以增強 AT-III 抗性、增強 TFPI 抗性、增強對 Zn^{2+}抑制作用之抗性、改良藥物動力學特性（諸如增加血清半衰期）、增強 TF 存在及/或不存在情況下之催化活性、增強與經活化血小板之結合、改變糖苷化、增強對血小板整合素$\alpha_{IIb}\beta_3$之親和力及/或結合、增強對血清白蛋白之親和力及/或結合及/或增強對經活化血小板之親和力及/或結合。舉例而言，FVII 多肽可包括增強催化活性及與血小板結合中之一或兩者的修飾。在其他實例中，可將本文中提供之任何修飾與熟習此項技術者已知之任何其他修飾組合，只要所得經修飾之 FVII 多肽呈雙鏈形式時展現增強之凝血活性。典型地，該增強之凝血活性係歸因於增強之 AT-III 抗性、增強之催化活性、增強之對 Zn^{2+}抑制作用之抗性、改良之藥物動力學特性（諸如增加之血清半衰期）、增強之 TFPI 抗性、改變之糖苷化、增強之對磷脂之結合及/或親和力、增強之對血清白蛋白之

結合及/或親和力，及/或增強之對血小板整合素$\alpha_{IIb}\beta_3$之結合及/或親和力。在一些實例中，引入 FVII 多肽中以改變比活性或特性的修飾亦可，或替代地影響另一活性或特性。因此，本文提供之修飾可影響經設計以影響一或多種其他特性或活性的特性或活性。舉例而言，對 FVII 多肽進行以增強催化活性之修飾亦可增強 AT-III 抗性。在一些實例中，諸如單一胺基酸取代之單一修飾改變 FVII 多肽之 2、3、4 種或 4 種以上特性或活性。可檢定本文中提供之經修飾之 FVII 多肽的各特性及活性，以鑑別修飾作用之範圍。該等檢定在此項技術中已知且在下文描述。本文中提供之經修飾之 FVII 多肽亦包括藉由細胞機構另外修飾的 FVII 多肽且包括例如糖苷化、γ-羧基化及β-羥基化多肽。

可藉由諸如對熟習此項技術者而言常規之標準重組 DNA 技術進行本文提供之修飾。可採用在此項技術中已知實現目標蛋白質之任一或多個胺基酸的突變之任何方法。方法包括編碼核酸分子之標準定點誘變（使用例如套組，諸如由 Stratagene 獲得諸如 QuikChange 之套組）或藉由固相多肽合成法。另外，可藉由常規重組 DNA 技術產生本文中提供之經修飾之嵌合蛋白(亦即 Gla 域交換)。舉例而言，可使用用於常規次選殖所需嵌合多肽組份之限制酶及選殖方法產生嵌合多肽。

在或不在多肽之一級序列中的其他修飾亦可包括於經修飾之 FVII 多肽或其接合物中，該等修飾包括(但不限於)添加碳水化合物部分、添加聚乙二醇（PEG）部分、添加

Fc 域等。舉例而言，可進行該等其他修飾以增加蛋白質之穩定性或半衰期。

所得經修飾之 FVII 多肽包括為單鏈酶原多肽或為雙鏈酶原樣多肽者。舉例而言，可自體活化或由其他凝血因子活化本文中提供的為單鏈多肽之任何經修飾之多肽以產生經修飾之雙鏈形式的 FVII（亦即 FVIIa）。典型地以雙鏈形式展現經修飾之 FVII 多肽的活性。

本文中提供之經修飾之 FVII 多肽可展現增強之 AT-III 抗性、在 TF 存在及/或不存在情況下增強之催化活性、增強之對 Zn^{2+}抑制作用之抗性、增強之 TFPI 抗性、改良之藥物動力學特性（諸如增加之血清半衰期）、改變之糖苷化、增強之對磷脂之結合及/或親和力、增強之對血清白蛋白之結合及/或親和力及/或增強之對血小板整合素 $\alpha_{IIb}\beta_3$ 之結合及/或親和力。典型地，產生本文中提供之經修飾之 FVII 多肽的該等特性及/或活性，同時保留其他 FVII 活性或特性，諸如（但不限於）與 TF 之結合及/或 FX 之結合及活化。因此，與野生型或起始形式之 FVII 多肽相比，本文中提供之經修飾之 FVII 多肽保留 TF 結合及/或 FX 結合及活化。典型地，與野生型或起始蛋白質相比，該活性實質上不變（改變小於 1%、5%或 10%）。在其他實例中，與野生型或起始 FVII 多肽相比，經修飾之 FVII 多肽的活性增加或降低。可試管內或活體內評估活性，且可將其與未經修飾之 FVII 多肽，諸如成熟野生型原生 FVII 多肽（SEQ ID NO: 3）、野生型前驅體 FVII 多肽（SEQ ID NO: 1 或 2）或熟習

此項技術者已知用作起始物質之任何其他 FVII 多肽相比較。

因此，藉助於本文中提供之修飾，經修飾之 FVII 多肽可展現增強之凝血活性、增加之凝血活性持續時間及/或提高之治療指數。此可以 TF 依賴性及/或 TF 獨立性方式觀測到。典型地，可在適當檢定中試管內或活體外或活體內（諸如向諸如人類或非人類個體之個體投藥後）觀測到本文中提供之經修飾之 FVII 多肽的增強之凝血活性、增加之凝血活性持續時間及/或提高之治療指數。與起始或未經修飾之 FVIIa 多肽的活性相比，經修飾之 FVII 多肽的活性增強可增加至少或約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、110%、120%、130%、140%、150%、160%、170%、180%、190%、200%、300%、400%、500%或 500 更高。

1. 增強之催化活性

FVII 在其活性中心中含有在裂解反應期間充當親核試劑之絲胺酸殘基（以標準胰凝乳蛋白酶（ogen）編號，位置 195）。絲胺酸蛋白酶之催化三合體亦包括兩個其他殘基：H57 及 D102（胰凝乳蛋白酶編號）。人類 FVIIa 之催化三合體對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之 H193、D242 及 S344。此等三個關鍵胺基酸在蛋白酶之催化活性中各起必需作用。絲胺酸蛋白酶經由形成四面體過渡態及醯基酶中間物來水解肽鍵。反應途徑開始於受質非共價結合於含有 H57 及 S195 的蛋白酶表面上之溝槽中（亦

即，活性位點裂口)以形成「米曼氏複合物(Michaelis Menton complex)」。沿反應途徑之生產性前進要求受質的 P1 羰基殘基隨後由酶之活性位點絲胺酸（亦即絲胺酸 195）的 O-γ 親核攻擊，以形成四面體過渡態，其迅速轉化成醯基酶中間物。包括殘基甘胺酸 193 及絲胺酸 195(對應於 SEQ ID NO:3 中所闡明的成熟 FVII 多肽之 G342 及 S344）且稱為氧陰離子洞之活性位點裂口內的結構藉由使過渡態穩定促進有效催化。特定言之，此等兩個殘基之主鏈醯胺氫與四面體過渡態中產生之氧陰離子（亦即，P1 殘基之羰基氧）形成穩定氫鍵。除此穩定化之外，氧陰離子洞內受質之結合使易斷裂鍵對於引起鍵裂解之生產性醯化及去醯化反應而言適當地定位。藉由以下觀測結果突出 FVII 活性中氧陰離子洞之重要性：胺基酸位置 342(根據胰凝乳蛋白酶編號對應於 193）之突變可引起 FVII 缺乏（參見例如 Bernardi 等人, (1994) Br. J. Haematol. 86:610-618 及 Bernardi 等人, (1996) Human Mut. 8:108-115）。

a. 增強催化活性之例示性修飾

本文提供展現增強之凝血活性的經修飾之 FVII 多肽。可藉由可影響氧陰離子洞之構形的一或多個殘基的胺基酸取代產生該等 FVII 多肽。在特定位置（例如，根據胰凝乳蛋白酶編號位置 143，或根據成熟 FVII 編號 286）引入不同胺基酸殘基可改變經修飾之 FVII 多肽的構形，以使得氧陰離子洞在催化期間更有效。此可產生與未經修飾之 FVII 多肽相比，具有增強之催化活性的經修飾之 FVII 多肽。由於

影響氧陰離子洞之突變導致的催化活性之變化可表現為凝血活性增強。可在組織因子存在及/或不存在之情況下（亦即可為 TF 依賴性及/或 TF 獨立性）觀測到本文中提供之經修飾之 FVII 多肽的催化及凝血活性之增強。因此，當諸如在作為促凝血治療劑向個體投藥後，在適當試管內、活體內或活體外檢定中評估時，與未經修飾之 FVII 多肽相比，經修飾之 FVII 多肽可顯示增強之凝血活性。

可改變氧陰離子洞之構形以藉由修飾參與氧陰離子洞形成或接近氧陰離子洞的一或多個胺基酸殘基誘導更有效構形。如本文所提供，該等胺基酸殘基之實例為 Q286（對應 SEQ ID NO: 3 中所闡明之成熟 FVII 多肽編號），其對應於根據胰凝乳蛋白酶編號之 Q143。可藉由例如胺基酸取代、缺失或插入來修飾 Q286。當藉由胺基酸取代實現修飾時，位置 286 之麩胺醯胺殘基可經任何其他胺基酸殘基置換。

Q286 鄰近且接觸形成 FVII 多肽之活性位點之區域及活性位點裂口的殘基定位。因而，據稱該位置之修飾應使得催化活性降低（參見例如美國專利第 6806063 號）。先前研究（參見例如國際專利公開案第 WO2007031559 號）已證明此點，其中麩胺醯胺殘基經丙胺酸（Q286A）置換。與野生型多肽相比，所得經修飾之 FVIIa 多肽展現降低之活化因子 X 的能力。在其他研究中，相同突變基本上對 FVIIa 突變體對於因子 X(Dickinson 等人, (1996) Proc. Nat. Acad. Sci. USA. 93:14379-14384）或合成受質（國際專利公開案

第 WO2007031559 號）之催化活性無影響。

然而，如本文所證明（參見實施例 4 及以下內容），FVII 多肽在位置 286（對應 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之編號；對應於根據胰凝乳蛋白酶編號位置 143）尤其經諸如精胺酸（Arg、R）之鹼性殘基之修飾產生具有增強之催化及凝血活性的經修飾之 FVII 多肽。

因此，本文提供經修飾之 FVII 多肽，其在對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之胺基酸位置 286（根據胰凝乳蛋白酶編號，胺基酸位置 143）的胺基酸位置含有修飾。可在任何 FVII 多肽中在胺基酸位置 286 進行本文提供之修飾，該 FVII 多肽包括 SEQ ID NO: 1 或 2 中所闡明之前驅體 FVII 多肽、SEQ ID NO: 3 中所闡明之成熟 FVII 多肽，或與 SEQ ID NO: 1-3 中所闡明之任一 FVII 多肽具有 40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%或 99%序列一致性的任何物種、對偶基因或經修飾變異體及其活性片段。

FVII 多肽在根據成熟 FVII 編號之胺基酸位置 286（對應於根據胰凝乳蛋白酶編號之胺基酸 143）之修飾可將氧陰離子洞之構形改變為促進受質之更有效催化的構形。該等經修飾之 FVII 多肽的增強之催化活性可在組織因子存在及/或不存在情況下展現，且可使用諸如以下實施例 4 及 7 所述之試管內檢定評估。除展現增強之催化活性之外，已在根據成熟 FVII 編號之胺基酸位置 286 修飾之 FVII 多肽亦可展現增強之 AT-III 抗性。此可歸因於例如在特定條件下（例

如注射於患者中後）經修飾 FVII 多肽與 AT-III 的結合降低，或 ATIII 之失活速率降低（亦即，降低之抑制二級速率常數），與未經修飾之 FVII 多肽相比，其在 AT-III 存在下可表現為增強之凝血活性。可使用諸如實施例 5 中所述之試管內檢定評估增強之 AT-III 抗性。

可藉由胺基酸缺失或經任何其他胺基酸置換或取代來修飾根據成熟 FVII 編號之胺基酸殘基 Q286(對應於根據胰凝乳蛋白酶編號之 Q143)。或者，可在改變胺基酸殘基 Q286 附近之構形之前或之後不久插入胺基酸。另外，含有 Q286 之修飾的 FVII 多肽亦可含有一或多個其他修飾，包括胺基酸插入、缺失、取代或置換，及多肽之一級序列中不存在的修飾，諸如碳水化合物部分之添加、聚乙二醇（PEG）部分之添加、Fc 域之添加等，或其任何組合。因此，在根據成熟 FVII 編號之胺基酸位置 286 含有修飾的 FVII 多肽可含有 2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、30、40、50 個或更多個經修飾之位置。該等多肽保留未經修飾之 FVII 多肽的至少一種活性。典型地，經修飾之 FVII 多肽展現增強之促凝血活性。

活性之此等變化可表現為增強之凝血活性、增加之凝血活性持續時間、增強之治療益處開始作用、增強之凝血活性開始作用及/或提高之治療指數。因此，本文提供與未經修飾之 FVII 多肽相比展現增強之凝血活性的經修飾之 FVII 多肽，其在根據成熟 FVII 編號之胺基酸位置 286 含有修飾。該等經修飾之 FVII 多肽可用於治療出血病症或事

件，諸如血友病、手術、外傷及損傷，其中 FVII 多肽可起作用以促進凝血。由於凝血活性增強，本文中提供的在根據成熟 FVII 編號之胺基酸位置 286 含有修飾的經修飾之 FVII 多肽提供優於以諸如 NovoSeven®之野生型 FVII 多肽治療的優勢，包括在血清中保持足夠濃度之活性 FVII 以供止血所需的所投予 FVII 之量下降。此可引起例如實現可比生物作用所需的較低劑量及/或劑量頻率，治療益處之較快開始，作用之較長持續時間，個體之較高舒適度及接受性及/或不當次級效應之減弱。

i. 鹼性胺基酸取代

提供經修飾之 FVII 多肽，其中位置 286（對應 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之編號；根據胰凝乳蛋白酶編號對應於位置 143）之麩胺醯胺經諸如精胺酸（Arg、R）、組胺酸（His、H）或離胺酸（Lys、K）中之任一者的鹼性胺基酸殘基置換。詳言之，本文提供經修飾之 FVII 多肽，其中位置 286 之麩胺醯胺經精胺酸置換（亦即 Q286R，根據胰凝乳蛋白酶編號對應於 Q143R）。模擬研究指示以精胺酸取代麩胺醯胺導致使 FVIIa 氧陰離子洞之無活性構形穩定的兩種關鍵交互作用喪失。原生 FVII 多肽中之去穩定交互作用包括 Q286（根據胰凝乳蛋白酶編號，對應於 Q143）之側鏈與 G342（根據胰凝乳蛋白酶編號，對應於 G193）之主鏈醯胺之間的交互作用，及 K341（根據胰凝乳蛋白酶編號，對應於 K141）之主鏈羰基與 S195（根據胰凝乳蛋白酶編號，對應於 S344）之主鏈醯胺之間的交互作用。

然而，藉由在位置 286 以精胺酸取代原生麩胺醯胺，產生兩種新的重要交互作用。此等新交互作用包括在經修飾之胺基酸 R286（根據胰凝乳蛋白酶編號，R143）之鹼性側鏈與原生 D289（根據胰凝乳蛋白酶編號，D146）之酸性側鏈之間產生鹽橋，及經修飾之胺基酸 R286 之主鏈醯胺與 K341 之主鏈羰基之間的穩定 FVIIa 之活性構形的交互作用。另外，預期經修飾之胺基酸 R286 與 D289 之間的新鹽橋改變形成活性位點裂口之部分的「自溶環」之構形及/或可撓性。自溶環與決定凝血蛋白酶之大分子受質及抑制子特異性有關。因此，此環之構形及/或可撓性改變可例如產生對受質（例如因子 X 及/或因子 IX)之催化活性增強及對抑制子(例如 TFPI 及/或 AT-III）之抗性增強。因此，與野生型 FVII 多肽相比，位置 286 之麩胺醯胺經諸如精胺酸（Arg、R）、組胺酸（His、H）或離胺酸（Lys、K）之鹼性胺基酸修飾可產生增強之催化及凝血活性。因此，本文提供含有根據成熟 FVII 編號之 Q286R、Q286K 或 Q286H 突變（根據胰凝乳蛋白酶編號，分別對應於 Q143R、Q143K 或 Q143H）之 FVII 多肽。該等多肽之實例為分別具有 SEQ ID NO: 118、119 及 129 中所闡明之胺基酸序列者。

可在任何 FVII 多肽中在對應於 SEQ ID NO: 3 中所闡明之成熟 FVII 多肽的胺基酸位置 286 之胺基酸位置進行麩胺醯胺（Gln、Q）經鹼性胺基酸殘基、尤其精胺酸（Arg、R）之胺基酸置換，該 FVII 多肽包括具有 SEQ ID NO: 1 或 2 中所闡明之序列的前驅體 FVII 多肽、SEQ ID NO: 3 中所闡

明之成熟 FVII 多肽或諸如彼等在此項技術中所述者之任何物種、對偶基因及經修飾變異體，及其活性片段，其與 SEQ ID NO: 1-3 中所闡明的任一 FVII 多肽具有 40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%或 99%序列一致性。舉例而言，可將 Q286R 突變併入在此項技術中所述之任何經修飾之 FVII 多肽中，包括本文中其他處所述的任一者中。該等經修飾之 FVII 多肽包括(但不限於）含有突變 M298Q（SEQ ID NO: 158）（參見例如 Persson 等人，(2001) Proc. Nat. Acad. Sci. USA 98: 13583-13588）、E296V/M298Q（SEQ ID NO: 343）、V158E（SEQ ID NO: 344）、E296R/M298K（SEQ ID NO: 345）、K337A（SEQ ID NO: 346）、V158D/E296V/M298Q（SEQ ID NO: 98；NN1731；參見例如 Persson 等人，(2007) Art. Thromb. Vasc. Biol. 27(3): 683-689）、V158D/E296V/M298Q/K337A（SEQ ID NO: 347；參見例如 Lisman 等人，(2003) J. Thromb. Haem. 1:2175-2178）、V253N（SEQ ID NO：348；參見例如 US7427592）、T106N（SEQ ID NO: 349；參見例如 US7427592）、T106N V253N（SEQ ID NO: 350；參見例如 US7427592）、K143N/N145T（SEQ ID NO: 351；US7442524）、R315N/V317T（SEQ ID NO:352；US7442524）或 K143N/N145T/R315N/V317T（SEQ ID NO:353；US7442524）的經修飾之 FVII 多肽。亦可將 Q286R 突變併入嵌合 FVII 多肽或 FVII 融合多肽或以其他方式、諸如藉由糖 PEG 化修飾之 FVII 多肽（參見例如

WO2007022512；Ghosh 等人，(2007) 美國血液學學會會議之報導錄（transcript of presentation at the Am. Society. Hematol. Meeting），2007 年 12 月 10 日）。在一實例中，在對應於 SEQ ID NO: 3 中所闡明之成熟 FVII 多肽的胺基酸位置 286 之胺基酸位置麩胺醯胺經精胺酸之胺基酸置換產生具有 SEQ ID NO: 118 中所闡明的胺基酸序列之 FVII 多肽。

本文提供經修飾之 FVII 多肽，其含有根據成熟 FVII 編號之胺基酸取代 Q286R（根據胰凝乳蛋白酶編號，對應於 Q143R)，其中經修飾之 FVII 多肽展現增強之凝血活性。該等經修飾之 FVII 多肽可含有 1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、30、40、50 個或更多個經修飾之位置，其中經修飾之位置中之一者為胺基酸位置 286。因此，本文提供經修飾之 FVII 多肽，其含有兩個或更多個修飾，其中一個修飾為胺基酸取代 Q286R（根據成熟 FVII 編號）且與未經修飾之 FVII 多肽相比，經修飾之 FVII 多肽展現增強之凝血活性。可將 Q286R 突變與本文所述或在此項技術中已知之任何其他突變組合。典型地，所得經修飾之 FVII 多肽顯示增強之凝血活性。熟習此項技術者可使用在此項技術中熟知且在本文中描述之試管內及活體內檢定測定含有 Q286R 修飾的 FVII 多肽之凝血活性。本文中提供之經修飾之 FVII 多肽包括含有 Q286R 突變以及含有一或多個突變者，該一或多種突變（例如）增強對於抗凝血酶-III 之抗性、增強對磷脂之結合及/

或親和力、增強對組織因子之親和力、增強固有活性、增強 TF 依賴性活性、增強凝血活性、改變多肽之構形以改變酶原性、藉由使高活性與較低活性 FVIIa 構形之間的平衡移動偏向高活性構形來增強催化或凝血活性、增強蛋白酶抗性、降低糖苷化、增加糖苷化、降低免疫原性、增強穩定性及/或促進化學基團連接。

含有胺基酸取代 Q286R 的經修飾之 FVII 多肽的凝血活性增強可為催化活性增強之結果。可在組織因子（TF）存在及/或不存在之情況下觀測到催化活性增強。因此，增強之催化活性可為 TF 依賴性及/或 TF 獨立性活性。可使用諸如實施例 4 及 7 中所述之檢定的試管內檢定評估含有 Q286R 突變的經修飾之 FVII 多肽的催化活性。該等檢定可在組織因子存在或不存在情況下測定經修飾之 FVII 多肽對諸如因子 X 的受質之催化活性。與未經修飾或野生型 FVII 多肽之活體內或試管內催化活性相比，在組織因子存在及/或不存在之情況下，含有 Q286R 突變的經修飾之 FVII 多肽可展現約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高的催化活性增強。舉例而言，如實施例 4 所表明，含有 Q286R 突變（根據胰凝乳蛋白酶編號，Q143R）之 FVIIa 多肽可在 TF 存在或不存在之情況下對 FX 展現比野生型 FVII 所展現之催化活性高約 2 至 4 倍之催化活性。

含有兩個或更多個修飾的經修飾之 FVII 多肽之非限制

性實例闡明於下表 5 及實施例 4 中，其中一個修飾為胺基酸取代 Q286R（根據成熟 FVII 編號）且與未經修飾之 FVII 多肽相比，該經修飾之 FVII 多肽在組織因子存在及/或不存在之情況下對 FX 展現增強之催化活性。鑑別闡明經修飾之 FVII 多肽的例示性胺基酸序列之序列識別符（SEQ ID NO）。如以下 D.6 部分更詳細論述，「Gla 交換 FIX」修飾包括藉由缺失胺基酸殘基 A1 至 Y44（對應於 SEQ ID NO: 3 中所闡明之成熟 FVII 多肽的殘基）使內源性 FVII Gla 域缺失及插入對應於 SEQ ID NO: 83 中所闡明的 FIX Gla 域之胺基酸殘基 Y1 至 Y45 的 45 個胺基酸殘基。在一些實例中，經「Gla 交換 FIX」修飾之 FVII 多肽中的異源 FIX Gla 域在對應於 SEQ ID NO: 83 中所闡明的 FIX Gla 域之 M19、E40、K43 及/或 Q44 之胺基酸位置含有一或多個胺基酸取代。該等取代由大括號表示（例如{Gla 交換 FIX/Q44S}）。在經修飾之胺基酸位置不具有對應胰凝乳蛋白酶編號（亦即，不在對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之胺基酸位置 153 至 406 中，且未闡明於上表 1 中）之情況下，使用成熟 FVII 編號在括號中表示位置。舉例而言，T158N 不具有對應胰凝乳蛋白酶編號且當提及胰凝乳蛋白酶編號時經闡明為 T[158]N。

表 5

修飾-成熟 FVII 編號	修飾-胰凝乳蛋白酶編號	SEQ ID NO
Q286R/ Gla交換FIX	Q143R/Gla交換FIX	131
Q286R/H257A	Q143R/H117A	132
Q286R/S222A	Q143R/S82A	133
Q286R/S222A/H257A	Q143R/S82A/H117A	134
Q286R/S222A/ Gla交換FIX	Q143R/S82A/Gla交換FIX	135

Q286R/H257A/ Gla交換FIX	Q143R/H117A/Gla交換FIX	136
Q286R/S222A/H257A/Gla交換FIX	Q143R/S82A/H117A/Gla交換FIX	137
Q286R/M298Q/K341Q	Q143R/M156Q/K192Q	139
Q286R/M298Q/K199E	Q143R/M156Q/K60cE	140
S222A/H257A/Q286R/M298Q	S82A/H117A/Q143R/M156Q	150
A175S/Q286R/Q366V	A39S/Q143R/Q217V	144
S222A/Q286R/Q366V	S82A/Q143R/Q217V	145
H257S/Q286R	H117S/Q143R	146
H257S/Q286R/Q366V	H117S/Q143R/Q217V	147
S222A/H257A/Q286R/Q366V	S82A/H117A/Q143R/Q217V	148
Q286R/H373A	Q143R/H224A	149
Q286R/Q366N	Q143R/Q217N	153
Q286R/M298Q/Q366N	Q143R/M156Q/Q217N	155
Q286R/H373F	Q143R/H224F	156
Q286R/M298Q/H373F	Q143R/M156Q/H224F	157
Q286R/M298Q	Q143R/M156Q	138
Q286R/M298Q/Gla交換FIX	Q143R/M156Q/Gla交換FIX	141
T128N/P129A/Q286R	T[128]N/P[129]A/Q143R	279
Gla 交換 FIX/ T128N/P129A/ S222A/Q286R	Gla 交換 FIX/ T[128]N/P[129]A/ S82A/Q143R	285
Gla 交換 FIX/ S52A/S60A/S222A/Q286R	Gla 交換 FIX/ S[52]A/S[60]A/S82A/Q143R	292
Gla 交換 FIX/ Q286R/M298Q	Gla 交換 FIX/ Q143R/M156Q	141
T128N/P129A/Q286R/ M298Q	T[128]N/P[129]A/Q143R/ M156Q	280
Gla 交換 FIX/T128N/P129A/Q286R/M298Q	Gla 交換 FIX/T[128]N/P[129]A/Q143R/ M156Q	286
{Gla 交換 FIX/E40L}/ Q286R/M298Q	{Gla 交換 FIX/E[40]L}/ Q143R/M156Q	274
{Gla 交換 FIX/K43I}/ Q286R/M298Q	{Gla 交換 FIX/K[43]I}/ Q143R/M156Q	275
{Gla 交換 FIX/Q44S}/ Q286R/M298Q	{Gla 交換 FIX/Q[44]S}/ Q143R/M156Q	276
{Gla 交換 FIX/M19K}/ Q286R/M298Q	{Gla 交換 FIX/M[19]K}/ Q143R/M156Q	277
S52A/S60A/Q286R/M298Q	S[52]A/S[60]A/Q143R/M156Q	293
T128N/P129A/S222A/H257A/Q286R/M298Q	T[128]N/P[129]A/S82A/H117A/Q143R/ M156Q	287
S52A/S60A/S222A/H257A/Q286R/M298Q	S[52]A/S[60]A/S82A/H117A/Q143R/M156Q	298
T128N/P129A/ Q286R/H373F	T[128]N/P[129]A/Q143R/H224F	281
S52A/S60A/ Q286R/H373F	S[52]A/S[60]A/Q143R/H224F	296
T128N/P129A/Q286R/M298Q/H373F	T[128]N/P[129]A/Q143R/M156Q/H224F	288
S52A/S60A/Q286R/M298Q/H373F	S[52]A/S[60]A/Q143R/M156Q/H224F	297
V21D/Q143R/E154V/M156Q	V21D/Q143R/E154V/M156Q	282

Gla 交換 FIX /S222A/T239V/Q286R	Gla 交換 FIX /S82A/T99V/Q143R	301
T239V/Q286R/M298Q	T99V/Q143R/M156Q	302
Gla 交換 FIX/ T239V/Q286R/M298Q	Gla 交換 FIX/ T99V/Q143R/M156Q	304
S222A/T239V/H257A/Q286R/M298Q	S82A/T99V/H117A/Q143R/M156Q	303
T239V/Q286R/H373F	T99V/Q143R/H224F	305
T239V/Q286R/M298Q/H373F	T99V/Q143R/M156Q/H224F	306
T239I/Q286R	T99I/Q143R	308
GlaSwapFIX/S222A/T239I/Q286R	Gla 交換 FIX /S82A/T99I/Q143R	310
T239I/Q286R/M298Q	T99I/Q143R/M156Q	311
Gla 交換 FIX /T239I/Q286R/M298Q	Gla 交換 FIX /T99I/Q143R/M156Q	313
S222A/T239I/H257A/Q286R/M298Q	S82A/T99I/H117A/Q143R/M156Q	312
T239I/Q286R/H373F	T99I/Q143R/H224F	314
T239V/Q286R	T99V/Q143R	299
T239I/Q286R/M298Q/ H373F	T99I/Q143R/M156Q/H224F	315
H257S/Q286R/M298Q	H117S/Q143R/M156Q	322
Gla 交換 FIX /Q286R/S222A/H257S	Gla 交換 FIX /Q143R/S82A/H117S	321
S222A/H257S/Q286R/ M298Q	S82A/H117S/Q143R/M156Q	324
H257S/Q286R/M298Q/ H373F	H117S/Q143R/M156Q/H224F	325
S222A/Q286R/M298Q/ H373F	S82A/Q143R/M156Q/H224F	326
Gla 交換 FIX/S222A/Q286R/M298Q/H373F	Gla 交換 FIX S82A/Q143R/M156Q/H224F	318
S222A/Q286R/M298Q	S82A/Q143R/M156Q	328
Gla 交換 FIX S222A/Q286R/M298Q	Gla 交換 FIX S82A/Q143R/M156Q	317
Gla 交換 FIX/ S222A/Q286R/H373F	Gla 交換 FIX/ S82A/Q143R/H224F	316
H257A/Q286R/M298Q	H117A/Q143R/M156Q	321
T128N/P129A/A175S/Q286R/M298Q	T[128]N/P[129]A/A39S/Q143R/M156Q	337
A122N/G124S/A175S/Q286R/M298Q	A[122]N/G[124]S/A39S/Q143R/M156Q	338
T128N/P129A/A175S/S222A/H257A/Q286R/ M298Q	T[128]N/P[129]A/A39S/S82A/H117A/Q 143R/M156Q	339
A122N/G124S/A175S/S222A/H257A/Q286R/ M298Q	A[122]N/G[124]S/A39S/S82A/H117A/Q 143R/M156Q	340
T128N/P129A/A175S/Q286R/M298Q/H373F	T[128]N/P[129]A/A39S/Q143R/M156Q/ H224F	341
A122N/G124S/A175S/Q286R/M298Q/H373F	A[122]N/G[124]S/A39S/Q143R/M156Q/ H224F	342
V158D/Q286R/E296V/M298Q/H373F	V21D/Q143R/E154V/M156Q/H224F	320
{Gla 交換 FIX /K43I}/T128N/P129A/Q286R/M298Q	{Gla 交換 FIX /K[43]I}/ T[128]N/P[129]A/Q143R/M156Q	355
T128N/P129A/Q286R/M298Q/Q366N	T[128]N/P[129]A/Q143R/M156Q/Q217 N	356
{Gla 交換 FIX /K43I}/Q286R/M298Q/Q366N	{Gla 交換 FIX	357

	/K[43]I}/Q143R/M156QQ217N	
{Gla 交換 FIX /K43I}/ T128N/P129A/Q286R/M298Q/Q366N	{Gla 交換 FIX /K[43]I}/ T[128]N/P[129]A/Q143R/M156QQ217N	358
V158D/Q286R/E296V/M298Q	V21D/Q143R/E154V/M156Q	360
T128N/P129A/Q286R/M298Q/Q366N/H373F	T[128]N/P[129]A/Q143R/M156Q/Q217N/H224F	364
T239V/Q286R/M298Q/Q366N	T99V/Q143R/M156Q/Q217N	365
T239I/Q286R/M298Q/Q366N	T99I/Q143R/M156Q/Q217N	366
T128N/P129A/T239V/Q286R/M298Q	T[128]N/P[129]A/T99V/Q143R/M156Q	367
T128N/P129A/S222A/T239V/H257A/Q286R/M298Q	T[128]N/P[129]A/S82A/T99V/H117A/Q143R/M156Q	368
T128N/P129A/T239V/Q286R/M298Q/H373F	T[128]N/P[129]A/T99V/Q143R/M156Q/H224F	369
T128N/P129A/T239I/Q286R/M298Q	T[128]N/P[129]A/T99I/Q143R/M156Q	370

含有根據成熟 FVII 編號之 Q286R 突變之 FVII 多肽亦可展現增強之 AT-III 抗性。增強之 AT-III 抗性可為在特定條件下，諸如注射於動物或患者中後，受 AT-III 抑制之速率降低或與 AT-III 之結合降低的結果。可藉由量測對野生型及變異型 FVIIa 多肽之抑制的二級速率常數來表明 AT-III 抗性。亦可使用諸如 BIAcore®檢定之其他試管內方法。與未經修飾之 FVII 多肽相比，經修飾之 FVII 多肽可展現增強之對 AT-III 之抑制作用的抗性，其可在諸如實施例 5 所述之試管內檢定中評估。與未經修飾或野生型 FVII 多肽之活體內或試管內催化活性相比，含有 Q286R 突變的經修飾之 FVII 多肽可展現約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高的 AT-III 抗性增強。舉例而言，如以下實施例 5 所表明，含有 Q286R 突變（根據胰凝乳蛋白酶編號，Q143R）之 FVIIa

多肽可在 AT-III 存在情況下對 FX 展現催化活性，其比野生型 FVII 所展現之催化活性高 4 倍。因此，經修飾之 Q286R FVII 多肽可展現比未經修飾之 FVII 多肽之抗性增強約 400%之 AT-III 抗性。

增強之催化活性及增強之 AT-III 抗性可在 TF 存在及/或不存在之情況下表現為增強之凝血活性。可諸如藉由向人類或動物個體投藥來試管內、活體外或活體內評估該等活性。與未經修飾或野生型 FVII 多肽之活體內或試管內之凝血活性相比，含有 Q286R 突變的經修飾之 FVII 多肽之凝血活性可增強至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。舉例而言，實施例 6 表明含有 Q286R 突變（根據胰凝乳蛋白酶編號，Q143R）的 FVIIa 多肽在小鼠出血模型中展現顯著大於（約 2 倍）野生型 FVII 多肽（NovoSeven®）所展現的凝血活性之凝血活性，且含有 Q286R 及 M298Q 突變（根據胰凝乳蛋白酶編號，分別為 Q143R 及 M156Q）之 FVIIa 多肽展現甚至更大凝血活性。

ii. 位置 286 之其他突變

對應於 SEQ ID NO:3 中所闡明之 FVII 多肽的位置 286 之胺基酸位置的麩胺醯胺可經除鹼性胺基酸以外（亦即除精胺酸、組胺酸或離胺酸以外）的胺基酸置換。該等取代可改變氧陰離子洞之構形，例如藉此產生與野生型 FVII 多肽相比使經修飾之 FVII 多肽的催化活性增強之構形。與未

經修飾或野生型 FVII 多肽之催化活性相比，當使用活體內、活體外或試管內檢定量測時，具有改變之氧陰離子洞構形的經修飾之 FVII 多肽可展現約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高之催化活性增強。

表 6 提供對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之胺基酸位置之 Q286 處例示性胺基酸置換（不為以精胺酸置換）之非限制性實例。如所述，該等 FVII 多肽經設計以將氧陰離子洞之構形改變為更有效構形，且因此具有增強之凝血活性。關於該等突變，第一胺基酸（單字母縮寫）對應於經置換之胺基酸，數字對應於成熟 FVII 多肽序列中關於 SEQ ID NO: 3 之位置，且第二胺基酸（單字母縮寫）對應於經選擇置換彼位置之第一胺基酸的胺基酸。亦根據胰凝乳蛋白酶編號方案提及用於突變之胺基酸位置。在下表 6 中，鑑別闡明經修飾之 FVII 多肽的例示性胺基酸序列之序列識別符（SEQ ID NO）。

表 6

修飾-成熟 PVII 編號	修飾-胰凝乳蛋白酶編號	SEQ ID NO
Q286N	Q143N	113
Q286E	Q143E	114
Q286D	Q143D	115
Q286S	Q143S	116
Q286T	Q143T	117
Q286A	Q143A	120
Q286V	Q143V	121
Q286M	Q143M	122
Q286L	Q143L	123
Q286Y	Q143Y	124
Q286G	Q143G	125
Q286F	Q143F	126

Q286I	Q143I	127
Q286P	Q143P	128
Q286W	Q143W	130

與未經修飾或野生型 FVII 多肽之催化活性相比，當使用活體內、活體外或試管內檢定量測時，具有改變之氧陰離子洞構形的經修飾之 FVII 多肽可展現約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高之催化活性增強。在一些實例中，與由未經修飾或野生型 FVII 多肽活體內、活體外或試管內所展現的內源性抑制子抑制速率或對內源性抑制子之親和力相比，具有改變之氧陰離子洞構形的經修飾之 FVII 多肽亦可展現約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高的對諸如 TFPI 或 AT-III 的內源性蛋白酶抑制子的抗性增強（亦即降低之抑制子抑制速率或降低之對抑制子的親和力）。該等經修飾之 FVII 多肽的增強之催化活性及/或內源性抑制子抗性(諸如 AT-III 抗性）亦可表現為增強之凝血活性、增加之凝血活性持續時間、凝血活性之較快起始及/或提高之治療指數。舉例而言，與未經修飾或野生型 FVII 多肽之活體內、活體外或試管內之凝血活性相比，經修飾之 FVII 多肽之凝血活性可增強至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。

2. 增強之 AT-III 抗性

抗凝血酶 III（亦稱為抗凝血酶或 AT-III）為重要抗凝絲胺酸蛋白酶抑制子。AT-III 經合成為含有 464 個胺基酸殘基之前驅體蛋白質（SEQ ID NO: 122）。在分泌過程中，裂解 32 個殘基之信號肽以產生 432 個胺基酸之成熟人類抗凝血酶（SEQ ID NO: 123）。58 kDa AT-III 醣蛋白在血液中循環且充當絲胺酸蛋白酶抑制子以抑制凝血系統之大量絲胺酸蛋白酶。AT-III 之主要目標為凝血酶及因子 Xa，儘管亦已展示 AT-III 抑制 FIXa、FXIa、FXIIa 及在較小程度上抑制 FVIIa 之活性。諸如在臨床實踐中廣泛用作抗凝劑的天然存在硫酸乙醯肝素或來源於各種組織之肝素之葡糖胺聚糖極大地增強 AT-III 之作用。AT-III 以高度特異性方式結合肝素中誘導反應中心環之構形變化的獨特五醣序列。在該構形中，AT-III 之反應中心環可更有效地與絲胺酸蛋白酶之反應性位點交互作用且實現抑制。

AT-III 甚至在肝素存在下通常對游離血漿 FVIIa 不具有抑制性，此可能由於防止與 AT-III 有效交互作用的 FVIIa 之酶原樣構形。然而，FVIIa 與 TF 複合後，AT-III 之抑制作用顯著增強。AT-III 與 TF/FVIIa 複合物之結合可自 TF 釋放 FVIIa，且保持其呈與 AT-III 之無活性複合物形式。與單獨 FVIIa 相比，AT-III 對與 TF 結合之 FVIIa 的增強之親和力大概反映當與 TF 複合時 FVIIa 之活性位點之成熟，因此使其易與 AT-III 結合（Rao 等人 (1993) Blood 81:2600-2607）。因此，AT-III 對 FVIIa 之影響與 FVIIa 分

子本身之固有活性成比例，除非介導 AT-III 抗性之突變已添加至 FVIIa 多肽。儘管 FVIIa 保留其酶原樣構形，但 AT-III 具有極少作用。然而，若 FVIIa 諸如藉由結合 TF 或藉由特定試管內修飾將構形改變為更具活性形式，則 AT-III 抑制顯著增強。經修飾以具有增強之固有活性的 FVIIa 多肽通常顯示對 AT-III 抑制之敏感性的同時提高。舉例而言，諸如藉由對應於 K337A、L305V、M298Q、V158D 及 E296V 取代（相對於 SEQ ID NO: 3 中所闡明之成熟 FVII 序列）之胺基酸置換，FVIIa 之活化袋中一或多個胺基酸之修飾使得 FVIIa 多肽對 AT-III 的敏感性增強，藉此抑制多達 90%之 FVIIa 活性（Persson 等人 (2001) PNAS 98:13583-13588）。在另一實例中，當增強經修飾之 FVIIa 蛋白質的活性時，藉由修飾參與 FVIIa 之 α 螺旋中的胺基酸誘導更具酶原樣構形亦增強其對 AT-III 的敏感性（Persson 等人 (2004) Biochem J 379:497-503）。

實現增強之 AT-III 抗性的例示性修飾

可對 FVII 多肽進行增強其 AT-III 抗性之修飾。通常，該等經修飾之 FVII 多肽保留 FVII 多肽之至少一種活性。典型地，該等修飾包括在 FVII 多肽中參與 FVIIa 與 AT-III 之交互作用的任何位置的一或多個胺基酸取代。該等修飾可例如使得經修飾 FVII 與 AT-III 的結合降低。因此，經修飾之 FVII 多肽對 AT-III 關於凝血起始之天然抑制作用具有抗性。當諸如作為促凝血治療劑向個體投藥後，在適當試管內檢定中或活體內評估時，與未經修飾之 FVII 多肽相比

較，經修飾之 AT-III 抗性 FVII 多肽顯示增強之凝血活性。

如本文以下所述，熟習此項技術者可憑經驗或合理地設計顯示增強之 AT-III 抗性的經修飾之 FVII 多肽。可在熟習此項技術者已知之檢定中測試該等經修飾之 FVII 多肽以測定該等經修飾之 FVII 多肽是否顯示增強之 AT-III 抗性。舉例而言，可測試該等經修飾之 AT-III 多肽與 AT-III 的結合。通常，具有增強之 AT-III 抗性的經修飾之 FVII 多肽將展現降低之與 AT-III 的結合及/或降低之對 AT-III 的親和力。典型地，對雙鏈形式之 FVII，諸如經活化形式之 FVII（FVIIa）進行該等檢定。另外，通常在肝素存在下及組織因子存在下進行測定 AT-III 之作用的檢定，儘管該等檢定亦可在一或兩種輔因子不存在之情況下進行。

本文提供展現增強之 AT-III 抗性的經修飾之 FVII 多肽。對 ATIII 抑制之抗性在 TF 存在及不存在之情況下均相關。本文中提供之 FVII 多肽變異體已經在胺基酸位置 239、931、366 及 373（根據胰凝乳蛋白酶編號，分別對應於胺基酸位置 99、170i、217 及 224）中之一或多者修飾。可諸如藉由胺基酸置換、缺失或取代來修飾此等胺基酸殘基。所鑑別殘基可經任何另一胺基酸置換或取代。或者，可使用胺基酸插入來改變目標胺基酸殘基之構形或目標胺基酸殘基附近的蛋白質結構。

可用任何胺基酸殘基來取代所鑑別位置處之內源性胺基酸殘基。典型地，置換胺基酸經選擇以使其干擾 FVII 與 AT-III 之間的交互作用。在一些實例中，位置 239（根據胰

凝乳蛋白酶編號，對應於位置 99）之蘇胺酸殘基經絲胺酸（Ser、S）、天冬醯胺（Asn、N）、麩胺醯胺（Gln、Q）、纈胺酸（Val、V）、白胺酸（Leu、L）、組胺酸（His、H）或異白胺酸（Ile、I）置換。在其他實例中，位置 321（根據胰凝乳蛋白酶編號，對應於位置 170i）之脯胺酸經離胺酸（Lys、K）、麩胺酸（Glu、E）、絲胺酸（Ser、S）或酪胺酸（Tyr、Y）置換。在其他實例中，位置 366（根據胰凝乳蛋白酶編號，對應於位置 217）之麩胺醯胺經天冬醯胺（Asn、N）、天冬胺酸（Asp、D）、麩胺酸（Glu、E）、絲胺酸（Ser、S）、蘇胺酸（Thr、T）、離胺酸（Lys、K）或纈胺酸（Val、V）置換。在其他實例中，位置 373（根據胰凝乳蛋白酶編號，對應於位置 224）之組胺酸經天冬胺酸（Asp、D）、麩胺酸（Glu、E）、絲胺酸（Ser、S）、苯丙胺酸（Phe、F）或丙胺酸（Ala、A）置換。在另一具體實例中，可產生組合突變體。該等組合突變體包括具有殘基 T239、P321、Q366 及 H373（根據胰凝乳蛋白酶編號，對應於 T99、P170i、Q217 及 H224）中之兩個或更多個突變者。舉例而言，經修飾之 FVII 多肽可在所鑑別位置之 2、3、4 或 5 者中具有胺基酸取代。因此，經修飾之多肽可顯示可產生 1、2、3、4 或 5 個增強之經修飾之 FVII 多肽對 AT-III 之抑制作用的抗性之突變。舉例而言，FVII 多肽可在胺基酸位置 366 及胺基酸位置 373 經修飾。在一些實例中，該等位置經胺基酸置換修飾，諸如以天冬胺酸置換位置 366 之麩胺醯胺且以麩胺酸置換位置 373 之組胺酸。

表 7 提供對應於如 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之胺基酸位置，所鑑別殘基處例示性胺基酸置換之非限制性實例。此等實例包括例示性組合突變。如所述，該等 FVII 多肽經設計以增強 AT-III 抗性且因此具有增強之凝血活性。關於該等突變，第一胺基酸（單字母縮寫）對應於經置換之胺基酸，數字對應於成熟 FVII 多肽序列中關於 SEQ ID NO: 3 之位置，且第二胺基酸（單字母縮寫）對應於經選擇置換彼位置之第一胺基酸的胺基酸。亦根據胰凝乳蛋白酶編號方案提及用於突變之胺基酸位置。在下表 7 中，鑑別闡明經修飾之 FVII 多肽的例示性胺基酸序列之序列識別符（SEQ ID NO）。

表 7

修飾-成熟 PVII 編號	修飾-胰凝乳蛋白酶編號	SEQ ID NO
T239S	T99S	159
T239N	T99N	160
T239Q	T99Q	161
T239V	T99V	162
T239L	T99L	163
T239H	T99H	164
T239I	T99I	165
P321K	P170iK	166
P321E	P170iE	167
P321Y	P170iY	168
P321S	P170iS	169
Q366D	Q217D	170
Q366E	Q217E	171
Q366N	Q217N	172
Q366T	Q217T	173
Q366S	Q217S	174

Q366V	Q217V	175
Q366I	Q217I	176
Q366L	Q217L	177
Q366M	Q217M	178
H373D	H224D	179
H373E	H224E	180
H373S	H224S	181
H373F	H224F	182
H373A	H224A	183
Q366D/H373E	Q217D/H224E	184
Q366V/H373V	Q217V/H224V	185
Q366V/H373L	Q217V/H224L	186
Q366V/H373I	Q217V/H224I	187

與未經修飾或野生型 FVII 多肽之活體內或試管內抑制程度或抑制之二級速率常數相比，具有增強之 AT-III 抗性的經修飾 FVII 多肽可展現在特定條件下 AT-III 之抑制程度或抑制之二級速率常數降低至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。因此，經修飾之 FVII 多肽可展現增強之 AT-III 抗性，其為至少或約為未經修飾之 FVII 多肽所展現的抗性之 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。該等經修飾之 FVII 多肽的增強之 AT-III 抗性在 AT-III 存在下亦可表現為增強之凝血活性，增加之凝血活性持續時間及/或提高之治療指數。與未經修飾或野生型 FVII 多肽之活體內或試管內凝血活性相比，AT-III 修飾之 FVII 多肽的凝血活性可增加至少約 1%、

2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。

3. 增強之對 Zn^{2+}抑制之抗性

藉由結合鈣離子及組織因子（TF）誘導之變構改變來調節 FVIIa 之醯胺水解活性。游離 FVII 典型地以無活性構形存在。結合 Ca^{2+}及 TF 誘導構形變化及增強之醯胺水解活性（Pederson 等人，(1990) J Biol. Chem. 265:16786-16793）。相反，已展示鋅離子與 FVIIa 之結合對活性具有抑制作用。Zn^{2+}與 FVIIa 之結合產生降低之醯胺水解活性及降低之對 TF 的親和力。研究指示 Ca^{2+}及 Zn^{2+}競爭結合 FVIIa，以使得在 Ca^{2+}存在下，Zn^{2+}之抑制作用得以降低。此外，與 TF 結合之 FVIIa 對鋅抑制較不敏感。

除 Gla 域中之 Zn^{2+}結合位點之外，其結合並不影響 FVIIa 醯胺水解活性，兩個 Zn^{2+}結合位點亦已定位於 FVII 之蛋白酶域（Petersen 等人，(2000) Protein Sci. 9:859-866；Bajaj 等人，(2006) J. Biol. Chem. 281:24873-24888）。蛋白酶域中此等結合位點之定位指示第一 Zn^{2+}結合位點包括胺基酸殘基 H216、E220 及 S222（根據胰凝乳蛋白酶編號，H76、E80 及 S82）之側鏈，且第二 Zn^{2+}結合位點包括胺基酸殘基 H257、D219 及 K161（根據胰凝乳蛋白酶編號，H117、D79 及 K24）之側鏈。

因此，Zn^{2+}作為 FVII 抑制劑在調節穩定中可具有生理學作用。已假定此等抑制作用作為血小板活化後凝塊部位

Zn^{2+}濃度增加之結果發生(Bajaj 等人, (2006) J. Biol. Chem. 281:24873-24888)。血小板在細胞質及α-顆粒中儲存大量Zn^{2+}，其在血小板活化後釋放。此可增加Zn^{2+}之局部濃度，其轉而可抑制 FVIIa 活性及 FVIIa 與 TF 之結合。

增強對 Zn^{2+}抑制之抗性的例示性修飾

本文中提供經修飾之 FVII 多肽，其展現增強之對Zn^{2+}抑制作用的抗性。此可例如藉由 FVII 中參與與Zn^{2+}交互作用及結合的一或多個殘基之降低或防止該結合的突變來實現，藉此製備關於催化活性及 TF 結合對Zn^{2+}之抑制作用具有抗性的經修飾之 FVII 多肽。當諸如作為促凝血治療劑向個體投藥後，在適當試管內檢定中或活體內評估時，與未經修飾之 FVII 多肽相比較，經修飾之 FVII 多肽可顯示增強之凝血活性。

本文中提供經修飾之 FVII 多肽，其在蛋白酶域中參與Zn^{2+}結合的殘基中具有一或多個突變。該等殘基包括(但不限於) K161、H216、D219、E220、S222 及 H257，其中編號係相對於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之胺基酸位置(根據胰凝乳蛋白酶編號，分別對應於 K24、H76、D79、E80、S82 及 H117)。在一些實例中，胺基酸殘基 H216、S222 及 H257(根據胰凝乳蛋白酶編號，分別對應於 H76、S82 及 H117)中之一或多者經諸如胺基酸置換或缺失修飾。可使用任何胺基酸殘基來置換所鑑別位置處之內源性殘基。舉例而言，本文中提供經修飾之 FVII 多肽，其中胺基酸位置 216 之組胺酸經絲胺酸、丙胺酸、離胺酸或精胺酸

殘基置換。在另一實例中，胺基酸位置 222 之絲胺酸經丙胺酸或離胺酸殘基置換，或位置 257 之組胺酸經丙胺酸或絲胺酸殘基置換。在另一具體實例中，位置 161 之離胺酸經絲胺酸、丙胺酸或纈胺酸殘基置換。修飾亦包括在經鑑別參與 Zn^{2+}結合的胺基酸位置處或其附近的胺基酸插入。該等插入可破壞 Zn^{2+}結合位點，產生具有降低之與 Zn^{2+}結合的經修飾之 FVII 多肽。

亦可產生在 FVII 多肽之一個以上上文所鑑別的殘基中進行胺基酸置換之組合突變體。該等組合突變體包括具有殘基 K161、H216、D219、E220、S222 及 H257（根據胰凝乳蛋白酶編號，分別對應於 K24、H76、D79、E80、S82 及 H117）中之兩個或更多個突變者。舉例而言，經修飾之 FVII 多肽可在所鑑別位置中之 2、3、4、5 或 6 者中具有胺基酸取代。因此，經修飾之多肽可顯示 1、2、3、4、5 或 6 個可使得經修飾之 FVII 多肽結合 Zn^{2+}的能力降低之突變。舉例而言，可藉由位置 222 之絲胺酸經離胺酸置換及位置 257 之組胺酸經丙胺酸殘基置換的胺基酸置換修飾 FVII 多肽。

與未經修飾或野生型 FVII 多肽之活體內或試管內抗性相比，具有增強之對 Zn^{2+}抑制作用的抗性的經修飾之 FVII 多肽可展現增強至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。該等經修飾之 FVII 多肽的 Zn^{2+}結合降低及因此針對 Zn^{2+}抑制作用之抗性增強亦可表現為在 Zn^{2+}存在下增強之凝血活性。與

未經修飾或野生型 FVII 多肽之活體內或試管內凝血活性相比，經修飾之 FVII 多肽的凝血活性可增強至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。

表 8 提供對應於如 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之胺基酸位置，所鑑別殘基處例示性胺基酸置換之非限制性實例。此等實例包括例示性組合突變。如所述，該等 FVII 多肽經設計以展現降低之結合 Zn^{2+}的能力，且因此針對 Zn^{2+}抑制作用的抗性增強。因此，經修飾之 FVII 多肽可具有增強之凝血活性。關於該等突變，第一胺基酸（單字母縮寫）對應於經置換之胺基酸，數字對應於成熟 FVII 多肽序列中關於 SEQ ID NO: 3 之位置，且第二胺基酸（單字母縮寫）對應於經選擇置換彼位置之第一胺基酸的胺基酸。亦根據胰凝乳蛋白酶編號方案提及用於突變之胺基酸位置。在下表 8 中，鑑別闡明經修飾之 FVII 多肽的例示性胺基酸序列之序列識別符（SEQ ID NO）。

表 8

修飾-成熟 PVII 編號	修飾-胰凝乳蛋白酶編號	SEQ ID NO
K161S	K24S	188
K161A	K24A	189
K161V	K24V	190
H216S	H76S	191
H216A	H76A	192
H216K	H76K	193
H216R	H76R	194
S222A	S82A	195
S222K	S82K	196
S222V	S82V	197
S222N	S82N	198
S222E	S82E	199

S222D	S82D	200
H257A	H117A	201
H257S	H117S	202
S222K/H257A	S82K/H117A	203
H216A/H257A	H76A/H117A	204
H216A/S222A	H76A/S82A	205

4. 改變之糖苷化

可藉由調節糖苷化之程度、量及/或類型改變蛋白質之特性及活性。舉例而言，糖苷化可藉由增加蛋白質之穩定性、溶解性且降低免疫原性來增加多肽之血清半衰期。糖苷化可藉由降低蛋白質之蛋白水解來增加蛋白質之穩定性且可保護蛋白質免於熱降解、暴露於變性劑、受氧自由基損壞及 pH 值變化。糖苷化亦可允許目標蛋白質避開可涉及與其他蛋白質（包括細胞表面受體）結合之清除機制。含有唾液酸之碳水化合物部分可影響蛋白質之溶解性。唾液酸部分具高度親水性且可屏蔽目標蛋白質之疏水性殘基。此降低目標蛋白質之聚集及沈澱。降低之聚集亦可幫助預防針對目標蛋白質之免疫反應。此外，碳水化合物可將免疫原性序列與免疫系統屏蔽。碳水化合物部分所佔據的空間之體積可降低由免疫系統所識別之可用表面積。此等特性使得目標蛋白質之免疫原性降低。

糖苷化位點提供用於經由糖苷鍵將單醣及寡醣與多肽連接，以使得當在能夠糖苷化之真核細胞中產生多肽時其經糖苷化之位點。兩個主要類型之糖苷化為 N-連接型糖苷化，其中糖單元經由天冬醯胺殘基之醯胺氮連接；及 O-連接型糖苷化，其中糖單元經由絲胺酸、蘇胺酸、羥離胺酸

或羥脯胺酸殘基之羥基連接。其他更次要形式之糖苷鍵包括半胱胺酸之 S-鍵聯及色胺酸之 C-鍵聯。N-連接型糖苷化發生在 Xaa 不為脯胺酸的一致序列-Asn-Xaa-Ser/Thr/Cys 中之天冬醯胺處。不存在 O-糖苷化之已知基元，儘管 O-糖苷化在具有高比例之絲胺酸、蘇胺酸及脯胺酸殘基的序列上更可能發生。然而，潛在糖苷化位點之存在並不確保該位點將在轉譯後加工期間在 ER 中糖苷化。此外，給定位點之糖苷化程度可變，且一個位點可具有許多不同聚糖結構。FVII 中存在四個天然存在糖苷化位點：對應於 SEQ ID NO:3 中所闡明之成熟 FVII 多肽中的胺基酸位置的處於 N145 及 N322 之兩個 N-糖苷化位點，及處於 S52 及 S60 之兩個 O-糖苷化位點。

改變糖苷化之例示性修飾

本文中提供與未經修飾之 FVII 多肽相比，已藉由改變糖苷化程度及/或類型修飾之 FVII 多肽。與未經修飾之 FVII 相比，糖苷化可增加或降低。在一些情況下，糖苷化程度增加，產生過糖苷化 FVII 多肽。可例如藉由併入至少一個未見於未經修飾之 FVII 多肽中連接碳水化合物部分的非原生糖苷化位點來實現此點。亦可藉由將碳水化合物部分連接至至少一個見於未經修飾之 FVII 多肽中但不在未經修飾之 FVII 多肽中糖苷化之原生糖苷化位點，產生過糖苷化 FVII 多肽。在其他實例中，與未經修飾之 FVII 多肽相比，經修飾之 FVII 多肽中的糖苷化程度降低。此可藉由諸如藉由胺基酸置換或缺失消除一或多個原生糖苷化位點實現。

對應於 SEQ ID NO: 3 中所闡明之成熟 FVII 多肽的胺基酸位置 52、60、145 及 322 之一或多個胺基酸殘基可經缺失或可經無法與碳水化合物部分連接之胺基酸殘基置換。舉例而言，位置 52 及/或 60 之絲胺酸殘基可經丙胺酸殘基置換，藉此消除原生 O-糖苷化位點之一或兩者。因此，可引入、改變、消除或重排 FVII 多肽中之糖苷化位點。

可在一或多個位置修飾 FVII 多肽以改變多肽之糖苷化。與未經修飾之 FVII 多肽相比，本文中提供的具有改變之糖苷化的經修飾之 FVII 多肽可不具有糖苷化、O-連接型糖苷化、N-連接型糖苷化及/或其組合。在一些實例中，經修飾之 FVII 多肽包括 1、2、3、4、5 個或更多個碳水化合物部分，其各自與不同糖苷化位點連接。糖苷化位點可為原生糖苷化位點及/或非原生糖苷化位點。在一些實例中，經修飾之 FVII 多肽在一個以上非原生糖苷化位點經糖苷化。舉例而言，經修飾之 FVII 多肽可經修飾以引入 1、2、3、4、5 個或更多個非原生糖苷化位點。

可藉由胺基酸置換引入非原生糖苷化位點。舉例而言，可藉由以絲胺酸或蘇胺酸對原生殘基進行胺基酸置換產生 O-糖苷化位點。可藉由建立 Xaa 不為脯胺酸之基元 Asn-Xaa-Ser/Thr/Cys 產生 N-糖苷化位點。藉由胺基酸修飾產生此一致序列可包括以天冬醯胺置換原生胺基酸殘基，以絲胺酸、蘇胺酸或半胱胺酸置換原生胺基酸殘基，或以天冬醯胺置換原生胺基酸殘基，及以絲胺酸、蘇胺酸或半胱胺酸對原生殘基進行胺基酸置換。舉例而言，使位置 109

（基於 SEQ ID NO: 3 中所闡明的成熟 FVII 之編號）之離胺酸可經天冬醯胺置換以在 EGF1 域中產生新 Asn-Xaa-Ser 基元且在胺基酸位置 109 產生新 N-糖苷化位點。在另一實例中，使位置 292 之丙胺酸經天冬醯胺置換且使位置 294 之丙胺酸經絲胺酸置換，以產生新 Asn-Xaa-Ser 基元且在胺基酸位置 292 產生新 N-糖苷化位點。在另一實例中，使位置 175 之丙胺酸經絲胺酸置換以在基於 SEQ ID NO:3 中所闡明的成熟 FVII 之編號的胺基酸位置 173-175 產生新 Asn-Xaa-Ser 基元，且在胺基酸位置 173 產生新 N-糖苷化位點。可在 FVII 多肽之任何區域中產生非原生糖苷化位點。舉例而言，可將一或多個糖苷化位點引入對應於 SEQ ID NO: 3 的成熟 FVII 多肽之胺基酸位置 46-82 的 EGF1 域中。在其他實例中，將非原生糖苷化位點引入 FVII 多肽之蛋白酶域區域或蛋白質摺疊後可與蛋白酶域區域相關聯的位置中。

原生糖苷化位點可經修飾以防止糖苷化或增強或降低糖苷化，而 FVII 多肽之其他位置可經修飾以引入非原生糖苷化位點。在一些實例中，FVII 多肽之碳水化合物含量可經修飾。舉例而言，可改變添加至 FVII 多肽的碳水化合物部分之碳水化合物鍵聯之編號位置、鍵強度、結構及組成（亦即，基於糖苷鍵之性質或碳水化合物之分枝的碳水化合物之結構）。

本文中提供的具有改變之糖苷化的經修飾之 FVII 多肽保留 FVII 之至少一種活性。典型地，與未經修飾之 FVII 相比，本文中提供的具有改變之糖苷化的經修飾之 FVII 多

肽展現增強之凝血活性。在一些實例中，FVII 多肽之糖苷化程度增加。與未經修飾或野生型 FVII 多肽之糖苷化程度相比，糖苷化程度可增加至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。在其他實例中，糖苷化程度降低。與未經修飾或野生型 FVII 多肽之糖苷化程度相比，糖苷化程度可降低至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。與未經修飾之 FVII 多肽相比，經修飾之 FVII 多肽上存在之改變之糖苷化程度或糖苷化類型變化可表現為凝血活性增強。與未經修飾或野生型 FVII 多肽之活體內或試管內凝血活性相比，具有改變之糖苷化的經修飾之 FVII 多肽的凝血活性可增強至少或約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。

表 9 提供對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之胺基酸位置的例示性胺基酸置換之非限制性實例，該等胺基酸置換係包括在經修飾之 FVII 多肽中以藉由添加或消除糖苷化位點來改變糖苷化程度。例示性胺基酸置換可產生非原生糖苷化位點或消除原生糖苷化位點。在一些情況下，需要兩個胺基酸置換來產生新糖苷化位點。表 9 亦包括在 FVII 多肽中產生一個以上新非原生糖苷化位點之

例示性組合突變。如上所述，糖苷化程度變化可例如增加半衰期。因此，經修飾之 FVII 多肽可具有增強之凝血活性。關於該等突變，第一胺基酸（單字母縮寫）對應於經置換之胺基酸，數字對應於成熟 FVII 多肽序列中關於 SEQ ID NO: 3 之位置，且第二胺基酸（單字母縮寫）對應於經選擇置換彼位置之第一胺基酸的胺基酸。適當時，亦根據胰凝乳蛋白酶編號方案提及用於突變之胺基酸位置。在經修飾之胺基酸位置不具有對應胰凝乳蛋白酶編號（亦即，不在對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之胺基酸位置 153 至 406，且未闡明於以上表 1 中）之情況下，位置係使用成熟 FVII 編號在括號中表示。舉例而言，A51N 不具有對應胰凝乳蛋白酶編號且當提及胰凝乳蛋白酶編號時經闡明為 A[51]N。在下表 9 中，鑑別闡明經修飾之 FVII 多肽的例示性胺基酸序列之序列識別符（SEQ ID NO）。表 9 亦鑑別藉由修飾產生之任何新非原生糖苷化位點。

表 9

修飾-成熟 FVII 編號	修飾-胰凝乳蛋白酶編號	非原生糖苷化位點（成熟 FVII 編號）	非原生糖苷化位點（胰凝乳蛋白酶編號）	SEQ ID NO
S52A	S[52]A	無	無	206
S60A	S[60]A	無	無	207
E394N/P395A/R396S	E245N/P246A/R247S	N394	N245	208
R202S	R62S	N200	N60d	209
A292N/A294S	A150N/A152S	N292	N150	210
G318N	G170fN	N318	N170f	211
A175S	A39S	N173	N37	212
K109N	K[109]N	N109	N[109]	213
A122N/G124S	A[122]N/G[124]S	N122	N[122]	214
A51N	A[51]N	N51	N[51]	215
T130N/E132S	T[130]N/E[132]S	N130	N[130]	216
A122N/G124S/ E394N/P395A/R396S	A[122]N/G[124]S / E245N/P246A/R247S	N122 及 N394	N[122]及 N245	217
A122N/G124S/ E394N/P395A/R396S/ G318N	A[122]N/G[124]S/ E245N/P246A/R247	N122, N394	N[122], N245 及	218

E394N/P395A/R396S/ G318N	E245N/P246A/R247S/ G170fN	及 N318	N245 及 N318	
S52A/S60A	S[52]A/S[60]A	無	無	219
S52N/P54S	S[52]N/P[54]S	N52	N[52]	220
S119N/L121S	S[119]N/L[121]S	N119	N[119]	221
T128N/P129A	T[128]N/P[129]A	N128	N[128]	222
Q66N/Y68S	Q[66]N/Y[68]S	N66	N[66]	223
S52N/P54S/A122N/G124S/E394N/P395A/R396S	S[52]N/P[54]S/A[122]N/G[124]S/E245N/P246A/R247S	N52, N122 及 N397	N[52], N[122]及 N245	224
K109N/A292N/A294S	K[109]N/A150N/A152S	N109 及 N292	N[109]及 N150	225
K109N/A175S	K[109]N/A39S	N109 及 N173	N[109]及 N37	226
S119N/L121S/A175S	S[119]N/L[121]S/A39S	N119 及 N173	N[119]及 N37	271
T128N/P129A/A175S	T[128]N/P[129]A/A39A	N128 及 N173	N[128]及 N37	272
A122N/G124S/A175S	A[122]N/G[124]S/A39S	N122 及 N173	N[122]及 N37	273

5. 增強之與血清白蛋白及/或血小板整合素 $\alpha_{IIb}\beta_3$ 的結合

重組未經修飾之 FVII 在人類中具有僅 1.5-3 小時之半衰期。增加 FVII 多肽之血清半衰期可降低治療作用所需的劑量之量及頻率。可採用數種策略來增加血清半衰期，包括（但不限於）增加糖苷化、增強蛋白酶抗性、PEG 化及與較大蛋白質（諸如血清白蛋白及 IgG 之 Fc 部分）接合或融合。該等修飾可產生（例如）減少之血清蛋白酶對 FVII 多肽的降解、降低之腎清除率、降低之肝清除率及降低之免疫系統的中和或清除率。可採用以增加 FVII 多肽之血清半衰期的另一策略包括將結合序列接枝於未經修飾之 FVII 多肽中以形成在未經修飾之 FVII 多肽中未觀察到的新或增強之蛋白質-蛋白質交互作用。

插入未經修飾之 FVII 多肽中之結合序列可含有約 5、6、7、8、9、10、11、12、13、14、15、20、25、30 個或更多個促進與另一蛋白質交互作用的胺基酸殘基。結合序列可對應於天然存在於原生蛋白質中的結合序列，或可為與天然存在於原生蛋白質中的結合序列具有極少或無序列相關性之合成結合序列。用以修飾本文之 FVII 多肽的結合序列與另一蛋白質上之結合位點特異性交互作用，形成非共價蛋白質-蛋白質交互作用。在一些實例中，結合序列具特異性之蛋白質為血清蛋白質，諸如血清白蛋白。在此項技術中熟知該等序列（參見例如 US20030069395、US20040009534、US20070202045）。在其他實例中，由結合序列識別之蛋白質為細胞表面受體或配位體，諸如血小板整合素 $\alpha_{IIb}\beta_3$（Smith 等人 (1995) J. Biol. Chem. 270:30486-30490）。經修飾之 FVII 多肽結合血清蛋白質或細胞表面受體之親和力之特徵典型地在於 1 μM、100 nM、10 nM、1 nM、100 pM、10 pM、1 pM 或 1 pM 以下之解離常數 Kd。與未經修飾之 FVII 多肽相比，經修飾之 FVII 多肽與血清蛋白或細胞表面受體經由結合序列的結合可降低例如經修飾之 FVII 多肽之腎清除率或肝清除率。在一些實例中，經修飾之 FVII 多肽與細胞表面受體的結合亦可使經修飾之 FVII 多肽靶向體內的所需細胞或組織類型或區域，藉此使彼 FVII 多肽「集中」在特定位點，諸如血凝塊。因此，與未經修飾之 FVII 多肽相比，含有接枝有結合序列的經修飾之 FVII 多肽可展現增加之半衰期。

a. 具有血清白蛋白結合序列之例示性 FVII 多肽

本文提供含有血清白蛋白結合序列的經修飾之 FVII 多肽。該等經修飾之 FVII 多肽可試管內或活體內結合血清白蛋白，使得半衰期增加。因此，本文中提供與未經修飾之 FVII 多肽相比，具有增加之半衰期的經修飾之 FVII 多肽。當諸如作為促凝血治療劑向個體投藥後，在適當試管內檢定中或活體內評估時，與未經修飾之 FVII 多肽相比較，經修飾之 FVII 多肽可顯示增強之凝血活性。

本文中提供之經修飾之 FVII 多肽可含有血清白蛋白結合序列。可將血清白蛋白結合序列插入未經修飾之 FVII 多肽內，或可將其連接至 FVII 多肽之 C 或 N 末端。舉例而言，血清白蛋白結合序列可自 FVII 多肽（對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽）之 C 末端的胺基酸位置 406 之脯胺酸殘基延伸。若將結合序列插入 FVII 多肽內，則插入在使得所得經修飾之 FVII 多肽保留未經修飾之 FVII 多肽的至少一種活性之位置。可在不移除 FVII 多肽內的任何胺基酸殘基之情況下，將結合序列插入 FVII 多肽中，或結合序列可置換 FVII 多肽中之一或多個胺基酸殘基。在一些實例中，血清白蛋白結合序列置換胺基酸殘基 S103 至 S111（對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽）以產生經修飾之 FVII 多肽。在其他實例中，血清白蛋白結合序列置換胺基酸殘基 H115 至 S126 或 T128 至 P134（對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽）。例示性血清白蛋白結合序列經闡明於 SEQ ID NO: 206-212 中。

表10提供可對FVII多肽進行以插入血清白蛋白結合序列的例示性修飾之非限制性實例。如上所述，血清白蛋白結合序列之包含可增加FVII多肽之半衰期。因此，經修飾之FVII多肽可具有增強之凝血活性。關於表10所列之修飾，血清白蛋白結合序列插入FVII多肽處的胺基酸殘基與結合序列之序列均呈示於表中。舉例而言，S103S111缺失插入QRLMEDICLPRWGCLWEDDF指示未經修飾之FVII多肽全長編號之胺基酸殘基S103至S111(對應於SEQ ID NO: 3中所闡明的成熟FVII多肽序列之殘基）已缺失且經具有胺基酸序列QRLMEDICLPRWGCLWEDDF（SEQ ID NO: 206）的血清白蛋白結合序列置換。僅單一胺基酸殘基（諸如P406)的敘述指示血清白蛋白結合序列插入在P406之後且FVII多肽中無胺基酸殘基缺失。適當時，亦根據胰凝乳蛋白酶編號方案提及用於突變之胺基酸位置。在經修飾之胺基酸位置不具有對應胰凝乳蛋白酶編號（亦即，不在對應於SEQ ID NO: 3中所闡明的成熟FVII多肽之胺基酸位置153至406，且未闡明於以上表1中）之情況下，位置係使用成熟FVII編號在括號中表示。舉例而言，S103不具有對應胰凝乳蛋白酶編號且當提及胰凝乳蛋白酶編號時經闡明為S[103]。在下表10中，鑑別闡明經修飾之FVII多肽的例示性胺基酸序列之序列識別符（SEQ ID NO）。

表 10

修飾-成熟PVII編號	修飾-胰凝乳蛋白酶編號	SEQ ID NO
S103S111缺失插入 QRLMEDICLPRWGCLWEDDF	S[103]S[111]缺失插入 QRLMEDICLPRWGCLWEDDF	227
H115S126缺失插入 QRLMEDICLPRWGCLWEDDF	H[115]S[126]缺失插入 QRLMEDICLPRWGCLWEDDF	228

T128P134 缺失插入 QRLMEDICLPRWGCLWEDDF	T[128]P[134]缺失插入 QRLMEDICLPRWGCLWEDDF	229
S103S111 缺失插入 IEDICLPRWGCLWE	S[103]S[111]缺失插入 IEDICLPRWGCLWE	230
H115S126 缺失插入 IEDICLPRWGCLWE	H[115]S[126]缺失插入 IEDICLPRWGCLWE	231
T128P134 缺失插入 IEDICLPRWGCLWE	T[128]P[134]缺失插入 IEDICLPRWGCLWE	232
S103S111 缺失插入 DICLPRWGCLWED	S[103]S[111]缺失插入 DICLPRWGCLWED	233
H115S126 缺失插入 DICLPRWGCLWED	H[115]S[126]缺失插入 DICLPRWGCLWED	234
T128P134 缺失插入 DICLPRWGCLWED	T[128]P[134]缺失插入 DICLPRWGCLWED	235
P406 插入 IEDICLPRWGCLW	P257 插入 IEDICLPRWGCLW	236
P406 插入 GGGSIEDICLPRWGCLW	P257 插入 GGGSIEDICLPRWGCLW	237
P406 插入 DICLPRWGCLWED	P257 插入 DICLPRWGCLWED	238
P406 插入 GGGSDICLPRWGCLWED	P257 插入 GGGSDICLPRWGCLWED	239

與未經修飾或野生型 FVII 多肽與血清白蛋白之活體內或試管內結合相比，含有血清白蛋白結合序列的經修飾之 FVII 多肽可展現至少或約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高的與血清白蛋白的結合增加。與未經修飾或野生型 FVII 多肽之活體內或試管內血清半衰期相比，可結合血清白蛋白的經修飾之 FVII 多肽可展現至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高的血清半衰期增加。該等經修飾之 FVII 多肽的增加之血清白蛋白結合及/或增加之血清半衰期亦可表現為增強之凝血活性、增加之凝血活性持續時間及/或提高之治療指數。與未經修飾或野生型 FVII 多肽之活體內或試管內凝血活性相比，經修飾之 FVII 多肽的凝血活性可增強至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。

b. 具有血小板整合素 $\alpha_{IIb}\beta_3$ 結合序列之例示性 FVII 多肽

本文提供含有血小板整合素 $\alpha_{IIb}\beta_3$ 結合序列的經修飾之 FVII 多肽。血小板整合素 $\alpha_{IIb}\beta_3$（亦稱為醣蛋白（GP）IIb/IIIa）為最豐富血小板黏附受體。其為充當包括（但不限於）血纖維蛋白原、纖連蛋白、玻連蛋白、溫韋伯氏因子及血小板反應蛋白之蛋白質的受體之鈣依賴性雜二聚體。與「同源」蛋白配位體結合可活化 $\alpha_{IIb}\beta_3$ 且經由蛋白質之細胞間域在細胞質中誘導信號轉導。因此，含有血小板整合素 $\alpha_{IIb}\beta_3$ 結合序列的經修飾之 FVII 多肽可結合血小板。經修飾之 FVII 多肽可試管內或活體內結合血小板整合素 $\alpha_{IIb}\beta_3$（經活化及/或未活化形式），使得半衰期增加。因此，彼等選擇性結合經活化之 $\alpha_{IIb}\beta_3$ 的 FVIIa 變異體可靶向經活化血小板且因此集中在正發展血凝塊之部位。預期使 FVIIa 選擇性靶向正發展之血凝塊將藉由提高功效與治療指數提高變異體之治療效用。因此，本文提供與未經修飾之 FVII 多肽及另外選擇性結合經活化血小板的變異體相比，具有增加之半衰期的經修飾之 FVII 多肽。當諸如作為促凝血治療劑向個體投藥後，在適當試管內檢定中或活體內評估時，與未經修飾之 FVII 多肽相比較，經修飾之 FVII 多肽可顯示增強之凝血活性。

本文中提供的經修飾之 FVII 多肽含有血小板整合素 $\alpha_{IIb}\beta_3$ 結合序列。可將血小板整合素 $\alpha_{IIb}\beta_3$ 結合序列插入未經修飾之 FVII 多肽，或可將其連接至 FVII 多肽之 C 或 N

末端。舉例而言，$\alpha_{IIb}\beta_3$結合序列可自 FVII 多肽（對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽）之 C 末端的胺基酸位置 406 之脯胺酸殘基延伸。若將結合序列插入 FVII 多肽內，則插入在使得所得經修飾之 FVII 多肽保留未經修飾之 FVII 多肽的至少一種活性之位置。可在不移除 FVII 多肽中的任何胺基酸殘基之情況下，將結合序列插入 FVII 多肽中，或結合序列可置換 FVII 多肽中之一或多個胺基酸殘基。在一些實例中，血小板整合素$\alpha_{IIb}\beta_3$結合序列置換胺基酸殘基 S103 至 S111（對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽）以產生經修飾之 FVII 多肽。在其他實例中，$\alpha_{IIb}\beta$3 結合序列置換胺基酸殘基 H115 至 S126 或 T128 至 P134（對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽）。例示性血小板整合素$\alpha_{IIb}\beta_3$結合序列經闡明於 SEQ ID NO: 213-215 中。

表 11 提供可對 FVII 多肽進行以插入血小板整合素$\alpha_{IIb}\beta_3$結合序列的例示性修飾之非限制性實例。如上所述，血小板整合素$\alpha_{IIb}\beta_3$結合序列之包含可增加 FVII 多肽之血清半衰期及/或使該蛋白質靶向正發展血凝塊。因此，經修飾之 FVII 多肽可具有增強之凝血活性。關於表 11 所列之修飾，血小板整合素$\alpha_{IIb}\beta_3$結合序列插入 FVII 多肽處的胺基酸殘基與結合序列之序列均呈示於表中。舉例而言，H115S126 缺失插入 QRLMEDICLPRWGCLWEDDF 指示未經修飾之 FVII 多肽全長編號之胺基酸殘基 H115 至 S126（對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽序列之殘基）

已缺失且經具有胺基酸序列 SFGRGDIRNV（SEQ ID NO:213）的 $\alpha_{IIb}\beta_3$ 結合序列置換。僅單一胺基酸殘基（諸如 P406）的敘述指示 $\alpha_{IIb}\beta_3$ 結合序列插入在 P406 之後且 FVII 多肽中無胺基酸殘基缺失。適當時，亦根據胰凝乳蛋白酶編號方案提及用於突變之胺基酸位置。在經修飾之胺基酸位置不具有對應胰凝乳蛋白酶編號（亦即，不在對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之胺基酸位置 153 至 406，且未闡明於以上表 1 中）之情況下，位置係使用成熟 FVII 編號在括號中表示。舉例而言，S103 不具有對應胰凝乳蛋白酶編號且當提及胰凝乳蛋白酶編號時經闡明為 S[103]。在下表 11 中，鑑別闡明經修飾之 FVII 多肽的例示性胺基酸序列之序列識別符（SEQ ID NO）。

表 11

修飾-成熟 PVII 編號	修飾-胰凝乳蛋白酶編號	SEQ ID NO
S103S111 缺失插入 SFGRGDIRNV	S[103]S[111]缺失插入 SFGRGDIRNV	240
H115S126 缺失插入 SFGRGDIRNV	H[115]S[126]缺失插入 SFGRGDIRNV	241
T128P134 缺失插入 SFGRGDIRNV	T[128]P[134]缺失插入 SFGRGDIRNV	242
P406 插入 CSFGRGDIRNVC	P257 插入 CSFGRGDIRNVC	243
P406 插入 GGGSCSFGRGDIRNVC	P257 插入 GGGSCSFGRGDIRNVC	244

與未經修飾或野生型 FVII 多肽與血小板整合素 α IIb β 3 之活體內結合相比，含有血小板整合素 α IIb β 3 結合序列的經修飾之 FVII 多肽可展現至少或約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500% 或更高的與血小板整合素 α IIb β 3 的結合增加。與未經修飾或野生型 FVII 多肽之試管內、活體內或活體外半衰期相

比，可經由血小板整合素αIIbβ3 結合血小板的經修飾之FVII 多肽可展現至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高的半衰期增加。該等經修飾之 FVII 多肽的增加之半衰期亦可表現為增強之凝血活性、增加之凝血活性持續時間及/或提高之治療指數。舉例而言，與未經修飾或野生型 FVII 多肽之活體內或試管內凝血活性相比，經修飾之 FVII 多肽的凝血活性可增強至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。

6. 藉由引入異源 Gla 域加以修飾

諸如 FVII、FIX、FX、凝血酶原、蛋白質 C 及蛋白質 S 的維生素 K 依賴性血漿蛋白質之γ-羧基化 Gla 域內的殘基與膜表面上帶負電磷脂之交互作用對於止血為重要的。維生素 K 依賴性血漿蛋白質之 Gla 域典型地含有約 45 個胺基酸，其中 9 至 12 個麩胺酸殘基經維生素 K 依賴性羧基化轉譯後修飾以形成γ-羧基麩胺酸（Gla）。形成 Gla 域之胺基酸直接位於形成蛋白質的信號肽及前肽之胺基酸之後，且因此在前驅體多肽被加工及裂解為成熟蛋白質後位於 N 末端。舉例而言，形成 FVII 的 Gla 域之胺基酸在 SEQ ID NO: 1 中所闡明的前驅體多肽之位置 39-83、SEQ ID NO: 2 中所闡明的前驅體多肽之位置 61-105 及 SEQ ID NO: 3 中所闡明的成熟多肽之位置 1 至 45。其中，SEQ ID NO: 3 中所闡明

之成熟 FVII 多肽的位置 E6、E7、E14、E19、E20、E25、E26、E29 及 E35 之 10 個麩胺酸殘基經羧基化修飾以產生 γ-羧基麩胺酸（Gla）殘基。

由於其對經活化血小板之相對低的結合親和力，FVII 之 Gla 域為修飾之目標，其目的為增強經修飾之 FVII 與磷脂膜之間的交互作用，藉此增強凝血活性。可藉由取代參與此交互作用的特定胺基酸實現修飾（參見例如，Shah 等人 PNAS 95: 4429-4234；Harvey 等人 (2003) J Biol Chem 278:8363-8369）。或者，可藉由以另一維生素 K 依賴性蛋白質之 Gla 域取代整個 Gla 域，亦即 Gla 域交換實現修飾。此類型之修飾產生嵌合蛋白，諸如當蛋白質 C 之 Gla 域經 FVII 之 Gla 域置換時產生之嵌合蛋白（Geng 等人 (1997) Thromb Haemost 77:926-933）。

典型地，該修飾包括諸如藉由添加或取代將異源 Gla 域或其足以實現磷脂結合之部分引入 FVII 多肽之區域中以產生嵌合經修飾之 FVII 多肽。通常，該嵌合 FVII 多肽保留 FVII 之至少一種活性。與未經修飾或野生型 FVII 多肽之活體內或試管內結合及/或親和力相比，Gla 經修飾之 FVII 多肽對經活化血小板之結合及/或親和力可增強至少約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。經修飾之 FVII 多肽對經活化血小板之結合及/或親和力亦可表現為增強之凝血活性。與未經修飾或野生型 FVII 多肽之活體內或試管內凝血活性相比，Gla

經修飾之 FVII 多肽的凝血活性可增強至少或約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。

任何多肽內所含的 Gla 域或其足以實現磷脂結合之部分，諸如異源 Gla 域之 30%、40%、50%、60%、70%、80%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或更高，可用作用於引入或置換 FVII 多肽之區域的異源 Gla 域之來源。典型地，該異源 Gla 域對磷脂，例如經活化血小板之表面上存在的磷脂展現結合親和力。通常，異源 Gla 域之選擇為與 FVII 之 Gla 域的親和力相比，對磷脂展現較高親和力者。可合理地或憑經驗確定用作用於修飾 FVII 多肽之異源域的確切 Gla 域或其足夠部分。其他含 Gla 之多肽的實例包括（但不限於）FIX、FX、凝血酶原、蛋白質 C、蛋白質 S、骨鈣蛋白、基質 Gla 蛋白、生長抑止特異性蛋白 6（Gas6）及蛋白質 Z。此等例示性蛋白質之 Gla 域經闡明於 SEQ ID NO: 83-91 之任一者中。舉例而言，可將異源 Gla 域之 2、3、4、5、6、7、8、9、10、20、30、40 個或更多個連續胺基酸或整個 Gla 域引入 FVII 多肽中。另外，將 Gla 域引入 FVII 多肽中亦可包括不為異源多肽之 Gla 域之部分的其他胺基酸，只要該等其他胺基酸不顯著削弱所引入 Gla 域之磷脂結合能力。

在一些實例中，藉由將 Gla 域添加至 FVII 多肽以使得異源 Gla 域得以插入 FVII 多肽之內源性 Gla 域或插入另一

區域或域中進行引入，只要經修飾之 FVII 多肽保留 FVII 之至少一種活性。在該等實例中，FVII 多肽之原生 Gla 域保留在多肽中，儘管在一些情況下，構成原生 Gla 域之胺基酸序列中斷。在其他實例中，異源 Gla 域或其足夠部分被插入於原生 Gla 域之 N 或 C 末端的鄰近處，或插入在 N 或 C 末端上，使得原生 Gla 域並不中斷。在另一實例中，異源 Gla 域或其足夠部分被插入 FVII 多肽之另一域中。

本文中亦提供經修飾之 Gla 域 FVII 多肽，其中 FVII 之內源性 Gla 域的所有或連續部分經移除且以異源 Gla 域或其足夠部分置換以實現磷脂結合，只要經修飾之 FVII 多肽保留 FVII 之至少一種活性。該等修飾亦稱為 Gla 域交換。例示性 Gla 交換修飾為內源性 Gla 域經 FIX（SEQ ID NO: 83）、FX（SEQ ID NO: 84）、凝血酶（SEQ ID NO: 85）、蛋白質 C（SEQ ID NO: 86）或蛋白質 S（SEQ ID NO: 87）中任一者的 Gla 域之全部或一部分置換者。該等修飾分別稱為「Gla 交換 FIX」、「Gla 交換 FX」、「Gla 交換凝血酶」、「Gla 交換蛋白質 C」及「Gla 交換蛋白質 S」。該等經修飾之 FVII 多肽可展現增強之與活化血小板的結合，使得凝血活性增強。「Gla 交換 FIX」修飾涉及藉由缺失胺基酸殘基 A1 至 Y44（對應於 SEQ ID NO: 3 中所闡明之成熟 FVII 多肽的殘基）使內源性 FVII Gla 域缺失及插入對應於 SEQ ID NO: 83 中所闡明的 FIX Gla 域之胺基酸殘基 Y1 至 Y45 的 45 個胺基酸殘基。Gla 交換 FX 修飾涉及使胺基酸殘基 A1 至 Y44（對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多

肽之殘基）缺失及插入對應於 SEQ ID NO: 84 中所闡明之 FX Gla 域的 A1 至 Y44 之 44 個胺基酸殘基。Gla 交換凝血酶修飾涉及使胺基酸殘基 A1 至 Y44(對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之殘基）缺失及插入對應於 SEQ ID NO: 85 中所闡明之凝血酶 Gla 域的胺基酸殘基 Y1 至 Y44 之 44 個胺基酸殘基。Gla 交換蛋白質 C 修飾涉及使胺基酸殘基 A1 至 Y44(對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之殘)缺失及插入對應於 SEQ ID NO: 86 中所闡明之蛋白質 C Gla 域的胺基酸殘基 A1 至 H44 之 44 個胺基酸殘基。Gla 交換蛋白質 S 修飾涉及使胺基酸殘基 A1 至 Y44（對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之殘)缺失及插入對應於 SEQ ID NO: 87 中所闡明之蛋白質 S Gla 域的胺基酸殘基 Y1 至 Y44 之 44 個胺基酸殘基。

在一些實例中，對引入 FVII 多肽中的異源 Gla 域進行包括（但不限於）胺基酸取代或置換、插入及/或缺失之修飾。與野生型異源 Gla 域所觀察到的結合相比，由於增強之磷脂結合，該等修飾可實現例如增強之與經活化血小板的結合。舉例而言，若將因子 IX Gla 域或其磷脂結合部分引入 FVII 多肽中以產生經修飾之 FVII 多肽，則因子 IX Gla 域可含有與野生型因子 IX Gla 域相比賦予增強之磷脂結合的胺基酸突變。本文中提供之含有異源 Gla 域的經修飾之 FVII 多肽可含有 1、2、3、4、5、6、7、8、9、10 個或更多個修飾，諸如胺基酸取代或置換、插入及/或缺失。

在一些實例中，異源 Gla 域內的修飾增強磷脂結合。在

其他實例中，異源 Gla 域可含有一或多個與異源 Gla 域之野生型形式相比對異源 Gla 域賦予 FVII 樣功能的突變。舉例而言，如上所述，SEQ ID NO: 119 中所闡明的 FVII Gla 域之 R36 可參與同 FX 之交互作用。因此，異源 Gla 域可含有其他修飾，諸如保持如 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽的位置 36 之精胺酸所需之任何修飾，或保持經修飾之 FVIIa 多肽的 FX 活化特性所需的任何其他修飾（Ruf 等人 (1999) Biochem 38:1957-1966）。因此，在一些實例中，可在異源 Gla 域中進行 R36 之對應突變。可藉由熟習此項技術者，諸如藉由比對胺基酸序列確定對應位置。

本文提供含有 Gla 交換修飾的經修飾之 FVII 多肽，其中與野生型異源 Gla 域相比，異源 Gla 域或其磷脂結合部分含有一或多個突變且藉由置換內源性 FVII Gla 域之一些或全部而引入 FVII 多肽中。在一實例中，本文中提供之經修飾之 FVII 多肽含有「Gla 交換 FIX」修飾，其如上所述涉及藉由缺失胺基酸殘基 A1 至 Y44（對應於 SEQ ID NO: 3 中所闡明之成熟 FVII 多肽的殘基）使內源性 FVII Gla 域缺失及插入對應於 SEQ ID NO: 83 中所闡明的 FIX Gla 域之胺基酸殘基 Y1 至 Y45 的 45 個胺基酸殘基。與 SEQ ID NO: 83 中所闡明的 FIX Gla 域之野生型形式相比，用於 Gla 交換修飾之 FIX Gla 域可含有一或多個突變，諸如 1、2、3、4、5 個或更多個突變，諸如胺基酸取代、缺失或插入。舉例而言，經「Gla 交換 FIX」修飾之 FVII 多肽中的異源 FIX Gla 域可在對應於 SEQ ID NO: 83 中所闡明的 FIX Gla 域之

M19、E40、K43 及/或 Q44 之胺基酸位置含有一或多個胺基酸取代。

在一實例中，FIX Gla 域含有 M19K 胺基酸取代。該修飾由{Gla 交換 FIX/M19K}表示，亦即對應於 SEQ ID NO: 83 中所闡明的 FIX Gla 域之胺基酸位置 19 的胺基酸位置之甲硫胺酸經離胺酸置換。在另一實例中，經修飾之 FVII 多肽中的經修飾異源 FIX Gla 域含有由{FIX Gla 交換/E40L}表示的 E40L 胺基酸取代，藉此對應於 SEQ ID NO: 83 中所闡明的 FIX Gla 域之胺基酸位置 40 的胺基酸位置之麩胺酸經白胺酸置換。本文中亦提供含有 K43I 取代（由{Gla 交換 FIX/K43I}表示）的經修飾之 FVII 多肽，其中對應於 SEQ ID NO: 83 中所闡明的 FIX Gla 域之胺基酸位置 43 的胺基酸位置之離胺酸經異白胺酸置換。在另一實例中，經修飾之 FVII 多肽中的經修飾異源 FIX Gla 域含有由{FIX Gla 交換/Q44S}表示的 Q44S 胺基酸取代，藉此對應於 SEQ ID NO: 83 中所闡明的 FIX Gla 域之胺基酸位置 44 的胺基酸位置之麩胺醯胺經絲胺酸置換。在一實例中，異源 FIX Gla 域含有 M19K/E40L/K43I/Q44S 胺基酸取代。

與諸如 NovoSeven®之野生型 FVII 分子相比，由於增強之對經活化血小板之結合及/或親和力，含有異源 Gla 域，諸如經修飾之異源 Gla 域的經修飾之 FVII 多肽在較低劑量下即可展現增強之凝血活性。與未經修飾或野生型 FVII 多肽之活體內、活體外或試管內凝血活性相比，Gla 經修飾之 FVII 多肽的凝血活性可增強至少或約 1%、2%、

3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、200%、300%、400%、500%或更高。

7. 組合及其他修飾

除 FVII 多肽之具有增強之 AT-III 抗性、增強之催化活性、增強之對 Zn^{2+}抑制的抗性、改變之糖苷化、改良之藥物動力學特性（諸如增加之半衰期）、增強之對血清白蛋白的結合及/或親和力、增強之對磷脂的結合及/或親和力或增強之對血小板整合素 $\alpha_{IIb}\beta_3$ 之結合及/或親和力的修飾外，本文中提供之經修飾之 FVII 多肽亦包括彼等展現一種以上上述特性者。典型地，該等其他修飾為本身使得經修飾之多肽的凝血活性增強及/或多肽的穩定性增強者。因此，所得經修飾之 FVII 多肽展現增強之凝血活性。其他修飾可包括例如在此項技術中已知之任何胺基酸取代、缺失或插入，典型地增強 FVII 多肽之凝血活性及/或穩定性的任何修飾。本文中提供的任何經修飾之 FVII 多肽可含有 1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20 個或更多個其他胺基酸修飾，只要所得經修飾之 FVII 多肽保留野生型或未經修飾之多肽的 FVII 活性即可。

在一實例中，可對 FVII 多肽序列進行其他修飾，以使得其與其他因子、分子及蛋白質的交互作用改變。舉例而言，參與同組織因子途徑抑制子（TFPI）之交互作用的胺基酸殘基可經置換以使得經修飾之 FVII 多肽對 TF 的親和

力及/或結合降低。其他修飾包括（但不限於）參與同因子X、因子 IX、組織因子（TF）及磷脂之交互作用的胺基酸之修飾。在一些實例中，對 FVII 多肽序列進行之修飾包括插入構成結合序列之胺基酸，該結合序列諸如血清白蛋白結合序列或醣蛋白 IIb-IIIa 結合序列。

亦可對本文中提供之經修飾之 FVII 多肽進行改變多肽之構形或摺疊的其他修飾。此等修飾包括例如以半胱胺酸置換一或多個胺基酸，以使得形成新雙硫鍵，或穩定 α 螺旋構形之修飾，藉此對經修飾之 FVII 多肽賦予增強之活性。

亦可對 FVII 多肽進行其他修飾以實現轉譯後修飾。舉例而言，可修飾多肽以包括額外糖苷化位點，以使得與未經修飾之 FVII 多肽相比，所得經修飾之 FVII 多肽具有增加之糖苷化。亦可進行修飾以引入可隨後與化學部分連接之胺基酸殘基，該化學部分諸如用於增強經修飾之 FVII 多肽的穩定性者。亦可藉由修飾潛在蛋白水解位點，藉此增強經修飾之 FVII 多肽的蛋白酶抗性來改變 FVII 多肽之穩定性。

另外，可在內源性 Gla 域中進行胺基酸取代、缺失或插入以使得經修飾之 FVII 多肽對磷脂膜顯示增強之結合及/或親和力。該等修飾可包括單一胺基酸取代、缺失及/或插入，或可包括多個胺基酸之胺基酸取代、缺失或插入。舉例而言，內源性 Gla 域之全部或部分可經異源 Gla 域之全部或部分置換。在其他實例中，本文中提供的經修飾之 FVII 多肽可顯示內源性 Gla 域中的缺失或通常經 γ 羧基化之位

置的取代（US20070037746）。

以下部分描述在此項技術中所述實現 FVII 多肽之增強之穩定性及/或凝血活性的例示性修飾之非限制性實例。如以上所討論，該等修飾亦可另外包括在本文中提供之任何經修飾之 FVII 多肽中。以下引用之胺基酸位置對應於如 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽。可在諸如 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之對偶基因、物種或剪接變異體的其他 FVII 多肽中進行對應突變。

a. 增強 TFPI 抗性的修飾

在一實例中，可對在根據成熟 FVII 編號之胺基酸位置 286 含有修飾的經修飾之 FVII 多肽進行使得 TFPI 抗性增強的其他修飾。舉例而言，可藉由 FVII 中參與同 TFPI 交互作用及結合的一或多個殘基之降低或防止該結合的突變來實現該 TFPI 抗性，藉此製備關於凝血起始對 TFPI 之天然抑制作用具有抗性的經修飾之 FVII 多肽。舉例而言，在為極其接近交互作用表面之 FVII/TFPI 接觸殘基的胺基酸殘基處進行修飾。

可包括於本文中提供的經修飾之 FVII 多肽中以增強 TFPI 抗性的其他修飾之實例包括（但不限於）彼等描述於國際專利公開案第 WO2004/083361 號；Neuenschwander 等人, (1995) Biochemistry 34:8701-8707；Chang 等人, (1999) Biochemistry 38:10940-10948；及 Iakhiaev 等人, (2001) Thromb. Haemost. 85:458-463 及相關申請案號代理人案號 119357 00059/4913 中者。在此項技術中所述可使得經修飾

之 FVII 多肽對 TFPI 之抗性增強的例示性胺基酸修飾之非限制性實例包括以下修飾中之任一或多者：Q176、D196K、D196R、D196A、D196Y、D196F、D196W、D196L、D196I、K197Y、K197A、K197E、K197D、K197L、K197M、K197I、K197V、K197F、K197W、K199A、K199D、K199E、G237W、G237T、G237I、G237V、T239A、R290A、R290E、R290D、R290N、R290Q、R290K、R290M、R290V、K341E、K341R、K341Q、K341N、K341M、K341D、G237T238 插入 A、G237T238 插入 S、G237T238 插入 V、G237T238 插入 AS、G237T238 插入 SA、D196K197 插入 K、D196K197 插入 R、D196K197 插入 Y、D196K197 插入 W、D196K197 插入 A、D196K197 插入 M、K197I198 插入 E、K197I198 插入 Y、K197I198 插入 A 及 K197I198 插入 S（其中，例如 G237T238 插入 AS 表示丙胺酸（A）及絲胺酸（S）已插入位置 237 之甘胺酸（G237）與位置 238 之蘇胺酸之間的修飾）。

b. 增強固有活性之修飾

在一實例中，可對本文中提供之經修飾之因子 VII 多肽進行使得對因子 X 之催化活性增強之其他修飾。舉例而言，可對參與同其輔因子 TF 交互作用的胺基酸進行修飾，以使得所得經修飾之 FVII 多肽對 TF 具有增強之親和力且藉此顯示增強之對 FX 的活性。亦可對 FVII 多肽之活化袋進行修飾，以使得與未經修飾之多肽的活性相比，經修飾之 FVII 多肽對 FX 之固有活性增強。產生增強之活性的另一修飾策略涉及使得蛋白質之摺疊及構形改變成為更具活性形式的

FVII 多肽之修飾。舉例而言，可進行胺基酸取代以使得蛋白酶域之 α-螺旋環區域(對應於如 SEQ ID NO: 3 中所闡明的成熟序列之位置 305 至 321)得以穩定且更緊固地摺疊為蛋白酶域主體以對經修飾之 FVII 多肽賦予更加酶原樣形狀。亦可藉由修飾參與 FVII 多肽之 β 鏈的胺基酸獲得具更高活性之多肽。舉例而言，可進行引入可形成新雙硫鍵的新半胱胺酸對的胺基酸取代，該新雙硫鍵可用於將經修飾之 FVII 多肽「鎖住」為更具活性形式。

可包括於本文中提供之經修飾之 FVII 多肽中以增強經修飾之 FVII 多肽的固有活性之其他修飾的實例包括（但不限於）彼等描述於 Persson 等人 (2004) Biochem J. 379:497-503；Maun 等人 (2005) Prot Sci 14:1171-1180；Persson 等人 (2001) PNAS 98:13583-13588；Persson 等人 (2002) Eur J Biochem 269:5950-5955；Soejima 等人 (2001) J Biol Chem 276:17229-17235；Soejima 等人 (2002) J Biol Chem 277:49027-49035；WO200183725；WO2002022776；WO2002038162；WO2003027147；WO200338162；WO2004029090；WO2004029091；WO2004108763 及 WO2004111242 中者。在此項技術中所述可使得經修飾之 FVII 多肽的固有活性增強的例示性胺基酸修飾之非限制性實例包括以下修飾中之任一或多者：S279C/V302C、L280C/N301C、V281C/V302C、S282C/V299C、S314E、L39E、L39Q、L39H、I42R、S43Q、S53N、K62E、K62R、K62D、K62N、K62Q、K62T、L65Q、L65S、F71D、F71Y、F71E、

F71Q、F71N、P74S、P74A、A75E、A75D、E77A、E82Q、E82N、T83K、E116D、K157V、K157L、K157I、K157M、K157F、K157W、K157P、K157G、K157S、K157T、K157C、K157Y、K157N、K157E、K157R、K157H、K157D、K157Q、V158L、V158I、V158M、V158F、V158W、V158P、V158G、V158S、V158T、V158C、V158Y、V158N、V158E、V158R、V158K、V158H、V158D、V158Q、A274M、A274L、A274K、A274R、A274D、A274V、A274I、A274F、A274W、A274P、A274G、A274T、A274C、A274Y、A274N、A274E、A274H、A274S、A274Q、F275H、E296V、E296L、E296I、E296M、E296F、E296W、E296P、E296G、E296S、E296T、E296C、E296Y、E296N、E296K、E296R、E296H、E296D、E296Q、M298Q、M298V、M298L、M298I、M298F、M298W、M298P、M298G、M298S、M298T、M298C、M298Y、M298N、M298K、M298R、M298H、M298E、M298D、R304Y、R304F、R304L、R304M、L305V、L305Y、L305I、L305F、L305A、L305M、L305W、L305P、L305G、L305S、L305T、L305C、L305N、L305E、L305K、L305R、L305H、L305D、L305Q、M306D、M306N、D309S、D309T、S314A、S314V、S314I、S314M、S314F、S314W、S314P、S314G、S314L、S314T、S314C、S314Y、S314N、S314E、S314K、S314R、S314H、S314D、S314Q、D334G、D334E、D334A、D334V、D334I、D334M、D334F、D334W、D334P、D334L、D334T、D334C、D334Y、D334N、D334K、D334R、D334H、D334S、D334Q、S336G、

S336E、S336A、S336V、S336I、S336M、S336F、S336W、S336P、S336L、S336T、S336C、S336Y、S336N、S336K、S336R、S336H、S336D、S336Q、K337L、K337V、K337I、K337M、K337F、K337W、K337P、K337G、K337S、K337T、K337C、K337Y、K337N、K337E、K337R、K337H、K337D、K337Q、F374P、F374A、F374V、F374I、F374L、F374M、F374W、F374G、F374S、F374T、F374C、F374Y、F374N、F374E、F374K、F374R、F374H、F374D、F374Q 及位置 300-322、305-322、300-312 或 305-312 經來自胰蛋白酶、凝血酶或 FX 的對應胺基酸之取代，及位置 310-329、311-322 或 233-329 經來自胰蛋白酶的對應胺基酸之取代。

c. 增強蛋白酶抗性的修飾

本文中提供的經修飾之 FVII 多肽亦可含有使得多肽對蛋白酶的抗性增強之其他修飾。舉例而言，可進行移除一或多個潛在蛋白水解裂解位點之胺基酸取代。因此，可使經修飾之 FVII 多肽對蛋白酶更具抗性，藉此增加經修飾之多肽的穩定性及半衰期。

可包括於本文中提供的經修飾之 FVII 多肽中以增強蛋白酶抗性的其他修飾之實例包括（但不限於）彼等描述於美國專利第 US5580560 號或國際公開申請案第 WO1988010295 號及第 WO2002038162 號中者。在此項技術中所述可使得經修飾之 FVII 多肽對抑制子及/或蛋白酶的抗性增強之例示性修飾之非限制性實例包括以下修飾中之任一或多者：K32Q、K32E、K32G、K32H、K32T、K32A、

K32S、K38T、K38D、K38L、K38G、K38A、K38S、K38N、K38H、I42N、I42S、I42A、I42Q、Y44N、Y44S、Y44A、Y44Q、F278S、F278A、F278N、F278Q、F278G、R290G、R290A、R290S、R290T、R290K、R304G、R304T、R304A、R304S、R304N、R315G、R315A、R315S、R315T、R315Q、Y332S、Y332A、Y332N、Y332Q、Y332G、K341E、K341Q、K341G、K341T、K341A 及 K341S。

d. 增強對磷脂之親和力的修飾

本文中提供的經修飾之 FVII 多肽亦可含有一或多個其他修飾以增強對磷脂的親和力。可藉由增強多肽對諸如彼等表現於經活化血小板之表面上的磷脂之結合及/或親和力增強 FVII 之凝血活性。此可例如藉由修飾內源性 FVII Gla 域達成。可藉由在 FVII 多肽之 Gla 域中的一或多個位置之產生具有增強之結合磷脂醯絲胺酸及其他帶負電磷脂的能力之經修飾之 FVII 多肽的胺基酸取代實現修飾。增強磷脂結合及/或親和力且可對本文中提供的含有內源性 FVII Gla 域之經修飾之 FVII 多肽進行之其他修飾的實例包括（但不限於）彼等描述於 Harvey 等人 (2003) J Biol Chem 278:8363-8369、US20030100506、US20040220106、US20060240526、US6017882、US6693075、US6762286、WO200393465 及 WO2004111242 中者。該等修飾之實例包括以下修飾中之任一或多者：位置 4 酪胺酸之插入或以下任一或多者之修飾：P10Q、P10E、P10D、P10N、R28F、R28E、K32E、K32D、D33F、D33E、D33K A34E、A34D、

A34I、A34L、A34M、A34V、A34F、A34W、A34Y、R36D、R36E、K38E 及 K38D。

e. 改變糖苷化之修飾

改變蛋白質糖苷化之程度、量及/或類型已作為降低免疫原性、增強穩定性、降低投藥頻率及/或降低諸如發炎之不良副作用的方式描述於此項技術中。通常，此藉由增加糖苷化程度實現。糖苷化位點提供用於在多肽上連接碳水化合物部分以使得當多肽在能夠糖苷化之真核細胞中產生時，其經糖苷化之位點。

FVII 中存在四個原生糖苷化位點：對應於 SEQ ID NO:3 中所闡明之成熟 FVII 多肽中的胺基酸位置處於 N145 及 N322 之兩個 N 糖苷化位點，及處於 S52 及 S60 之兩個 O 糖苷化位點。在一具體實例中，可對本文中提供之經修飾之 FVII 多肽進行其他修飾以使得上述位點之糖苷化受到破壞。此可產生具有增強之凝血活性的經修飾之 FVII 多肽(參見例如 WO2005123916)。與未經修飾之 FVII 多肽相比，在此項技術中所述可使得經修飾之 FVII 多肽的糖苷化降低及活性增強的例示性修飾之非限制性實例包括(但不限於)：S52A、S60A、N145Y、N145G、N145F、N145M、N145S、N145I、N145L、N145T、N145V、N145P、N145K、N145H、N145Q、N145E、N145R、N145W、N145D、N145C、N322Y、N322G、N322F、N322M、N322S、N322I、N322L、N322T、N322V、N322P、N322K、N322H、N322Q、N322E、N322R、N322W 及 N322C。

在另一具體實例中，可對本文中提供之經修飾之 FVII 多肽的胺基酸序列進行其他修飾，以使得引入額外糖苷化位點，因此與未經修飾之 FVII 多肽相比，增加經修飾之 FVII 多肽之糖苷化程度。糖苷化位點可為 N-連接型或 O-連接型糖苷化位點。可對 FVII 多肽進行之引入一或多個新糖苷化位點的修飾之實例包括（但不限於）彼等描述於 US6806063 及 WO200393465 中者。與未經修飾之 FVII 多肽相比，在此項技術中所述可使得經修飾之 FVII 多肽的糖苷化增加的例示性修飾之非限制性實例包括（但不限於）：F4S、F4T、P10N、Q21N、W41N、S43N、A51N、G58N、L65N、G59S、G59T、E82S、E82T、N95S、N95T、G97S、G97T、Y101N、D104N、T106N、K109N、G117N、G124N、S126N、T128N、A175S、A175T、G179N、I186S、I186T、V188N、R202S、R202T、I205S、I205T、D212N、E220N、I230N、P231N、P236N、G237N、V253N、E265N、T267N、E270N、R277N、L280N、G291N、P303S、P303ST、L305N、Q312N、G318N、G331N、D334N、K337N、G342N、H348N、R353N、Y357N、I361N、V376N、R379N、M391N、K32N/A34S、K32N/A34T、F31N/D33S、F31N/D33T、I30N/K32S、I30N/K32T、A34N/R36S、A34N/R36T、K38N/F40S、K38N/F40T、T37N/L39S、T37N/L39T、R36N/K38S、R36N/K38T、L39N/W41S、L39N/W41T、F40N/I42S、F40N/I42T、I42N/Y44S、I42N/Y44T、Y44N/D46S、Y44N/D46T、D46N/D48S、D46N/D48T、G47N/Q49S、G47N/Q49T、

S52N/P54S、Q66N/Y68S、S119N/L121S、A122N/G124S、
T128N/P129A、T130N/E132S、K143N/N145S、
K143N/N145T、E142N/R144S、E142N/R144T、
L141N/K143S、L141N/K143T、I140N/E142S/、
I140N/E142T、R144N/A146S、R144N/A146T、
A146N/K148S、A146N/K148T、S147N/P149S/、
S147N/P149T、R290N/A292S、R290N/A292T、
A292N/A294S、D289N/G291S、D289N/G291T、
L288N/R290S、L288N/R290T、L287N/D289S、
L287N/D289T、A292N/A294S、A292N/A294T、
T293N/L295S、T293N/L295T、R315N/V317S、
R315N/V317T、S314N/K316S、S314N/K316T、
Q313N/R315S、Q313N/R315T、K316N/G318S、
K316N/G318T、V317N/D319S、V317N/D319T、
K341N/D343S、K341N/D343T、S339N/K341S、
S339N/K341T、D343N/G345S、D343N/G345T、
R392N/E394S、R392N/E394T、L390N/R392S、
L390N/R392T、K389N/M391S、K389N/M391T、
S393N/P395S、S393N/P395T、E394N/R396S、E394N/R396T、
E394N/P395A/R396S、P395N/P397S、P395N/P397T、
R396N/G398S、R396N/G398T、P397N/V399S、
P397N/V399T、G398N/L400S、G398N/L400T、
V399N/L401S、V399N/L401T、L400N/R402S、
L400N/R402T、L401N/A403S、L401N/A403T、

R402N/P404S、R402N/P404T、A403N/F405S、A403N/F405T、P404N/P406S 及 P404N/P406T。

f. 促進化學基團連接之修飾

亦可進行本文中提供的經修飾之 FVII 多肽的其他修飾以促進化學基團之後續連接。可進行一或多個胺基酸取代或插入以使得可經由該經取代之胺基酸將化學基團連接至經修飾之 FVII 多肽。舉例而言，可將半胱胺酸引入經修飾之 FVII 多肽中，聚乙二醇（PEG）部分可與該連接半胱胺酸以賦予增加之穩定性及血清半衰期。其他連接殘基包括離胺酸、天冬胺酸及麩胺酸殘基。在一些具體實例中，胺基酸殘基經置換以減少潛在連接位置之數目。舉例而言，可減少離胺酸之數目。可對 FVII 多肽之胺基酸序列進行的可促進與化學基團的後續連接之修飾之實例包括（但不限於）彼等描述於 US20030096338、US20060019336、US6806063、WO200158935 及 WO2002077218 中者。FVII 多肽的可促進與化學基團之後續連接之例示性修飾的非限制性實例包括（但不限於）：Q250C、R396C、P406C、I42K、Y44K、L288K、D289K、R290K、G291K、A292K、T293K、Q313K、S314K、R315K、V317K、L390K、M391K、R392K、S393K、E394K、P395K、R396K、P397K、G398K、V399K、L400K、L401K、R402K、A403K、P404K、F405K、I30C、K32C、D33C、A34C、T37C、K38C、W41C、Y44C、S45C、D46C、L141C、E142C、K143C、R144C、L288C、D289C、R290C、G291C、A292C、S314C、R315C、K316C、V317C、

L390C、M391C、R392C、S393C、E394C、P395C、R396C、P397C、G398C、V399C、L401C、R402C、A403C、P404C、I30D、K32D、A34D、T37D、K38D、W41D、Y44D、S45D、D46C、L141D、E142D、K143D、R144D、L288D、R290D、G291D、A292D、Q313D、S314D、R315D、K316D、V317D、L390D、M391D、R392D、S393D、P395D、R396D、P397D、G398D、V399D、L401D、R402D、A403D、P404D、130E、K32E、A34E、T37E、K38E、W41E、Y44E、S45E、D46C、L141E、E142E、K143E、R144E、L288E、R290E、G291E、A292E、Q313E、S314E、R315E、K316E、V317E、L390E、M391E、R392E、S393E、P395E、R396E、P397E、G398E、V399E、L401E、R402E、A403E、P404E、K18R、K32R、K38R、K62R、K85R、K109R、K137R、K143R、K148R、K157R、K161R、K197R、K199R、K316R、K337R、K341R、K389R、K18Q、K32Q、K38Q、K62Q、K85Q、K109Q、K137Q、K143Q、K148Q、K157Q、K161Q、K197Q、K199Q、K316Q、K337Q、K341Q、K389Q、K18N、K32N、K38N、K62N、K85N、K109N、K137N、K143N、K148N、K157N、K161N、K197N、K199N、K316N、K337N、K341N、K389N、K18H、K32H、K38H、K62H、K85H、K109H、K137H、K143H、K148H、K157H、K161H、K197H、K199H、K316H、K337H、K341H 及 K389H。

g. 例示性組合突變

本文提供經修飾之 FVII 多肽，其具有兩個或更多個經

設計以影響未經修飾之 FVII 多肽的一或多種特性或活性的修飾。在一些實例中，兩個或更多個修飾改變 FVII 多肽之兩種或兩種以上特性或活性。可對 FVII 多肽進行修飾，以使得催化活性、AT-III 抗性、TFPI 抗性、對 Zn^{2+}抑制之抗性、固有活性、醯胺水解活性、磷脂結合及/或親和力、糖苷化、蛋白酶抗性、半衰期及與諸如 FX、FIX、血清白蛋白及血小板整合素 $\alpha_{IIb}\beta_3$ 之其他因子或分子的交互作用中之一或多者得以改變。典型地，組合兩個或更多個修飾以使得與未經修飾之 FVII 多肽相比，所得經修飾之 FVII 多肽具有增強之凝血活性、增加之凝血活性持續時間及/或提高之治療指數。修飾可包括胺基酸取代、插入或缺失。與起始或未經修飾之 FVIIa 多肽的活性相比，含有兩個或更多個修飾的經修飾之 FVII 多肽的增強之凝血活性、增加之凝血活性持續時間及/或提高之治療指數可增加至少或約 1%、2%、3%、4%、5%、6%、7%、8%、9%、10%、20%、30%、40%、50%、60%、70%、80%、90%、100%、110%、120%、130%、140%、150%、160%、170%、180%、190%、200%、300%、400%、500%或更高。

本文中提供經修飾之 FVII 多肽，其含有兩個或更多個經引入未經修飾之 FVII 多肽中以改變兩種或兩種以上活性或特性的修飾。經修飾之 FVII 多肽可含有 2、3、4、5、6 個或更多個修飾。另外，各修飾可涉及一或多個胺基酸殘基。舉例而言，經修飾之 FVII 多肽可含有兩個修飾，其各自為單一胺基酸取代。在另一實例中，經修飾之 FVII 多肽

可含有兩個修飾，其中一者為單一胺基酸取代且另一者涉及使一個以上胺基酸殘基缺失且隨後插入一個以上胺基酸殘基。舉例而言，本文中提供的經修飾之 FVII 多肽可含有破壞 Zn^{2+}結合的胺基酸取代 S222A（對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之殘基），及 Gla 交換 FIX 修飾，其涉及藉由缺失胺基酸殘基 A1 至 Y44（對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之殘基）使內源性 FVII Gla 域缺失且插入對應於 SEQ ID NO: 110 中所闡明的 FIX Gla 域之胺基酸殘基 Y1 至 Y45 之 45 個胺基酸殘基。

本文中提供的經修飾之 FVII 多肽可具有僅選自表 5 至 13 中所闡明者的兩個或更多個修飾。在其他實例中，經修飾之 FVII 多肽含有兩個或更多個修飾，其中一或多個修飾係選自表 5 至 13 中所闡明者，且一或多個修飾為表 5 至 13 中未闡明之其他修飾，諸如在此項技術中所述之修飾。在一些實例中，該一或多種其他修飾可選自以上 D.6.a-e 部分中所闡明者。舉例而言，經修飾之 FVII 多肽可在基於 SEQ ID NO:3 中所闡明的成熟 FVII 之編號的胺基酸殘基 D196、K197、K199、G237、T239、R290 或 K341（基於胰凝乳蛋白酶編號，分別對應於 D60、K60a、K60c、G97、T99、R147 及 K192）中之一或多者含有增強 TFPI 抗性之修飾，且在一或多個胺基酸殘基處含有影響固有活性之修飾，諸如 V158 及 M298（基於胰凝乳蛋白酶編號，分別為 V21 及 M156）。舉例而言，經修飾之 FVII 多肽可含有增強 TFPI 抗性之兩個胺基酸取代，諸如 K197E 及 G237V，及一個增強固有活

性之胺基酸取代，諸如 M298Q，藉此產生具有增強之凝血活性的 FVII 多肽。

本文中提供之例示性組合修飾為包括至少 Q286R 突變（對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽之編號；根據胰凝乳蛋白酶編號，對應於 Q143R）的組合修飾。含有 Q286R 修飾之經修飾之 FVII 多肽可含有 1、2、3、4、5、6 個或更多個其他修飾。可包括此等其他修飾以例如改變催化活性、AT-III 抗性、TFPI 抗性、對 Zn^{2+}抑制之抗性、固有活性、醯胺水解活性、磷脂結合及/或親和力、糖苷化、蛋白酶抗性、半衰期，及與諸如 FX、FIX、血清白蛋白及血小板整合素 $\alpha_{IIb}\beta_3$ 之其他因子或分子的交互作用。典型地，與野生型 FVII 多肽相比，本文中提供的含有兩個或更多個修飾（其中一個修飾為胺基酸取代 Q286R）之經修飾之 FVII 多肽展現增強之凝血活性。

在一些實例中，含有兩個或更多個修飾（其中一個修飾為 Q286R）的經修飾之 FVII 多肽與野生型多肽相比以及與僅含有該等突變中之任一者的 FVII 多肽相比展現增強之催化及凝血活性。舉例而言，本文中提供經修飾之 FVII 多肽，其含有 Q286R 與 M289Q 胺基酸取代（Q286R/M298Q 編號對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽；根據胰凝乳蛋白酶編號，對應於 Q143R/M156Q）。與野生型 FVII、Q286R 單一突變體及 M298Q 單一突變體相比，Q286R/M298Q 組合 FVII 突變體對其受質因子 X 展現增強之催化活性（參見例如以下實施例 4）。舉例而言，在一研

究中，M298Q 突變體在 TF 存在下對 FX 展現比野生型多肽高約 1.5 倍之催化活性，Q286R 突變體之催化活性比野生型 FVII 多肽高約 1.8 倍，且 Q286R/M298Q 突變體對 FX 展現約為野生型多肽對 FX 之催化活性的 3.3-3.8 倍之催化活性（參見下表 15）。

表 12 提供非限制性例示性組合修飾。此等例示性組合修飾包括經設計以改變 FVII 多肽的兩種或兩種以上活性或特性之兩個或更多個修飾，該等活性或特性包括（但不限於）TFPI 抗性、AT-III 抗性、固有活性、醯胺水解活性、催化活性、Zn^{2+}結合、磷脂結合及/或親和力、糖苷化、蛋白酶抗性、半衰期及與諸如 FX 及 FIX 的其他因子或分子之交互作用。含有該等組合修飾的經修飾之 FVII 多肽可具有增強之凝血活性、增加之凝血活性持續時間及/或提高之治療指數。下表 12 中闡明的修飾使用與以上表 5 至 11 中所述相同的命名法及編號系統。舉例而言，如上所述，「Gla 交換 FIX」修飾涉及藉由缺失胺基酸殘基 A1 至 Y44（對應於 SEQ ID NO: 3 中所闡明之成熟 FVII 多肽的殘基）使內源性 FVII Gla 域缺失及插入對應於 SEQ ID NO: 83 中所闡明的 FIX Gla 域之胺基酸殘基 Y1 至 Y45 的 45 個胺基酸殘基。在一些實例中，如以上所討論，與野生型 FIX Gla 域相比，「Gla 交換 FIX」修飾亦在 FIX Gla 域部分中含有一或多個胺基酸取代。舉例而言，Gla 交換 FIX 修飾亦可包括 M19K 胺基酸取代（對應 SEQ ID NO: 83 中所闡明的 FIX Gla 域之胺基酸位置之編號）。該修飾由{Gla 交換 FIX/M19K}表示，

亦即經修飾之 FVII 多肽含有對應於 SEQ ID NO: 83 中所闡明的 FIX Gla 域的位置 19 之位置之甲硫胺酸經離胺酸置換的異源 FIX Gla 域。因此，使用對應於成熟野生型 FIX 多肽或 SEQ ID NO: 83 中所闡明的野生型 FIX Gla 域的胺基酸位置之胺基酸位置提及對異源 FIX Gla 域部分進行之修飾。使用對應於如 SEQ ID NO:3 中所闡明之成熟 FVII 多肽的胺基酸位置之胺基酸位置提及對 FVII 多肽中之胺基酸位置進行的修飾，且其亦根據胰凝乳蛋白酶編號方案加以提及。舉例而言，由{Gla 交換 FIX/M19K}/Q286R 表示含有 Q286R 修飾(編號對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽)及 Gla 交換 FIX 修飾(其中 FIX Gla 域含有 M19K 胺基酸取代(編號對應 SEQ ID NO: 83 中所闡明的 FIX Gla 域之胺基酸位置))的經修飾之 FVII 多肽。類似地，修飾{Gla 交換 FIX/Q44S}/Q286R/M298Q 表示 FVII 多肽含有 Gla 交換 FIX 修飾，其中對應於 SEQ ID NO: 83 中所闡明的 FIX Gla 域之胺基酸位置 44 的胺基酸位置之麩胺醯胺經絲胺酸置換，且亦含有 Q286R 及 M298Q 胺基酸取代，其中編號對應於 SEQ ID NO: 3 中所闡明的成熟 FVII 多肽。在下表 12 中，鑑別闡明經修飾之 FVII 多肽的例示性胺基酸序列之序列識別符(SEQ ID NO)。

表 12

修飾-成熟 PVII 編號	修飾-胰凝乳蛋白酶編號	SEQ ID NO
Q286R/Gla 交換 FIX	Q143R/Gla 交換 FIX	131
Q286R/H257A	Q143R/H117A	132
Q286R/S222A	Q143R/S82A	133
Q286R/S222A/H257A	Q143R/S82A/H117A	134
Q286R/S222A/Gla 交換 FIX	Q143R/S82A/Gla 交換 FIX	135
Q286R/H257A/Gla 交換 FIX	Q143R/H117A/Gla 交換 FIX	136
Q286R/S222A/H257A/Gla 交換 FIX	Q143R/S82A/H117A/Gla 交換 FIX	137

Q286R/M298Q	Q143R/M156Q	138
Q286R/M298Q/K341Q	Q143R/M156Q/K192Q	139
Q286R/M298Q/K199E	Q143R/M156Q/K60cE	140
Q286R/M298Q/Gla 交換 FIX	Q143R/M156Q/Gla 交換 FIX	141
Q286R/Q366V	Q143R/Q217V	142
Q286R/A292N/A294S/Q366V	Q143R/A150N/A152S/Q217V	143
A175S/Q286R/Q366V	A39S/Q143R/Q217V	144
S222A/Q286R/Q366V	S82A/Q143R/Q217V	145
H257S/Q286R	H117S/Q143R	146
H257S/Q286R/Q366V	H117S/Q143R/Q217V	147
S222A/H257A/Q286R/Q366V	S82A/H117A/Q143R/Q217V	148
Q286R/H373A	Q143R/H224A	149
S222A/H257A/Q286R/M298Q	S82A/H117A/Q143R/M156Q	150
Q286R/K341D	Q143R/K192D	151
Q286R/Q366D	Q143R/Q217D	152
Q286R/Q366N	Q143R/Q217N	153
Q286R/M298Q/Q366D	Q143R/M156Q/Q217D	154
Q286R/M298Q/Q366N	Q143R/M156Q/Q217N	155
Q286R/H373F	Q143R/H224F	156
Q286R/M298Q/H373F	Q143R/M156Q/H224F	157
S222A/Gla 交換 FIX	S82A/ Gla 交換 FIX	245
H257A/ Gla 交換 FIX	H117A/ Gla 交換 FIX	246
S222A/H257A/ Gla 交換 FIX	S82A/H117A/ Gla 交換 FIX	247
S222A/M298Q	S82A/M156Q	248
H257A/M298Q	H117A/M156Q	249
S222A/H257A/M298Q	S82A/H117A/M156Q	250
S222A/A292N/A294S/Q366V	S82A/A150N/A152S/Q217V	251
A175S/S222A/Q366V	A39S/S82A/Q217V	252
S222A/Q366V	S82A/Q217V	253
H257S/Q366V	H117S/Q217V	254
S222A/H373A	S82A/H224A	255
V158T/L287T/M298K	V21T/L144T/M156K	256
V158D/L287T/M298K	V21D/L144T/M156K	257
S103S111 缺失插入 IEDICLPRWGCLWE/G237V	S[103]S[111]缺失插入 IEDICLPRWGCLWE/G97V	258
S103S111 缺失插入 DICLPRWGCLWED/G237V	S[103]S[111]缺失插入 DICLPRWGCLWED/G97V	259
H115S126 缺失插入 QRLMEDICLPRWGCLWEDDF/G237V	H[115]S[126]缺失插入 QRLMEDICLPRWGCLWEDDF/G97V	260
H115S126 缺失插入 IEDICLPRWGCLWE/G237V	H[115]S[126]缺失插入 IEDICLPRWGCLWE/G97V	261
H115S126 缺失插入 DICLPRWGCLWED/G237V	H[115]S[126]缺失插入 DICLPRWGCLWED/G97V	262
T128P134 缺失插入 QRLMEDICLPRWGCLWEDDF/G237V	T[128]P[134]缺失插入 QRLMEDICLPRWGCLWEDDF/G97V	263
T128P134 缺失插入 IEDICLPRWGCLWE/G237V	T[128]P[134]缺失插入 IEDICLPRWGCLWE/G97V	264
S103S111 缺失插入 QRLMEDICLPRWGCLWEDDF/G237V	S[103]S[111]缺失插入 QRLMEDICLPRWGCLWEDDF/G97V	265
T128P134 缺失插入 DICLPRWGCLWED/G237V	T[128]P[134]DICLPRWGCLWED/G97V	266
S103S111 缺失插入 SFGRGDIRNV/G237V	S[103]S[111]缺失插入 SFGRGDIRNV/G97V	267
H115S126 缺失插入 SFGRGDIRNV/G237V	H[115]S[126]缺失插入 SFGRGDIRNV/G97V	268

T128P134 缺失插入 SFGRGDIRNV/G237V	T[128]P[134]缺失插入 SFGRGDIRNV/G97V	269
M298Q/H373F	M156Q/H224F	270
S119N/L121S/A175S	S[119]N/L[121]S/A39S	271
T128N/P129A/A175S	T[128]N/P[129]A/A39S	272
A122N/G124S/A175S	A[122]N/G[124]S/A39S	273
{Gla 交換 FIX /E40L}/Q286R/M298Q	{Gla 交換 FIX /E[40]L}/Q143R/M156Q	274
{Gla 交換 FIX /K43I}/Q286R/M298Q	{Gla 交換 FIX /K[43]I}/Q143R/M156Q	275
{Gla 交換 FIX /Q44S}/Q286R/M298Q	{Gla 交換 FIX /Q[44]S}/Q143R/M156Q	276
{Gla 交換 FIX /M19K}/Q286R/M298Q	{Gla 交換 FIX /M[19]K}/Q143R/M156Q	277
{Gla 交換 FIX /M19K/E40L/K43I/Q44S}/Q286R/M298Q	{Gla 交換 FIX/M[19]K/E[40]L/K[43]I/Q[44]S}/ Q143R/ M156Q	278
T128N/P129A/Q286R	T[128]N/P[129]A/Q143R	279
T128N/P129A/Q286R/M298Q	T[128]N/P[129]A/Q143R/M156Q	280
T128N/P129A/Q286R/H373F	T[128]N/P[129]A/Q143R/H224F	281
V158D/Q286R/E296V/M298Q	V21D/Q143R/E154V/M156Q	282
T128N/P129A/V158D/E296V/M298Q	T[128]N/P[129]A/V21D/E154V/M156Q	283
T128N/P129A/S222A	T[128]N/P[129]A/S82A	284
Gla 交換 FIX/T128N/P129A/S222A/Q286R	Gla 交換 FIX/T[128]N/P[129]A/S82A/Q143R	285
Gla 交換 FIX/T128N/P129A/Q286R/M298Q	Gla 交換 FIX/T[128]N/P[129]A/Q143R/M156Q	286
T128N/P129A/S222A/H257A/Q286R/M298Q	T[128]N/P[129]A/S82A/H117A/Q143R/M156Q	287
T128N/P129A/Q286R/M298Q/H373F	T[128]N/P[129]A/Q143R/M156Q/H224F	288
S52A/S60A/V158D/E296V/M298Q	S[52]A/S[60]A/V21D/E154V/M156Q	289
S52A/S60A/Q286R	S[52]A/S[60]A/Q143R	290
S52A/S60A/S222A	S[52]A/S[60]A/S82A	291
Gla 交換 FIX/S52A/S60A/S222A/Q286R	Gla 交換 FIX/S[52]A/S[60]A/S82A/Q143R	292
S52A/S60A/Q286R/M298Q	S[52]A/S[60]A/Q143R/M156Q	293
Gla 交換 FIX/S52A/S60A/Q286R/M298Q	Gla 交換 FIX/S[52]A/S[60]A/Q143R/M156Q	294
S52A/S60A/S222A/H257A/Q286R/M298Q	S[52]A/S[60]A/S82A/H117A/Q143R/ M156Q	298
S52A/S60A/Q286R/H373F	S[52]A/S[60]A/Q143R/H224F	296
S52A/S60A/Q286R/M298Q/H373F	S[52]A/S[60]A/Q143R/M156Q/H224F	297
V158D/T239V/E296V/M298Q	V21D/T99V/E154V/M156Q	298
T239V/Q286R	T99V/Q143R	299
S222A/T239V	S82A/T99V	300
Gla 交換 FIX /S222A/T239V/Q286R	Gla 交換 FIX /S82A/T99V/Q143R	301
T239V/Q286R/M298Q	T99V/Q143R/M156Q	302
S222A/T239V/H257A/Q286R/M298Q	S82A/T99V/H117A/Q143R/M156Q	303
Gla 交換 FIX/T239V/Q286R/M298Q	Gla 交換 FIX/T99V/Q143R/M156Q	304
T239V/Q286R/H373F	T99V/Q143R/H224F	305
T239V/Q286R/M298Q/H373F	T99V/Q143R/M156Q/H224F	306
V158D/T239I/E296V/M298Q	V21D/T99I/E154V/M156Q	307
T239I/Q286R	T99I/Q143R	308
S222A/T239I	S82A/T99I	309

Gla 交換 FIX/S222A/T239I/Q286R	Gla 交換 FIX/S82A/T99I/Q143R	310
T239I/Q286R/M298Q	T99I/Q143R/M156Q	311
S222A/T239I/H257A/Q286R/M298Q	S82A/T99I/H117A/Q143R/M156Q	312
Gla 交換 FIX/T239I/Q286R/M298Q	Gla 交換 FIX/T99I/Q143R/M156Q	313
T239I/Q286R/H373F	T99I/Q143R/H224F	314
T239I/Q286R/M298Q/H373F	T99I/Q143R/M156Q/H224F	315
Gla 交換 FIX/S222A/Q286R/H373F	Gla 交換 FIX/S82A/Q143R/H224F	316
Gla 交換 FIX/S222A/Q286R/M298Q	Gla 交換 FIX/S82A/Q143R/M156Q	317
Gla 交換 FIX/S222A/Q286R/M298Q/H373F	Gla 交換 FIX/S82A/Q143R/M156Q/H224F	318
V158D/E296V/M298Q/H373F	V21D/E154V/M156Q/H224F	319
V158D/Q286R/E296V/M298Q/H373F	V21D/Q143R/E154V/M156Q/H224F	320
H257A/Q286R/M298Q	H117A/Q143R/M156Q	321
H257S/Q286R/M298Q	H117S/Q143R/M156Q	322
Gla 交換 FIX/S222A/H257S/Q286R/	Gla 交換 FIX/S82A/H117S/Q143R	323
S222A/H257S/Q286R/M298Q	S82A/H117S/Q143R/M156Q	324
H257S/Q286R/M298Q/H373F	H117S/Q143R/M156Q/H224F	325
S222A/Q286R/M298Q/H373F	S82A/Q143R/M156Q/H224F	326
Gla 交換 FIX/Q366V	Gla 交換 FIX/Q217V	327
S222A/Q286R/M298Q	S82A/Q143R/M156Q	328
T128N/P129A/A175S/Q366V	T[128]N/P[129]A/A39S/Q217V	329
A122N/G124S/A175S/Q366V	A[122]N/G[124]S/A39S/Q217V	330
T128N/P129A/A175S/S222A	T[128]N/P[129]A/A39S/S82A	331
A122N/G124S/A175S/S222A	A[122]N/G[124]S/A39S/S82A	332
T128N/P129A/A175S/Q286R	T[128]N/P[129]A/A39S/Q143R	333
A122N/G124S/A175S/Q286R	A[122]N/G[124]S/A39S/Q143R	334
Gla 交換 FIX/T128N/P129A/A175S/S222A/Q286R	Gla 交換 FIX/T[128]N/P[129]A/A39S/S82A/Q143R	335
Gla 交換 FIX/A122N/G124S/A175S/S222A/Q286R	Gla 交換 FIX/A[122]N/G[124]S/A39S/S82A/Q143R	336
T128N/P129A/A175S/Q286R/M298Q	T[128]N/P[129]A/A39S/Q143R/M156Q	337
A122N/G124S/A175S/Q286R/M298Q	A[122]N/G[124]S/A39S/Q143R/M156Q	338
T128N/P129A/A175S/S222A/H257A/Q286R/M298Q	T[128]N/P[129]A/A39S/S82A/H117A/Q143R/M156Q	339
A122N/G124S/A175S/S222A/H257A/Q286R/M298Q	A[122]N/G[124]S/A39S/S82A/H117A/Q143R/M156Q	340
T128N/P129A/A175S/Q286R/M298Q/H373F	T[128]N/P[129]A/A39S/Q143R/M156Q/H224F	341
A122N/G124S/A175S/Q286R/M298Q/H373F	A[122]N/G[124]S/A39S/Q143R/M156Q/H224F	342
T128N/P129A/M298Q	T[128]N/P[129]A/M156Q	354
{Gla 交換 FIX /K43I}/T128N/P129A/Q286R/M298Q	{Gla 交換 FIX /K[43]I}/ T[128]N/P[129]A/Q143R/M156Q	355
T128N/P129A/Q286R/M298Q/Q366N	T[128]N/P[129]A/Q143R/M156Q/Q217N	356
{Gla 交換 FIX /K43I}/Q286R/M298Q/Q366N	{Gla 交換 FIX /K[43]I}/Q143R/M156QQ217N	357
{Gla 交換 FIX /K43I}/ T128N/P129A/Q286R/M298Q/Q366N	{Gla 交換 FIX /K[43]I}/ T[128]N/P[129]A/Q143R/M156QQ217N	358
T128N/P129A/M298Q/H373F	T[128]N/P[129]A/M156Q/H224F	359
V158D/Q286R/E296V/M298Q	V21D/Q143R/E154V/M156Q	360
M298Q/Q366N/H373F	M156Q/Q217N/H224F	361

T239V/M298Q/H373F	T99V/M156Q/H224F	362
T239I/M298Q/H373F	T99I/M156Q/H224F	363
T128N/P129A/Q286R/M298Q/Q366N/H373F	T[128]N/P[129]A/Q143R/M156Q/Q217N/H224F	364
T239V/Q286R/M298Q/Q366N	T99V/Q143R/M156Q/Q217N	365
T239I/Q286R/M298Q/Q366N	T99I/Q143R/M156Q/Q217N	366
T128N/P129A/T239V/Q286R/M298Q	T[128]N/P[129]A/T99V/Q143R/M156Q	367
T128N/P129A/S222A/T239V/H257A/Q286R/M298Q	T[128]N/P[129]A/S82A/T99V/H117A/Q143R/M156Q	368
T128N/P129A/T239V/Q286R/M298Q/H373F	T[128]N/P[129]A/T99V/Q143R/M156Q/H224F	369
T128N/P129A/T239I/Q286R/M298Q	T[128]N/P[129]A/T99I/Q143R/M156Q	370
T128N/P129A/T239I/Q286R/M298Q/H373F	T[128]N/P[129]A/T99I/Q143R/M156Q/H224F	371

E. FVII 多肽之產生

可藉由在此項技術中熟知用於蛋白質純化及重組蛋白質表現之方法獲得 FVII 多肽，包括經修飾之 FVII 多肽或 FVII 或其他維生素 K 多肽的域。可使用熟習此項技術者已知用於鑑別編碼所需基因的核酸之任何方法。可使用在此項技術中可用之任何方法諸如自細胞或組織來源（諸如自肝臟）獲得編碼 FVII 多肽或其他維生素 K 多肽之全長（亦即涵蓋整個編碼區域）cDNA 或基因組 DNA 純系。可如本文所述，諸如藉由定點誘變工程化經修飾之 FVII 多肽。

可使用在此項技術中已知用於選殖及分離核酸分子之任何可用方法來選殖或分離 FVII。該等方法包括 PCR 擴增核酸及篩選文庫，包括核酸雜交篩選、抗體基篩選及活性基篩選。

可使用用於擴增核酸之方法來分離編碼 FVII 多肽的核酸分子，包括例如聚合酶鏈反應（polymerase chain reaction，PCR）方法。可使用含有核酸的材料作為分離 FVII

編碼核酸分子之起始物質。舉例而言，DNA 及 mRNA 製劑、細胞萃取物、組織萃取物（例如自肝臟）、流體樣品（例如血液、血清、唾液）、來自健康及/或患病個體的樣品可用於擴增方法。亦可使用核酸文庫作為起始物質之來源。引子可經設計以擴增 FVII 編碼分子。舉例而言，可基於產生 FVII 的表現序列來設計引子。可基於 FVII 胺基酸序列之反向轉譯來設計引子。藉由擴增產生之核酸分子可經定序且證實編碼 FVII 多肽。

出於將合成基因選殖於載體中之目的，該載體例如蛋白質表現載體或經設計以供擴增編碼核心蛋白質之 DNA 序列的載體，可將其他核苷酸序列與 FVII 編碼核酸分子聯接，包括含有限制性內切酶位點之連接子序列。此外，可將指定功能性 DNA 元件之其他核苷酸序列與 FVII 編碼核酸分子操作性連接。該等序列之實例包括（但不限於）經設計以促進細胞內蛋白質表現之啟動子序列及經設計以促進蛋白質分泌之分泌序列。亦可將諸如指定蛋白結合區域的序列之其他核苷酸序列與 FVII 編碼核酸分子連接。該等區域包括（但不限於）促進 FVII 吸收至特定目標細胞中或者以其他方式增強合成基因之藥物動力學之序列。

可隨後將經鑑別且經分離之核酸插入適當選殖載體中。可使用在此項技術中已知之大量載體-宿主系統。可能的載體包括（但不限於）質體或經修飾之病毒，但載體系統必須與所用宿主細胞相容。該等載體包括（但不限於）諸如 λ 衍生物之噬菌體或諸如 pBR322 或 pUC 質體衍生物

的質體或 Bluescript 載體（Stratagene, La Jolla, CA）。例如可藉由將 DNA 片段連接於具有互補黏性末端的選殖載體中實現於選殖載體中的插入。可使用 TOPO 選殖載體（Invitrogen, Carlsbad, CA）實現插入。若用以分割 DNA 之互補限制性位點並不存在於選殖載體中，則可酶促修飾 DNA 分子之末端。或者，可藉由將核苷酸序列（連接子）連接於 DNA 末端上來產生所需的任何位點；此等經連接之連接子可含有化學合成之編碼限制性內切酶識別序列的特定寡核苷酸。在一替代性方法中，可藉由均聚加尾反應修飾經裂解之載體及 FVII 蛋白質基因。可經由例如轉型、轉染、感染、電穿孔及聲致穿孔將重組分子引入宿主細胞中，以便產生基因序列之許多複本。

在特定具體實例中，用併有經分離 FVII 蛋白質基因、cDNA 或合成 DNA 序列之重組 DNA 分子轉型宿主細胞能夠產生多個基因複本。因此，可藉由使轉型子生長、自轉型子分離重組 DNA 分子且必要時自所分離重組 DNA 回收所插入之基因來大量地獲得基因。

1. 載體及細胞

對於一或多種 FVII 蛋白之重組表現而言，可將含有編碼 FVII 蛋白之核苷酸序列的全部或一部分之核酸插入適當表現載體中，亦即含有轉錄及轉譯所插入蛋白質編碼序列之必要元件之載體。該載體之實例為任何哺乳動物表現載體，諸如 pCMV。必要轉錄及轉譯信號亦可由 FVII 基因之原生啟動子及/或其側接區域提供。

亦提供含有編碼 FVII 或經修飾之 FVII 的核酸之載體。亦提供含有載體之細胞。該等細胞包括真核及原核細胞，且載體為任何適用於其中之載體。

提供包括內皮細胞之含有載體的原核及真核細胞。該等細胞包括細菌細胞、酵母菌細胞、真菌細胞、古細菌細菌、植物細胞、昆蟲細胞及動物細胞。該等細胞藉由使上述細胞在所編碼 FVII 蛋白由細胞表現之條件下生長且回收所表現 FVII 蛋白來用以產生 FVII 多肽或經修飾之 FVII 多肽。出於本文之目的，FVII 可分泌於培養基中。

在一具體實例中，提供含有編碼具有 FVII 活性且含有 FVII 多肽之全部或一部分之多肽的核苷酸之序列或其多個複本之載體。載體可經選擇用於在細胞中表現 FVII 多肽或其經修飾之 FVII 多肽或使得 FVII 蛋白以分泌蛋白質形式表現。當表現 FVII 時，將核酸連接至編碼諸如釀酒酵母菌（*Saccharomyces cerevisiae*）α-配合因子信號序列或其部分或原生信號序列的分泌信號之核酸。

可使用多種宿主-載體系統表現蛋白質編碼序列。此等系統包括（但不限於）經病毒（例如痘瘡病毒、腺病毒及其他病毒）感染之哺乳動物細胞系統；經病毒（例如桿狀病毒）感染之昆蟲細胞系統；微生物，諸如含有酵母菌載體之酵母菌；或經噬菌體、DNA、質體 DNA 或黏質體 DNA 轉型之細菌。載體之表現元件的強度及特異性可變。視所用宿主-載體系統而定，可使用許多適當轉錄及轉譯元件中之任一者。

可使用熟習此項技術者已知用於將DNA片段插入載體中的任何方法來構築含有包含適當轉錄/轉譯控制信號及蛋白質編碼序列的嵌合基因之表現載體。此等方法可包括試管內重組DNA及合成技術及活體內重組（遺傳重組）。可由第二核酸序列調節編碼FVII多肽或經修飾之FVII多肽或其域、衍生物、片段或同源物之核酸序列的表現，以便基因或其片段表現於經重組DNA分子轉型之宿主中。舉例而言，可藉由在此項技術中已知之任何啟動子/強化子控制蛋白質之表現。在一特定具體實例中，啟動子不為FVII蛋白之基因的原生啟動子。可使用之啟動子包括（但不限於）SV40早期啟動子(Bernoist及Chambon, *Nature 290*:304-310 (1981))、含於勞氏肉瘤病毒（Rous sarcoma virus）之3'長末端重複中的啟動子（Yamamoto 等人 *Cell 22*:787-797 (1980))、疱疹胸苷激酶啟動子（Wagner 等人, *Proc. Natl. Acad. Sci. USA 78*:1441-1445 (1981))、金屬硫蛋白基因之調節序列（Brinster 等人, *Nature 296*:39-42 (1982)）；原核表現載體，諸如β-內醯胺酶啟動子（Jay 等人, (1981) *Proc. Natl. Acad. Sci. USA 78*:5543）或tac啟動子（DeBoer 等人, *Proc. Natl. Acad. Sci. USA 80*:21-25 (1983)）；亦參見「Useful Proteins from Recombinant Bacteria」：於Scientific American *242*:79-94 (1980)中）；含有胭脂鹼合成酶啟動子之植物表現載體（Herrar-Estrella 等人, *Nature 303*:209-213 (1984)或花椰菜花葉病毒 35S RNA 啟動子（Garder 等人, *Nucleic Acids Res. 9*:2871 (1981))，及光合

成酶二磷酸核酮糖羧化酶之啟動子（Herrera-Estrella 等人，*Nature 310*:115-120 (1984)）；來自酵母菌及其他真菌之啟動子元件，諸如 Gal4 啟動子、乙醇脫氫酶啟動子、磷酸甘油激酶啟動子、鹼性磷酸酶啟動子及展現組織特異性且已用於轉殖基因動物中之下列動物轉錄控制區域：在胰腺腺泡細胞中具有活性之彈性蛋白酶 I 基因控制區域（Swift 等人，*Cell 38*:639-646 (1984)；Ornitz 等人，*Cold Spring Harbor Symp. Quant. Biol. 50*:399-409 (1986)；MacDonald, *Hepatology 7*:425-515 (1987)），在胰腺 β 細胞中具有活性之胰島素基因控制區域（Hanahan 等人，*Nature 315*:115-122 (1985)），在淋巴樣細胞中具有活性之免疫球蛋白基因控制區域（Grosschedl 等人，*Cell 38*:647-658 (1984)；Adams 等人，*Nature 318*:533-538 (1985)；Alexander 等人，*Mol. Cell Biol. 7*:1436-1444 (1987)），在睾丸、乳房、淋巴及肥大細胞中具有活性之小鼠乳腺瘤病毒控制區域（Leder 等人，*Cell 45*:485-495 (1986)），在肝臟中具有活性之白蛋白基因控制區域（Pinckert 等人，*Genes and Devel. 1*:268-276 (1987)），在肝臟中具有活性之 α-胎蛋白基因控制區域（Krumlauf 等人，*Mol. Cell. Biol. 5*:1639-1648 (1985)；Hammer 等人，*Science 235*:53-58 1987)），在肝臟中具有活性之 α-1 抗胰蛋白酶基因控制區域（Kelsey 等人，*Genes and Devel. 1*:161-171 (1987)），在骨髓細胞中具有活性之 β 珠蛋白基因控制區域（Mogram 等人，*Nature 315*:338-340 (1985)；Kollias 等人，*Cell 46*:89-94 (1986)），在腦之寡樹突神經膠

質細胞中具有活性之髓磷脂鹼性蛋白基因控制區域（Readhead 等人, *Cell 48*:703-712 (1987)），在骨骼肌中具有活性之肌凝蛋白輕鏈-2 基因控制區域（Shani, *Nature 314*:283-286 (1985)）及在下丘腦之促性腺激素細胞中具有活性之促性腺釋放激素基因控制區域（Mason 等人, *Science 234*:1372-1378 (1986)）。

在一特定具體實例中，使用含有與編碼 FVII 多肽或經修飾之 FVII 多肽、或其域、片段、衍生物或同源物之核酸操作連接的啟動子、一或多個複製起點及視情況一或多個可選擇性標誌（例如抗生素抗性基因）之載體。用於表現 FVII 多肽之載體及系統包括熟知畢赤酵母菌（*Pichia*）載體（例如，可獲自 Invitrogen, San Diego, CA），尤其彼等經設計用於分泌所編碼蛋白質者。用於在哺乳動物細胞中表現之例示性質體載體包括例如 pCMV。用於轉型大腸桿菌（*E.coli*）細胞之例示性質體載體包括例如 pQE 表現載體（可獲自 Qiagen, Valencia, CA；亦參見由 Qiagen 出版描述該系統之文獻）。pQE 載體具有噬菌體 T5 啟動子（由大腸桿菌 RNA 聚合酶識別）及雙重 lac 操縱子阻遏模組以在大腸桿菌中提供重組蛋白質之緊密調節高水準表現、用於有效轉譯的合成核糖體結合位點（RBS II）、6×His 標籤編碼序列、t_0 及 T1 轉錄終止子、ColE1 複製起點及賦予胺苄青黴素（ampicillin）抗性之 β-內醯胺酶基因。pQE 載體能夠將 6×His 標籤放置在重組蛋白質之 N 或 C 末端。該等質體包括 pQE 32、pQE 30 及 pQE 31，其為所有三個閱讀框架提

供多個選殖位點且提供經 N 末端 6×His 標記之蛋白質的表現。用於轉型大腸桿菌細胞之其他例示性質體載體包括 pET 表現載體（參見美國專利 4,952,496；可獲自 NOVAGEN, Madison, WI；亦參見由 Novagen 出版描述該系統之文獻）。該等質體包括 pET 11a，其含有 T7lac 啟動子、T7 終止子、誘導型大腸桿菌 lac 操縱子及 lac 阻遏蛋白基因；pET 12a-c，其含有 T7 啟動子、T7 終止子及大腸桿菌 ompT 分泌信號；及 pET 15b 及 pET19b(NOVAGEN, Madison, WI)，其含有用於以 His 管柱純化之 His-Tag™ 前導序列及允許經管柱純化後裂解之凝血酶裂解位點、T7-lac 啟動子區及 T7 終止子。

2. 表現系統

可藉由在此項技術中已知用於蛋白質產生之任何方法產生 FVII 多肽（經修飾及未經修飾），該等方法包括試管內及活體內方法，諸如將編碼 FVII 之核酸分子引入宿主細胞、宿主動物中且自編碼 FVII 之核酸分子試管內表現。可在任何適於產生投藥及治療所需的所需量及形式之 FVII 多肽之生物體中表現 FVII 及經修飾之 FVII 多肽。表現宿主包括原核及真核生物體，諸如大腸桿菌、酵母菌、植物、昆蟲細胞、哺乳動物細胞，包括人類細胞系及轉殖基因動物。表現宿主之蛋白質產生量以及所表現蛋白上存在的轉譯後修飾類型可不同。可基於此等及其他因素，諸如管理及安全性考慮、生產成本及純化之需要及方法進行表現宿主之選擇。

真核宿主中之表現可包括在諸如釀酒酵母菌及巴斯德畢赤酵母菌（*Pichia pastoria*）的酵母菌，諸如果蠅（*Drosophila*）細胞及鱗翅目（*lepidopteran*）細胞的昆蟲細胞，諸如煙草、玉米、稻穀、藻類及浮萍屬的植物及植物細胞中之表現。用於表現之真核細胞亦包括哺乳動物細胞系，諸如中國倉鼠卵巢（Chinese hamster ovary，CHO）細胞或幼小倉鼠腎臟（baby hamster kidney，BHK）細胞。真核表現宿主亦包括在轉殖基因動物中產生，例如包括在血清、乳汁及卵中產生。在此項技術中已知用於產生野生型FVII多肽之轉殖基因動物(美國專利公開案第20020166130號及第20040133930號）且其可適合於產生本文中提供之經修飾之FVII多肽。

熟習此項技術者可用且已知許多用於表現FVII之表現載體。表現載體之選擇受宿主表現系統之選擇影響。該選擇充分處於熟習此項技術者之技能範圍內。通常，表現載體可包括轉錄啟動子及視情況強化子、轉譯信號及轉錄及轉譯終止信號。用於穩定轉型之表現載體典型地具有可選擇性標誌，其允許選擇及維持經轉型細胞。在一些情況下，可使用複製起點在細胞中擴增載體之複本數。

FVII或經修飾之FVII多肽亦可以蛋白質融合體形式使用或表現。舉例而言，可產生融合體以將其他功能性添加至多肽。融合蛋白質之實例包括（但不限於）信號序列、諸如用於定位之標籤（例如 his_6 標籤或 myc 標籤）或用於純化之標籤之融合體，例如 GST 融合體，及用於引導蛋白

質分泌及/或膜結合之序列。

在一具體實例中，FVII 多肽或經修飾之 FVII 多肽可以活性形式表現，藉此在分泌後藉由多肽之自體活化實現活化。在另一具體實例中，蛋白酶以無活性酶原形式表現。

FVII 多肽之產生方法可包括共表現可幫助產生 FVII 多肽之一或多種其他異源多肽。舉例而言，該等多肽可促進 FVII 多肽之轉譯後加工。例示性多肽包括（但不限於）幫助裂解諸如前肽序列的 FVII 前驅體序列之肽酶，及諸如藉由例如糖苷化、羥基化、羧基化或磷酸化參與 FVII 多肽之修飾的酶。可與 FVII 一起共表現之一例示性肽酶為 PACE/弗林蛋白酶（或 PACE-SOL），其幫助裂解 FVII 前肽序列。幫助 FVII 多肽羧基化之一例示性蛋白質為華法林（warfarin）敏感性酶維生素 K 2,3-環氧化物還原酶（VKOR），其對於作為輔因子由維生素 K 依賴性 γ 羧化酶利用而言產生減少之維生素 K（Wajih 等人, *J. Biol. Chem.* 280(36)31603-31607）。此酶之亞單元 VKORC1 可與經修飾之 FVII 多肽一起共表現以增加 γ-羧基化。可自與 FVII 多肽相同的表現載體或自不同載體表現該一或多種其他多肽。

a. 原核表現

原核生物，尤其大腸桿菌，提供用於產生大量 FVII 之系統(參見例如 Platis 等人 (2003) Protein Exp. Purif. 31(2): 222-30；及 Khalilzadeh 等人 (2004) J. Ind. Microbiol. Biotechnol. 31(2): 63-69）。大腸桿菌之轉型為熟習此項技

術者所熟知之簡單且快速之技術。大腸桿菌之表現載體可含有誘導型啟動子，其適用於誘導高含量之蛋白質表現且適用於表現對宿主細胞展現某些毒性之蛋白質。誘導型啟動子之實例包括 lac 啟動子、trp 啟動子、雜交 tac 啟動子、T7 及 SP6 RNA 啟動子及溫度調節 λ P_L 啟動子。

FVII 可表現於大腸桿菌之細胞質環境中。細胞質為還原環境且對於某些分子，此可引起不溶性包涵體之形成。可使用諸如二硫蘇糖醇及 β-巯基乙醇之還原劑及變性劑（例如胍 HCl 鹽及脲）使蛋白質再溶解。一替代方法為在提供氧化環境及使得產生可溶性蛋白質之伴侶蛋白（chaperonin）樣及雙硫異構酶的細菌之細胞周質間隙中表現 FVII。典型地，將引導蛋白質至細胞周質之前導序列與待表現蛋白質融合。該前導序列接著由細胞周質中之信號肽酶移除。靶向細胞周質之前導序列之實例包括來自果膠酸裂合酶基因之 pelB 前導序列及來源於鹼性磷酸酶基因之前導序列。在一些情況下，細胞周質表現允許使所表現蛋白質洩漏於培養基中。蛋白質之分泌允許自培養上清液迅速且簡單的純化。可藉由滲透溶解自細胞周質獲得未分泌之蛋白質。類似於細胞質表現，在一些情況下，蛋白質可變得不溶，且可使用變性劑及還原劑促進溶解及再摺疊。誘導及生長之溫度亦可影響表現量及溶解性。典型地，使用 25℃ 與 37℃ 之間的溫度。亦可使用突變來增加所表現蛋白質之溶解性。典型地，細菌產生糖苷化蛋白質。因此，若蛋白質之功能要求糖苷化，則可在自宿主細胞純化後試

管內添加糖苷化。

b. 酵母菌

諸如釀酒酵母菌、粟酒裂殖酵母菌（*Schizosaccharomyces pombe*）、解脂耶氏酵母菌（*Yarrowia lipolytica*）、乳酸刻魯維酵母菌（*Kluyveromyces lactis*）及巴斯德畢赤酵母菌（*Pichia pastoris*）之酵母菌對於 FVII 而言為適用表現宿主（參見例如，Skoko 等人 (2003) Biotechnol. Appl. Biochem. 38(Pt3):257-65）。可以游離型複製載體或藉由同源重組穩定染色體整合將酵母菌轉型。典型地，使用誘導型啟動子來調節基因表現。該等啟動子之實例包括 GAL1、GAL7 及 GAL5 及諸如 CUP1 之金屬硫蛋白啟動子。表現載體通常包括可選擇性標誌，諸如 LEU2、TRP1、HIS3 及 URA3，以供選擇且維持經轉型 DNA。酵母菌中表現之蛋白質通常可溶且與諸如 Bip 的伴侶蛋白及蛋白質雙硫異構酶之共表現可提高表現量及溶解性。另外，可使用諸如來自釀酒酵母菌的酵母菌配合型 α 因子分泌信號之分泌信號肽融合體及與諸如 Aga2p 配合黏附受體或黑麴黴（*Arxula adeninivorans*）葡糖澱粉酶之酵母菌細胞表面蛋白質之融合體引導酵母菌中表現之蛋白質分泌。蛋白酶裂解位點（例如 Kex-2 蛋白酶）可經工程化以當多肽脫離分泌途徑時，自該多肽移除所融合之序列。酵母菌亦能夠在 Asn-X-Ser/Thr 基元進行糖苷化。

c. 昆蟲及昆蟲細胞

昆蟲及昆蟲細胞（尤其使用桿狀病毒表現系統）適用

於表現諸如 FVII 或其修飾形式之多肽（參見例如 Muneta 等人 (2003) J. Vet. Med. Sci. 65(2):219-23）。昆蟲細胞及昆蟲幼蟲（包括在血淋巴中之表現）表現高含量之蛋白質且能夠進行較高等真核生物使用之大多數轉譯後修飾。桿狀病毒具有限制性宿主範圍，其提高真核表現之安全性且降低管理問題。典型地，表現載體使用諸如桿狀病毒之多角體蛋白（polyhedrin）啟動子之啟動子用於高含量表現。常用桿狀病毒系統包括桿狀病毒，諸如苜蓿銀紋夜蛾（*Autographa californica*）核型多角體病毒（AcNPV）及家蠶（*Bombyx mori*）核型多角體病毒（BmNPV），及昆蟲細胞株，諸如來源於草地黏蟲（*Spodoptera frugiperda*）、美洲黏蟲（*Pseudaletia unipuncta*）（A7S）及黑脈金斑蝶（*Danaus plexippus*）（DpN1）之 Sf9。對於高含量表現，將待表現分子之核苷酸序列直接融合於病毒之多角體蛋白起始密碼子的下游。哺乳動物分泌信號在昆蟲細胞中精確處理，且可用於將所表現蛋白質分泌於培養基中。另外，細胞系美洲黏蟲（A7S）及黑脈金斑蝶（DpN1）產生具有與哺乳動物細胞系統相似之糖苷化模式的蛋白質。

昆蟲細胞中之一替代表現系統係使用經穩定轉型之細胞。可使用諸如 Schnieder 2（S2）及 Kc 細胞（黑腹果蠅（*Drosophila melanogaster*））及 C7 細胞（白紋伊蚊（*Aedes albopictus*））之細胞系用於表現。可使用果蠅金屬硫蛋白啟動子在鎘或銅之重金屬誘導存在下誘導高含量表現。典型地藉由使用諸如新黴素（neomycin）及勻黴素

（hygromycin）之可選擇性標誌維持表現載體。

d. 哺乳動物細胞

可使用哺乳動物表現系統來表現 FVII 多肽。可藉由諸如腺病毒之病毒感染，或藉由諸如脂質體、磷酸鈣、DEAE-葡聚糖之直接 DNA 轉移，且藉由諸如電穿孔及顯微注射之物理手段，將表現構築體轉移至哺乳動物細胞中。哺乳動物細胞之表現載體典型地包括 mRNA 加帽位點、TATA 盒、轉譯起始序列（Kozak 一致序列）及聚腺嘌呤化元件。該等載體通常包括用於高含量表現之轉錄啟動子-強化子，例如 SV40 啟動子-強化子、人類細胞巨大病毒（CMV）啟動子及 Rous 肉瘤病毒（RSV）之長末端重複。此等啟動子-強化子在許多細胞類型中具有活性。亦可使用組織及細胞類型啟動子及強化子區域用於表現。例示性啟動子/強化子區域包括（但不限於）彼等來自諸如以下之基因者：彈性蛋白酶 I、胰島素、免疫球蛋白、小鼠乳腺瘤病毒、白蛋白、α-胎蛋白、α 1-抗胰蛋白酶、β-珠蛋白、髓磷脂鹼性蛋白、肌凝蛋白輕鏈-2，及促性腺激素釋放激素基因對照。可使用可選擇性標誌來選擇及維持具有表現構築體之細胞。可選擇性標誌基因之實例包括（但不限於）勻黴素 B 磷酸轉移酶、腺苷脫胺酶、黃嘌呤-鳥嘌呤磷酸核糖轉移酶、胺基糖苷磷酸轉移酶、二氫葉酸還原酶及胸苷激酶。與諸如 TCR-ζ 及 FcεRI-γ 的細胞表面信號分子之融合體可指引活性狀態之蛋白質表現於細胞表面上。

許多細胞系可用於哺乳動物表現，包括小鼠、大鼠、

人類、猴及雞及倉鼠細胞。例示性細胞系包括（但不限於）BHK（亦即 BHK-21 細胞）、293-F、CHO、Balb/3T3、HeLa、MT2、小鼠 NS0（非分泌）及其他骨髓瘤細胞系、融合瘤及雜交融合瘤細胞系、淋巴細胞、纖維母細胞、Sp2/0、COS、NIH3T3、HEK293、293S、293T、2B8 及 HKB 細胞。細胞系亦可適應於無血清培養基，該無血清培養基利於自細胞培養基純化所分泌蛋白質。一種該實例為無血清 EBNA-1 細胞系（Pham 等人，(2003) *Biotechnol. Bioeng.* 84:332-42）。在此項技術中已知展現與來源於血漿之 FVII 類似的結構及轉譯後修飾的重組 FVII 多肽之表現（參見例如 Jurlander 等人 (2003) Semin Throm Hemost）。已知優化維生素 K 依賴性蛋白質表現之方法。舉例而言，在培養基中補充維生素 K 或維生素 K 依賴性 γ-羧化酶之共表現（Wajih 等人, *J. Biol. Chem.* 280(36)31603-31607）可幫助諸如 FVII 多肽之維生素 K 依賴性蛋白質的轉譯後修飾。

e. 植物

可使用轉殖基因植物細胞及植物用於表現 FVII。典型地，使用諸如微粒轟擊之直接 DNA 轉移，及 PEG 介導轉移至原生質體中，及使用農桿菌介導之轉型將表現構築體轉移至植物中。表現載體可包括啟動子及強化子序列、轉錄終止元件及轉譯控制元件。表現載體及轉型技術通常在諸如芥菜屬（Arabidopsis）及煙草之雙子葉植物宿主與諸如玉米及稻穀的單子葉植物宿主之間不同。用於表現之植物啟動子的實例包括花椰菜花葉病毒啟動子、胭脂鹼合成酶啟

動子、核糖二磷酸羧化酶啟動子及泛素及 UBQ3 啟動子。通常使用諸如勻黴素、磷酸甘露糖異構酶及新黴素磷酸轉移酶之可選擇性標誌促進所轉型細胞的選擇及維持。經轉型植物細胞可以細胞、聚集體（愈傷組織）形式維持於培養物中或再生為完整植物。由於植物具有與哺乳動物細胞不同的糖苷化模式，因此此可影響在此等宿主中產生 FVII 之選擇。轉殖基因植物細胞亦可包括經工程化以產生蛋白質之藻類（參見例如 Mayfield 等人 (2003) PNAS 100:438-442）。由於植物具有與哺乳動物細胞不同的糖苷化模式，因此此可影響在此等宿主中產生 FVII 之選擇。

2. 純化

自宿主細胞純化 FVII 多肽之方法取決於所選宿主細胞及表現系統。對於分泌型分子，通常在移除細胞之後自培養基純化蛋白質。對於細胞內表現，可將細胞溶解且自萃取物純化蛋白質。當使用諸如轉殖基因植物及動物之轉殖基因生物體表現時，組織或器官可用作製備溶解細胞萃取物之起始物質。另外，轉殖基因動物產生可包括在乳汁或卵中產生多肽，其可收集且必要時可使用此項技術中之標準方法進一步提取及進一步純化蛋白質。

可使用在此項技術中已知之標準蛋白質純化技術純化 FVII，該等技術包括（但不限於）SDS-PAGE、尺寸分級分離及尺寸排阻層析法、硫酸銨沈澱、螯合層析及離子交換層析。舉例而言，可藉由陰離子交換層析純化 FVII 多肽。純化 FVII 多肽之例示性方法係使用允許具有功能性 Gla 域

的任何多肽結合，接著在鈣存在下溶離之離子交換柱（參見例如實施例 2）。亦可使用親和力純化技術來提高製備效率及製劑純度。舉例而言，可在親和力純化中使用結合 FVII 之抗體、受體及其他分子。在另一實例中，亦可使用可溶性 TF（sTF）親和力管柱增強純化（Maun 等人 (2005) Prot Sci 14:1171-1180）。表現構築體亦可經工程化以添加諸如 myc 抗原決定基、GST 融合體或 His_6 之親和標籤且分別以 myc 抗體、麩胱甘肽樹脂及 Ni 樹脂親和力純化為蛋白質。可藉由在此項技術中已知之包括凝膠電泳及染色及分光光度技術的任何方法評估純度。

FVII 蛋白酶可經表現且純化為無活性形式（酶原形式），或者所表現蛋白酶可諸如藉由自體催化而純化為活性形式。舉例而言，可試管內製備已經由蛋白水解裂解 Arg^{152}-Ile^{153} 而活化之 FVII 多肽（亦即 FVIIa，雙鏈形式）。可藉由本文所述之任何產生方法首先製備 FVII 多肽，該等方法包括（但不限於）在哺乳動物細胞中產生，接著純化。可藉由數種方式實現將 FVII 多肽裂解為活性蛋白酶形式 FVIIa。舉例而言，可在 45 分鐘內實現在鈣存在下與磷脂微脂粒一起培育期間的自體活化（Nelsestuen 等人 (2001) J Biol Chem 276:39825-31）。亦可在鈣存在下，存在或不存在磷脂之情況下，藉由與因子 Xa、因子 XIIa 或 TF 一起培育將 FVII 多肽活化至完成（參見例如實施例 2 及 Broze 等人 (1980) J Biol Chem 255:1242-1247; Higashi 等人 (1996) J Biol Chem 271:26569-26574；Harvey 等人 J Biol Chem

278:8363-8369）。

3. 融合蛋白

亦提供含有經修飾之 FVII 多肽及一或多種其他多肽的融合蛋白。提供含有該等經調配用於藉由適當途徑投藥之融合蛋白之醫藥組成物。藉由以任何順序連接經修飾之 FVII 多肽與諸如抗體或其片段、生長因子、受體、配位體及其他用於促進 FVII 多肽純化，藉由指引、例如藉由指引多肽至目標細胞或組織來改變 FVII 多肽的藥效學特性及/或增加 FVII 多肽之表現或分泌之目的之此類藥劑來形成融合蛋白。典型地，與非融合 FVII 多肽相比，任何 FVII 融合蛋白保留至少約 30%、40%、50%、60%、70%、80%、90%或 95%凝血活性，包括與非融合多肽相比 96%、97%、98%、99%或更高的凝血活性。

可直接或經由連接子間接實現 FVII 多肽與另一多肽之連接。在一實例中，連接可藉由化學鍵，諸如經由雙異官能性試劑或硫醇鍵或其他此類鍵聯來實現。亦可藉由重組方式實現融合。FVII 多肽與另一多肽之融合可融合至 FVII 多肽之 N 或 C 末端。可用於與本文中提供之 FVII 多肽的融合蛋白的多肽之非限制性實例包括例如 GST（麩胱甘肽 S 轉移酶）多肽、免疫球蛋白之 Fc 域或異源信號序列。融合蛋白可含有其他組份，諸如幫助使蛋白質被細胞吸收的大腸桿菌麥芽糖結合蛋白（MBP）（參見國際 PCT 申請案第 WO 01/32711 號）。

可藉由標準重組技術產生融合蛋白。舉例而言，可根

據習知技術將編碼不同多肽序列之 DNA 片段同框連接在一起，例如藉由採用用於連接的鈍端或交錯端末端，提供適當末端之限制酶消化、適當時填充黏性末端、避免不當聯接之鹼性磷酸酶處理及酶促連接。在另一具體實例中，可藉由包括自動 DNA 合成儀之習知技術合成融合基因。或者，可使用在兩個連續基因片段之間產生互補突出端的錨固引子進行基因片段之 PCR 擴增，該等互補突出端可隨後黏接且再擴增以產生嵌合基因序列(參見例如 Ausubel 等人(編) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, 1992)。此外，已編碼融合體部分(例如 GST 多肽)之許多表現載體可購得。可將 FVII 編碼核酸選殖入該表現載體中，以使得融合體部分與蛋白酶蛋白質同框連接。

4. 多肽修飾

經修飾之 FVII 多肽可經製備為裸多肽鏈或複合物。對於一些應用而言，製備呈「裸」形式而無轉譯後或其他化學修飾的經修飾之 FVII 可為合意的。可在不轉譯後修飾 FVII 的適當宿主中製備裸多肽鏈。亦可在試管內系統中且使用化學多肽合成製備該等多肽。對於其他應用，可需要特定修飾，包括聚乙二醇化、白蛋白化、糖苷化、羧基化、羥基化、磷酸化或其他已知修飾。可試管內或例如藉由在產生此類修飾的適當宿主中產生經修飾之 FVII 進行修飾。

5. 核苷酸序列

本文中提供編碼 FVII 或經修飾之 FVII 多肽的核酸分

子。核酸分子包括任何所編碼 FVII 多肽的對偶基因變異體或剪接變異體。本文中提供之例示性核酸分子為編碼本文中提供的經修飾之 FVII 多肽之任何核酸分子，諸如編碼 SEQ ID NO: 113-273 之任一者中所闡明的多肽之任何核酸分子。在一具體實例中，本文中提供之核酸分子具有至少 50、60、65、70、75、80、85、90、91、92、93、94、95 或 99%序列一致性，或在中或高嚴格度條件下沿編碼本文中提供之 FVII 多肽之任何核酸的全長之至少 70%雜交。在另一具體實例中，核酸分子可包括彼等具有編碼本文中提供之任何 FVII 多肽的簡并密碼子序列者。

F. 評估經修飾之 FVII 多肽之活性

可試管內及/或活體內評估 FVII 多肽之活性及特性。熟習此項技術者已知用於該評估之檢定，且已知其使所測試活性及結果與治療及活體內活性相關聯。在一實例中，可與未經修飾及/或野生型 FVII 相比較評估 FVII 變異體。在另一實例中，可在試管內或活體內暴露於 AT-III 後評估經修飾之 FVII 多肽的活性，且將其與未暴露於 AT-III 之經修飾之 FVII 多肽的活性相比較。可在 TF 存在或不存在之情況下進行該等檢定。試管內檢定包括熟習此項技術者已知之任何實驗室檢定，諸如細胞基檢定，包括凝血檢定、結合檢定、蛋白質檢定及分子生物學檢定。活體內檢定包括動物模型中之 FVII 檢定以及對人類之投藥。在一些情況下，可藉由評估檢定指定體之血液、血清或其他體液測定來 FVII 之活體內活性。亦可活體內測試 FVII 變異體以評估

諸如治療作用之活性或特性。

典型地，本文所述之檢定與雙鏈活化形式之 FVII，亦即 FVIIa 有關。亦可以單鏈形式進行該等檢定，以便提供陰性對照，因為該形式典型地不含 FVII 之凝血活性所需的蛋白水解或催化活性。另外，亦可在諸如 TF 之在一些情況下加強 FVII 活性之輔因子存在下進行該等檢定。

1. ***試管內檢定***

例示性試管內檢定包括評估多肽修飾及活性之檢定。可使用在此項技術中已知之評估 γ-羧基化及其他轉譯後修飾之試管內檢定、蛋白質檢定及構形檢定評估修飾。用於活性之檢定包括（但不限於）量測 FVII 與諸如 TF、因子 X 及因子 IX 之其他凝血因子之交互作用，測定 FVII 多肽之蛋白水解活性的蛋白水解檢定，測定 FVII 多肽對磷脂醯絲胺酸及其他磷脂的結合及/或親和力之檢定，及測定 FVII 多肽對凝血之作用的細胞基檢定。

可藉由在此項技術中熟知之方法評估經修飾之 FVII 多肽的濃度，包括（但不限於）酶聯免疫吸附檢定（ELISA）、SDS-PAGE；Bradford、Lowry、BCA 法；UV 吸光率及其他可計量蛋白質標記法，諸如（但不限於）免疫學、放射性及螢光方法及相關方法。

可使用包括（但不限於）以下方法之方法進行對蛋白水解反應之裂解產物(包括 FVII 多肽裂解或由 FVII 蛋白酶活性產生的產物)的評估：發色受質裂解、HPLC、SDS-PAGE 分析、ELISA、西方墨漬（Western blotting）、免疫組織化

學、免疫沈澱、NH_2末端定序及蛋白質標記。

亦可評估經修飾之FVII多肽的結構特性。舉例而言，可進行經修飾之 FVII 多肽的 X-射線結晶學、核磁共振（NMR）及低溫電子顯微鏡（低溫 EM）以評估 FVII 多肽之三維結構及/或 FVII 多肽之其他特性，諸如 Ca^{2+}或輔因子結合。

另外，可藉由諸如十二烷基硫酸鈉聚丙烯醯胺凝膠電泳（SDS-PAGE）及經電泳之含 FVII 樣品的西方墨漬之標準技術量測 FVII 降解之存在及程度。亦可使已暴露於蛋白酶之 FVII 多肽經受 N 末端定序以測定經修飾之 FVII 多肽的裂解位點之位置或變化。

a. 轉譯後修飾

亦可評估 FVII 多肽之轉譯後修飾的存在。該等檢定在此項技術中已知且包括量測糖苷化、羥基化及羧基化之檢定。在糖苷化之一例示性檢定中，可例如以暴露於胼解或內切糖苷酶處理之 FVII 多肽的 SDS-Page 分析進行碳水化合物分析。藉由與無水胼一起培育，胼解自醣蛋白釋放 N-及 O-連接型多醣，而內切糖苷酶釋放包括 PNG 酶 F，其自醣蛋白釋放大多數 N-多醣。FVII 多肽之胼解或內切糖苷酶處理產生可以螢光團或發色團標記之還原末端。可藉由螢光團輔助碳水化合物電泳（FACE）分析經標記 FVII 多肽。亦可使用多醣之螢光標籤用於藉由 HPLC 進行複合糖苷化模式之單醣分析、譜分析或指紋圖譜分析。例示性 HPLC 方法包括親水性交互作用層析、電子交互作用、離子交換、

疏水性交互作用及尺寸排阻層析。例示性多醣探針包括（但不限於）3-(乙醯胺基)-6-胺基吖啶（AA-Ac）及 2-胺基苯甲酸（2-AA）。亦可經由使用識別糖苷化 FVII 多肽之特異性抗體來偵測碳水化合物部分。

量測 β-羥基化之一例示性檢定包含對已經受鹼水解的 FVII 多肽之逆相 HPLC 分析（Przysiecki 等人 (1987) PNAS 84:7856-7860）。如此項技術中所述，可使用質譜分析以基質輔助雷射脫附電離飛行時間（MALDI-TOF）分析評估 FVII 多肽之羧基化及 γ-羧基化（參見例如 Harvey 等人 J Biol Chem 278:8363-8369；Maun 等人 Prot Sci 14:1171-1180）。亦可評估含有前肽之 FVII 多肽（前 FVII）與負責轉譯後 γ-羧基化修飾的羧化酶之交互作用。可藉由各向異性測定所結合羧化酶之量來量測將羧化酶與螢光素標記之前 FVII 多肽一起培育後的解離常數（K_d）（Lin 等人 (2004) J Biol Chem 279:6560-6566）。

b. 蛋白水解活性

可測試經修飾之 FVII 多肽的蛋白水解活性。可使用發色受質量測 FVII 之蛋白水解活性，該等發色受質諸如 Chromozym t-PA（$MeSO_2$-D-Phe- Gly-Arg-pNA）、S-2288（H-D-Ile-Pro-Arg-pNA）、S-2266（H-D-Val-Leu-Arg-pNA）、S-2765（Z-D-Arg-Gly-Arg-pNA）、Spectrozyme FXa 及 Spectrozyme FVIIa（CH3SO2-D-CHA-But-Arg-pNA）。單獨或在 TF 存在下將 FVII 多肽與不同濃度之發色受質一起培育。可藉由吸

光率監測受質之裂解且藉由線性回歸使用易於獲得之軟體測定受質水解速率。

亦可評估 FVII 多肽對諸如 FX 之凝血因子受質的活化。在存在或不存在與 TF 一起預培育之情況下，可將 FVII 多肽與經純化 FX（可購得）一起培育。作為經由吸光率變化監測的 FXa 對諸如 S-2222 或 Spectrafluor FXa（CH3SO2-D-CHA-Gly-Arg-AMC.AcOH）之發色受質的活性，量測由於與 FVII 多肽一起培育產生之活性 FXa 的量（Harvey 等人 J Biol Chem 278:8363-8369；亦參見以下實施例 4）。亦可將磷脂源包括於 FVII 及 FX 之培育中（Nelsestuen 等人 (2001) J Biol Chem 276:39825-31）。

c. 凝血活性

可藉由使用在此項技術中熟知之檢定測試 FVII 多肽的凝血活性。舉例而言，一些檢定包括（但不限於）二級凝結檢定（Liebman 等人, (1985) PNAS 82:3879-3883）；凝血酶原時間檢定（PT，其可量測 FVIIa 在外在途徑中之 TF 依賴性活性）；為 PT 測試之改進的檢定；活化部分凝血酶原激酶時間（aPTT，其可量測 FVIIa 之 TF 獨立性活性）；活化凝結時間（ACT）；複鈣活化凝結時間；李-懷特凝結時間（Lee-White Clotting time）；或凝血彈性描記法（TEG）（Pusateri 等人 (2005) Critical Care 9:S15-S24）。舉例而言，可藉由 PT 基檢定測定經修飾之 FVII 多肽之凝血活性，其中將 FVII 稀釋於 FVII 缺乏血漿中且與凝血酶原時間試劑（重組 TF 與磷脂及鈣）（諸如可自 Dade Behring 作為

Innovin™ 獲得者）混合。光學偵測凝塊形成且測定凝結時間且相對於僅 FVII 缺乏血漿進行比較。

d. 與其他蛋白質及分子結合及/或受其他蛋白質及分子抑制

可使用抑制檢定量測經修飾之 FVII 多肽對諸如 AT-III 及 TFPI 之 FVII 抑制子或諸如 Zn^{2+}之分子的抗性。亦可測試對其他抑制子之抑制的評估且其包括（但不限於）其他絲胺酸蛋白酶抑制子及 FVII 特異性抗體。可藉由培育例如 AT-III、TFPI 或 Zn^{2+}與已在 TF 存在及/或不存在情況下預培育的 FVII 多肽評估抑制。可隨後使用上述活性或凝血檢定中之任一或多者量測 FVII 之活性，且可藉由比較與抑制子一起培育的 FVII 多肽之活性與未與抑制子一起培育的 FVII 多肽之活性評估 AT-III、TFPI 或 Zn^{2+}之抑制。

可測試 FVII 多肽與其他凝血因子及抑制子之結合。舉例而言，可使用在此項技術中已知之任何結合檢定評估 FVII 與諸如 TF 之輔因子，諸如 FX 及 FIX 之受質及諸如抗凝血酶 III、TFPI 及肝素之抑制子的直接及間接交互作用，該結合檢定包括（但不限於）免疫沈澱、管柱純化、非還原性 SDS-PAGE、BIAcore®檢定、表面電漿共振（SPR）、螢光共振能量轉移（FRET）、螢光偏振（FP）、等溫滴定量熱法（ITC）、圓二色性（CD）、蛋白質片段互補檢定（PCA）、核磁共振（NMR）光譜、光散射、沈降平衡、小區凝膠過濾層析、凝膠阻滯、遠端西方墨漬（Far western blotting）、螢光偏振、羥基自由基蛋白質足紋圖譜分析、

噬菌體呈現及各種雙雜交系統。在一實例中，使用平衡分析來評估 Zn^{2+}結合（Petersen 等人, (2000) Protein Science 9:859-866）。

e. 磷脂親和力

可使用在此項技術中熟知之檢定測定經修飾之 FVII 多肽對磷脂醯絲胺酸（PS）及其他磷脂的結合及/或親和力。可使用有機溶劑中之高純磷脂（例如已知濃度之牛 PS 及卵磷脂醯膽鹼（PC），其可自諸如 Sigma 購得）製備小型單層磷脂微脂粒。可藉由與入射光成 90° 之相對光散射來測定 FVII 多肽與此等 PS/PC 微脂粒之結合。量測使用僅 PC/PS 及 PC/PS/FVII 情況下之光散射強度以測定解離常數（Harvey 等人 J Biol Chem 278:8363-8369）。亦可使用諸如在 BIAcore 生物傳感器儀器上之表面電漿共振來量測 FVII 多肽對磷脂膜之親和力（Sun 等人 Blood 101:2277-2284）。

2. 非人類動物模型

可使用非人類動物模型評估經修飾之 FVII 多肽的活性、功效及安全性。舉例而言，非人類動物可用作疾病或病狀模型。非人類動物可在投予諸如 SEQ ID NO: 113-273 之任一者所闡明的任何FVII變異體之FVII變異體之前注射誘發疾病及/或表型之物質以監測對疾病進展之作用。遺傳模型亦適用。可產生諸如小鼠之動物，其藉由過度表現、表現不足或剔除一或多個基因來模擬疾病或病狀，諸如顯示 A 型血友病的因子 VIII 剔除小鼠（Bi 等人 (1995) Nat

Gen 10:119-121）。可藉由在此項技術中熟知之轉殖基因動物產生技術或使用天然存在或誘導突變品系產生該等動物。與 FVII 相關的疾病之適用非人類動物模型之實例包括（但不限於）出血病症、尤其血友病或血栓形成疾病之模型。亦可使用損傷之非人類動物模型來評估 FVII 多肽之活性，諸如凝血活性。可與野生型 FVII 多肽相比較，使用此等非人類動物模型監測 FVII 變異體之活性。

亦可使用動物模型監測經修飾之 FVII 多肽的穩定性、半衰期及清除率。該等檢定適用於比較經修飾之 FVII 多肽且適用於計算其他非人類動物及人類試驗之劑量及給藥方案。舉例而言，可將諸如本文中提供之任何 FVII 變異體（包括例如 SEQ ID NO: 113-273 之任一者中所闡明的任何 FVII 變異體）的經修飾之 FVII 多肽注入小鼠之尾靜脈。接著，在注射後之時間點（諸如其後數分鐘、數小時及數天）取血樣，且隨後可在特定時間點，例如藉由 ELISA 或放射免疫檢定監測包括（但不限於）血清或血漿的身體樣品中經修飾之 FVII 多肽的含量。亦使用諸如實施例 9 所述之各種方法測試注射 FVII 多肽後各時間點之血樣的凝血活性。此等類型之藥物動力學研究可提供關於 FVII 多肽的半衰期、清除率及穩定性之資訊，其可幫助確定用於作為促凝血劑投藥之適當劑量。

可使用血友病動物模型測試諸如 SEQ ID NO: 113-273 之任一者所闡明的任何 FVII 多肽之經修飾之 FVII 多肽的療效。在一非限制性實例中，可使用諸如小鼠之動物模型。

血友病之小鼠模型在此項技術中可獲得且可用以測試經修飾之 FVII 多肽。舉例而言，可使用藉由注射抗 FVIII 抗體產生的 A 型血友病之小鼠模型評估 FVII 多肽之凝血活性（參見例如實施例 6 及 Tranholm 等人 Blood (2003)102:3615-3620）。亦可使用 B 型血友病之小鼠模型測試 FVII 多肽（Margaritis 等人 (2004) J Clin Invest 113:1025-1031）。亦存在出血病症之非小鼠模型。可在患有華法林誘導之出血或美拉加群（melagatran）誘導之出血的大鼠（Diness 等人 (1992) Thromb Res 67:233-241；Elg 等人 (2001) Thromb Res 101:145-157）及患有肝素誘導之出血的兔（Chan 等人 (2003) J Thromb Haemost 1:760-765）中評估 FVII 多肽活性。顯示嚴重出血的近交 A 型血友病、B 型血友病及溫韋伯氏病犬亦可用於 FVII 多肽之非人類動物研究中（Brinkhous 等人 (1989) PNAS 86:1382-1386）。亦可在藉由組合 γ 輻射及使用血小板抗體誘導血小板減少症的出血之兔模型中評估 FVII 多肽之活性（Tranholm 等人 (2003) Thromb Res 109:217-223）。

除患有廣泛性出血病症之動物之外，亦可使用損傷及外傷模型評估 FVII 多肽之活性及其作為凝血治療劑之安全性及功效。該等模型之非限制性實例包括兔冠狀動脈狹窄症模型（Fatorutto 等人 (2004) Can J Anaesth 51:672-679）、豬 V 級肝臟損傷模型（Lynn 等人 (2002) J Trauma 52:703-707）、豬 V 級肝臟損傷模型（Martinowitz 等人 (2001) J Trauma 50:721-729）及豬主動脈切開術模型

（Sondeen 等人 (2004) Shock 22:163-168）。

3. 臨床檢定

許多檢定可用來評估用於臨床用途之 FVII 之活性。該等檢定可包括評估凝血、蛋白質穩定性及活體內半衰期及表型檢定。表型檢定及評估 FVII 治療之治療作用的檢定包括評估 FVII 之血液含量（例如，在投藥之前及投藥後之時間點量測血清 FVII，投藥後之時間點包括第一次投藥後，最後一次投藥後不久及之間的時間點，校正體重指數（BMI））、以 FVII 治療後使用上述方法試管內評估凝血（例如 PT 檢定），及對 FVII 治療之表型反應，包括與以未經修飾及/或野生型 FVII 或安慰劑治療的個體相比，隨時間之症狀改善。可監測以 FVII 多肽治療的患者之失血、輸血要求及血紅素。可在常規或重複投藥之某段時間內，或在回應諸如出血、外傷或手術程序之急性事件投藥後定期監測患者。

G. 調配物及投藥

本文提供用於治療出血病症的組成物。該等組成物含有治療有效量之如本文所述的因子 VII 多肽。將有效濃度之 FVII 多肽或其醫藥學上可接受之衍生物與適當醫藥載劑或媒劑混合用於全身性、局部性或局部投藥。包括有效治療所選擇病症的量之化合物。組成物中活性化合物之濃度將取決於活性化合物之吸收、失活、排泄速率，劑量時程及所投予量以及熟習此項技術者已知的其他因素。

適於投予本文中提供的化合物之醫藥載劑或媒劑包括

熟習此項技術者已知適合於特定投藥模式的任何此類載劑。亦可以在投藥之前不久與諸如無菌水重構之凍乾粉末形式提供包括治療有效量之本文所述之 FVII 多肽的醫藥組成物。

1. 調配物

可以任何習知方式藉由混合所選量的多肽與一或多種生理上可接受之載劑或賦形劑來調配含有經修飾之 FVII 的醫藥組成物。載劑或賦形劑之選擇在投藥行當之技能範圍內且可取決於許多參數。此等參數包括例如投藥模式（亦即，全身性、經口、經鼻、肺部、局部、局部性或任何其他模式）及所治療病症。可調配本文中提供之醫藥組成物用於單劑（直接）投藥或用於稀釋或其他改進形式。調配物中化合物之濃度在投藥後有效傳遞對預期治療有效的量。典型地，調配組成物用於單劑投藥。為調配組成物，將重量分率之化合物或其混合物在所選媒劑中以使得所治療病狀得以緩解或改善的有效濃度溶解、懸浮、分散或以其他方式混合。

可調配本文中提供的經修飾之 FVII 多肽用於以雙鏈 FVIIa 蛋白形式向個體投藥。可在調配之前藉由在此項技術中已知之任何方法活化經修飾之 FVII 多肽。舉例而言，FVII 可在藉由離子交換層析純化期間經歷自體活化（Jurlander 等人 (2001) Semin Thromb Hemost 27:373-384）。亦可藉由與固定於珠粒上的 FXa 一起培育（Kemball-Cook 等人 (1998) J Biol Chem 273:8516-8521）或藉由在此項技術中已

知之任何其他方法活化經修飾之 FVII 多肽（亦參見以下實施例 2）。在此等過程中包含鈣確保經修飾之 FVIIa 蛋白的充分活化及恰當摺疊。亦可調配本文中提供之經修飾之 FVII 多肽用於以單鏈蛋白質形式投藥。可以諸如防止裂解之方式純化單鏈 FVII 多肽（參見例如 US6677440）。可藉由適當選擇介質以消除或控制自體活化，調配本文中提供的經修飾之 FVII 多肽以使得單鏈及雙鏈形式以任何比率含於醫藥組成物中。

化合物可以微粒化或其他適當形式懸浮或可經衍生以產生更可溶之活性產物。所得混合物之形式取決於許多因素，包括預期投藥模式及化合物在所選載劑或媒劑中之溶解性。所得混合物為溶液、懸浮液、乳液及其他此類混合物，且可調配為非水性或水性混合物、乳膏劑、凝膠、軟膏劑、乳液、溶液、酏劑、洗劑、懸浮液、酊劑、糊劑、發泡體、氣溶膠、沖洗劑、噴霧、栓劑、繃帶或適於全身性、局部性或局部投藥之任何其他調配物。對於局部內部投藥，諸如肌肉內、非經腸或關節內投藥而言，可將多肽調配為在水基介質中的溶液懸浮液，諸如等張緩衝鹽水，或將其與意欲內部投藥之生物相容性載體或生物黏合劑相組合。有效濃度足以改善目標病狀且可憑經驗確定。為調配組成物，將重量分率之化合物在所選媒劑中以使得目標病狀得以緩解或改善的有效濃度溶解、懸浮、分散或者混合。

通常，根據管理機構之批准製備醫藥學上可接受之組

成物或根據用於動物及人類之通常公認之藥典製備其他組成物。醫藥組成物可包括載劑，諸如稀釋劑、佐劑、賦形劑或媒劑，同功異型物與其一起投予。該等醫藥載劑可為無菌液體，諸如水及油，包括石油、動物、植物或合成來源之油，諸如花生油、大豆油、礦物油及芝麻油。當靜脈內投予醫藥組成物時，水為典型載劑。亦可採用生理食鹽水溶液及右旋糖水溶液及甘油溶液作為液體載劑，尤其用於可注射溶液。連同活性成份一起，組成物可含有以下各物：稀釋劑，諸如乳糖、蔗糖、磷酸氫鈣或羧甲基纖維素；潤滑劑，諸如硬脂酸鎂、硬脂酸鈣及滑石；及黏結劑，諸如澱粉、天然膠（諸如阿拉伯膠）、明膠、葡萄糖、糖蜜、聚乙烯吡咯啶、纖維素及其衍生物、聚乙烯吡咯酮、交聯聚乙烯吡咯酮及熟習此項技術者已知之其他此類黏結劑。適當醫藥賦形劑包括澱粉、葡萄糖、乳糖、蔗糖、明膠、麥芽、稻穀、麵粉、白堊、矽膠、硬脂酸鈉、單硬脂酸甘油酯、滑石、氯化鈉、脫脂奶粉、甘油、丙烯、乙二醇、水及乙醇。需要時，組成物亦可含有微量濕潤劑或乳化劑或 pH 值緩衝劑，例如乙酸鹽、檸檬酸鈉、環糊精衍生物、脫水山梨糖醇單月桂酸酯、三乙醇胺乙酸鈉、油酸三乙醇胺及其他此類試劑。此等組成物可呈溶液、懸浮液、乳液、錠劑、丸劑、膠囊、散劑及持續釋放調配物形式。可調配含有治療化合物與適當粉末主劑（諸如乳糖或澱粉）的粉末混合物之用於吸入器或吹入器中之（例如）明膠之膠囊及濾筒。組成物可以傳統黏結劑及諸如甘油三酯之載劑調

配成栓劑形式。經口調配物可包括標準載劑，諸如醫藥級甘露糖醇、乳糖、澱粉、硬脂酸鎂、糖精鈉、纖維素、碳酸鎂及其他此類試劑。亦可以蛋白酶抑制劑適當地調配用於經口投藥之製劑，該等抑制劑諸如包曼-伯克抑制劑（Bowman-Birk inhibitor）、經接合包曼-伯克抑制劑、抑蛋白酶肽及卡莫司他（camostat）。適當醫藥載劑之實例描述於 E. W. Martin 之「Remington' s Pharmaceutical Sciences」中。該等組成物將含有治療有效量之通常呈經純化形式的化合物以及適當量之載劑以便提供用於適當投予個體或患者之形式。

調配物應適合投藥模式。舉例而言，經修飾之 FVII 可經調配用於藉由注射來非經腸投藥（例如藉由快速注射或連續輸液）。可注射組成物可採用諸如於油性或水性媒劑中的懸浮液、溶液或乳液之形式。無菌可注射製劑亦可為於無毒非經腸可接受之稀釋劑或溶劑中之無菌可注射性溶液或懸浮液，例如作為於 1,4-丁二醇中之溶液。無菌、不揮發性油類通常可用作溶劑或懸浮介質。出於此目的，可採用任何無刺激不揮發性油，包括（但不限於）合成單-或二甘油酯、脂肪酸（包括油酸）、天然存在植物油，如芝麻油、椰子油、花生油、棉籽油及其他油，合成脂肪媒劑，如油酸乙酯。需要時可併入緩衝劑、防腐劑、抗氧化劑及適當成份，或者，其可構成調配物。

多肽可經調配為組成物中之唯一醫藥活性成份，或可與其他活性成份組合。可諸如藉由與諸如抗體之靶向劑接

合使多肽靶向傳遞。包括組織靶向脂質體之脂質體懸浮液亦可適用作醫藥學上可接受之載劑。可根據熟習此項技術者已知之方法製備此等載劑。舉例而言，可如美國專利第4,522,811 號中所述製備脂質體調配物。脂質體傳遞亦可包括緩釋調配物，包括諸如膠原凝膠及經纖連蛋白改質之脂質體之醫藥基質(參見例如 Weiner 等人 (1985) J Pharm Sci. 74(9): 922-5）。本文中提供之組成物可進一步含有一或多種促進傳遞之佐劑，諸如（但不限於）惰性載劑，或膠態分散系統。該等惰性載劑之代表性及非限制性實例可選自水、異丙醇、氟態碳氟化合物、乙醇、聚乙烯吡咯啶酮、丙二醇、凝膠產生材料、十八烷醇、硬脂酸、鯨蠟、脫水山梨糖醇單油酸酯、甲基纖維素以及其兩種或兩種以上之適當組合。

活性化合物以足以在無不當副作用情況下對所治療個體發揮治療有效作用之量包括於醫藥學上可接受之載劑中。可藉由在已知試管內及活體內系統中，諸如在本文中提供之檢定中測試化合物來憑經驗確定治療有效濃度。

a. 劑量

所投予治療劑之精確量或劑量取決於特定 FVII 多肽，投藥途徑及其他考慮因素，諸如疾病之嚴重程度及個體的體重及總體狀態。局部投予治療劑典型地要求比任何全身性投藥模式小的劑量，儘管在一些情況下局部投藥後，治療劑之局部濃度可高於全身性投藥後可安全地實現之濃度。必要時，可憑經驗確定或外推出特定劑量及持續時間

及治療方案。舉例而言，可使用重組及原生 FVII 多肽之例示性劑量作為起始點來確定適當劑量。舉例而言，已藉由快速輸液經 2 至 5 分鐘以 90 μg/kg 之劑量向患有 A 型血友病或 B 型血友病之經歷出血事件的患者投予已活化為 rFVIIa Novoseven®的重組 FVII（rFVIIa）多肽，獲得至少 2 μg/ml 之有效循環含量。每 2 小時重複劑量，直至實現止血。與該重組 FVII 相比，本文中提供的經修飾之 FVII 多肽在低給藥量及/或頻率下便可有效。舉例而言，可以 80 μg/kg、70 μg/kg、60 μg/kg、50 μg/kg、40 μg/kg、30 μg/kg、20 μg/kg、15 μg/kg 或 15 μg/kg 以下之劑量投予本文提供之經修飾之 FVII 多肽。在一些具體實例中，劑量可較高，諸如 100 μg/kg、110 μg/kg、120 μg/kg 或 120 μg/kg 以上。治療持續時間及注射之間的時間間隔將隨出血嚴重程度及患者對治療之反應而變化，且可相應地調節。當作劑量確定時，可考慮與未經修飾之 FVII 相比，諸如經修飾之 FVII 之活性程度及半衰期的因素。可憑經驗確定特定劑量及方案。

在另一實例中，已藉由快速輸液經 2 至 5 分鐘以 15-30 μg/kg 之劑量向患有先天性 FVII 缺乏之經歷出血事件的患者投予已活化為 rFVIIa Novoseven®之重組 FVII（rFVIIa）多肽。每 4-6 小時重複劑量，直至實現止血。與該重組 FVII 相比，本文中提供的經修飾之 FVII 多肽在低給藥量及/或頻率下便可有效。舉例而言，可以 20 μg/kg、15 μg/kg、10 μg/kg、5 μg/kg、3 μg/kg 或 3 μg/kg 以下之劑量投予本文中

提供的經修飾之 FVII 多肽。在一些實例中，劑量可較高，諸如 35 μg/kg、40 μg/kg、45 μg/kg 或 45 μg/kg 以上。治療持續時間及注射之間的時間間隔將隨出血嚴重程度及患者對治療之反應而變化，且可相應地調節。與未經修飾之 FVII 相比，諸如經修飾之 FVII 之活性程度及半衰期的因素可用於作劑量確定。舉例而言，可以與未經修飾之 FVII 多肽相比較低之劑量及/或較低之頻率投予展現比未經修飾之 FVII 多肽長的半衰期之經修飾之 FVII 多肽。類似地，使用與未經修飾之 FVII 多肽相比，顯示凝血活性增強之經修飾之 FVII 多肽情況下治療作用所需的劑量之頻率及量可降低。可由熟習此項技術者憑經驗確定特定劑量及方案。

b. 劑型

以單位劑型或多劑型典型地調配且投予醫藥治療活性化合物及其衍生物。可提供調配物用於以包括（但不限於）以下的劑型向人類及動物投藥：錠劑、膠囊、丸劑、散劑、顆粒、無菌非經腸溶液或懸浮液、經口溶液或懸浮液及油水乳液，其含有適當量之化合物或其醫藥學上可接受之衍生物。各單位劑量含有預定量之足以產生所需治療作用的治療活性化合物與所需醫藥載劑、媒劑或稀釋劑。單位劑型之實例包括安瓿及注射器及單獨封裝之錠劑或膠囊。在一些實例中，以在投藥之前重構的凍乾粉末形式提供單位劑量。舉例而言，可提供呈以適當溶液重構以產生用於注射的單劑溶液之凍乾粉末形式之 FVII 多肽。在一些具體實例中，凍乾粉末可含有 FVII 多肽及其他組份，諸如鹽，以

使得用無菌蒸餾水重構產生於緩衝或生理食鹽水溶液中的FVII 多肽。可按份或以多份投予單位劑型。多劑型為封裝在單一容器中以用隔離單位劑型投予之複數個相同單位劑型。多劑型之實例包括小瓶、錠劑或膠囊瓶或品脫或加侖瓶。因此，多劑型為未在封裝中隔離之多個單位劑量。

2. 經修飾之 FVII 多肽之投藥

可藉由使諸如體液或其他組織樣品之混合物與 FVII 多肽接觸來試管內、活體外或活體內投予本文中提供之 FVII 多肽（亦即活性化合物）。舉例而言，當活體外投予化合物時，可使來自個體的體液或組織樣品與塗佈於諸如旁路機（bypass machine）中之管或過濾器的管或過濾器上之 FVII 多肽接觸。當活體內投予時，活性化合物可以液體、半液體或固體形式藉由任何合適途徑投予，例如經口、經鼻、肺部、非經腸、靜脈內、皮內、皮下、關節內、腦池內、眼內、腦室內、鞘內、肌肉內、腹膜內、氣管內或局部性投予，以及藉由其任何兩種或兩種以上之任何組合投予，且以適於各投藥途徑之方式調配。可一次或一次以上，諸如兩次、三次、四次或實現治療作用所需的任何次數投予經修飾之 FVII 多肽。多次投藥可經由任何途徑或途徑組合實現，或可每小時、每 2 小時、每 3 小時、每 4 小時或更長時間投予。

用於投藥之最適當途徑將視待治療疾病病況而不同，例如出血病症之位置。通常，將藉由靜脈內快速注射經約 2-5 分鐘之投藥（輸液）時間投予 FVII 多肽。在其他實例

中，如藉由血漿含量所確定，可藉由活性劑之連續輸液保持 FVII 之所需血液含量。應注意由於毒性或骨髓、肝臟或腎臟功能異常，主治醫師將知曉如何且何時終止、中斷或調節療法至較低劑量。相反地，若臨床反應並不充分（排除毒性副作用），則主治醫師亦將知曉如何且何時調整治療至較高含量。在其他實例中，出血病症之位置可指示經由替代途徑投予 FVII 調配物。舉例而言，當患者經歷腦出血時，可在該區域中進行局部投藥，包括向腦投藥（例如腦室內）。類似地，對於治療關節中之出血，可採用藉由將治療劑注射於關節中（亦即關節內、靜脈內或皮下方式）來進行局部投藥。在其他實例中，當出血定位於皮膚或肺時，向皮膚局部性投予治療劑，例如調配為乳膏劑、凝膠或軟膏劑，或藉由吸入或氣管內向肺投藥可為適當的。

在經修飾之 FVII 多肽經調配為儲槽式製劑的情況下，可藉由植入（例如皮下或肌肉內）或藉由肌肉內注射投予長效調配物。因此（例如）可使用合適之聚合或疏水性材料（例如呈於可接受之油中之乳液形式）或離子交換樹脂、或作為微溶性衍生物（例如呈微溶性鹽形式）來調配治療化合物。

必要時，組成物可存在於可含有一或多個含有活性成份的單位劑型之包裝、套組或分配器裝置中。包裝（例如）含有金屬或塑料箔，諸如起泡包裝。包裝或分配器裝置可附有投藥用法說明書。可將含有活性劑的組成物封裝為含有封裝材料、本文中提供之藥劑及指示所提供藥劑適用之

病症的標籤之製品。

3. 編碼經修飾之FVII多肽的核酸之投藥(基因療法)

亦提供編碼經修飾之FVII多肽的核酸分子及編碼其之表現載體之適於基因療法的組成物。可活體內(諸如全身或藉由其他途徑)或活體外(諸如藉由移除包括淋巴細胞之細胞,將核酸引入其中且再引入宿主或相容性接受者中)投予核酸,而非傳遞蛋白質。

可藉由表現核酸分子將經修飾之FVII多肽傳遞至細胞及組織。可以編碼經修飾之FVII多肽的核酸分子形式,包括活體外技術及直接活體內表現,投予經修飾之FVII多肽。可藉由熟習此項技術者已知之任何方法將核酸傳遞至細胞及組織。可將經分離核酸序列併入載體用於進一步操縱。如本文中所用,載體(或質體)係指用以將異源DNA引入細胞以供其表現或複製的獨立元件。該等媒介之選擇及使用完全處於熟習此項技術者之技能範圍內。

藉由表現編碼核酸分子來投予經修飾之FVII多肽的方法包括投予重組載體。載體可經設計以諸如藉由包含複製起點來保持游離或可經設計以整合於細胞之染色體中。經修飾之FVII多肽亦可使用非病毒載體用於活體外基因表現療法。舉例而言,細胞可諸如藉由使經修飾之FVII多肽編碼核酸整合於基因組位置中、操作性連接至調節序列或使得其與基因組位置內之調節序列操作性連接安置經工程化以表現經修飾之FVII多肽。接著,可將該等細胞局部或全身性投予個體,諸如需要治療之患者。

病毒載體包括例如腺病毒、腺相關病毒（AAV）、痘病毒、疱疹病毒、逆轉錄病毒，且可採用經設計用於基因療法之其他病毒載體。載體可保持游離或可整合於所治療個體之染色體中。經修飾之 FVII 多肽可由向需要治療之個體所投予的病毒表現。適於基因療法之病毒載體包括腺病毒、腺相關病毒（AAV）、逆轉錄病毒、慢病毒、痘瘡病毒及其他上述病毒載體。舉例而言，在此項技術中熟知腺病毒表現技術且亦熟知腺病毒產生及投藥方法。腺病毒血清型可獲自例如美國典型培養物保藏所（American Type Culture Collection；ATCC，Rockville, MD）。可活體外使用腺病毒，例如自需要治療之患者分離細胞且以表現經修飾之 FVII 多肽之腺病毒載體轉導。適當培養期後，將經轉導細胞局部及/或全身性地投予個體。或者，分離且在醫藥學上可接受之載劑中調配表現經修飾之 FVII 多肽之腺病毒顆粒以傳遞治療有效量來預防、治療或改善個體之疾病或病狀。典型地，以每公斤個體體重 1 個顆粒至 10^{14} 個顆粒、通常在每公斤個體體重 10^{6} 或 10^{8} 個顆粒至 10^{12} 個顆粒之間的範圍內之劑量傳遞腺病毒顆粒。在一些情況下，需要向核酸來源提供靶向細胞之藥劑，諸如對細胞表面膜蛋白或目標細胞具特異性之抗體，或目標細胞上受體之配位體。FVII 亦可靶向傳遞於特異細胞類型中。舉例而言，可使用編碼 FVII 多肽的腺病毒載體在諸如肝細胞之非分裂細胞中穩定表現（Margaritis 等人 (2004) J Clin Invest 113:1025-1031）。在另一實例中，可將編碼 FVII 多肽的病

毒或非病毒載體轉導於經分離細胞中用於後續傳遞。用於表現且傳遞 FVII 之其他細胞類型可包括（但不限於）纖維母細胞及內皮細胞。

可將核酸分子引入人工染色體及其他非病毒載體中。諸如 ACES（參見 Lindenbaum 等人 (2004) Nucleic Acids Res. 32(21): e172）之人工染色體可經工程化以編碼且表現同功異型物。簡言之，哺乳動物人工染色體（MAC）提供以自主複製非整合形式將遺傳資訊之大有效載荷引入細胞中的方式。在 MAC 之中獨特地，基於哺乳動物衛星 DNA 之人工染色體表現（ACE）可在不同物種之細胞系中從頭可再現地產生且易於自宿主細胞染色體純化。隨後，可將經純化哺乳動物 ACE 再引入多種受體細胞系中，其中其已在選擇壓力不存在情況下使用 ACE 系統穩定地長期保持。使用此方法，已在 LMTK (-)及 CHO 細胞中取得一或兩個基因目標之特定負載。

引入編碼經修飾之 FVII 多肽的核酸之另一方法為酵母菌中的兩步基因置換技術，其以在酵母菌人工染色體（YAC）中選殖之完全腺病毒基因組（Ad2；Ketner 等人 (1994) PNAS 91: 6186-6190）及含有靶向 YAC 純系內的特定區域之腺病毒序列之質體、所關注之基因之表現卡匣及陽性及陰性可選擇性標誌起始。尤其關注 YAC，因為其允許併入較大基因。可使用此方法構築承載編碼所述經修飾之 FVII 多肽中的任一者之核酸的腺病毒基載體以供基因轉移至哺乳動物細胞或所有動物。

可將核酸囊封於諸如脂質體之媒介中或引入諸如細菌細胞、尤其減毒細菌之細胞中或引入病毒載體中。舉例而言，當採用脂質體時，結合與內飲作用相關的細胞表面膜蛋白之蛋白質可用於靶向及/或促進吸收，例如對特定細胞類型具有向性之衣殼蛋白或其片段，在循環中經歷內化的蛋白質之抗體，及靶向細胞內定位且增強細胞內半衰期之蛋白質。

對於活體外及活體內方法，將編碼經修飾之 FVII 多肽的核酸分子引入來自適當供體或待治療個體之細胞中。出於治療目的可引入核酸之細胞包括（例如）適合於待治療疾病或病狀的任何所需可用細胞類型，包括（但不限於）上皮細胞、內皮細胞、角質細胞、纖維母細胞、肌細胞、肝細胞；血細胞，諸如 T 淋巴細胞、B 淋巴細胞、單核細胞、巨噬細胞、嗜中性白血球、嗜伊紅細胞、巨核細胞、粒細胞；各種幹細胞或祖細胞，尤其造血幹細胞或祖細胞，例如獲自骨髓、臍帶血、周邊血液、胎兒肝臟及其他來源之幹細胞。

對於活體外治療，自與待治療個體相容之供體或待治療個體移除細胞，將核酸引入此等經分離細胞中且向該個體投予經修飾之細胞。治療包括直接投藥，諸如囊封在植入患者中之多孔膜內（參見例如，美國專利第 4,892,538 號及第 5,283,187 號，其各自以引用的方式全部併入本文中）。適於試管內將核酸轉移於哺乳動物細胞中的技術包括使用脂質體及陽離子脂質（例如 DOTMA、DOPE 及 DC-Chol）

電穿孔、顯微注射、細胞融合、DEAE-葡聚糖及磷酸鈣沈澱法。可使用 DNA 傳遞方法活體內表現經修飾之 FVII 多肽。該等方法包括脂質體傳遞核酸及裸 DNA 傳遞，包括局部及全身性傳遞，諸如使用電穿孔、超音波及磷酸鈣傳遞。其他技術包括顯微注射、細胞融合、染色體介導之基因轉移、小細胞介導之基因轉移及球形體融合。

經修飾之 FVII 多肽之活體內表現可與其他分子之表現相關聯。舉例而言，經修飾之 FVII 多肽的表現可與諸如經工程化病毒中或表現於細胞毒性病毒中的細胞毒性產物之表現相關聯。可使該等病毒靶向為治療作用之目標的特定細胞類型。可使用所表現經修飾之 FVII 多肽增強病毒之細胞毒性。

經修飾之 FVII 多肽之活體內表現可包括將編碼經修飾之 FVII 多肽的核酸分子操作連接至諸如細胞特異性或組織特異性啟動子的特定調節序列。亦可自在目標細胞類型及/或組織中特異性感染及/或複製的載體表現經修飾之 FVII 多肽。可使用誘導型啟動子選擇性調節經修飾之 FVII 多肽表現。一例示性可調節表現系統為多西環素（doxycycline）誘導型基因表現系統，其已用以調節重組 FVII 表現（Srour 等人(2003) Thromb Haemost. 90(3): 398-405）。

可藉由全身性投藥、局部性、局部及其他投藥途徑向個體投予呈裸核酸形式或在載體、人工染色體、脂質體及其他媒介中之核酸分子。當全身性且活體內投藥時，可使核酸分子或含有核酸分子之媒介靶向細胞。

亦可藉由諸如投予典型地靶向細胞或組織之載體或細胞指引投藥。舉例而言，腫瘤細胞及增生細胞可為用於活體內表現經修飾之 FVII 多肽的目標細胞。用於活體內表現經修飾之 FVII 多肽的細胞亦包括患者自體的細胞。可自患者移除該等細胞，引入用於表現經修飾之 FVII 多肽的核酸且隨後諸如藉由注射或移植向患者投予。

H. 治療用途

可使用本文中提供的經修飾之 FVII 多肽來治療可採用重組 FVII 來治療的任何病狀。典型地，該等治療包括彼等需要增強凝血，諸如增強止血反應者。經修飾之 FVII 多肽單獨或與其他藥劑組合具有治療活性。本文中提供之經修飾之多肽經設計以保留治療活性，但展現改進之特性，尤其增強之 AT-III 抗性及增強之催化活性。本文中提供之經修飾之多肽亦可展現增強之 TFPI 抗性、增強之對 Zn^{2+} 抑制作用之抗性、改良之藥物動力學特性（諸如血清半衰期）、對經活化血小板增強之結合及/或親和力、對血清白蛋白增強之結合及/或親和力及/或對血小板整合素 $\alpha_{IIb}\beta_3$ 增強之結合及/或親和力。由於經修飾之 FVII 多肽的凝血活性增強，因此該等經修飾之特性可例如提高多肽之療效。此部分提供例示性用途及投藥方法。此等所述療法為例示性的且並不限制經修飾之 FVII 多肽的應用。

本文中提供之經修飾之 FVII 多肽可用於採用 FVII 的各種療法以及診斷方法。該等方法包括（但不限於）以下所述及列舉之生理學及醫學病狀的治療方法。與野生型 FVII

相比，本文中提供的經修飾之 FVII 多肽可展現活體內活性及治療作用改良，包括實現相同作用之較低劑量，及其他投藥及治療之其他改良，諸如較少及/或較低頻率投藥、副作用減少及治療作用增加。儘管應瞭解經修飾之 FVII 多肽可以 FVII 酶原形式（亦即單鏈形式）投予，但典型地，例如在自體活化或在諸如純化期間由其他凝血因子活化之後，以經活化雙鏈形式投予本文中提供的經修飾之 FVII 多肽。

詳言之，經修飾之 FVII 多肽意欲用於已使用 FVII 來治療的治療方法中。該等方法包括（但不限於）疾病及病症之治療方法，該等疾病及病症諸如（但不限於）凝血病症、血液學病症、出血性病症、血友病（諸如 A 型血友病、B 型血友病及因子 VII 缺乏）及後天性血液病症，諸如由肝病所引起的後天性因子 VII 缺乏。經修飾之 FVII 多肽亦可用於治療其他出血疾病及病症，諸如（但不限於）血小板減少症（例如，由於化療方案）、溫韋伯氏病、遺傳性血小板病症（例如貯存池疾病，諸如契-東（Chediak-Higashi）症候群及赫曼斯基-普德拉克症候群（Hermansky-Pudlak syndromes）、凝血烷 A2 功能異常、格蘭士文氏血小板功能不足及伯-蘇氏症候群（Bernard-Soulier syndrome））、溶血性尿毒癥候群、亦稱為朗奧韋氏症候群（Rendu Osler-Weber syndrome）之遺傳性出血性毛細血管擴張症、過敏性紫癜（亨-舒紫癜（Henoch Schonlein purpura））及彌漫性血管內凝血。

在一些具體實例中，待由 FVII 多肽治療之出血發生在諸如腦、內耳區域、眼睛、肝臟、肺、腫瘤組織、胃腸道之器官中。在其他具體實例中，出血在諸如出血性胃炎及血崩中擴散。患有諸如 A 型血友病及 B 型血友病之出血病症之患者在手術或外傷期間通常處於出血併發症之風險中。該等出血可表現為急性關節血腫（關節內出血）、慢性血友病性關節病、血腫（例如肌肉、腹膜後、舌下及咽後）、血尿（腎道出血）、中樞神經系統出血、胃腸出血（例如 UGI 出血）及腦出血，其亦可以經修飾之 FVII 多肽治療。另外，可以經修飾之 FVII 多肽治療任何與手術（例如肝切除術）或拔牙相關的出血。在一具體實例中，可使用經修飾之 FVII 多肽治療個體由於外傷或手術導致之出血事件或降低之血小板計數或活性。用於經歷手術之患者的例示性方法包括治療以預防出血及在手術前、期間或之後治療，該等手術諸如（但不限於）心臟手術、血管成形術、肺手術、腹部手術、脊椎手術、腦手術、血管手術、牙手術或器官移植手術，包括骨髓、心臟、肺、胰腺或肝臟移植。

可使用如本文所述之適當調配物藉由任何適當投藥途徑（包括（但不限於）注射、肺部、經口及經皮投藥）實現以經修飾之 FVII 多肽對疾病及病狀的治療。典型地藉由靜脈內快速投藥實現治療。

必要時，可憑經驗確定或外推出特定劑量及持續時間及治療方案。舉例而言，可使用重組及原生 FVII 多肽之例

示性劑量作為起始點確定適當劑量。舉例而言，已藉由快速輸液經 2 至 5 分鐘以 90 μg/kg 之劑量向患有 A 型血友病或 B 型血友病之經歷出血事件的患者投予已活化為 rFVIIa Novoseven®的重組 FVII（rFVIIa）多肽，實現平均半衰期為 2.7 小時的至少 2 μg/ml 之有效循環含量。每 2 小時重複劑量，直至實現止血。由於增強之 AT-III 抗性、增強之催化活性、增強之對 Zn^{2+}抑制作用之抗性、增強之 TFPI 抗性、改良之藥物動力學特性（諸如增加之血清半衰期）、對經活化血小板增強之結合及/或親和力、對血清白蛋白增強之結合及/或親和力及/或對血小板整合素 $\alpha_{IIb}\beta_3$ 增強之結合及/或親和力而具有增強之凝血活性的經修飾之 FVII 多肽與該重組 FVII 相比可在低給藥量及/或頻率下有效。野生型或未經修飾之 FVII 多肽的劑量可用作確定經修飾之 FVII 多肽的劑量之指導。與未經修飾之 FVII 相比，諸如經修飾之 FVII 之活性程度及半衰期的因素可用於作該等確定。可憑經驗確定特定劑量及方案。

可基於已知劑量及方案確定劑量含量及方案，且必要時其可基於經修飾之多肽的特性變化外推出及/或可基於多種因素憑經驗確定。該等因素包括個體之體重、總體健康狀況、年齡、所用特定化合物之活性、性別、飲食、投藥時間、排泄速率、藥物組合、疾病嚴重程度及疾病過程及患者對疾病之傾向及治療醫師之判斷。典型地，組合活性成份多肽與醫藥有效載劑。可與載劑物質組合以產生單一劑型或多劑型之活性成份的量可視所治療宿主及特定投藥

方式而改變。

可使用在此項技術中已知之任一凝結測試監測 FVII 多肽對血液凝結時間之作用，該等凝結測試包括（但不限於）全血凝血酶原時間（PT）、活化部分凝血酶原激酶時間（aPTT）、活化凝結時間（ACT）、複鈣活化凝結時間或李-懷特凝結時間（Lee-White Clotting time）。

改善患者病狀後，必要時可投予化合物或組成物之維持劑量；可改變投藥之劑量、劑型或頻率或其組合。在一些情況下，疾病症狀之任何復發後，個體可要求在長期基礎上或基於預定劑量間歇治療。在其他情況下，可回應諸如出血、外傷或手術程序之急性事件要求另外投藥。

以下為 FVII（以 FVIIa 形式投予）已單獨或組合其他藥劑用作治療劑之某些例示性病狀。

1. 先天性出血病症

a. 血友病

先天性血友病為隱性血液病症，其中血漿中存在降低含量之凝血因子，導致凝血級聯中斷及凝塊凝結時間增加。佔所有血友病病例的約 85%之 A 型血友病由 X 染色體上因子 VIII 基因突變引起，導致 FVIII 蛋白缺乏或功能異常。B 型血友病由通常由 X 染色體上 FIX 基因點突變或缺失導致的凝血因子 FIX 缺乏或功能異常引起。A 型血友病之全世界發生率為每 5000 個男性個體約 1 例，且對於 B 型血友病而言為每 25000 個男性個體 1 例。將 A 型血友病及 B 型血友病進一步分類為輕度、中度或嚴重。具有 5%-25%功

能正常因子 VIII 或 IX 之血漿含量經分類為輕度，1%-5%為中度，且低於 1%為嚴重。通常稱為 FIX 缺乏之 C 型血友病為相對輕度且罕見之疾病，其以自體隱性方式影響 100000 人中之約 1 個人。

A 型血友病及 B 型血友病臨床上表現多個方面。小傷口及擦傷將不會導致大量出血，但外傷及手術會。患者亦將具有許多關節及肌肉出血且易於碰傷。關節積血或血液洩漏入關節為血友病之一種主要併發症，且可自發地或回應外傷發生。諸如膝、肘及踝之鉸鏈關節最頻繁地受影響。髖及肩部受影響頻率低的多，此係因為球窩關節在其周圍具有更多肌肉組織，因此更常保護其免於損傷。出血可引起嚴重劇痛、限制運動且導致包括滑液增生之二級併發症。此外，關節之復發出血可引起慢性滑膜炎，其可引起關節損壞，進而破壞滑膜、軟骨及骨骼。諸如顱內出血及中樞神經系統出血的危及生命之出血亦折磨血友病個體。顱內出血發生在約 10%之患有嚴重血友病的患者中，導致 30%之死亡率。相反，C 型血友病為較輕度血友病。罕見自發性出血，且血液洩漏入關節、軟組織及肌肉亦不常見。通常以輸入新鮮冰凍血漿（FFP）、FXI 替代療法治療出血，或對於局部性治療，諸如外部創傷或拔牙之治療，使用血纖蛋白膠。

A 型血友病或 B 型血友病之最常見療法為替代療法，其中向患者投予 FVIII 或 FIX。調配物可作為來源於血漿之產物或重組產物購得，現在重組蛋白為先前未經治療患者

之所選療法。儘管此等療法可極為成功，但若患者發展針對新近投予因子 VIII 或因子 IX 的抑制子，則出現併發症。抑制子為 IgG 抗體，主要為 IgG4 子類，其與 FVIII 或 FIX 反應且干擾促凝血功能。抑制子影響約 1/5 患有嚴重 A 型血友病之患者。大多數個體在投予第一次因子 VIII 輸液後不久發展此等抑制子，其通常在幼年早期，儘管個體在生命稍後階段亦發展該等抑制子。抑制子亦影響約 1/15 患有輕度或中度 A 型血友病之人。此等抑制子通常在成年期間發展，且不僅破壞所投予外源 FVIII，且亦破壞內源性 FVIII。因此，輕度及中度血友病患者變得嚴重。臨床上，根據再次暴露於 FVIII 時所經歷的回憶反應之強度，將具有抑制子的 A 型血友病患者分類為高及低反應者。抑制子影響約 1/100 患有 B 型血友病之患者。在大多數情況下，抑制子在治療因子 IX 之第一次輸液後發展且可伴隨有過敏性反應。

可使用本文中提供的經修飾之 FVII 多肽治療患有血友病之患者，尤其具有抑制子的血友病患者。已批准且許可重組 FVIIa 產品（NovoSeven, Novo Nordisk）用於治療具有針對 FVIII 或 FIX 之抑制子的 A 型血友病或 B 型血友病患者之出血事件，且用於在具有針對 FVIII 或 FIX 的抑制子之 A 型血友病或 B 型血友病患者之外科手術或侵襲性程序中預防出血。rFVIIa 治療增加凝血酶產生，同時繞過對 FVIIIa 及/或 FIXa 之需求。藉由 rFVIIa 與 TF 之交互作用在損傷部位起始凝血，引起初始 FX 活化、凝血酶產生及血小板活化。

可藉由 TF 依賴性及 TF 獨立性機制實現藉由 rFVIIa 完全凝血，其中所產生的一些凝血酶可由經活化血小板上 FX 受 rFVIIa 單獨之直接活化引起，rFVIIa 本身經由與磷脂膜之低親和力交互作用結合經活化血小板。

本文中提供的經修飾之 FVII 多肽可用於血友病療法，包括在外科手術介入或侵襲性程序中治療出血事件及預防出血。本文中的經修飾之 FVII 多肽可提供增強之 AT-III 抗性、增強之催化活性、增強之對 Zn^{2+}抑制作用之抗性、增強之 TFPI 抗性、改良之藥物動力學特性（諸如血清半衰期）、對經活化血小板增強之結合及/或親和力、對血清白蛋白增強之結合及/或親和力及/或對血小板整合素 $\alpha_{IIb}\beta_3$ 增強之結合及/或親和力。因此，FVII 多肽可以 TF 依賴性方式（諸如經由增強之 TFPI 抗性）及/或 TF 獨立性方式（諸如經由對經活化血小板增強之結合及/或親和力）顯示較高凝血活性。因此，可使用經修飾之 FVII 多肽傳遞對血友病之更有效療法。使用經修飾之 FVII 多肽之治療改良的實例包括例如（但不限於）較低劑量、較少及/或較低頻率之投藥、降低之副作用及增加之治療作用。

典型地，經修飾之 FVII 多肽係以經活化 FVII（FVIIa）多肽形式投予。例如，可藉由使用動物模型來測試經修飾之 FVII 多肽的療效。舉例而言，可以經修飾之 FVII 多肽治療抗體誘導之血友病小鼠或血友病之任何其他已知疾病模型。監測疾病症狀及表型之進展以評估經修飾之 FVII 多肽的作用。亦可諸如在臨床試驗中將經修飾之 FVII 多肽投予

個體以與安慰劑對照及/或使用未經修飾之 FVII 的對照相比較，活體內評估有效性。

b. FVII 缺乏

因子 VII 缺乏為影響 500000 人中之約 1 個人的自體隱性出血病症。FVII 缺乏在臨床上可為輕度、中度或嚴重，輕度至中度缺乏特徵在於手術及外傷後出血增加。患有嚴重 FVII 缺乏（小於 1% FVII 活性）之患者經歷類似於血友病之症狀。舉例而言，FVII 缺乏個體傾向於關節積血、自發性鼻出血、胃腸出血、尿路出血。亦已報導腦內出血及肌肉出血，而女性可經歷嚴重月經過多（月經大出血）。可藉由替代療法實現治療。已批准且許可重組 FVIIa 產品（NovoSeven®，Novo Nordisk）用於治療患有先天性 FVII 缺乏的患者之出血事件，且用於在患有先天性 FVII 缺乏的患者之外科手術或侵襲性程序中預防出血。因此，可類似地使用本文的經修飾之 FVII 多肽。本文中提供的經修飾之 FVII 多肽可用於在 FVII 缺乏患者之外科手術或侵襲性程序中治療出血事件及預防出血。舉例而言，可藉由靜脈內快速注射向表現嚴重 FVII 缺乏的患有顱內出血的新生患者投予經修飾之 FVII 多肽以實現凝血且保持止血。通常，經修飾之 FVII 多肽係以經活化 FVII（FVIIa）多肽形式投予。

c. 其他

可以本文中提供的 FVII 多肽治療其他出血病症以促進凝血。因子 V 及 X 之先天性缺乏亦表現為凝血時間增加且可潛在地以投予治療劑量之 FVII 治療。舉例而言，可向患

有因子 X 缺乏之患者投予 rFVIIa 以控制與脾切除術相關的出血（Boggio 等人 (2001) Br J Haematol 112:1074-1075）。亦可使用本文中提供的經修飾之 FVII 多肽治療與溫韋伯氏病（vWD）相關的自發性及手術相關出血事件。VWD 為由血液凝結蛋白溫韋伯氏因子（vWF）之缺陷或缺乏所引起的出血病症且據估算在群體中發生率為 1%至 2%。具有 vWD 碰傷之個體易於患有復發性鼻出血，拔牙、扁桃體切除術或其他手術後出血，且女性患者可具有增加之月經出血。可使用經修飾之 FVII 多肽改善 vWD 患者的自發性及手術相關出血（von Depka 等人 (2006) Blood Coagul Fibrin 17:311-316）。其他血小板相關出血病症，諸如格蘭士文氏血小板功能不全及赫曼斯基-普德拉克症候群，亦與降低之內源性凝結活性相關。亦可藉由治療劑量之經修飾之 FVII 多肽控制患有血小板相關出血病症的患者之過度自發性或手術相關出血。舉例而言，可以經修飾之 FVII 多肽在手術之前、期間及/或之後治療患有格蘭士文氏血小板功能不全之經歷手術的患者以預防大失血（van Buuren 等人 (2002) Dig Dis Sci 47:2134-2136）。通常，經修飾之 FVII 多肽係以經活化 FVII（FVIIa）多肽形式投予。

2. 後天性出血病症

a. 化學療法-後天性血小板減少症

出血病症亦可為後天性而非先天性的。舉例而言，諸如對白血病及其他癌症之化學療法治療可引起血小板減少症。此可能由於接受化學療法的患者之骨髓中血小板產生

損失且典型地發生在藥物治療 6-10 天之後。通常藉由用來預防可由血小板缺乏引起之任何異常自發性出血的血小板、紅血球或血漿輸入治療後天性血小板減少症。亦可藉由投予治療量之本文中提供的經修飾之 FVII 多肽控制患有化學療法誘發之血小板減少症或任何其他後天性或先天性血小板減少症的患者之出血。舉例而言，可靜脈內快速注射向具有諸如胃腸道不受控出血之血小板減少症患者投予治療量之 FVII 多肽以停止出血（Gerotziafas 等人 (2002) Am J Hematol 69:219-222)。通常，經修飾之 FVII 多肽係以經活化 FVII（FVIIa）多肽形式投予。

b. 其他凝血病

可使用本文中提供的經修飾之 FVII 多肽治療其他後天性凝血病。凝血病可由包括（但不限於）以下之病狀引起：爆發性肝衰竭（FHF；諸如由肝毒性藥物、毒素、代謝疾病、傳染性疾病及局部缺血所引起），其他肝臟疾病，包括硬化及與威爾森氏症（Wilson’s disease）相關的疾病，維生素 K 缺乏（諸如由抗生素治療或飲食所引起）、溶血性尿毒癥綜合征、血栓形成血小板減少症（TTC）及彌漫性血管內凝血病（DIC）。通常藉由輸入血漿、紅血球（RBC）或血小板進行習知治療，但其可能不成功。在一具體實例中，可將經修飾之 FVII 多肽投予患有 FHF 經歷侵襲性程序之患者以預防出血。使用新鮮冰凍血漿（FFP）之習知治療通常並不成功且可要求大量血漿，從而引起容量過載及全身水腫（水腫流體廣泛滲入皮下結締組織中）。在諸如肝活組

織檢查或肝臟移植之侵襲性手術期間、之前及/或之後，藉由靜脈內快速注射治療量之經修飾之 FVII 多肽來治療可預防出血且在 FHF 患者中形成止血。可藉由血液之 PT 監測患者以確定治療功效（Shami 等人 (2003) Liver Transpl 9:138-143）。在另一具體實例中，可向患有與凝血病相關之嚴重出血（諸如與肝臟功能異常及 DIC 相關的嚴重剖宮產術後腹內出血）的對習知輸血並不作出反應之患者投予 FVII（Moscardo 等人 (2001) Br J Haematol 113:174-176）。另外，可使用經修飾之 FVII 多肽治療新生兒及兒童患者之凝血病。在一特定具體實例中，新生兒及兒童患者對諸如 RBC 及血小板輸入之習知治療並不作出反應。舉例而言，可向患有與增加之 PT 相關的嚴重肺出血之對 RBC 及血小板輸入並不作出反應之新生兒投予經修飾之 FVII 多肽以降低 PT 且形成止血（Olomu 等人 (2002) J Perinatol 22:672-674）。與未經修飾之 FVII 多肽相比，本文中提供的經修飾之 FVII 多肽展現增強之凝血活性，且因此可例如以較低劑量、較低頻率且具有較小副作用情形下投予。通常，經修飾之 FVII 多肽係以經活化 FVII（FVIIa）多肽形式投予。

c. 移植-後天性出血

由於血小板減少，骨髓移植（BMT）及幹細胞移植（SCT）後之嚴重出血為與此等程序相關之相對常見且危及生命之併發症。舉例而言，彌漫性肺泡出血（DAH）為在移植群體中具有 1-21%之估算發生率及 60-100%之死亡率的 BMT

之肺部併發症。該等出血事件之習知治療包括皮質類固醇治療及輸入血漿、血小板及/或 RBC，儘管此等治療在很大程度上並不成功，總體死亡率為約 50%(Hicks 等人 (2002) Bone Marrow Transpl 30:975-978)。可在存在或不存在皮質類固醇及/或血小板輸液並行治療之情況下，進行藉由靜脈內快速注射投予 FVII 以治療 DAH 且形成止血(Hicks 等人 (2002) Bone Marrow Transpl 30:975-978)。與未經修飾之 FVII 多肽相比，本文中提供的經修飾之 FVII 多肽展現增強之凝血活性，且因此可例如以較低劑量、較低頻率經較短治療持續時間且對於相同生物活性及功效而言具有較小副作用情形下投予。通常，經修飾之 FVII 多肽係以經活化 FVII(FVIIa)多肽形式投予。

d. 抗凝血療法誘發之出血

經歷用於治療諸如血栓栓塞症之病狀的抗凝血療法之患者可在急性投予諸如華法林、肝素及方達珀魯(fondaparinux)之抗凝劑後展現出血事件或由於長期使用該等療法發展出血性病症。用於出血事件之治療典型地包括投予諸如維生素 K、血漿、外源 FIX 及魚精蛋白之促凝血劑以中和肝素。亦可投予外源 FVII 以中和抗凝劑之作用，增加 PT、aPTT 及/或凝血之其他標誌且形成止血(Deveras 等人 (2002) Ann Inten Med 137:884-888)。本文中提供的經修飾之 FVII 多肽可用於治療以控制由於抗凝血治療而患上後天性出血病症的患者之出血事件。通常，經修飾之 FVII 多肽係以經活化 FVII(FVIIa)多肽形式投予。

e. 後天性血友病

因子 VIII 抑制子可在健康個體中另外自發地產生，導致稱為「後天性血友病」之病狀。後天性血友病為罕見病狀，年發生率為每百萬群體 0.2-1.0 例。自體抗體主要為 IgG4 抗體，其當與 FVIII 結合時，藉由干擾凝血酶裂解、溫韋伯氏因子交互作用及/或磷脂結合而抑制 FVIII 活性。此在約 87%之受影響患者中導致危及生命的出血。與患有遺傳性血友病之主要在關節及肌肉中出血的患者相對照，常見出血部位為皮膚、黏膜、肌肉及腹膜後腔。可以經活化凝血酶原複合物濃縮物或重組經活化因子 VII(NovoSeven®，Novo Nordisk）治療後天性血友病以控制出血事件。與未經修飾之 FVII 多肽相比，本文中提供的經修飾之 FVII 多肽展現增強之凝血活性，且因此可例如以較低劑量、較低頻率經較短治療持續時間且對於相同生物活性及功效而言具有較小副作用情形下投予。通常，經修飾之 FVII 多肽係以經活化 FVII（FVIIa）多肽形式投予。

3. 外傷及手術出血

可使用 FVII 多肽作為治療具有正常凝血系統之個體的與圍手術期及外傷性失血相關之出血的療法。舉例而言，可向患者投予 FVII 多肽以促進凝血且減少與手術相關的失血，且進一步降低輸血需求。在一具體實例中，可向經歷恥骨後前列腺切除術的個體投予 FVII 多肽。恥骨後前列腺切除術通常與大失血及後續輸血需要相關。經歷此類或類似手術之個體可在手術階段初期靜脈內快速注射給予治療

量之 FVII 以藉由增強手術部位之凝血而減少圍手術期失血。失血之減少使得此等患者消除對輸血之需要(Friederich 等人 (2003) Lancet 361:201-205)。可向具有正常凝血經歷其他類型之手術的患者投予 FVII 多肽以實現快速止血且預防失血。典型地療法可使用以經活化形式(亦即 FVIIa)投予之 FVII 以減少手術期出血的手術程序之非限制性實例包括(但不限於)貴門瓣手術(Al Douri 等人 (2000) Blood Coag Fibrinol 11:S121-S127)、主動脈瓣置換(Kastrup 等人 (2002) Ann Thorac Surg 74:910-912)、復發性血管外皮瘤切除術(Gerlach 等人 (2002) J Neurosurg 96:946-948)、癌症手術(Sajdak 等人 (2002) Eur J Gynaecol Oncol 23:325-326)及十二指腸潰瘍手術(Vlot 等人 (2000) Am J Med 108:421-423)。用 FVII 治療可促進手術部位之止血且減少或預防失血,藉此減少或消除輸血需要。與未經修飾之 FVII 多肽相比,本文中提供的經修飾之 FVII 多肽經設計以展現增強之凝血活性,且因此可例如以較低劑量、較低頻率且具有較小副作用情形下投予。通常,經修飾之 FVII 多肽係以經活化 FVII(FVIIa)多肽形式投予。

亦可使用因子 VII 多肽來促進具有外傷性損傷之個體的凝血且預防失血。外傷經定義為外在性作用物對活組織的損傷,且為美國死亡之第四大原因。外傷經分類為鈍外傷(引起內壓縮、器官損壞及內出血)或穿透性外傷(作用物穿透身體且破壞組織、血管及器官,引起外出血之後果)。外傷可由包括(但不限於)以下之數種事件造成:

車輛事故（導致鈍及/或穿透性外傷）、槍射傷（導致穿透性外傷）、刺穿創傷（導致穿透性外傷）、機械事故（導致穿透性及/或鈍外傷）及自顯著高度跌下（導致穿透性及/或鈍外傷）。由外傷導致之不受控出血造成相關死亡率中之大多數。彌漫性凝血病為與外傷患者相關的相對常見併發症，其發生在多達 25-36%之個體中。凝血病可在損傷後早期發展，其由諸如凝血因子及血小板稀釋及消耗、纖維蛋白溶解、酸毒症及體溫過低之多種因素引起。習知控制涉及藉由輸入新鮮冰凍血漿（FFP）、血小板、RBC 及/或冷沈澱物進行替代療法、矯正酸毒症及治療體溫過低。此等步驟通常不足以停止出血及預防死亡。藉由投予治療量之 FVII 來治療可促進外傷患者凝血且減少失血。舉例而言，除外科手術之外，亦可向具有槍射傷之大量出血的患者投予 FVII 以控制凝血病出血（Kenet 等人 (1999) Lancet 354:1879）。使用 FVII 之凝血療法可有效減少具有鈍及穿透外傷的患者之失血及出血（Rizoli 等人 (2006) Crit Care 10:R178）。與未經修飾之 FVII 多肽相比，本文中提供的經修飾之 FVII 多肽經設計以展現增強之凝血活性，且因此可例如以較低劑量、較低頻率且具有較小副作用情形下投予。通常，經修飾之 FVII 多肽係以經活化 FVII（FVIIa）多肽形式投予。

I. 組合療法

可組合其他治療劑或程序，在其他治療劑或程序之前，與其他治療劑或程序間歇或在其他治療劑或程序之後

投予本文所述之任何經修飾之 FVII 多肽，該等治療劑或程序包括（但不限於）其他生物製品、小分子化合物及手術。對於包括所有以上所例示者之 FVII（包括 FVIIa 及 rFVIIa）經指示或已使用且其他藥劑及治療可用之任何疾病或病狀，FVII 可與其組合使用。因此，可類似地使用本文中提供的經修飾之 FVII 多肽。視待治療疾病或病狀而定，例示性組合包括（但不限於）與其他血漿純化或重組凝血因子、促凝血劑（諸如維生素 K、維生素 K 衍生物及蛋白質 C 抑制子）、血漿、血小板、紅血球及皮質類固醇之組合。

J. 製品及套組

經修飾之 FVII 多肽或編碼經修飾之 FVII 多肽之核酸或其衍生物或生物活性部分的醫藥化合物可以含有封裝材料、有效治療止血疾病或病症之醫藥組成物及指示經修飾之 FVII 多肽或核酸分子用於治療止血疾病或病症之標籤的製品形式封裝。

本文中提供之製品含有封裝材料。熟習此項技術者熟知用於封裝醫藥產品之封裝材料。參見例如美國專利第 5,323,907 號、第 5,052,558 號及第 5,033,352 號，其各自全部併入本文中。醫藥封裝材料之實例包括（但不限於）起泡包裝、瓶、管、吸入器、泵、袋、小瓶、容器、注射器、瓶及適於所選調配物及預期投藥及治療模式的任何封裝材料。涵蓋本文中提供之化合物及組成物的多種調配物作為用於任何止血疾病或病症的多種療法。

亦可以套組形式提供經修飾之 FVII 多肽及核酸分子。

套組可包括本文所述之醫藥組成物及用於投藥之項目。舉例而言，可以用於投藥之諸如注射器、吸入器、劑量杯、滴管或敷塗器的裝置提供經修飾之 FVII。套組可視情況包括應用之用法說明書，包括劑量、給藥方案及投藥模式用法說明書。套組亦可包括本文所述之醫藥組成物及用於診斷之項目。舉例而言，該套組可包括用於量測 FVII 的濃度、量或活性或個體之 FVII 調節系統之項目。

以下實施例僅出於說明性目的包括在本文中，且不欲限制本發明之範疇。

K. 實施例

實施例 1

FVII 之選殖及表現

A. 選殖 FVII

將編碼 466 個胺基酸之人類 FVII 同功異型物前驅體多肽（P08709；闡明於 SEQ ID NO: 1 中）的核苷酸選殖入含有細胞巨大病毒（CMV）啟動子的哺乳動物表現載體 pCMV Script（Stratagene；SEQ ID NO: 99）中。簡言之，分別使用 CBO-125（SEQ ID NO: 100）及 CBO-126（SEQ ID NO: 101）寡核苷酸作為正向及反向引子以藉由 PCR 使用人類 FVII cDNA（Invitrogen）作為模板擴增 FVII 序列。CBO-125 引子含有 BamHI 限制性位點（粗體）、Kozak 序列（雙下劃線），接著為與 FVII cDNA 序列的 5' 端同源之 18 個核苷酸（下劃線），包括 ATG 起始密碼子。CBO-126 引子含有 EcoRI 限制性位點（粗體）、終止密碼子（雙下劃線）

及與 FVII cDNA 序列之 3' 端同源的 21 個核苷酸(下劃線)。

CBO-125 正向引子

5' gcatcatgacgtgacggatccgccaccatggtctcccaggccctc 3'

CBO-126 反向引子

5' gatcgtacgatacgtgaattcctagggaaatggggctcgcaggag 3'

如製造商所推薦，聯合 KoD HiFi PCR 套組（EMD Biosciences）使用標準 PCR 反應及熱循環條件。以 BamH I 及 EcoR I 限制酶消化 PCR 產物且使用標準分子技術將其連接至 pCMV Script 載體之 BamH I 及 EcoR I 限制性位點中。接著，將載體轉型入大腸桿菌中。使所選菌落生長且收集細菌細胞用於使用常規分子生物學技術純化質體。

B. 產生 FVII 變異體

根據製造商用法說明書，使用特異性設計之充當將特定突變併入新近合成之 DNA 的引子之寡核苷酸使用 QuikChange II XL 定點誘變套組（Stratagene）產生 FVII 變異體。QuikChange 方法涉及藉由 PfuUltra 高保真度 DNA 聚合酶線性擴增模板 DNA。在循環期間，使用含有作為模板之所選殖 FVII cDNA 序列之經純化雙鏈超螺旋 pCMV Script 載體延伸包括所需突變之互補引子。引子之延伸使得所關注之突變併入新近合成鏈中且產生具有交錯缺口的突變型質體。擴增後，以消化來源於大腸桿菌的 pCMV Script 載體之 dam 甲基化親本鏈之 Dpn I 處理核酸。此舉產生新近合成之並未甲基化的突變型質體之「選擇」。將含有所需突變之載體 DNA 轉型入 XL10-Gold 超勝任大腸桿菌細胞

中，其中細菌連接酶修復缺口且允許正常複製發生。

下表 13 闡明所產生的 FVII 變異體。在一些情況下，產生將血小板整合素 $\alpha_{IIb}\beta_3$ 之結合序列插入 FVII 多肽之不同區域中的 FVII 變異體。插入三種不同整合素 $\alpha_{IIb}\beta_3$ 結合序列中之一者：SFGRGDIRNV（SEQ ID NO: 110）；CSFGRGDIRNVC（SEQ ID NO: 111）；或 GGGSCSFGRGDIRNVC（SEQ ID NO: 112）。將整合素 $\alpha_{IIb}\beta_3$ 結合序列插入在（根據成熟 FVII 編號）胺基酸殘基 P406 之後 FVII 多肽之的 C 末端，或藉由缺失且置換 FVII 胺基酸殘基 S103 為 S111、置換 H115 為 S126 或置換 T127 為 P134（根據成熟 FVII 編號）插入。亦產生插入血清白蛋白結合序列之其他 FVII 變異體。此等 FVII 變異體含有 7 種不同血清白蛋白結合序列中之一者：QRLMEDICLPRWGCLWEDDF（SEQ ID NO: 103）、IEDICLPRWGCLWE（SEQ ID NO: 104）、DICLPRWGCLWED（SEQ ID NO: 105）、IEDICLPRWGCLW（SEQ ID NO: 106）、GGGSIEDICLPRWGCLW（SEQ ID NO: 107）、DICLPRWGCLWED（SEQ ID NO: 108）或 GGGSDICLPRWGCLWED（SEQ ID NO: 109）。將血清白蛋白結合序列插入在（根據成熟 FVII 編號）胺基酸殘基 P406 之後 FVII 多肽之的 C 末端，或藉由缺失且置換 FVII 胺基酸殘基 S103 為 S111、置換 H115 為 S126 或置換 T127 為 P134（根據成熟 FVII 編號）插入。「Gla 交換 FIX」FVII 變異體（亦即內源性 Gla 域已經來自 FIX 的 Gla 域置換之 FVII

多肽）在 N 末端含有 SEQ ID NO: 83 之胺基酸殘基 Y1 至 Y45。在一些實例中，「Gla 交換 FIX」變異體在 FIX Gla 域部分中含有一或多個胺基酸取代。處於 FIX Gla 域部分內之突變由大括號包圍且使用對應於成熟野生型 FIX 多肽或 SEQ ID NO: 83 中所闡明之野生型 FIX Gla 域的胺基酸位置之胺基酸位置引述。舉例而言，{Gla 交換 FIX/M19K}表示經修飾之 FVII 多肽含有異源 FIX Gla 域，其中 SEQ ID NO: 83 中所闡明的 FIX Gla 域的位置 19 之甲硫胺酸經離胺酸置換。在下表 13 中，呈示血小板整合素 $\alpha_{IIb}\beta_3$ 或血清白蛋白結合序列插入 FVII 多肽中之胺基酸殘基及結合序列之胺基酸序列。舉例而言，H115S126 缺失插入 QRLMEDICLPRWGCLWEDDF 指示胺基酸殘基 H115 至 S126 已缺失且經具有胺基酸序列 QRLMEDICLPRWGCLWEDDF（SEQ ID NO: 103）之血清白蛋白結合序列置換。

表 13. 因子 VII 變異體

變異體（成熟 FVII 編號）	變異體（胰凝乳蛋白酶編號）	FVII 多肽 SEQ ID NO
野生型	野生型	3
Q286N	Q143N	113
Q286E	Q143E	114
Q286D	Q143D	115
Q286S	Q143S	116
Q286T	Q143T	117
Q286R	Q143R	118
Q286K	Q143K	119
Q286A	Q143A	120
Q286V	Q143V	121
Q286M	Q143M	122
Q286L	Q143L	123
Q286Y	Q143Y	124
Q286R/ Gla 交換 FIX	Q143R/ Gla 交換 FIX	131
Q286R/H257A	Q143R/H117A	132
Q286R/S222A	Q143R/S82A	133
Q286R/S222A/H257A	Q143R/S82A/H117A	134
Q286R/S222A/ Gla 交換 FIX	Q143R/S82A/Gla 交換 FIX	135

Q286R/H257A/ Gla 交換 FIX	Q143R/H117A/Gla 交換 FIX	136
Q286R/S222A/H257A/Gla 交換 FIX	Q143R/S82A/H117A/Gla 交換 FIX	137
Q286R/M298Q	Q143R/M156Q	138
Q286R/M298Q/K341Q	Q143R/M156Q/K192Q	139
Q286R/M298Q/K199E	Q143R/M156Q/K60cE	140
Q286R/M298Q/Gla 交換 FIX	Q143R/M156Q/Gla 交換 FIX	141
Q286R/Q366V	Q143R/Q217V	142
Q286R/A292N/A294S/Q366V	Q143R/A150N/A152S/Q217V	143
A175S/Q286R/Q366V	A39S/Q143R/Q217V	144
S222A/Q286R/Q366V	S82A/Q143R/Q217V	145
H257S/Q286R	H117S/Q143R	146
H257S/Q286R/Q366V	H117S/Q143R/Q217V	147
S222A/H257A/Q286R/Q366V	S82A/H117A/Q143R/Q217V	148
Q286R/H373A	Q143R/H224A	149
S222A/H257A/Q286R/M298Q	S82A/H117A/Q143R/M156Q	150
V158D/E296V/M298Q	V158D/E296V/M298Q	158
Q286R/K341D	Q143R/K192D	151
Q286R/Q366D	Q143R/Q217D	152
Q286R/Q366N	Q143R/Q217N	153
Q286R/M298Q/Q366D	Q143R/M156Q/Q217D	154
Q286R/M298Q/Q366N	Q143R/M156Q/Q217N	155
Q286R/H373F	Q143R/H224F	156
Q286R/M298Q/H373F	Q143R/M156Q/H224F	157
T239S	T99S	159
T239N	T99N	160
T239Q	T99Q	161
T239V	T99V	162
T239L	T99L	163
T239H	T99H	164
T239I	T99I	165
P321K	P170iK	166
P321E	P170iE	167
P321Y	P170iY	168
P321S	P170iS	169
Q366D	Q217D	170
Q366E	Q217E	171
Q366N	Q217N	172
Q366T	Q217T	173
Q366S	Q217S	174
Q366V	Q217V	175
Q366I	Q217I	176
Q366L	Q217L	177
Q366M	Q217M	178
H373D	H224D	179
H373E	H224E	180
H373S	H224S	181
H373F	H224F	182
H373A	H224A	183
Q366D/H373E	Q217D/H224E	184
Q366V/H373V	Q217V/H224V	185
Q366V/H373L	Q217V/H224L	186
Q366V/H373I	Q217V/H224I	187
K161S	K24S	188
K161A	K24A	189
K161V	K24V	190
H216S	H76S	191
H216A	H76A	192
H216K	H76K	193
H216R	H76R	194

S222A	S82A	195
S222K	S82K	196
S222V	S82V	197
S222D	S82D	200
S222N	S82N	198
S222E	S82E	199
H257A	H117A	201
H257S	H117S	202
S222K/H257A	S82K/H117A	203
H216A/H257A	H76A/H117A	204
H216A/S222A	H76A/S82A	205
S52A	S[52]A	206
S60A	S[60]A	207
E394N/P395A/R396S	E245N/P246A/R247S	208
R202S	R62S	209
A292N/A294S	A150N/A152S	210
G318N	G170fN	211
A175S	A39S	212
K109N	K-26N	213
A122N/G124S	A[122]N/G[124]S	214
A51N	A-84N	215
T130N/E132S	T[130]N/E[132]S	216
S50A/S62A	S[50]A/S[62]A	217
A122N/G124S/ E394N/P395A/R396S	A[122]N/G[124]S / E245N/P246A/R247S	218
A122N/G124S/ E394N/P395A/R396S/ G318N	A[122]N/G[124]S/E245N /P246A/R247S/G170fN	219
S52N/P54S	S[52]N/P[54]S	220
S119N/L121S	S[119]N/L[121]S	221
T128N/P129A	T[128]N/P[129]A	222
Q66N/Y68S	Q[66]N/Y[68]S	223
S52N/P54S/A122N/G124S/E394N/P395A/ R396S	S[52]N/P[54]S/A[122]N/G[124]S /E245N/P246A/R247S	224
K109N/A292N/A294S	[K109N] /A150N/A152S	225
K109N/A175S	[K109N] /A39S	226
V158T/L287T/M298K	V21T/L144T/M156K	256
V158D/L287T/M298K	V21D/L144T/M156K	257
S103S111 缺失插入 QRLMEDICLPRWGCLWEDDF	S[103]S[111]缺失插入 QRLMEDICLPRWGCLWEDDF	227
H115S126 缺失插入 QRLMEDICLPRWGCLWEDDF	H[115]S[126]缺失插入 QRLMEDICLPRWGCLWEDDF	228
T128P134 缺失插入 QRLMEDICLPRWGCLWEDDF	T[128]P[134]缺失插入 QRLMEDICLPRWGCLWEDDF	229
S103S111 缺失插入 IEDICLPRWGCLWE	S[103]S[111]缺失插入 IEDICLPRWGCLWE	230
H115S126 缺失插入 IEDICLPRWGCLWE	H[115]S[126]缺失插入 IEDICLPRWGCLWE	231
T128P134 缺失插入 IEDICLPRWGCLWE	T[128]P[134]缺失插入 IEDICLPRWGCLWE	232
S103S111 缺失插入 DICLPRWGCLWED	S[103]S[111]缺失插入 DICLPRWGCLWED	233
H115S126 缺失插入 DICLPRWGCLWED	H[115]S[126]缺失插入 DICLPRWGCLWED	234
T128P134 缺失插入 DICLPRWGCLWED	T[128]P[134]缺失插入 DICLPRWGCLWED	235
P406 插入 IEDICLPRWGCLW	P257 插入 IEDICLPRWGCLW	236
P406 插入 GGGSIEDICLPRWGCLW	P257 插入 GGGSIEDICLPRWGCLW	237
P406 插入 DICLPRWGCLWED	P257 插入 DICLPRWGCLWED	238
P406 插入 GGGSDICLPRWGCLWED	P257 插入 GGGSDICLPRWGCLWED	239

S103S111 缺失插入 SFGRGDIRNV	S[103]S[111]缺失插入 SFGRGDIRNV	240
H115S126 缺失插入 SFGRGDIRNV	H[115]S[126]缺失插入 SFGRGDIRNV	241
T127P134 缺失插入 SFGRGDIRNV	T[128]P[134]缺失插入 SFGRGDIRNV	242
P406 插入 CSFGRGDIRNVC	P257 插入 CSFGRGDIRNVC	243
P406 插入 GGGSCSFGRGDIRNVC	P257 插入 GGGSCSFGRGDIRNVC	244
S222A/ Gla 交换 FIX	S82A/ Gla 交换 FIX	245
H257A/ Gla 交换 FIX	H117A/ Gla 交换 FIX	246
S222A/H257A/ Gla 交换 FIX	S82A/H117A/ Gla 交换 FIX	247
S222A/M298Q	S82A/M156Q	248
H257A/M298Q	H117A/M156Q	249
S222A/H257A/M298Q	S82A/H117A/M156Q	250
S222A/A292N/A294S/Q366V	S82A/A150N/A152S/Q217V	251
A175S/S222A/Q366V	A39S/S82A/Q217V	252
S222A/Q366V	S82A/Q217V	253
H257S/Q366V	H117S/Q217V	254
S222A/H373A	S82A/H224A	255
S103S111 缺失插入 IEDICLPRWGCLWE/G237V	S[103]S[111]缺失插入 IEDICLPRWGCLWE/G97V	258
S103S111 缺失插入 DICLPRWGCLWED/G237V	S[103]S[111]缺失插入 DICLPRWGCLWED/G97V	259
H115S126 缺失插入 QRLMEDICLPRWGCLWEDDF/G237V	H[115]S[126]缺失插入 QRLMEDICLPRWGCLWEDDF/G97V	260
H115S126 缺失插入 IEDICLPRWGCLWE/G237V	H[115]S[126]缺失插入 IEDICLPRWGCLWE/G97V	261
H115S126 缺失插入 DICLPRWGCLWED/G237V	H[115]S[126]缺失插入 DICLPRWGCLWED/G97V	262
T128P134 缺失插入 QRLMEDICLPRWGCLWEDDF/G237V	T[128]P[134]缺失插入 QRLMEDICLPRWGCLWEDDF/G97V	263
T128P134 缺失插入 IEDICLPRWGCLWE/G237V	T[128]P[134]缺失插入 IEDICLPRWGCLWE/G97V	264
S103S111 缺失插入 QRLMEDICLPRWGCLWEDDF/G237V	S[103]S[111]缺失插入 QRLMEDICLPRWGCLWEDDF/G97V	265
T128P134 缺失插入 DICLPRWGCLWED/G237V	T[128]P[134]缺失插入 DICLPRWGCLWED/G97V	266
S103S111 缺失插入 SFGRGDIRNV/G237V	S[103]S[111]缺失插入 SFGRGDIRNV/G97V	267
H115S126 缺失插入 SFGRGDIRNV/G237V	H[115]S[126]缺失插入 SFGRGDIRNV/G97V	268
T128P134 缺失插入 SFGRGDIRNV/G237V	T[128]P[134]缺失插入 SFGRGDIRNV/G97V	269
M298Q/H373F	M156Q/H224F	270
S119N/L121S/A175S	S[119]N/L[121]S/A39S	271
T128N/P129A/A175S	T[128]N/P[129]A/A39S	272
A122N/G124S/A175S	A[122]N/G[124]S/A39S	273
{Gla 交换 FIX/E40L}/Q286R/M298Q	{Gla 交换 FIX/E[40]L}/Q143R/M156Q	274
{Gla 交换 FIX/K43I}/Q286R/M298Q/	{Gla 交换 FIX/K[43]I}/Q143R/M156Q	275
{Gla 交换 FIX/Q44S}/Q286R/M298Q/	{Gla 交换 FIX/Q[44]S}/Q143R/M156Q	276
Gla 交换 FIX/M19K}/Q286R/M298Q/	{Gla 交换 FIX/M[19]K}/Q143R/M156Q	277
{Gla 交换 FIX/M19K/E40L/K43I/Q44S}/Q286R/M298Q/	{Gla 交换 FIX/M[19]K/E[40]L/K[43]I/Q[44]S}/Q143R/M156Q	278
T128N/P129A/Q286R	T[128]N/P[129]A/Q143R	279
T128N/P129A/Q286R/M298Q	T[128]N/P[129]A/Q143R/M156Q	280
T128N/P129A/Q286R/H373F	T[128]N/P[129]A/Q143R/H224F	281
V158D/Q286R/E296V/M298Q	V21D/Q143R/E154V/M156Q	282

T128N/P129A/V158D/E296V/M298Q	T[128]N/P[129]A/V21D/E154V/M156Q	283
T128N/P129A/S222A	T[128]N/P[129]A/S82A	284
Gla 交換 FIX/T128N/P129A/S222A/Q286R	Gla 交換 FIX/T[128]N/P[129]A/S82A/Q143R	285
Gla 交換 FIX/T128N/P129A/Q286R/M298Q	Gla 交換 FIX/T[128]N/P[129]A/Q143R/M156Q	286
T128N/P129A/S222A/H257A/Q286R/M298Q	T[128]N/P[129]A/S82A/H117A/Q143R/M156Q	287
T128N/P129A/Q286R/M298Q/H373F	T[128]N/P[129]A/Q143R/M156Q/H224F	288
S52A/S60A/V158D/E296V/M298Q	S[52]A/S[60]A/V21D/E154V/M156Q	289
S52A/S60A/Q286R	S[52]A/S[60]A/Q143R	290
S52A/S60A/S222A	S[52]A/S[60]A/S82A	291
Gla 交換 FIX/S52A/S60A/S222A/Q286R	Gla 交換 FIX/S[52]A/S[60]A/S82A/Q143R	292
S52A/S60A/Q286R/M298Q	S[52]A/S[60]A/Q143R/M156Q	293
S52A/S60A/S222A/H257A/Q286R/M298Q	S[52]A/S[60]A/S82A/H117A/Q143R/M156Q	298
S52A/S60A/Q286R/H373F/	S[52]A/S[60]A/Q143R/H224F	296
S52A/S60A/ Q286R/M298Q/H373F	S[52]A/S[60]A/Q143R/M156Q/H224F	297
V158D/T239V/E296V/M298Q	V21D/T99V/E154V/M156Q	298
T239V/Q286R	T99V/Q143R	299
S222A/T239V	S82A/T99V	300
Gla 交換 FIX/S222A/T239V/Q286R	Gla 交換 FIX/S82A/T99V/Q143R	301
T239V/Q286R/M298Q	T99V/Q143R/M156Q	302
S222A/T239V/H257A/Q286R/M298Q	S82A/T99V/H117A/Q143R/M156Q	303
Gla 交換 FIX/T239V/Q286R/M298Q	Gla 交換 FIX/T99V/Q143R/M156Q	304
T239V/Q286R/H373F	T99V/Q143R/H224F	305
T239V/Q286R/M298Q/H373F	T99V/Q143R/M156Q/H224F	306
V158D/T239I/E296V/M298Q	V21D/T99I/E154V/M156Q	307
T239I/Q286R	T99I/Q143R	308
S222A/T239I	S82A/T99I	309
Gla 交換 FIX/S222A/T239I/Q286R	Gla 交換 FIX/S82A/T99I/Q143R	310
T239I/Q286R/M298Q	T99I/Q143R/M156Q	311
S222A/T239I/H257A/Q286R/M298Q	S82A/T99I/H117A/Q143R/M156Q	312
Gla 交換 FIX/T239I/Q286R/M298Q	Gla 交換 FIX/T99I/Q143R/M156Q/	313
T239I/Q286R/H373F	T99I/Q143R/H224F	314
T239I/Q286R/M298Q/H373F	T99I/Q143R/M156Q/H224F	315
Gla 交換 FIX/S222A/Q286R/H373F	Gla 交換 FIX/S82A/Q143R/H224F	316
Gla 交換 FIX/S222A/Q286R/M298Q	Gla 交換 FIX/S82A/Q143R/M156Q	317
Gla 交換 FIX/S222A/Q286R/M298Q/H373F	Gla 交換 FIX/S82A/Q143R/M156Q/H224F	318
V158D/E296V/M298Q/H373F	V21D/E154V/M156Q/H224F	319
V158D/Q286R/E296V/M298Q/H373F	V21D/Q143R/E154V/M156Q/H224F	320
H257A/Q286R/M298Q	H117A/Q143R/M156Q	321
H257S/Q286R/M298Q	H117S/Q143R/M156Q	322
Gla 交換 FIX/S222A/H257S/Q286R/	Gla 交換 FIX/S82A/H117S/Q143R	323
S222A/H257S/Q286R/M298Q	S82A/H117S/Q143R/M156Q	324
H257S/Q286R/M298Q/H373F	H117S/Q143R/M156Q/H224F	325
S222A/Q286R/M298Q/H373F	S82A/Q143R/M156Q/H224F	326
Gla 交換 FIX/Q366V	Gla 交換 FIX/Q217V	327
S222A/Q286R/M298Q	S82A/Q143R/M156Q	328
T28N/P129A/A175S/Q366V	T[128]N/P[129]A/A39S/Q217V	329
A122N/G124S/A175S/Q366V	A[122]N/G[124]S/A39S/Q217V	330
T128N/P129A/A175S/S222A	T[128]N/P[129]A/A39S/S82A	331
A122N/G124S/A175S/S222A	A[122]N/G[124]S/A39S/S82A	332
T128N/P129A/A175S/Q286R	T[128]N/P[129]A/A39S/Q143R	333
A122N/G124S/A175S/Q286R	A[122]N/G[124]S/A39S/Q143R	334
Gla 交換	Gla 交換	335

FIX/T128N/P129A/A175S/S222A/Q286R	FIX/T[128]N/P[129]A/A39S/S82A/Q143R	
Gla 交換 FIX/A122N/G124S/A175S/S222A/Q286R	Gla 交換 FIX/A[122]N/G[124]S/A39S/S82A/Q143R	336
T128N/P129A/A175S/Q286R/M298Q	T[128]N/P[129]A/A39S/Q143R/M156Q	337
A122N/G124S/A175S/Q286R/M298Q	A[122]N/G[124]S/A39S/Q143R/M156Q	338
T128N/P129A/A175S/S222A/H257A/Q286R/M298Q	T[128]N/P[129]A/A39S/S82A/H117A/Q143R/M156Q	339
A122N/G124S/A175S/S222A/H257A/Q286R/M298Q	A[122]N/G[124]S/A39S/S82A/H117A/Q143R/M156Q	340
T128N/P129A/A175S/Q286R/M298Q/H373F	T[128]N/P[129]A/A39S/Q143R/M156Q/H224F	341
A122N/G124S/A175S/Q286R/M298Q/H373F	A[122]N/G[124]S/A39S/Q143R/M156Q/H224F	342
T128N/P129A/M298Q	T[128]N/P[129]A/M156Q	354
{Gla 交換 FIX /K43I}/T128N/P129A/Q286R/M298Q	{Gla 交換 FIX /K[43]I}/T[128]N/P[129]A/Q143R/M156Q	355
T128N/P129A/Q286R/M298Q/Q366N	T[128]N/P[129]A/Q143R/M156Q/Q217N	356
{Gla 交換 FIX /K43I}/Q286R/M298Q/Q366N	{Gla 交換 FIX /K[43]I}/Q143R/M156QQ217N	357
{Gla 交換 FIX /K43I}/T128N/P129A/Q286R/M298Q/Q366N	{Gla 交換 FIX /K[43]I}/T[128]N/P[129]A/Q143R/M156QQ217N	358
T128N/P129A/M298Q/H373F	T[128]N/P[129]A/M156Q/H224F	359
V158D/Q286R/E296V/M298Q	V21D/Q143R/E154V/M156Q	360
M298Q/Q366N/H373F	M156Q/Q217N/H224F	361
T239V/M298Q/H373F	T99V/M156Q/H224F	362
T239I/M298Q/H373F	T99I/M156Q/H224F	363
T128N/P129A/Q286R/M298Q/Q366N/H373F	T[128]N/P[129]A/Q143R/M156Q/Q217N /H224F	364
T239V/Q286R/M298Q/Q366N	T99V/Q143R/M156Q/Q217N	365
T239I/Q286R/M298Q/Q366N	T99I/Q143R/M156Q/Q217N	366
T128N/P129A/T239V/Q286R/M298Q	T[128]N/P[129]A/T99V/Q143R/M156Q	367
T128N/P129A/S222A/T239V/H257A/Q286R/M298Q	T[128]N/P[129]A/S82A/T99V/H117A/Q143R/M156Q	368
T128N/P129A/T239V/Q286R/M298Q/H373F	T[128]N/P[129]A/T99V/Q143R/M156Q/H224F	369
T128N/P129A/T239I/Q286R/M298Q	T[128]N/P[129]A/T99I/Q143R/M156Q	370
T128N/P129A/T239I/Q286R/M298Q/H373F	T[128]N/P[129]A/T99I/Q143R/M156Q/H224F	371

C. FVII 多肽之表現

為藉由 ELISA 及西方墨漬進行初始表現分析，在 BHK-21 細胞中表現 FVII 多肽。對於諸如下文所述者之生物化學檢定，在 Freestyle™ 293-F 細胞（Invitrogen）中表現 FVII 多肽。

最初在幼小倉鼠腎臟細胞系 BHK-21(ATCC CRL 1632) 中表現野生型因子 VII 多肽（SEQ ID NO: 3）及變異型 FVII 多肽。於 100 mm 培養皿中在具有 10%胎牛血清（FCS）之伊格爾最低必需培養基（Eagle' s minimal essential medium；EMEM，Invitrogen）中在 37℃及 5% CO_2 下培養 BHK-21 細胞。生長至約 90%長滿後，如製造商所指示使用 Lipofectamine 2000 套組（Invitrogen）以 24 μg FVII 質體 DNA 轉染細胞。轉染 6 小時後，以無血清之含有 1 μg/ml 維生素 K1（Sigma）的 EMEM 置換培養基且將細胞進一步培育 72 小時。藉由 ELISA 或西方墨漬檢定細胞培養基中 FVII 之表現。

對於使用生物化學檢定進行後續分析，在 Freestyle™ 293-F 細胞（Invitrogen）中表現野生型因子 VII 多肽（SEQ ID NO: 3）及變異型 FVII 多肽。在具有通風蓋之錐形瓶中在 Freestyle™ 293 培養基（Invitrogen）中在 37℃及 8% CO_2 下培養細胞。使用製造商提議之方案轉染細胞。簡言之，生長至 1×10^6 個細胞/毫升後，離心細胞且交換培養基。接著，對於每 240 ml 細胞使用 293fectin（Invitrogen），以 240 μg FVII 質體 DNA 轉染細胞。另外，對於每 240 ml 細胞，添加 50 μl 之 1 mg/mL 維生素 K_1（Sigma）在乙醇中之儲備液。使細胞生長 5 天，接著收集培養物上清液。藉由 ELISA 檢定細胞培養基中 FVII 之表現。

在一些實例中，在 CHO 表現（CHOX）細胞（Excellgene）中表現野生型及變異型 FVII 多肽。將 CHO 表現（CHOX）

細胞維持在 DM202 完全培養基（SAFC BioSciences）中，且用於接種製備種子培養物。使種子培養物生長至 5×10^6 個活細胞/毫升且使用約 60 mL 接種約 0.6 L DM202 完全培養基（接種密度為 0.4×10^6 vc/mL）以產生製備培養物。在轉染當天，使此製備培養物生長 4 天達到 $8\text{-}12\times10^6$ vc/mL。使用因子 VII 質體 DNA(6 mg)及 23.1 mg 聚伸乙亞胺(PEI)形成轉染複合物。接著，在 0.5 L 無血清 Opti-MEM 轉染培養基（Invitrogen）中稀釋轉染複合物，將其添加至 0.6 L 製備培養物中。轉染 5 小時後，以補充有 8 mM L-麩胺醯胺及 4 mg/L 維生素 K1 之約 1 L ProCHO5 培養基（Lonza）進一步稀釋培養物。使 2.2L 搖瓶培養物表現 5-7 天，接著收集粗因子 VII。接著，藉由過濾收集培養物上清液且純化 FVII。

在穩定細胞系中進行一種 FVII 變異體(Q286R/M298Q)的表現。藉由轉染 CHOX 細胞在 Excellgene(Monthey, Valais, Switzerland)產生此細胞系。簡言之，使細胞在甲胺喋呤存在下生長，接著藉由限制稀釋法在 96 孔板中以每孔 1 個細胞塗板。藉由 ELISA 測定產生最高含量的變異型 FVII 之純系。藉由第二次限制稀釋法且在 96 孔板中塗板進一步次選殖一個純系(純系 52)。使群落在 37℃下在補充有 8 mM L-麩胺醯胺、1 mM 半胱胺酸、1 mg/L 維生素 K1 的 DM204A 培養基（SAFC BioSciences）中生長。藉由 ELISA 分析發現 24 個純系具有比原始純系 52 高的 Q286R/M298Q 表現量。在 6 孔板中進一步擴增此等 24 個純系用以生長 6 天，

接著在 40 mL 搖瓶中生長 4 天。在 37℃下在經如上所述補充之 DM204A 培養基中進行各生長步驟。生長 4 天後，以 1 $\times 10^7$ 個活細胞/毫升冷凍純系。藉由 ELISA 測定各純系所產生的 Q286R/M298Q 之含量。純系 5F7 為最高產生者，典型地產生 25-35 mg/L Q286R/M298Q。

1. ELISA

使用免疫檢定量化樣品中人類 FVII 及 FVIIa 之量。使用針對人類 FVII 之多株抗體捕獲及偵測溶液中的蛋白酶。可使用免疫檢定測定條件培養基或經純化儲備液之蛋白質濃度，或測定例如人類或小鼠血漿樣品的另一樣品中 FVII 之濃度。人類血液中 FVII 之基線濃度為約 50 nM 且酶促活性形式 FVIIa 為約 1 nM。

為測定樣品中人類 FVII 或 FVIIa 蛋白之量，進行夾層 ELISA。以 100 微升/孔之 5 ng/μl 抗生物素蛋白（NeutrAvidin, Pierce Biotech）塗佈 96 孔平底 Maxisorp 免疫板（Nunc）。覆蓋板且在振盪情況下在室溫下（RT）培育 1 小時，接著在具有 0.01%吐溫-20（Tween-20）之 PBS（PBST）中洗滌 4 次。在 RT 下在振盪情況下，藉由以在 200 微升/孔添加至各孔的於 PBS 中之 1%牛血清白蛋白（BSA）（w/v）培育將板阻斷至少 1 小時。接著在 4℃下儲存經阻斷板直至使用（至多 2 週）。

使用前，將板在 PBST 中洗滌 4 次以移除 BSA，且將 100 微升/孔之生物素化抗因子 VII 抗體（R & D Systems）的 1 ng/μl 溶液添加至各孔，且在室溫下在振盪情況下將板

培育 45 分鐘以允許與所塗佈抗生物素蛋白複合。藉由以 PBST 洗滌板（4 次）移除過量未結合抗體。

以 100 微升/孔將範圍介於 50 ng/μl 至 0.8 ng/μl 的 FVII 標準（American Diagnostica；在 PBST 中稀釋）之連續兩倍稀釋液添加至板。亦包括含有 PBST 而無任何 FVII 之孔作為僅緩衝液對照。為檢定 FVII 或 FVIIa 之經純化樣品（活化前及活化後，參見實施例 3），首先在 PBST 中以 1:25 稀釋樣品，且隨後進行連續 2 倍稀釋以便測試 25 倍、50 倍、100 倍及 200 倍稀釋液。以 100 微升/孔將所稀釋樣品一式兩份添加至孔中。為檢定含有 FVII 或 FVIIa 之血漿樣品，在 PBST 中以 1:100 及 1:400 稀釋血漿樣品，且以 100 微升/孔一式兩份添加至孔中。亦包括無 FVII 或 FVIIa 之血漿樣品以測定背景含量。接著，在 RT 下在振盪情況下將板培育 30 分鐘，以允許樣品中之任何 FVII 或 FVIIa 與抗 FVII 抗體複合。

培育樣品後，以 PBST 將板洗滌 4 次。在 PBST 中以 1:5000 稀釋二級抗體馬類抗人類 FVII 或鼠類單株抗人類 FVII（American Diagnostica）且以 100 μl 之體積添加至各孔中。在室溫下在振盪情況下將板培育 30 分鐘，以允許所添加抗體與板上的 FVII 或 FVII 複合物結合。為移除過量二級抗體，以 PBST 洗滌板（4 次）。為偵測所結合二級抗體，將在 PBST 中以 1:5000 稀釋之 100 μl 山羊抗馬類 HRP 接合物或在 PBST 中以 1:20,000 稀釋之 100 μl 山羊抗小鼠 HRP 接合物添加至各孔中。在室溫下在振盪情況下培育 30

分鐘後，以 PBST 將板洗滌 4 次，且添加 100 微升/孔之含有 TMB 受質與過氧化氫溶液（Pierce Biotech）的 1:1 混合物之溶液。在室溫下，將板震盪約 1 分鐘，隨後添加 100 微升/孔之 2M H_2SO_4 以停止反應。使用 Molecular Device M5 板讀取器量測 450 nm 下之光學密度，且自各孔之量測值減去板之背景值（以 PBST 單獨量測）。藉由將 FVII 標準之濃度相對於吸光率作圖，產生標準曲線。典型地在上述 ELISA 條件下產生約 0.2-50 ng/ml 之標準曲線範圍。接著使用標準曲線且乘以稀釋係數測定各樣品之濃度，報導平均值及標準偏差。

2. 西方墨漬

亦藉由西方墨漬來檢定細胞培養基中 FVII 之表現。

含有經 FVII 轉染之細胞（BHK-21 或 CHOX 細胞）的細胞培養基之未經稀釋樣品或兩個於 PBS 中連續 2 倍稀釋液之等分試樣經標記為濃度 1（未經稀釋）、濃度 2（2 倍稀釋）及濃度 3（4 倍稀釋）。將樣品加載於 SDS page 凝膠上 10、25 及 50 毫微克之對照血漿經純化 rFVII(American Diagnostica)之後。藉由西方墨漬使用一級多株馬類抗 FVII 抗體（American Diagnostica；在製造商所提議之濃度下使用）及 HRP 接合之抗馬類 IgG 二級抗體（來自 Zymed Laboratories 的以 1:2000 稀釋之 1 mg/ml 溶液)偵測 BHK-21 或 CHOX 細胞所產生之 FVII 蛋白。在一些實例中，藉由西方墨漬使用一級兔抗人類因子 VIIa 抗體（Hematologic Technologies)及 HRP 接合之抗兔 IgG 二級抗體(Invitrogen)

偵測 FVII。與對照血漿經純化 rFVII 比較表現量。結果展示細胞培養物等分試樣中存在範圍為約 20 ng 至 50 ng 以上 FVII 的濃度。

實施例 2

FVII 多肽之純化及活化

使用吸附有具有功能性 Gla 域之 FVII 多肽的 Q Sepharose Fast Flow 或 CaptoQ 管柱（GE Healthcare）純化 FVII 多肽，接著進行鈣溶離步驟。典型地，以含有 20 mM Tris pH 8.0 及 0.01%吐溫 20 之溶液將經轉染細胞之培養物上清液稀釋 2 倍，且隨後將 500 mM EDTA pH 8.0 添加至經稀釋樣品中至 1.5 mM 之最終濃度。過濾樣品，隨後加載於首先經緩衝液 B（20 mM Tris pH 8.0、1 M NaCl、0.01%吐溫 20），接著經緩衝液 A（20 mM Tris pH 8.0、0.15 M NaCl、0.01%吐溫 20）預平衡之 Q Sepharose Fast Flow 或 CaptoQ 管柱上。加載後，以緩衝液 A 洗滌管柱直至 280 nm 下之流動吸光率達到基線。以緩衝液 C（20 mM Tris pH 8.0、0.15 M NaCl、0.01%吐溫 20、5 mM $CaCl_2$）置換緩衝液 A 且進行泵洗滌以完全置換管線內之緩衝液。泵洗滌完成後，以 8 mL/min 將緩衝液 C 施加至管柱以溶離 FVII 多肽，其收集於溶離份中。溶離後，以緩衝液 B 洗滌管柱，同時仍收集溶離份，直至自管柱洗滌除去粉紅色顏料（來自培養基）。接著，以緩衝液 A 洗滌管柱以使其再平衡以便再次使用。

使用最初經緩衝液 B 且隨後經緩衝液 A 預平衡之 Mono Q 或 QHiTrap 管柱（GE Healthcare）進一步純化所溶離溶

離份。彙集含有 FVII 之以上述緩衝液 C 收集的溶離份且以緩衝液 A 稀釋 2 倍，隨後添加 EDTA pH 8.0 至 40 mM 之最終濃度。視情況在此點取小等分試樣（例如 100 μl）用於諸如藉由 ELISA 進行分析。將經合併樣品加載於 Mono Q（或 QHiTrap）管柱上，接著以緩衝液 A 洗滌。為溶離經結合 FVII 多肽，使緩衝液 B 之 0%至 30%梯度穿過管柱且收集溶離份。接著，以緩衝液 B 接著以緩衝液 A 洗滌管柱以使其再平衡以便再次使用。

在一些實例中，在第一 Capto Q 管柱之後，藉由透濾至緩衝液 D（20 mM MES pH 6.0、10 mM $CaCl_2$、0.1 M NaCl、0.01%吐溫 20）中使所彙集溶離份進行緩衝液交換，接著將其加載於已經緩衝液 D 預平衡之 SP-HP 管柱上。以緩衝液 D 洗滌後，將 0.1M NaCl 至 1.0M NaCl 之梯度施加至管柱且收集溶離份。接著，將含有 FVII 之溶離份調整至 pH 8.0 且在緩衝液 E（20 mM Tris pH 8.0、10 mM $CaCl_2$、0.01%吐溫 20）中稀釋 2 倍且施加至已經緩衝液 E 預平衡之 Q H-HP 管柱。接著，以緩衝液 E 洗滌此管柱且藉由緩衝液 E 中 0-1 M NaCl 之梯度溶離 FVII。

使用來自限制性蛋白酶因子 Xa 裂解及移除套組（Roche）之生物素化因子 Xa 將經純化 FVII 多肽活化為 FVIIa。典型地，將來自 Mono Q 純化之 7 個溶離份彙集在 15 ml 錐形管中，且添加 388 μl 500 mM $CaCl_2$、38.9 μl 於蒸餾水中之 10% BSA 及 3.2 μg 生物素化因子 Xa。在 37 ℃下培育 14-16 小時後，添加 250 μl 經固定抗生物素蛋白

（Pierce）且在 4℃下將樣品混合 30 分鐘。接著，經由 Econo-pak 管柱（Bio-Rad）過濾所得溶液，且將濾液再與另外 250 μl 經固定抗生物素蛋白混合 30 分鐘。再次過濾溶液且使用 Amicon Ultra-4 10kDa 離心過濾器（Millipore）將濾液濃縮至約 300-500 μl。接著藉由 ELISA 分析 FVIIa 濃度（如實施例 1.C.1 所述）且藉由西方墨漬監測因子 VII 活化程度。基本上如實施例 1.C.2 所述進行西方墨漬，但改為使用以 1:2000 稀釋之兔抗人類因子 VIIa 抗體（Haematologic Technologies, Inc）歷時 1 小時作為一級抗體，接著使用以 1:5000 稀釋之 HRP-山羊抗兔 IgG（H+L）（Invitrogen）歷時 30 分鐘。

實施例 3

測定溶液中催化活性蛋白酶之濃度

藉由以 FVIIa 之不可逆肽抑制劑 Phe-Phe-Arg-氯甲基酮（FFR-CMK）滴定因子 VIIa 與可溶性組織因子（sTF）之複合物來測定儲備溶液中催化活性 FVIIa 之濃度。抑制劑與 FVIIa 而非 FVII 結合。在高濃度 FVIIa（50 nM）下延長培育確保蛋白酶之完全滴定。量測以 FFR-CMK 培育後 FVIIa/TF 複合物之殘餘活性以測定原始儲備溶液中催化活性 FVIIa 之濃度。

藉由添加 150 微升/孔之 1x板緩衝液（100 mM Tris pH 8.4、100 mM NaCl、0.01% BSA、0.01%吐溫 20）至各孔中且在 37℃下將板培育至少 1 小時預處理 96 孔透明半區域檢定板（Nunc）。藉由點漬於紙巾上且倒轉離心板以移除任

何剩餘緩衝液來完全移除緩衝液，且將板風乾 1 小時且覆蓋儲存在室溫下（RT）。

為製備 FVIIa/sTF/FFR-CMK 反應混合物，首先在 1×直接檢定緩衝液（100 mM Tris pH 8.4、100 mM NaCl、5 mM $CaCl_2$、0.01% BSA）中將 FVIIa（American Diagnostica；在 50%甘油中稀釋至 5 μM（v/v）且在-20℃下以等分試樣冷儲存）或 FVIIa 變異體之儲備液稀釋至 500 nM。接著，藉由混合 90 μl 蒸餾水與 36 μl 5×直接檢定緩衝液、18 μl 500 nM FVIIa 及 18 μl 5 μM sTF（重組人類凝血因子 III/可溶性組織因子；R & D Systems；所用儲備溶液為 50%甘油中 19.6 μM 且將其在 1×直接檢定緩衝液中稀釋至 5 μM 且在 4℃下儲存至多兩週）製備 FVIIa/sTF 混合物。接著，允許組份在室溫下複合 5 分鐘。

將 10 mM FFR-CMK（BaChem）在 DMSO 中之儲備溶液（在-20℃下儲存）於水中稀釋至 3.5 μM。使用聚丙烯不透明儲存板（Costar）之一列，在 96 孔不透明板之 11 個孔中製備 FFR-CMK 於水中之連續兩倍稀釋液，該列之最後一個孔僅含有水作為對照。此為 10×FFR-CMK 抑制劑系列溶液。向經預處理 96 孔透明半區域檢定板之一列中的各孔中添加 10.8 μl FVIIa/sTF 混合物，接著添加 1.2 μl 10× FFR-CMK 抑制劑系列。充分混合溶液，且在<3000 rpm 下離心板 5 分鐘以移除孔中之液滴。覆蓋板且在 37℃下培育 8 小時。

為檢定 FVIIa/TF 複合物之殘餘活性，首先藉由混合 360

μl 5×直接檢定緩衝液與 180 μl Spectrozyme FVIIa 之 10 mM 溶液及 1080 μl 水來製備受質 Spectrozyme FVIIa（American Diagnostica, # 217L；50 微莫耳小瓶之在 5 mL 蒸餾水中至 10 mM 且儲存在 4℃下之重構儲備液）與 5×直接緩衝液（500 mM Tris pH 8.4、500 mM NaCl、25 mM $CaCl_2$ 及 0.05% BSA）之混合物。向檢定板之各孔中添加 108 μl 所製備受質溶液。混合孔且在 37℃下培育板。在 37℃下於來自 Molecular Devices 之 Spectramax Gemini M5 板讀取器上每 30 秒量測 405 nm 下之吸光率增加歷時 1 小時。

使用 SoftMax Pro 軟體（Molecular Devices），量測吸光率且藉由將所量測吸光率除以未受抑制蛋白酶之吸光率來測定與抑制劑一起培育的蛋白酶之比活性（fractional activity）。相對於 FFR-CMK 之濃度將比活性作圖，且拋棄為未受抑制活性之>90%或<10%之點。接著經由剩餘點畫線，以確定 x 截距，其表示溶液中活性蛋白酶之濃度。量測多個檢定之值且求平均值且測定標準差。

實施例 4

測定 FVIIa 對其受質因子 X 之催化活性

在螢光檢定中藉由檢定受 FVIIa 活化後產生的 FXa 對合成受質 Spectrafluor FXa 之活性，間接評估 FVIIa 變異體對其受質因子 X（FX）之催化活性。

A. 野生型 FVIIa 對其受質因子 X 之 TF 依賴性催化活性

在包括脂化形式之經純化組織因子（TF）以提供 FVIIa

之最佳活性的螢光檢定中評估野生型 FVIIa 之 TF 依賴性催化活性。藉由作為時間函數量測所產生游離螢光團 AMC(7-胺基-4-甲基香豆素)吸光率之增加，測定 FXa 對 Spectrafluor FXa（CH3SO2-D-CHA-Gly-Arg-AMC.AcOH）之酶活性。

簡言之，最初在 1x檢定緩衝液（100 mM Tris pH 8.4、100 mM NaCl、5 mM $CaCl_2$ 及 0.01% BSA)中將野生型 FVIIa 多肽稀釋至 0.5 μM，接著在檢定緩衝液中進一步稀釋至 0.1 nM。在 20 mL 水中重構脂化全長 TF（Innovin；Dade Behring）以製備 3 nM 溶液且將其在 1x檢定緩衝液中稀釋至 0.2 nM。將 400 μl 之 0.1 nM FVIIa 與 400 μl 之 0.2 nM TF 混合且在室溫下培育 5 分鐘。藉由兩次 2 倍稀釋於含有 0.2 nM TF 之 1x檢定緩衝液中進一步稀釋溶液，以獲得各含有 0.2 nM TF 的 0.05 nM、0.025 nM 或 0.0125 nM FVIIa 之總共三種 FVIIa 稀釋液（FVIIa/TF 溶液）。

在 135.6 μl 蒸餾水中重構受質因子 X（FX；American Diagnostica；80 μg）以提供 10 μM 儲備液且將其以等分試樣儲存在-80℃。等分試樣並未經冷凍且解凍一次以上。在直接檢定緩衝液中將 FX 儲備液稀釋至 800 nM，接著連續稀釋 2 倍以獲得範圍介於 800 nM 至 50 nM 之 FX 溶液。

在蒸餾水中重構 Spectrofluor Xa（American Diagnostica；10 微莫耳）至 5 mM 且儲存在 4℃。向 96 孔黑色半區域檢定板（Costar）中每孔添加 5 μl Spectrofluor Xa（American Diagnostica）。接著，將 25 μl FX 溶液添加至各孔中。在檢定中板之最後一列孔亦包括未添加 FX 的

陰性對照。一式兩份以 20 μl 向板之各別行的孔添加三種濃度之 TF/FVIIa 溶液，以便針對各 FX 稀釋液檢定各 TF/FVIIa 稀釋液，其中一組行不含所添加之 TF/FVIIa（亦即僅 FX）。藉由振盪混合平板。以經設定以每 30 秒讀取之螢光光譜儀在 37℃下隨時間量測螢光歷時 1 小時（Ex：380 nm；EM：450 nm；截斷：435 nm），且以時間平方單位報導時間。檢定後，在同一板讀取器中產生 AMC 螢光之標準曲線以由螢光單位轉化為檢定中所釋放之 μM 受質。在 1× 檢定緩衝液中將於 DMSO（Invitrogen）中之 1 mM AMC 稀釋至 0.02 mM。在 1×檢定緩衝液中製備範圍介於 20 nM 至 0.625 nM 的 AMC 之 6 個兩倍連續稀釋液。使用與上述相同的檢定條件量測 AMC 之螢光且作螢光相對於 AMC 濃度之圖。計算線的斜率，其在後續計算中充當 RFU 至 mM 之轉換係數。

藉由對受質濃度之倒數相對於受質裂解速度（單位為秒 ^{2}）之倒數進行線性回歸分析，以 $V_{max,\ FVIIa}$ 計算為 Y 截距之倒數，$K_{m,\ FVIIa}$ 為 Y 截距處之斜率且 $V_{max}/K_{m,\ FVIIa}$ 為斜率之倒數，計算 FX 之 FVIIa 活化之動力學常數。接著使用以下方程式獲得 k_{cat} 值：

$k_{cat}/K_{m,\ FVIIa} = V_{max}/K_{m,\ FVIIa} \times 1/(0.5 \times k_2 \times$ [FVIIa，以 μM 計] × (RFU/μM 轉換係數))

其中：$k_2 = ([S] \times k_{cat,\ FXa})/(K_{m,\ FXa} + [S])$，其中 $k_{cat,\ FXa}$ 及 $K_{m,\ FXa}$ 為當 $k_{cat,\ FXa} = 117\ sec^{-1}$ 且 $K_{m,\ FXa} = 164\ \mu M$ 時，使用 FXa 標準憑經驗確定之 SpectrofluorXa 的 FXa 裂解之

常數。

使用上述檢定條件，動力學常數k2經測定為88.1 sec^{-1}。

測定各FVIIa變異體之K_m及k_{cat}以評估催化活性，其各自對受質FX之k_{cat}/K_m（$M^{-1}sec^{-1}$）（表14）。評估野生型FVIIa蛋白酶且發現其展現1.8 × 10^7 $M^{-1}sec^{-1}$之活性。如Krishnaswamy等人（J. Biol. Chem. (1998) 273:8 4378-86）所量測因子X之因子VIIa活化為2.9 X 10^7 $M^{-1}sec^{-1}$。

B. FVIIa變異體對受質因子X之催化活性的分析

在2種類型之發色檢定中藉由檢定由FVIIa活化後產生的FXa對所合成受質Spectrafluor FXa之活性，間接評估FVIIa變異體對受質因子X（FX）之催化活性。該等兩個檢定係在脂化組織因子存在或不存在情況下進行，以評估TF依賴性與TF獨立性活性。如以上實施例1及2所述，表現、純化FVII變異體且將其活化為FVIIa。儘管大多數FVII變異體僅在Freestyle™ 293-F細胞中表現，但某些亦在BHK-21細胞中表現。

脂化組織因子依賴性間接檢定

使用具有微小修改之以上實施例4之A部分中所述的檢定，評估FVIIa變異體在組織因子存在下之催化活性。一種該修改為使用已以ERG-CMK及FFR-CMK處理以降低背景活性之因子X受質蛋白酶（Molecular Innovations）。使用兩個獨立檢定進行2種類型之資料分析：線性範圍分析檢定及雙曲線型範圍分析檢定。線性範圍分析檢定使用在0

與 150 nM 之間的一系列因子 X 濃度以確保在劑量曲線之線性範圍中精確量測動力學常數。相反，雙曲線型範圍分析檢定使用在 0 與 1.44 μM 之間的一系列因子 X 濃度以確保使用飽和（雙曲線型）劑量曲線精確量測動力學常數。

使用以下修改，基本上如以上實施例 4 之 A 部分中所述使用線性範圍資料分析進行脂化組織因子間接檢定。將 FVIIa 變異體/TF 溶液製備為 0.1 nM FVIIa/0.4 nM TF 溶液且培育 30 分鐘，隨後在 0.4 nM TF 中兩倍稀釋下降至含有 1.5625 pM FVIIa/0.4 nM TF 之溶液。將 25 μL FVIIa/TF 溶液與含有 1.0 mM Spectrofluor FXa（American Diagnostica）及 300 nM、200 nM、133.3 nM、88.9 nM、59.3 nM、39.5 nM、36.3 nM 或 0 nM 因子 X（Molecular Innovations）中之一者的 25 μL 受質溶液混合。因此，檢定之最終濃度為 50 微升/孔中 0.8 pM FVIIa、0.2 nM TF、0.5 mM Spectrofluor FXa 及 150 nM、100 nM、66.7 nM、44.4 nM、29.6 nM、19.8 nM、13.2 nM 或 0 nM 因子 X（Molecular Innovations）。延伸在後續計算中充當 RFU 至 mM 的轉換係數之 AMC 標準曲線以包括涵蓋 0 μM 至 100 μM AMC 的劑量範圍。

使用以下修改，基本上如以上實施例 4 之 A 部分中所述使用雙曲線型範圍資料分析進行脂化組織因子間接檢定。將 FVIIa 變異體/TF 溶液製備為 0.1 nM FVIIa/0.4 nM TF 溶液且培育 30 分鐘，隨後在 0.4 nM TF 中兩倍稀釋下降至 1.5625 pM（或對於預期具有高活性之蛋白酶而言 0.78 pM）

FVIIa/0.4 nM TF。將 25 μL FVIIa/TF 溶液與含有 1.0 mM Spectrofluor FXa（American Diagnostica）及 1440 nM、720 nM、360 nM、180 nM、90 nM、45 nM、22.5 nM 或 0 nM 因子 X（Molecular Innovations）中之一者的 25 μL 受質溶液混合。因此，檢定之最終濃度為 50 微升/孔中 0.8（或 0.39）pM FVIIa、0.2 nM TF、0.5 mM Spectrofluor FXa 及 7 nM、720 nM、360 nM、180 nM、90 nM、45 nM、22.5 nM、11.25 nM 或 0 nM 因子 X（Molecular Innovations）。使用形式（$V_{max}/(1+(K_m/x))$）之 Michaelis Menton 雙曲線方程計算 k_{cat} 及 K_m 參數。延伸在後續計算中充當 RFU 至μM 的轉換係數之 AMC 標準曲線以包括涵蓋 0 μM 至 100 μM AMC 的劑量範圍。

為測定 FX 之 FVIIa 或 FVIIa 變異體活化之動力學速率常數，將以 SoftMax Pro 應用（Molecular Devices）收集的原始資料輸出為.XML 文件。另外，以 XLfit4，一種用於在 Microsoft Excel 試算表環境（IDBS Software）內進行自動曲線擬合及統計分析之軟體套件進行資料線性及非線性分析。

對於使用線性範圍檢定收集之資料，由 FX 濃度相對於螢光受質裂解速度（以μM/sec^2 計）之線性回歸分析之斜率直接計算 k_{cat}/K_m（$M^{-1}sec^{-1}$）動力學常數，其中 k_{cat}/K_m = 斜率/[FVIIa] $\times 0.5 \times k_2$。使用實施例 4 之 A 部分所述的方法測定校正係數 k_2 為 45，且以先前經 AT-III/肝素活性位點滴定之經活化 FX（FXa）實驗測定 Spectrofluor FXa 之 FXa 裂

解的動力學常數 $k_{cat,FXa}$ = 56 sec^{-1} 且 $K_{m,FXa}$ = 126 nM。排除使 R^2 值小於 0.98 的資料點確保擬合程序中所用資料組的線性。

由 FX 濃度相對於螢光受質裂解速度（以 μM/sec^2 計）之非線性回歸分析計算使用雙曲線型範圍檢定所收集資料之分析。使用形式（$V_{max}/(1+(K_m/x))$）之 Michaelis Menton 雙曲線方程，將個別 k_{cat} 及 K_m 參數計算為擬合參數，其中 $k_{cat} = V_{max}/[FVIIa] \times 0.5 \times k_2$。由個別 k_{cat} 及 K_m 擬合參數計算出動力學常數 k_{cat}/K_M。

組織因子獨立性間接檢定

在類似於如上所述之間接檢定中評估在組織因子存在下 FVIIa 變異體之催化活性，但例外為組織因子並未包括在檢定中。因此，使用以下修改，基本上如上所述進行評估 TF 獨立性活性之檢定。將 FVIIa 變異體溶液稀釋為 50 nM（或對於預期具有高 TF 獨立性活性之變異體而言，5 nM）。將 25 μL 各 FVIIa 溶液與含有 1.0 mM Spectrofluor FXa（American Diagnostica）及 1050 nM、700 nM、466.7 nM、311.1 nM、207.4 nM、138.3 nM、92.2 nM 或 0 nM 因子 X（Molecular Innovations）中之一者的 25 μL 受質溶液混合。因此，檢定之最終濃度為在 50 微升/孔中 25 nM FVIIa（或對於高活性變異體而言 2.5 nM）、0.5 mM Spectrofluor FXa 及 525 nM、350 nM、233.3 nM、155.6 nM、103.7 nM、69.1 nM、46.1 nM 或 0 nM 因子 X（Molecular Innovations）。如對於以上無修改之線性範圍檢定所述進行

資料分析。

表 13 提供如在 TF 依賴性間接檢定中使用由 293-F 細胞及 BHK-21 細胞表現之 FVIIa 多肽量測的 FVIIa 變異體之催化活性，及如在 TF 獨立性間接檢定中使用由 293-F 細胞及/或 BHK-21 細胞表現的 FVIIa 多肽量測的催化活性。結果呈示為催化活性之動力學常數 k_{cat}/K_m（$M^{-1}sec^{-1}$），且亦表示為野生型 FVIIa 之活性之百分數，其中活性為催化活性，各 FVIIa 變異體對其受質 FX 的 k_{cat}/K_m（$M^{-1}sec^{-1}$）。線性或雙曲線型範圍資料分析之使用亦指示該等表中呈示之值。在各檢定中並非檢定所有 FVIIa 變異體。與野生型 FVIIa 分子相比，數種 FVIIa 變異體展現增強之催化活性。舉例而言，僅含有 Q286R 突變的 FVIIa 多肽（Q286R-FVIIa）具有在野生型 FVIIa 之 2 倍與 3 倍之間的催化活性，且含有 Q286R 及 M298Q 突變之 FVIIa 多肽（Q286R/M298Q-FVIIa）具有超過野生型 FVIIa 之 3 倍的催化活性。

表 14. FVIIa 變異體之催化活性

使用來自 293-F 細胞之 FVIIa 多肽的 TF 依賴性間接檢定				
突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	檢定格式	k_{cat}/K_M ($M^{-1}s^{-1}$)	k_{cat}/K_M (WT%)
Q286N	Q143N	雙曲線型	4.88×10^7	100
Q286E	Q143E	雙曲線型	1.14×10^7	23
Q286D	Q143D	雙曲線型	6.04×10^6	12
Q286S	Q143S	雙曲線型	4.64×10^7	95
Q286T	Q143T	雙曲線型	2.44×10^7	50
Q286R	Q143R	線性	1.11×10^8	323
Q286K	Q143K	雙曲線型	5.44×10^7	112
Q286A	Q143A	雙曲線型	8.55×10^7	175
Q286V	Q143V	雙曲線型	1.65×10^7	34
H216S	H76S	線性	4.74×10^7	138
H216A	H76A	線性	5.98×10^7	175
H216K	H76K	雙曲線型	6.51×10^7	133
H216R	H76R	雙曲線型	9.44×10^7	193
S222A	S82A	線性	5.73×10^7	167
S222K	S82K	線性	8.02×10^7	234

H257A	H117A	線性	3.90×10^7	114
H257S	H117S	線性	5.90×10^7	172
K161S	K24S	雙曲線型	5.99×10^7	123
K161A	K24A	線性	4.22×10^7	123
K161V	K24V	雙曲線型	5.45×10^7	112
H373D	H224D	線性	1.79×10^7	52
H373E	H224E	線性	2.79×10^7	81
H373S	H224S	線性	2.75×10^7	80
H373F	H224F	線性	5.11×10^7	149
H373A	H224A	線性	3.11×10^7	91
S52A	S[52]A	線性	4.66×10^7	136
S60A	S[60]A	線性	5.15×10^7	150
Q366D	Q217D	線性	1.88×10^7	55
Q366E	Q217E	線性	4.77×10^7	139
Q366N	Q217N	線性	5.64×10^7	165
Q366T	Q217T	線性	3.42×10^7	100
Q366S	Q217S	線性	2.70×10^7	79
Q366V	Q217V	線性	6.59×10^7	192
E394N/P395A/R396S	E245N/P246A/R247S	線性	5.32×10^7	155
R202S	R62S	線性	2.57×10^7	75
A292N/A294S	A150N/A152S	線性	0	0
G318N	G170fN	線性	5.50×10^7	161
A175S	A39S	線性	3.32×10^7	97
K109N	K[109]N	線性	5.97×10^7	174
A122N/G124S	A[122]N/G[124]S	線性	5.27×10^7	154
T130N/E132S	T[130]N/E[132]S	線性	6.35×10^7	185
A122N/G124S/ E394N/P395A/R396S	A[122]N/G[124]S/E245N/P246 A/R247S	線性	4.88×10^7	142
V158T/L287T/M298K	V21T/L144T/M156K	線性	4.50×10^6	13
V158D/L287T/M298K	V21D/L144T/M156K	線性	4.48×10^6	13
S103S111缺失插入 SFGRGDIRNV	S[103]S[111]缺失插入 SFGRGDIRNV	線性	4.83×10^7	141
P406插入 CSFGRGDIRNVC	P257插入CSFGRGDIRNVC	線性	6.16×10^7	180
P406插入 GGGSCSFGRGDIRN VC	P257插入 GGGSCSFGRGDIRNVC	線性	7.47×10^7	218
T128N/P129A	T[128]N/P[129]A	線性	5.96×10^7	174
S222A/ Gla交換FIX	S82A/Gla交換FIX	線性	6.55×10^7	189
H257A/ Gla交換FIX	H117A/Gla交換FIX	線性	6.45×10^7	186
S222A/H257A/ Gla交換FIX	S82A/H117A/Gla交換FIX	線性	5.77×10^7	168
Q286R/ Gla交換FIX	Q143R/Gla交換FIX	線性	1.11×10^8	323
Q286R/H257A	Q143R/H117A	線性	1.27×10^8	371
Q286R/S222A	Q143R/S82A	線性	1.42×10^8	415
Q286R/S222A/H257A	Q143R/S82A/H117A	線性	9.51×10^7	278
Q286R/S222A/ Gla交換FIX	Q143R/S82A/Gla交換FIX	線性	1.61×10^8	470
Q286R/H257A/ Gla交換FIX	Q143R/H117A/Gla交換FIX	線性	8.09×10^7	234
Q286R/S222A/H257A/ Gla交換FIX	Q143R/S82A/H117A/Gla交換 FIX	線性	7.75×10^7	226
Q286R/M298Q/K341Q	Q143R/M156Q/K192Q	線性	3.93×10^7	115
Q286R/M298Q/K199E	Q143R/M156Q/K60cE	線性	7.74×10^7	226

T239S	T99S	線性	1.74×10^7	51
T239Q	T99Q	線性	1.74×10^7	51
T239V	T99V	線性	9.57×10^7	279
T239L	T99L	線性	3.77×10^7	110
T239H	T99H	線性	9.90×10^6	29
T239I	T99I	線性	3.50×10^7	102
S222A/H257A/M298Q	S82A/H117A/M156Q	線性	7.75×10^7	224
S222A/H257A/Q286R/M298Q	S82A/H117A/Q143R/M156Q	線性	2.00×10^8	583
S222A/H257A	S82A/H117A	線性	5.02×10^7	147
A175S/Q286R/Q366V	A39S/Q143R/Q217V	線性	8.08×10^7	236
A175S/S222A/Q366V	A39S/S82A/Q217V	線性	3.78×10^7	109
K109N/A175S	K[109]N/A39S	線性	3.67×10^7	107
S222A/Q286R/Q366V	S82A/Q143R/Q217V	線性	1.27×10^8	369
Q286M	Q143M	線性	5.25×10^7	153
Q286L	Q143L	線性	2.02×10^7	59
Q286Y	Q143Y	線性	1.61×10^7	47
Q366I	Q217I	線性	9.37×10^7	274
Q366L	Q217L	線性	6.87×10^7	201
Q366M	Q217M	線性	6.61×10^7	193
S222V	S82V	線性	6.04×10^7	176
S222D	S82D	線性	5.34×10^7	156
S222N	S82N	線性	6.82×10^7	199
S222E	S82E	線性	5.48×10^7	160
H216A/H257A	H76A/H117A	線性	6.62×10^7	193
H216A/S222A	H76A/S82A	線性	5.46×10^7	159
H257S/Q286R	H117S/Q143R	線性	3.93×10^7	115
H257S/Q366V	H117S/Q217V	線性	6.71×10^7	194
H257S/Q286R/Q366V	H117S/Q143R/Q217V	線性	1.58×10^8	457
S222A/H257A/Q286R/Q366V	S82A/H117A/Q143R/Q217V	線性	1.86×10^8	538
Q366V/H373V	Q217V/H224V	線性	1.84×10^7	53
Q366V/H373L	Q217V/H224L	線性	3.07×10^7	89
Q286R/H373A	Q143R/H224A	線性	5.89×10^7	172
S222A/H373A	S82A/H224A	線性	3.64×10^7	106
Q286R/M298Q/K341D	Q143R/M156Q/K192D	線性	1.18×10^7	34
Q286R/K341D	Q143R/K192D	線性	1.11×10^7	32
Q286R/Q366D	Q143R/Q217D	線性	1.53×10^7	45
Q286R/Q366N	Q143R/Q217N	線性	5.42×10^7	158
Q286R/M298Q/Q366D	Q143R/M156Q/Q217D	線性	1.91×10^7	56
Q286R/M298Q/Q366N	Q143R/M156Q/Q217N	線性	1.04×10^8	305
Q286R/H373F	Q143R/H224F	線性	9.08×10^7	265
Q286R/M298Q/H373F	Q143R/M156Q/H224F	線性	1.51×10^8	440
M298Q/H373F	M156Q/H224F	線性	8.49×10^7	248
S119N/L121S/A175S	S[119]N/L[121]S/A39S	線性	2.92×10^7	85
T128N/P129A/A175S	T[128]N/P[129]A/A39S	線性	2.98×10^7	87
A122N/G124S/A175S	A[122]N/G[124]S/A39S	線性	2.79×10^7	81
使用來自 BHK-21 細胞之 FVIIa 多肽的 TF 依賴性間接檢定				
突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	檢定格式	k_{cat}/K_M ($M^{-1}s^{-1}$)	k_{cat}/K_M (WT%)
Q286R	Q143R	線性	1.01×10^8	187

H216A	H76A	線性	5.98×10^7	110
S222A	S82A	線性	6.42×10^7	118
H257A	H117A	線性	4.96×10^7	91
H257S	H117S	線性	7.65×10^7	141
H373F	H224F	線性	4.82×10^7	89
S52A	S[52]A	線性	3.50×10^7	65
S60A	S[60]A	線性	3.22×10^7	59
Q366D	Q217D	線性	9.80×10^6	18
Q366N	Q217N	線性	3.44×10^7	63
Q366V	Q217V	線性	1.86×10^8	342
G318N	G170fN	線性	5.46×10^7	101
A175S	A39S	線性	2.12×10^7	39
A122N/G124S	A[122]N/G[124]S	線性	8.05×10^7	148
A51N	A[51]N	線性	1.02×10^8	188
S52A/S60A	S[52]A/S[60]A	線性	1.05×10^8	193
P406插入 GGGSCSFGRGDIRNVC	P257插入 GGGSCSFGRGDIRNVC	線性	9.54×10^7	176
S119N/L121S	S[119]N/L[121]S	線性	5.75×10^7	106
T128N/P129A	T[128]N/P[129]A	線性	8.76×10^7	161
Q286R/S222A	Q143R/S82A	線性	1.24×10^8	229
Q286R/S222A/H257A	Q143R/S82A/H117A	線性	1.06×10^8	196
Q286R/S222A/ Gla交換FIX	Q143R/S82A/Gla交換FIX	線性	8.52×10^7	157
Q286R/M298Q	Q143R/M156Q	線性	1.85×10^8	341
Q286R/M298Q/K341Q	Q143R/M156Q/K192Q	線性	3.11×10^7	57
Q286R/M298Q/K199E	Q143R/M156Q/K60cE	線性	9.18×10^7	169
P321K	P170iK	線性	3.43×10^7	63
P321E	P170iE	線性	5.59×10^7	103
P321Y	P170iY	線性	4.48×10^7	83
P321S	P170iS	線性	5.53×10^7	102
T239N	T99N	線性	1.64×10^7	30
T239Q	T99Q	線性	1.70×10^7	31
T239V	T99V	線性	9.81×10^7	181
T239L	T99L	線性	5.24×10^7	97
T239H	T99H	線性	1.25×10^7	23
T239I	T99I	線性	4.67×10^7	86
S222A/M298Q	S82A/M156Q	線性	7.13×10^7	131
H257A/M298Q	H117A/M156Q	線性	1.28×10^8	236
S222A/H257A/Q286R/M298Q	S82A/H117A/Q143R/M156Q	線性	1.94×10^8	358
Q286R/M298Q/Gla交換FIX	Q143R/M156Q/Gla交換FIX	線性	2.64×10^8	487
Q286R/Q366V	Q143R/Q217V	線性	7.92×10^7	146
A175S/Q286R/Q366V	A39S/Q143R/Q217V	線性	7.63×10^7	141
K109N/A175S	K[109]N/A39S	線性	2.45×10^7	45
S222A/Q286R/Q366V	S82A/Q143R/Q217V	線性	1.44×10^8	265
Q286R/M298Q/K341D	Q143R/M156Q/K192D	線性	1.35×10^7	25
Q286R/H373F	Q143R/H224F	線性	1.18×10^8	218
Q286R/M298Q/H373F	Q143R/M156Q/H224F	線性	2.01×10^8	371
M298Q/H373F	M156Q/H224F	線性	8.69×10^7	160
A122N/G124S/A175S	A[122]N/G[124]S/A39S	線性	1.93×10^7	36

TF-獨立性間接檢定					
突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	293-F 細胞		BHK-21 細胞	
		k_{cat}/K_M ($M^{-1}s^{-1}$)	k_{cat}/K_M (WT%)	k_{cat}/K_M ($M^{-1}s^{-1}$)	k_{cat}/K_M (WT%)
Q286N	Q143N	$3.03x\ 10^1$	134		
Q286E	Q143E	4.80	21		
Q286D	Q143D	$3.50x\ 10^{-1}$	2		
Q286S	Q143S	$2.66x\ 10^1$	118		
Q286T	Q143T	$1.51x\ 10^1$	67		
Q286R	Q143R	$4.87x\ 10^1$	215	$4.08x\ 10^1$	259
Q286K	Q143K	$3.95x\ 10^1$	175		
Q286A	Q143A	$2.11x\ 10^1$	93		
Q286V	Q143V	2.35	10		
S222A	S82A	$7.36x\ 10^1$	326	$3.10x\ 10^1$	197
H257A	H117A	$2.02x\ 10^1$	89	$1.18x\ 10^1$	75
H257S	H117S	$1.75x\ 10^1$	77	$1.33x\ 10^1$	84
Q366D	Q217D	6.30	28	2.30	15
Q366E	Q217E	$2.38x\ 10^1$	105		
Q366N	Q217N	$2.26x\ 10^1$	100	$1.36x\ 10^1$	86
Q366T	Q217T	$2.48x\ 10^1$	110		
Q366S	Q217S	$1.02x\ 10^1$	45		
Q366V	Q217V	$2.90x\ 10^1$	128	$8.36x\ 10^1$	530
A51N	A[51]N			$2.07x\ 10^1$	91
V158T/L287T/M298K	V21T/L144T/M156K	4.65	21		
V158D/L287T/M298K	V21D/L144T/M156K	2.50	11		
S52A/S60A	S[52]A/S[60]A			$1.68x\ 10^1$	106
T128N/P129A	T[128]N/P[129]A			$1.43x\ 10^1$	91
Q286R/ Gla交換FIX	Q143R/Gla交換FIX	$4.37x\ 10^1$	193		
Q286R/H257A	Q143R/H117A	$1.07x\ 10^1$	47		
Q286R/S222A	Q143R/S82A	$1.00x\ 10^2$	444	$3.18x\ 10^1$	202
Q286R/S222A/H257A	Q143R/S82A/H117A			9.60x 10	61
Q286R/S222A/ Gla交換FIX	Q143R/S82A/Gla交換FIX	$1.82x\ 10^2$	804	$3.63x\ 10^1$	230
Q286R/S222A/H257A/ Gla交換FIX	Q143R/S82A/H117A/Gla交換FIX	$2.79x\ 10^1$	123		
Q286R/M298Q	Q143R/M156Q			$3.02x\ 10^2$	1916
Q286R/M298Q/K341Q	Q143R/M156Q/K192Q	$1.50x\ 10^2$	665	$3.65x\ 10^2$	2319
Q286R/M298Q/K199E	Q143R/M156Q/K60cE	$8.69x\ 10^1$	385	$2.29x\ 10^2$	1451
P321K	P170iK			$1.13x\ 10^1$	71
S222A/M298Q	S82A/M156Q			$7.85x\ 10^2$	4981
H257A/M298Q	H117A/M156Q			$4.12x\ 10^1$	262
S222A/H257A/Q286R/ M298Q	S82A/H117A/Q143R/M156 Q	$6.09x\ 10^2$	2695	$1.90x\ 10^2$	1208
Q286R/M298Q/Gla交換FIX	Q143R/M156Q/Gla交換 FIX			$7.52x\ 10^2$	4775
Q286R/Q366V	Q143R/Q217V			$2.38x\ 10^1$	151
A175S/Q286R/Q366V	A39S/Q143R/Q217V	$3.87x\ 10^1$	171	$1.23x\ 10^1$	78
S222A/Q286R/Q366V	S82A/Q143R/Q217V			$3.21x\ 10^1$	204
Q286M	Q143M	$1.07x\ 10^1$	47		
Q286L	Q143L	3.20	14		
Q286Y	Q143Y	$9.50x\ 10^{-1}$	4		
Q366I	Q217I	$6.29x\ 10^1$	278		
Q366L	Q217L	$2.54x\ 10^1$	112		
Q366M	Q217M	$4.05x\ 10^1$	179		
Q286R/K341D	Q143R/K192D	1.80	8		
Q286R/Q366D	Q143R/Q217D	1.00	4		

Q286R/Q366N	Q143R/Q217N	2.75	12		
Q286R/M298Q/Q366D	Q143R/M156Q/Q217D	6.80	30		
Q286R/M298Q/Q366N	Q143R/M156Q/Q217N	2.12×10^{1}	94		
Q286R/H373F	Q143R/H224F			2.20×10^{1}	139
Q286R/M298Q/H373F	Q143R/M156Q/H224F	2.16×10^{2}	957	3.17×10^{2}	2009
M298Q/H373F	M156Q/H224F			2.36×10^{2}	1499

在另一組實驗中，使用具有微小修改之如上所述之 TF 獨立性及 TF 依賴性間接檢定分析在 BHK-21 細胞中產生的 FVIIa 多肽之催化活性。數種變異體亦在除 BHK-21 細胞之外的 CHOX 細胞中產生或僅在 CHOX 細胞中產生。與所用細胞系無關，在相同條件下檢定變異體。對於 TF 依賴性催化檢定（使用線性分析）而言，如以下實施例 12 中所述，首先以香豆素(4)p'-胍基苯甲酸酯（4-methylumbelliferl p'-guanidinobenzoate；MUGB）活性位點滴定 FVIIa 多肽以測定 FVIIa 濃度。為最大化線性範圍內資料點之數目，將檢定中 FX 之最大濃度設定為 25 nM（亦即 0-25 nM，替代 0-150 nM）。如以下實施例 15 中所述，將檢定中所用之 FX 活化（亦即 FXa）且以螢光素-單-p'胍基苯甲酸酯（FMGB）滴定。就此活性位點滴定之 FXa 測定 Spectrafluor FXa 受質裂解之動力學常數，且證明為 190.2 μM 之 K_m 及 340 s^{-1} 之 k_{cat}。主要差異在於 k_{cat} 且主要由於改良之活性位點測定。此等參數提供 246.4 之修正 k_2 校正係數值，其用於線性分析中以測定 FVIIa 多肽在 TF 存在下之催化活性。

對於 TF 獨立性催化檢定而言，如以下實施例 12 中所述，首先以香豆素(4)p'-胍基苯甲酸酯（MUGB）活性位點滴定 FVIIa 多肽以測定 FVIIa 濃度。如實施例 15 中所述，將檢定中所用之 FX（亦即 FXa）活化且以螢光素-單-p'胍

基苯甲酸酯（FMGB）滴定。就此活性位點滴定之 FXa 測定 Spectrafluor FXa 受質裂解之動力學常數，且證明為 190.2 μM 之 K_m 及 340 s^{-1} 之 k_{cat}。此等參數提供 246.4 之修正 k_2 校正係數值，其用於線性分析中以測定 FVIIa 多肽在 TF 不存在情況下之催化活性。

表 15 闡明所檢定各 FVIIa 變異體多肽的催化活性。結果呈示為催化活性之動力學常數 k_{cat}/K_m（$M^{-1}sec^{-1}$），且亦表示為野生型 FVIIa 之活性之百分數，其中活性為催化活性，各 FVIIa 變異體對其受質 FX 的 k_{cat}/K_m（$M^{-1}sec^{-1}$）。亦提供標準偏差（SD）、變異係數（以百分數計；%CV）及所進行檢定之數目（n）。與野生型 FVII 多肽相比，一些變異體顯著顯示增強之催化活性。舉例而言，Gla 交換 FIX/Q286R/M298Q 變異體展現比野生型 FVII 多肽高 6 倍的 TF 依賴性催化活性。FVIIa 變異體的催化活性增強在 TF 獨立性檢定中更顯著。舉例而言，Gla 交換 FIX/Q366V 變異體具有比野生型 FVIIa 高 9 倍以上的催化活性，Gla 交換 FIX/Q286R/M298Q、{Gla 交換 FIX/E40L}/Q286R/M298Q、{Gla 交換 FIX/K43I}/Q286R/M298Q 及 {Gla 交換 FIX/Q44S}/Q286R/M298Q 變異體具有比野生型 FVIIa 高 70-80 倍以上的催化活性，且 S52A/S60A/V158D/E296V/M1298Q 變異體具有比野生型 FVIIa 高 220 倍以上的催化活性。

表 15. FVIIa 變異體之催化活性

TF 依賴性檢定						
突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	k_{cat}/K_M ($M^{-1}s^{-1}$)	SD	CV%	k_{cat}/K_M(WT)	n
WT (NovoSeven®)	WT (NovoSeven®)	3.98E+07	1.02E+07	26%	106%	30
WT (NovoSeven-RT®)	WT (NovoSeven-RT®)	3.48E+07	8.33E+06	24%	93%	10
WT	WT	3.75E+07	5.44E+06	15%	100%	13
WT †	WT †	3.76E+07	7.09E+06	19%	100%	10
T128N/P129A	T[128]N/P[129]A	4.65E+07	1.09E+07	23%	124%	5
Gla 交換 FIX	Gla 交換 FIX	5.38E+07	9.08E+05	2%	144%	2
K109N	K[109]N	5.54E+07	8.57E+06	15%	148%	2
A122N/G124S	A[122]N/G[124]S	3.87E+07	4.96E+06	13%	103%	2
S52A/S60A	S[52]A/S[60]A	3.56E+07	4.63E+06	13%	95%	2
M298Q	M156Q	6.76E+07	7.38E+06	11%	180%	6
M298Q †	M156Q †	7.46E+07	9.42E+06	13%	198%	4
T128N/P129A/M298Q †	T[128]N/P[129]A/M156Q †	6.29E+07	1.28E+07	20%	167%	4
V158D/E296V/M298Q	V21D/E154V/M156Q	1.81E+08	4.43E+07	25%	482%	8
V158D/E296V/M298Q †	V21D/E154V/M156Q †	1.65E+08	4.08E+07	25%	441%	10
T128N/P129A/V158D/E296V/M298Q	T[128]N/P[129]A/V21D/E154V/M156Q	2.01E+08	1.54E+07	8%	537%	4
S52A/S60A/V158D/E296V/M1298Q	S[52]A/S[60]A/V21D/E154/M156Q	2.00E+08	4.31E+05	0%	532%	2
Q286R	Q143R	8.06E+07	1.43E+07	18%	215%	5
T128N/P129A/Q286R	T[128]N/P[129]A/Q143R	8.45E+07	1.90E+07	22%	226%	6
T128N/P129A/Q286R †	T[128]N/P[129]A/Q143R †	6.20E+07			165%	1
S52A/S60A/Q286R	S[52]A/S[60]A/Q143R	4.10E+07	6.71E+06	16%	109%	4
S222A	S82A	4.07E+07	1.17E+07	29%	109%	4
T128N/P129A/S222A	T[128]N/P[129]A/S82A	6.25E+07	6.78E+06	11%	167%	4
S52A/S60A/S222A	S[52]A/S[60]A/S82A	3.91E+07	8.75E+06	22%	104%	3
H257S	H117S	1.18E+08	2.02E+07	17%	316%	2
H373F	H224F	5.58E+07	2.05E+07	37%	149%	2
Q366V	Q217V	5.48E+07	2.69E+06	5%	146%	2
Gla 交換 FIX/Q366V	Gla 交換 FIX/Q217V	9.11E+07	2.50E+07	27%	243%	3
A175S	A39S	2.11E+07	6.10E+06	29%	56%	3
K109N/A175S	K[109]N/A39S	1.74E+07	4.29E+06	25%	46%	5
S119N/L121S/A175S	S[119]N/L[121]S/A39S	1.73E+07	1.28E+06	7%	46%	2
T128N/P129A/A175S	T[128]N/P[129]A/A39S	8.59E+06	1.82E+06	21%	23%	2
A122N/G124S/A175S	A[122]N/G[124]S/A39S	1.05E+07	1.12E+06	11%	28%	2
Q286R/H257A	Q143R/H117A	9.91E+07	1.74E+07	18%	264%	2
Q286R/H257A †	Q143R/H117A †	3.08E+07	1.52E+07	49%	82%	4
Q286R/S222A	Q143R/S82A	1.11E+08	3.21E+07	29%	296%	4
Gla 交換 FIX/ T128N/P129A/ S222A/Q286R	Gla 交換 FIX/ T[128]N/P[129]A/ S82A/Q143R	1.47E+08	2.53E+07	17%	393%	3
Gla 交換 FIX/ T128N/P129A/ S222A/Q286R †	Gla 交換 FIX/ T[128]N/P[129]A/ S82A/Q143R †	1.43E+08	1.63E+07	11%	379%	2
Gla 交換 FIX/ S52A/S60A/S222A/Q286R	Gla 交換 FIX/ S[52]A/S[60]A/S82A/Q143R	7.24E+07	2.36E+06	3%	193%	2
Q286R/S222A/H257A	Q143R/S82A/H117A	6.98E+07	1.64E+07	23%	186%	3
Q286R/M298Q	Q143R/M156Q	1.66E+08	3.86E+07	23%	442%	14
Q286R/M298Q †	Q143R/M156Q †	1.34E+08	2.37E+07	18%	356%	15

Q286R/M298Q §	Q143R/M156Q §	1.54E+08	3.86E+07	25%	408%	6
Gla 交換 FIX/ Q286R/M298Q	Gla 交換 FIX/ Q143R/M156Q	2.55E+08	6.16E+07	24%	680%	6
Gla 交換 FIX/ Q286R/M298Q †	Gla 交換 FIX/ Q143R/M156Q †	2.30E+08	5.10E+07	22%	613%	4
T128N/P129A/Q286R/ M298Q	T[128]N/P[129]A/Q143 R/ M156Q	1.86E+08	2.64E+07	14%	497%	6
T128N/P129A/Q286R/ M298Q †	T[128]N/P[129]A/Q143 R/ M156Q †	1.50E+08	4.16E+07	28%	398%	4
Gla 交換 FIX /T128N/P129A/Q286R/ M298Q	Gla 交換 FIX /T[128]N/P[129]A/Q143 R/ M156Q	2.11E+08	4.41E+07	21%	562%	3
Gla 交換 FIX /T128N/P129A/Q286R/ M298Q †	Gla 交換 FIX /T[128]N/P[129]A/Q143 R/ M156Q †	1.99E+08	6.79E+07	34%	529%	5
{Gla 交換 FIX/E40L}/ Q286R/M298Q	{Gla 交換 FIX/E[40]L}/ Q143R/M156Q	2.08E+08	4.39E+07	21%	556%	4
{Gla 交換 FIX/K43I}/ Q286R/M298Q	{Gla 交換 FIX/K[43]I}/ Q143R/M156Q	2.73E+08	5.21E+07	19%	727%	5
{Gla 交換 FIX/K43I}/ Q286R/M298Q †	{Gla 交換 FIX/K[43]I}/ Q143R/M156Q †	2.91E+08	4.30E+07	15%	774%	5
{Gla 交換 FIX/Q44S}/ Q286R/M298Q	{Gla 交換 FIX/Q[44]S}/ Q143R/M156Q	1.98E+08	2.75E+07	14%	529%	3
{Gla 交換 FIX/M19K}/ Q286R/M298Q	{Gla 交換 FIX/M[19]K}/ Q143R/M156Q	1.41E+08	5.22E+06	4%	375%	2
S52A/S60A/ Q286R/M298Q	S[52]A/S[60]A/Q143R/ M156Q	1.25E+08	1.14E+07	9%	333%	4
Gla 交換 FIX /S52A/S60A/ Q286R/M298Q †	Gla 交換 FIX /S[52]A/S[60]A/Q143R/ M156Q †	1.80E+08	1.81E+07	10%	480%	3
{Gla 交換 FIX/M19K/E40L/K43I/ Q44S}/ Q286R/M298Q	{Gla 交換 FIX/M[19]K/E[40]L/K[4 3]I/Q[44]}/ Q286R/M298Q	1.21E+08	7.07E+06	6%	322%	2
{Gla 交換 FIX/K43I}/T128N/P129 A/ Q286R/M298Q †	{Gla 交換 FIX/K[43]I}/T128N/P12 9A/Q143R/M156Q †	2.71E+08	6.41E+07	24%	720%	5
T239V	T99V	4.64E+07	8.38E+06	18%	124%	2
T239I	T99I	2.62E+07	6.51E+06	25%	70%	2
H257A/ M298Q	H117A/Q143R/M156Q	1.67E+07	4.27E+06	26%	45%	5
S222A/H257A/Q286R/ M298Q	S82A/H117A/Q143R/M 156Q	1.65E+08	1.76E+07	11%	440%	4
T128N/P129A/S222A/ H257A/Q286R/M298Q	T[128]N/P[129]A/S82A/ H117A/Q143R/M156Q	1.55E+08	5.77E+07	37%	414%	9
T128N/P129A/S222A/ H257A/Q286R/M298Q †	T[128]N/P[129]A/S82A/ H117A/Q143R/M156Q †	1.73E+08	1.41E+07	8%	461%	2
S52A/S60A/S222A/H25 7A/Q286R/M298Q	S[52]A/S[60]A/S82A/H 117A/Q143R/M156Q	2.49E+08	8.78E+06	4%	665%	3
H257S/Q286R/Q366V	H117S/Q143R/Q217V	7.10E+07	3.16E+07	44%	189%	11
S222A/H257A/Q286R/ Q366V	S82A/H117A/Q143R/Q2 17V	1.00E+08	1.03E+07	10%	268%	4
Q286R/M298Q/Q366N	Q143R/M156Q/Q217N	1.17E+08	3.05E+07	26%	312%	7
T128N/P129A/Q286R/M 298Q/Q366N †	T[129]N/P[129]A/Q143 R/M156Q/Q217N †	1.42E+08	4.17E+07	29%	377%	3
{Gla 交換 FIX/K43I}/Q286R/M298 Q/Q366N †	{Gla 交換 FIX/K43I}/Q143R/M15 6Q/Q217N †	1.69E+08	3.89E+07	23%	450%	5

{Gla 交換 FIX/K43I}/T128N/P129A/Q286R/M298Q/Q366N †	{Gla 交換 FIX/K43I}/T[128]N/P[129]A/Q143R/M156Q/Q217N †	2.52E+08	1.36E+07	5%	669%	2
Q286R/H373F	Q143R/H224F	9.01E+07	7.73E+06	9%	240%	2
T128N/P129A/Q286R/H373F	T[128]N/P[129]A/Q143R/H224F	6.91E+07	2.15E+07	31%	184%	12
S52A/S60A/Q286R/H373F	S[52]A/S[60]A/Q143R/H224F	9.44E+07	1.43E+07	15%	252%	3
Q286R/M298Q/H373F	Q143R/M156Q/H224F	1.36E+08	1.92E+07	14%	364%	5
T128N/P129A/Q286R/M298Q/H373F	T[128]N/P[129]A/Q143R/M156Q/H224F	1.33E+08	4.77E+07	36%	354%	17
S52A/S60A/Q286R/M298Q/H373F	S[52]A/S[60]A/Q143R/M156Q/H224F	1.77E+08	3.63E+07	21%	472%	3
M298Q/H373F	M156Q/H224F	7.21E+07	1.76E+07	24%	192%	4
T128N/P129A/M298Q/H373F †	T[128]N/P[129]A/M156Q/H224F †	6.07E+07	1.29E+07	21%	161%	2
V158D/Q286R/E296V/M298Q	V21D/Q143R/E154V/M156Q	1.49E+08	3.59E+07	24%	397%	11
S222A/T239V	S82A/T99V	7.49E+07	2.57E+06	3%	200%	3
Gla 交換 FIX /S222A/T239V/Q286R	Gla 交換 FIX /S82A/T99V/Q143R	2.03E+08	3.16E+07	16%	541%	3
Gla 交換 FIX /S222A/T239V/Q286R †	Gla 交換 FIX /S82A/T99V/Q143R †	9.94E+07	1.83E+07	18%	264%	3
T239V/Q286R/M298Q	T99V/Q143R/M156Q	1.72E+08	4.92E+07	29%	459%	5
Gla 交換 FIX/T239V/Q286R/M298Q	Gla 交換 FIX/T99V/Q143R/M156Q	2.53E+08	4.78E+07	19%	675%	3
Gla 交換 FIX/T239V/Q286R/M298Q †	Gla 交換 FIX/T99V/Q143R/M156Q †	1.79E+08	3.81E+07	21%	477%	4
T128N/P129A/T239V/Q286R/M298Q †	T[128]N/P[129]A/T99V/Q143R/M156Q †	1.04E+08	2.43E+07	23%	276%	4
S222A/T239V/H257A/Q286R/M298Q	S82A/T99V/H117A/Q143R/M156Q	2.14E+08	4.48E+07	21%	571%	5
T128N/P129A/S222A/T239V/H257A/Q286R/M298Q †	T[128]N/P[129]A/S82A/T99V/H117A/Q143R/M156Q †	1.21E+08	5.58E+06	5%	323%	3
T239V/Q286R/H373F	T99V/Q143R/H224F	1.06E+08	1.34E+07	13%	283%	2
T239V/Q286R/M298Q/H373F	T99V/Q143R/M156Q/H224F	1.70E+08	1.13E+07	7%	454%	2
T128N/P129A/T239V/Q286R/M298Q/H373F †	T[128]N/P[129]A/T99V/Q143R/M156Q/H224F †	2.36E+08	2.77E+07	12%	627%	3
V158D/T239I/E296V/M298Q	V21D/T99I/E154V/M156Q	1.45E+08	1.18E+07	8%	387%	4
T239I/Q286R	T99I/Q143R	5.79E+07	1.39E+07	24%	155%	3
S222A/T239I	S82A/T99I	3.05E+07	9.26E+06	30%	81%	4
Gla 交換 FIX/S222A/T239I/Q286R	Gla 交換 FIX /S82A/T99I/Q143R	6.77E+07	4.44E+06	7%	181%	2
T239I/Q286R/M298Q	T99I/Q143R/M156Q	1.13E+08	3.68E+06	3%	301%	2
Gla 交換 FIX / T239I/Q286R/M298Q	Gla 交換 FIX /T99I/Q143R/M156Q	1.25E+08	2.13E+07	17%	334%	2
T128N/P129A/T239I/Q286R/M298Q †	T[128]N/P[129]A/T99I/Q143R/M156Q †	8.17E+07	8.17E+06	10%	217%	3
S222A/T239I/H257A/Q286R/M298Q	S82A/T99I/H117A/Q143R/M156Q	1.14E+08	2.22E+07	19%	304%	3
T239I/Q286R/H373F	T99I/Q143R/H224F	6.18E+07	9.27E+06	15%	165%	3
V158D/T239V/E296V/M298Q	V21D/T99V/E154V/M156Q	2.22E+08	1.39E+07	6%	591%	2
V158D/T239V/E296V/	V21D/T99V/E154V/M1	1.65E+08	2.12E+06	1%	438%	2

M298Q †	56Q †					
T239V/Q286R	T99V/Q143R	8.84E+07	7.16E+05	1%	236%	2
T239I/Q286R/M298Q/ H237F	T99I/Q143R/M156Q/H224F	1.08E+08	2.32E+07	21%	289%	7
T128N/P129A/T239I/Q286R/M298Q/ H237F †	T[128]N/P[129]A/T99I/ Q143R/M156Q/H224F †	1.30E+08	2.51E+07	19%	345%	5
H257S/Q286R/M298Q	H117S/Q143R/M156Q	1.40E+08	8.97E+06	6%	372%	4
Gla 交換 FIX /Q286R/S222A/H257S	Gla 交換 FIX /Q143R/S82A/H117S	8.53E+07	1.66E+07	20%	227%	3
S222A/H257S/Q286R/ M298Q	S82A/H117S/Q143R/M156Q	1.58E+08	1.76E+07	11%	420%	2
H257S/Q286R/M298Q/ H373F	H117S/Q143R/M156Q/ H224F	1.52E+08	3.35E+07	22%	407%	7
S222A/Q286R/M298Q/ H373F	S82A/Q143R/M156Q/H224F	1.48E+08	2.23E+06	2%	395%	2
Gla 交換 FIX/S222A/ Q286R/M298Q/H373F	Gla 交換 FIX S82A/Q143R/M156Q/H224F	2.84E+08	4.85E+07	17%	758%	3
S222A/Q286R/M298Q	S82A/Q143R/M156Q	1.29E+08	1.86E+07	14%	343%	3
Gla 交換 FIX/ S222A/Q286R/M298Q	Gla 交換 FIX S82A/Q143R/M156Q	2.10E+08	4.28E+07	20%	559%	5
T128N/P129A/A175S/ Q366V	T[128]N/P[129]A/A39S/ Q217V	3.38E+07	3.06E+06	9%	90%	2
A122N/G124S/A175S/ Q366V	A[122]N/G[124]S/A39S /Q217V	3.02E+07	7.05E+06	23%	80%	5
T128N/P129A/A175S/ S222A	T[128]N/P[129]A/A39S/ S82A	1.72E+07	3.18E+06	18%	46%	3
A122N/G124S/A175S/ S222A	A[122]N/G[124]S/A39S /S82A	2.08E+07	5.05E+06	24%	56%	5
T128N/P129A/A175S/ Q286R	T[128]N/P[129]A/A39S/ Q143R	3.33E+07	1.46E+06	4%	89%	3
A122N/G124S/A175S/ Q286R	A[122]N/G[124]S/A39S /Q143R	4.11E+07	5.27E+06	13%	110%	5
Gla 交換 FIX/ S222A/Q286R/H373F	Gla 交換 FIX/ S82A/Q143R/H224F	1.22E+08	3.17E+07	26%	327%	8
V158D/E296V/M298Q/ H373F	V21D/E154V/M156Q/H224F	1.51E+08	8.39E+06	6%	402%	3
H257A/Q286R/M298Q	H117A/Q143R/M156Q	1.13E+08	1.55E+07	14%	301%	3
Gla 交換 FIX/ T128N/P129A/A175S/ S222A/Q286R	Gla 交換 FIX/ T[128]N/P[129]A/A39S/ S82A/Q143R	3.88E+07	2.74E+06	7%	104%	3
Gla 交換 FIX/ A122N/G124S/A175S/ S222A/Q286R	Gla 交換 FIX/ A[122]N/G[124]S/A39S /S82A/Q143R	4.13E+07	8.99E+06	22%	110%	6
T128N/P129A/A175S/ Q286R/M298Q	T[128]N/P[129]A/A39S/ Q143R/M156Q	7.21E+07	1.14E+07	16%	192%	3
A122N/G124S/A175S/ Q286R/M298Q	A[122]N/G[124]S/A39S /Q143R/M156Q	7.43E+07	1.10E+07	15%	198%	3
T128N/P129A/A175S/ S222A/H257A/Q286R/ M298Q	T[128]N/P[129]A/A39S/ S82A/H117A/Q143R/M156Q	6.89E+07	3.36E+06	5%	184%	3
A122N/G124S/A175S/ S222A/H257A/Q286R/ M298Q	A[122]N/G[124]S/A39S /S82A/H117A/Q143R/M156Q	8.40E+07	5.72E+06	7%	224%	3
T128N/P129A/A175S/ Q286R/M298Q/H373F	T[128]N/P[129]A/A39S/ Q143R/M156Q/H224F	5.72E+07	3.36E+06	6%	153%	3
A122N/G124S/A175S/ Q286R/M298Q/H373F	A[122]N/G[124]S/A39S /Q143R/M156Q/H224F	8.39E+07	9.99E+06	12%	224%	3
V158D/Q286R/E296V/	V21D/Q143R/E154V/M	2.39E+08	3.82E+07	16%	638%	5

M298Q/H373F	156Q/H224F					
M298Q/Q366N/H373F †	M156Q/Q217N/H224F †	7.05E+07	1.78E+07	25%	188%	3
T239V/M298Q/H373F †	T99V/M156Q/H224F †	4.43E+07	1.10E+07	25%	118%	3
T239I/M298Q/H373F †	T99I/M156Q/H224F †	3.47E+07	4.57E+06	13%	92%	3
T128N/P129A/Q286R/M298Q/Q366N/H373F †	T[128]N/P[129]A/Q143R/M156Q/Q217N/H224F †	1.33E+08	1.81E+07	14%	355%	2
T239V/Q286R/M298Q/Q366N †	T99V/Q143R/M156Q/Q217N †	1.85E+08	5.96E+07	32%	491%	4
T239I/Q286R/M298Q/Q366N †	T99I/Q143R/M156Q/Q217N †	7.40E+07	1.40E+07	19%	197%	4
TF 獨立性檢定						
突變（成熟 FVII 編號）	**突變（胰凝乳蛋白酶編號）**	**k_{cat}/K_M ($M^{-1}s^{-1}$)**	**SD**	**CV%**	**k_{cat}/K_M (WT%)**	**n**
WT (NovoSeven®)	WT (NovoSeven®)	9.8	3.0	30%	88%	14
WT (NovoSeven-RT®)	WT (NovoSeven-RT®)	12.4	4.3	35%	112%	12
WT	WT	11.1	2.7	25%	100%	5
WT †	WT †	6.9	2.2	31%	100%	7
T128N/P129A	T[128]N/P[129]A	17.0	5.2	31%	153%	3
Gla 交換 FIX	Gla 交換 FIX	41.3	3.0	7%	373%	2
A122N/G124S	A[122]N/G[124]S	3.4	0.6	16%	31%	2
S52A/S60A	S[52]A/S[60]A	3.8			34%	1
M298Q †	M156Q †	69.9	49.4	71%	1013%	3
T128N/P129A/M156Q †	T[128]N/P[129]A/M156Q †	90.8	70.8	78%	1316%	5
V158D/E296V/M298Q	V21D/E154V/M156Q	1221.7	307.0	25%	11025%	4
V158D/E296V/M298Q †	V21D/E154V/M156Q †	984.5	308.4	31%	14265%	2
T128N/P129A/V158D/E296V/M298Q	T[128]N/P[129]A/V21D/E154V/M156Q	1375.8	140.3	10%	12415%	3
S52A/S60A/V158D/E296V/M1298Q	S[52]A/S[60]A/V21D/E154V/M156Q	1760.1	575.0	33%	15883%	3
Q286R	Q143R	10.3	0.7	7%	93%	3
T128N/P129A/Q286R	T[128]N/P[129]A/Q143R	8.7	4.3	50%	78%	5
T128N/P129A/Q286R †	T[128]N/P[129]A/Q143R †	10.5	5.6	53%	152%	6
S52A/S60A/S82A	S[52]A/S[60]A/S82A	10.2	4.7	47%	92%	3
T128N/P129A/S222A	T[128]N/P[129]A/S82A	4.8			43%	1
S52A/S60A/S222A	S[52]A/S[60]A/S82A	19.6			177%	1
H257S	H117S	3.1	1.1	35%	28%	7
Q366V	Q217V	4.3	0.6	14%	39%	2
Gla 交換 FIX/Q366V	Gla 交換 FIX/Q217V	90.0	17.7	20%	812%	2
Q286R/H257A	Q143R/H117A	4.3	2.1	49%	39%	3
Q286R/H257A †	Q143R/H117A †	2.5	0.0	0%	36%	2
Gla 交換 FIX/T128N/P129A/S222A/Q286R	Gla 交換 FIX/T[128]N/P[129]A/S82A/Q143R	15.5	2.9	18%	140%	4
Gla 交換 FIX/T128N/P129A/S222A/Q286R †	Gla 交換 FIX/T[128]N/P[129]A/S82A/Q143R †	21.3	6.5	31%	309%	5
Gla 交換 FIX/S52A/S60A/S222A/Q286R	Gla 交換 FIX/S[52]A/S[60]A/S82A/Q143R	2.9			26%	1
Q286R/S222A/H257A	Q143R/S82A/H117A	21.3	6.5	31%	193%	5
Q286R/M298Q	Q143R/M156Q	79.9	18.9	24%	721%	5
Q286R/M298Q †	Q143R/M156Q †	162.4	79.9	49%	2353%	12
Q286R/M298Q §	Q143R/M156Q §	135.1	7.3	5%	1957%	2

Gla 交換 FIX/ Q286R/M298Q	Gla 交換 FIX/ Q143R/M156Q	672.7	79.1	12%	6070%	4
Gla 交換 FIX/ Q286R/M298Q †	Gla 交換 FIX/ Q143R/M156Q †	678.2	249.0	37%	9826%	11
T128N/P129A/Q286R/ M298Q	T[128]N/P[129]A/Q143 R/ M156Q	81.6	13.4	16%	736%	4
T128N/P129A/Q286R/ M298Q †	T[128]N/P[129]A/Q143 R/ M156Q †	212.5	135.4	64%	3079%	10
Gla 交換 FIX /T128N/P129A/Q286R/ M298Q	Gla 交換 FIX /T[128]N/P[129]A/Q143 R/ M156Q	83.8	35.3	42%	756%	6
Gla 交換 FIX /T128N/P129A/Q286R/ M298Q †	Gla 交換 FIX /T[128]N/P[129]A/Q143 R/ M156Q †	751.9	305.3	41%	10895%	6
{Gla 交換 FIX/E40L}/ Q286R/M298Q	{Gla 交換 FIX/E[40]L}/ Q143R/M156Q	814.1	89.0	11%	7346%	2
{Gla 交換 FIX/K43I}/ Q286R/M298Q	{Gla 交換 FIX/K[43]I}/ Q143R/M156Q	902.4	360.6	40%	8144%	11
{Gla 交換 FIX/K43I}/ Q286R/M298Q †	{Gla 交換 FIX/K[43]I}/ Q143R/M156Q †	794.2	178.7	23%	11508%	6
{Gla 交換 FIX/Q44S}/ Q286R/M298Q	{Gla 交換 FIX/Q[44]S}/ Q143R/M156Q	729.0	4.5	1%	6578%	2
{Gla 交換 FIX/M19K}/ Q286R/M298Q	{Gla 交換 FIX/M[19]K}/ Q143R/M156Q	512.0	51.4	10%	4620%	2
S52A/S60A/ Q286R/M298Q	S[52]A/S[60]A/Q143R/ M156Q	216.8	1.6	1%	1956%	2
Gla 交換 FIX /S52A/S60A/ Q286R/M298Q	Gla 交換 FIX/S[52]A/ S[60]A/Q143R/M156Q	988.7	207.5	21%	14327%	2
{Gla 交換 FIX/K43I} /T128N/P129A/Q286R/ M298Q †	{Gla 交換 FIX/K[43]I}/ T[128]N/P[129]A/ Q143R/M156Q †	389.4	34.3	9%	5642%	2
S222A/H257A/Q286R/ M298Q	S82A/H117A/Q143R/M 156Q	345.3	99.9	29%	3116%	3
T128N/P129A/S222A/ H257A/Q286R/M298Q	T[128]N/P[129]A/S82A/ H117A/Q143R/M156Q	24.8	17.2	69%	224%	4
T128N/P129A/S222A/ H257A/Q286R/M298Q †	T[128]N/P[129]A/S82A/ H117A/Q143R/M156Q †	82.6	40.2	49%	1196%	3
S52A/S60A/S222A/H25 7A/Q286R/M298Q	S[52]A/S[60]A/S82A/H 117A/Q143R/M156Q	115.6	62.9	54%	1043%	2
H257S/Q286R/Q366V	H117S/Q143R/Q217V	7.7	1.8	23%	69%	2
S222A/H257A/Q286R/Q 366V	S82A/H117A/Q143R/Q2 17V	12.5	2.8	23%	113%	2
Q286R/M298Q/Q366N	Q143R/M156Q/Q217N	65.9	33.4	51%	595%	5
T129N/P129A/Q286R/M 298Q/Q366N †	T[129]N/P[129]A/Q143 R/M156Q/Q217N †	64.6	28.7	44%	936%	4
{Gla 交換 FIX/K43I} /Q286R/M298Q/Q217N †	{Gla 交換 FIX/K[43]I} /Q143R/M156Q/Q217N †	84.9	76.5	90%	1230%	4
{Gla 交換 FIX/K43I} /T128N/P129A/Q286R/ M298Q/Q366N †	{Gla 交換 FIX/K[43]I} /T[128]N/P[129]A/Q143 R/M156Q/Q217N †	218.5	137.8	63%	3166%	3
Q286R/H373F	Q143R/H224F	81.6	123.7	152%	736%	9
T128N/P129A/ Q286R/H373F	T[128]N/P[129]A/Q143 R/H224F	6.6	0.9	13%	59%	2
S52A/S60A/Q286R/H37 3F	S[52]A/S[60]A/Q143R/ H224F	30.1			272%	1

Q286R/M298Q/H373F	Q143R/M156Q/H224F	114.8	24.7	22%	1036%	5
T128N/P129A/Q286R/M298Q/H373F †	T[128]N/P[129]A/Q143R/M156Q/H224F †	30.7	8.9	29%	277%	4
S52A/S60A/Q286R/M298Q/H373F	S[52]A/S[60]A/Q143R/M156Q/H224F	63.3	10.8	17%	571%	3
M298Q/H373F	M156Q/H224F	96.4	47.0	49%	870%	5
T128N/P129A/M298Q/H373F	T[128]N/P[129]A/M156Q/H224F	91.6	48.0	52%	1327%	3
V158D/Q286R/E296V/M298Q	V21D/Q143R/E154V/M156Q	1023.9	339.3	33%	9240%	5
S222A/T239V	S82A/T99V	3.0			27%	1
Gla 交換 FIX /S222A/T239V/Q286R	Gla 交換 FIX /S82A/T99V/Q143R	17.4	2.2	13%	157%	3
Gla 交換 FIX /S222A/T239V/Q286R †	Gla 交換 FIX /S82A/T99V/Q143R †	87.9	61.7	70%	1274%	4
T239V/Q286R/M298Q	T99V/Q143R/M156Q	29.3	6.2	21%	264%	4
Gla 交換 FIX/ T239V/Q286R/M298Q	Gla 交換 FIX/ T99V/Q143R/M156Q	277.7	64.2	23%	2506%	3
Gla 交換 FIX/ T239V/Q286R/M298Q †	Gla 交換 FIX/ T99V/Q143R/M156Q †	902.4	323.5	36%	13076%	6
T128N/P129A/ T239V/Q286R/M298Q †	T[128]N/P[129]A/ T99V/Q143R/M156Q †	229.7	134.1	58%	3329%	5
S222A/T239V/H257A/ Q286R/M298Q	S82A/T99V/H117A/Q143R/M156Q	143.0	93.1	65%	1290%	10
T128N/P129A/ S222A/T239V/H257A/ Q286R/M298Q	T[128]N/P[129]A/ S82A/T99V/H117A/Q143R/M156Q	179.0	80.5	45%	2593%	5
T239V/Q286R/H373F	T99V/Q143R/H224F	12.2			110%	1
T239V/Q286R/M298Q/ H373F	T99V/Q143R/M156Q/H224F	40.7	5.2	13%	367%	2
T128N/P129A/T99V/Q143R/M156Q/H224F	T[128N]/P129]A/T99V/ Q143R/M156Q/H224F	290.0	72.9	25%	4203%	4
V158D/T239I/E296V/M298Q	V21D/T99I/E154V/M156Q	216.3	32.5	15%	1951%	2
T239I/Q286R	T99I/Q143R	4.6	1.3	28%	41%	4
S222A/T239I	S82A/T99I	1.7			15%	1
Gla 交換 FIX /S222A/T239I/Q286R	Gla 交換 FIX /S82A/T99I/Q143R	20.3			184%	1
T239I/Q286R/M298Q	T99I/Q143R/M156Q	11.3	4.0	35%	102%	4
Gla 交換 FIX / T239I/Q286R/M298Q	Gla 交換 FIX /T99I/Q143R/M156Q	244.0	9.6	4%	2202%	2
T128N/P129A/T239I/Q286R/M298Q	T[128N]/P129]A/T99I/Q143R/M156Q	77.8	40.3	52%	1128%	5
S222A/T239I/H257A/Q286R/M298Q	S82A/T99I/H117A/Q143R/M156Q	51.6	5.7	11%	466%	2
V158D/T239V/E296V/ M298Q	V21D/T99V/E154V/M156Q	1864.3	374.0	20%	16823%	2
V158D/T239V/E296V/ M298Q †	V21D/T99V/E154V/M156Q †	4231.6	913.4	22%	61315%	4
T239V/Q286R	T99V/Q143R	11.8	4.1	35%	106%	4
T239I/Q286R/M298Q/H373F	T99I/Q143R/M156Q/H224F	13.1	3.8	29%	118%	3
T128N/P129A/T239I/Q286R/M298Q/H373F †	T[128]N/P[129]A/T99I/ Q143R/M156Q/H224F †	113.3	43.7	39%	1642%	5
H257S/Q286R/M298Q	H117S/Q143R/M156Q	27.4	4.1	15%	247%	4
Gla 交換 FIX /S8222A/H257S/Q143R	Gla 交換 FIX /S82A/H117S/Q143R	20.5	3.6	18%	185%	2
S222A/Q286R/M298Q/ H373F	S82A/Q143R/M156Q/H224F	41.7	9.1	22%	376%	4

H257S/Q286R/M298Q/H373F	H117S/Q143R/M156Q/H224F	30.4	9.1	30%	274%	3
S82A/Q143R/M156Q/H224F	S82A/Q143R/M156Q/H224F	430.2	126.8	29%	3883%	3
Gla 交換 FIX/S222A/Q286R/M298Q/H373F	Gla 交換 FIX/S82A/Q143R/M156Q/H224F	192.1	36.8	19%	1733%	2
S222A/Q286R/M298Q	S82A/Q143R/M156Q	252.9	7.4	3%	2282%	2
Gla 交換 FIX/S222A/Q286R/M298Q	Gla 交換 FIX/S82A/Q143R/M156Q	414.7	81.3	20%	3742%	2
T128N/P129A/A175S/Q366V	T[128]N/P[129]A/A39S/Q217V	3.4	1.0	29%	30%	2
A122N/G124S/A175S/Q366V	A[122]N/G[124]S/A39S/Q217V	3.0	0.8	26%	27%	4
T128N/P129A/A175S/S222A	T[128]N/P[129]A/A39S/S82A	1.9	0.5	26%	17%	2
T128N/P129A/A175S/Q286R	T[128]N/P[129]A/A39S/Q143R	3.3	1.2	37%	29%	4
A122N/G124S/A175S/Q286R	A[122]N/G[124]S/A39S/Q143R	3.0	0.7	23%	27%	2
Gla 交換 FIX/S222A/Q286R/H373F	Gla 交換 FIX/S82A/Q143R/H224F	81.2	66.7	82%	732%	2
V158D/E296V/M298Q/H373F	V21D/E154V/M156Q/H224F	1297.2	486.1	37%	11706%	4
H257A/Q286R/M298Q	H117A/Q143R/M156Q	61.5	43.8	71%	555%	2
Gla 交換 FIX/T128N/P129A/A175S/S222A/Q286R	Gla 交換 FIX/T[128]N/P[129]A/A39S/S82A/Q143R	30.5			276%	1
T128N/P129A/A175S/S222A/H257A/Q286R/M298Q	T[128]N/P[129]A/A39S/S82A/H117A/Q143R/M156Q	20.3	3.8	19%	183%	2
V158D/Q286R/E296V/M298Q/H373F	V21D/Q143R/E154V/M156Q/H224F	573.6	100.4	18%	5176%	6
M298Q/Q366N/H373F †	M156Q/Q217N/H224F †	125.9	75.2	60%	1825%	4
T239V/M298Q/H373F †	T99V/M156Q/H224F †	319.5	125.0	39%	4629%	6
T239I/M298Q/H373F †	T99I/M156Q/H224F †	138.2	101.9	74%	2003%	7
T128N/P129A/Q286R/M298Q/Q366N/H373F †	T[128]N/P[129]A/Q143R/M156Q/Q217N/H224F †	160.9	43.3	27%	2331%	4
T239V/Q286R/M298Q/Q366N †	T99V/Q143R/M156Q/Q217N †	64.2	36.3	57%	931%	3
T239I/Q286R/M298Q/Q366N †	T99I/Q143R/M156Q/Q217N †	88.8	23.5	26%	1287%	5

† 在 CHOX 細胞中產生

§ 在 CHOX 穩定細胞系純系 52-5F7 中產生

實施例 5

測定 AT-III/肝素對 FVIIa/TF 或 FVIIa 之抑制

藉由量測各種濃度之 AT-III 對 FVIIa/sTF 對受質甲磺

醯基-FPR-ACC 之催化活性的抑制程度評估在可溶性組織因子（sTF）存在或不存在情況下（亦即 TF 依賴性或 TF 獨立性），AT-III/肝素複合物與 FVIIa 之間的交互作用之效能。測定所測試各 FVIIa 變異體之 $K_{0.5}$ 值，其對應於在 30 分鐘檢定中在室溫下（約 25°）50%抑制（IC50）FVIIa 變異體所需的 AT-III 之莫耳濃度。

準備兩個獨立檢定，一個具有 sTF 且一個無 sTF。藉由混合 26.4 μL 151.7 μM AT-III（血漿經純化人類 AT-III；Molecular Innovations）與 50 μL 0.2 mM LMW 肝素（CalBiochem）、400 μL 5x檢定緩衝液（100 mM Hepes、750 mM NaCl、25 mM $CaCl_2$、0.05% BSA、0.5% PEG 8000，pH 7.4）及 1.523 mL 試劑級水製備 AT-III/肝素之 2 μM 溶液（最終 5 μM 肝素）。該溶液在 TF 依賴性檢定中以最高濃度形式使用。藉由混合 52.8 μL 151.7 μM AT-III（Molecular Innovations）與 50 μL 0.2 mM LMW 肝素（CalBiochem）、400 μL 5x檢定緩衝液及 1.497 mL 試劑級水製備含有 4 μM AT-III/肝素（最終 5 μM 肝素）之溶液以便用於 TF 獨立性檢定中。在室溫下將 AT-III/肝素溶液培育 5-10 分鐘，且隨後以含有 5 μM 肝素之 1 mL 最終體積兩倍稀釋於 96 深孔聚丙烯板中，產生 2000、1000、500、250、125、62.5、31.25 及 0 nM 或 4000、2000、1000、500、250、125、62.5 及 0 nM 之稀釋液。將 FVIIa 變異體及野生型 FVIIa 在 1x檢定緩衝液（20 mM Hepes、150 mM NaCl、5 mM $CaCl_2$、0.01% BSA、0.1% PEG 8000，pH 7.4）中稀

釋至 250 nM。對於 TF 依賴性檢定，藉由混合 20 μL FVIIa 與 10 μL 5 μM sTF（R & D Systems 人類凝血因子 III：#2339-PA）、200 μL 5×檢定緩衝液及 770 μL 試劑級水且將溶液在室溫下培育 10-15 分鐘形成 5 nM FVIIa/50 nM sTF 複合物。對於 TF 獨立性檢定，混合 100 μL FVIIa 與 200 μL 5×檢定緩衝液及 700 μL 試劑級水以產生 25 nM FVIIa 溶液。為起始檢定，在 96 孔黑色半區域檢定板（Nunc）之孔中獨立地混合 25 μL FVIIa/TF 或僅 FVIIa 之溶液與 25 μL 各 AT-III/肝素稀釋液。TF 依賴性檢定之最終檢定條件為 2.5 nM FVIIa/25 nM sTF 及濃度範圍為 1000 nM 至 0 nM 之 AT-III/肝素。對於 TF 獨立性檢定，FVIIa 濃度為 12.5 nM FVIIa 且 AT-III/肝素濃度範圍為 2000 nM 至 0 nM。在振盪情況下在室溫下（約 25℃）將板培育 30 分鐘。

藉由在 DMSO 中溶解受質至 20 mM，接著製備在 1×檢定緩衝液中之 0.5 mM 工作溶液製備 FVIIa 受質（甲磺醯基-FPR-ACC）之儲備溶液。培育上述檢定板後，將 50 μl FVIIa 受質添加至檢定板之各孔中。混合反應且藉由在設定為 30℃之螢光讀取器中追蹤受質裂解初始速率 15 分鐘評估 FVIIa 之殘餘活性。

為測定 FVIIa 或 FVIIa 變異體受 AT-III/肝素抑制之程度，將以 SoftMax Pro 應用（Molecular Devices）收集的原始資料輸出為.XML 文件。另外，以 XLfit4，一種用於在 Microsoft Excel 試算表環境（IDBS Software）內進行自動曲線擬合及統計分析之軟體套件進行非線性資料分析。使

用試算表模板計算 AT-III 稀釋系列，AT-III 與 FVIIa 之比率及各 FVIIa 重複在各實驗性 AT-III 濃度下之 Vi/Vo 比率。使用 XLfit4 及形式（(C+(Amp*(1-(X/($K_{0.5}$+X))))）之雙曲線型抑制方程式處理殘餘 FVIIa 活性（表示為 Vi/Vo）相對於 AT-III 濃度之非線性回歸分析；其中 C = 偏移值（固定在 0 以允許外推在檢定過程中未達到 100%抑制之資料組），Amp = 擬合幅度，且 $K_{0.5}$ 對應於在檢定條件下半最大抑制所需的 AT-III 之濃度。對於數種 FVIIa 變異體，AT-III 在 AT-III 之最高測試濃度下抑制小於 20-25%之總蛋白酶活性，表示檢定之偵測上限。因此，具有小於 20-25%最大抑制之變異體經指定下限 $K_{0.5}$ 值（對於 TF 依賴性為 5 μM 且對於 TF 獨立性為 10 μM），且在大多數情況下預期具有大於所報導值之 AT-III 抗性。

表 15 及 16 提供分別在 TF 存在及不存在情況下使用在 Freestyle TM 293-F 細胞及/或 BHK-21 細胞中表現之 FVIIa 變異體進行的檢定之結果。結果呈示為經擬合 $K_{0.5}$ 參數與同野生型 FVIIa 相比各變異體 AT-III 抗性之程度的表示，其表示為其經擬合 $K_{0.5}$ 值之比率（$K_{0.5}$ 變異體/$K_{0.5}$ 野生型）。與野生型 FVIIa 相比，數種 FVIIa 變異體展現增強之 AT-III 抗性。舉例而言，Q286R-FVIIa、Q286R/S222A-FVIIa、Q286R/S222A/Gla 交換 FIX-FVIIa、A175S/Q286R/Q366V-FVIIa、Q286M-FVIIa、Q286L-FVIIa 及 Q286Y-FVIIa 處於 TF 不存在情況下展現比野生型 FVIIa 高 4 倍以上的 AT-III 抗性之組中。

表 16. TF 存在下 AT-III/肝素對 FVIIa 變異體之抑制

突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	TF-依賴性 ATIII 抗性檢定			
		293-F 細胞		BHK-21 細胞	
		$K_{0.5}$ (nM)	$K_{0.5mut}/K_{0.5wt}$	$K_{0.5}$ (nM)	$K_{0.5mut}/K_{0.5wt}$
WT	WT	72.3	1.0	56.0	1.0
V158D/E296V/M298Q	V21D/E154V/M156Q	75.1	1.0	79.0	1.4
Q286R	Q143R	60.6	0.8	59.1	1.1
S222A	S82A	47.6	0.7	43.9	0.8
H257S	H117S	50.6	0.7	52.9	0.9
H373D	H224D	423.6	5.9		
H373E	H224E	152.1	2.1		
H373S	H224S	64.2	0.9		
H373F	H224F	38.7	0.5		
H373A	H224A	76.9	1.1		
Q366D	Q217D	2239.2	31.0		
Q366E	Q217E	116.2	1.6		
Q366N	Q217N	75.3	1.0		
Q366T	Q217T	57.5	0.8		
Q366S	Q217S	107.2	1.5		
Q366V	Q217V	25.8	0.4	20.0	0.4
A175S	A39S	112.4	1.6		
A122N/G124S	A[122]N/G[124]S	48.2	0.7		
Q286R/S222A	Q143R/S82A			53.3	1.0
Q286R/S222A/ Gla 交換 FIX	Q143R/S82A/Gla 交換 FIX	83.7	1.2		
Q286R/M298Q	Q143R/M156Q			74.2	1.3
Q286R/M298Q/K341Q	Q143R/M156Q/K192Q			21.8	0.4
Q286R/M298Q/K199E	Q143R/M156Q/K60cE			101.1	1.8
P321K	P170iK			97.5	1.7
P321E	P170iE			66.0	1.2
P321Y	P170iY			49.5	0.9
P321S	P170iS			60.7	1.1
T239S	T99S	254.6	3.5		
T239Q	T99Q			117.2	2.1
T239V	T99V			42.5	0.8
T239L	T99L			81.1	1.4
T239H	T99H			52.0	0.9
T239I	T99I			125.3	2.2
H257A/M298Q	H117A/M156Q			89.1	1.6
S222A/H257A/Q286R/M298Q	S82A/H117A/Q143R/M156Q	66.6	0.9		
Q286R/Q366V	Q143R/Q217V			62.0	1.1
A175S/Q286R/Q366V	A39S/Q143R/Q217V			72.0	1.3
S222A/Q286R/Q366V	S82A/Q143R/Q217V			38.5	0.7
Q286M	Q143M	53.1	0.7		
Q286L	Q143L	114.4	1.6		
Q286Y	Q143Y	131.3	1.8		
Q366I	Q217I	23.2	0.3		
Q366L	Q217L	23.0	0.3		
Q366M	Q217M	35.4	0.5		

表 17. TF 不存在情況下 AT-III/肝素對 FVIIa 變異體之抑制

突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	TF-依賴性 ATIII 抗性檢定			
		293-F 細胞		BHK-21 細胞	
		$K_{0.5}$ (nM)	$K_{0.5mut}/K_{0.5wt}$	$K_{0.5}$ (nM)	$K_{0.5mut}/K_{0.5wt}$
WT	WT	2265	1.0	2222	1.0
V158D/E296V/M298Q	V21D/E154V/M156Q	389	0.2	415	0.2
Q286R	Q143R	10000	>4.4	10000	>4.5
S222A	S82A	2338	1.0	2088	0.9
H257S	H117S	5884	2.6	5584	2.5
H373D	H224D	10000	>4.4		
H373E	H224E	6949	3.1		
H373S	H224S	9513	4.2		
H373F	H224F	1306	0.6		
H373A	H224A	10000	>4.4		
Q366D	Q217D	10000	>4.4		
Q366E	Q217E	6901	3.0		
Q366N	Q217N	5186	2.3		
Q366T	Q217T	5885	2.6		
Q366S	Q217S	10000	>4.4		
Q366V	Q217V	487	0.2	531	0.2
A175S	A39S	5785	2.6		
A122N/G124S	A[122]N/G[124]S	2926	1.3		
Q286R/S222A	Q143R/S82A			10000	>4.5
Q286R/S222A/ Gla 交換 FIX	Q143R/S82A/Gla 交換 FIX	10000	>4.4		
Q286R/M298Q	Q143R/M156Q			3663	1.6
Q286R/M298Q/K341Q	Q143R/M156Q/K192Q			72	
Q286R/M298Q/K199E	Q143R/M156Q/K60cE			5182	2.3
P321K	P170iK			5274	2.4
P321E	P170iE			3666	1.6
P321Y	P170iY			705	0.3
P321S	P170iS			2689	1.2
T239S	T99S	10000	>4.4		
T239Q	T99Q			2222	1.0
T239V	T99V			2644	1.2
T239L	T99L			8532	3.8
T239H	T99H			10000	>4.5
T239I	T99I			10000	>4.5
H257A/M298Q	H117A/M156Q			1344	0.6
S222A/H257A/Q286R/M298Q	S82A/H117A/Q143R/M156Q	7742	3.4		
Q286R/Q366V	Q143R/Q217V			2251	1.0
A175S/Q286R/Q366V	A39S/Q143R/Q217V			10000	>4.5
S222A/Q286R/Q366V	S82A/Q143R/Q217V			3398	1.5
Q286M	Q143M	10000	>4.4		
Q286L	Q143L	10000	>4.4		
Q286Y	Q143Y	10000	>4.4		
Q366I	Q217I	599	0.3		
Q366L	Q217L	1708	0.8		
Q366M	Q217M	914	0.4		

進行另一組實驗以使用具有微小修改之與如上所述相同之檢定評估 FVIIa 變異體在 TF 不存在情況下受 AT-III/肝素之抑制。使用全長未分級肝素（Calbiochem）替代低分子量肝素（LMW 肝素）以增加抑制反應之速率（參見例如，Olson 等人. (2004) Thromb Haemost 92(5), 929-939）。將檢定之培育時間增加至 60 分鐘，且將用以確定殘餘活性的甲磺醯基-FPR-ACC 受質之濃度增加至 0.5 mM 之最終濃度。

表 18 提供 TF 不存在情況下使用 BHK-21 細胞及 CHOX 細胞中表現的 FVIIa 變異體進行之檢定之結果。結果呈示為經擬合 $K_{0.5}$ 參數與同野生型 FVIIa 相比各變異體 AT-III 抗性之程度的表示，其表示為經擬合 $K_{0.5}$ 值之比率（$K_{0.5}$ 突變體/$K_{0.5}$ 野生型）。亦展示標準偏差（SD）及檢定數目（n）。

表 18. TF 不存在情況下 AT-III/肝素對 FVIIa 變異體之抑制

突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	$K_{0.5}$ (nM)	SD	%CV	$K_{0.5mut}/K_{0.5wt}$	n
WT (NovoSeven®)	WT (NovoSeven®)	424.3	70.9	17%	1.08	33
WT (NovoSeven-RT®)	WT (NovoSevenRT®)	424.2	60.5	14%	1.08	5
WT	WT	393.8	67.8	17%	1.00	4
WT †	WT †	503.0	120.0	24%	1.00	4
T128N/P129A	T[128]N/P[129]A	465.3	28.1	6%	1.18	2
Gla 交換 FIX	Gla 交換 FIX	298.9			0.76	1
K109N	K[109]N	330.1	72.3	22%	0.84	2
A122N/G124S	A[122]N/G[124]S	372.5	28.6	8%	0.95	2
S52A/S60A	S[52]A/S[60]A	360.6			0.92	1
M298Q	M156Q	120.1	14.1	12%	0.31	5
M298Q †	M156Q †	130.0	14.3	11%	0.26	2
T128N/P129A/M298Q †	T[128]N/P[129]A/M156Q †	143.9	14.5	10%	0.29	2
V158D/E296V/M298Q	V21D/E154V/M156Q	75.5	10.1	13%	0.19	27
V158D/E296V /M298Q †	V21D/E154V/M156Q †	77.4	18.0	23%	0.15	7
T128N/P129A/V158D/E296V/M298Q	T[128]N/P[129]A/V21D/E154V/M156Q	81.6	3.8	5%	0.21	2

S52A/S60A/V158D/E296V/M1298Q	S[52]A/S[60]A/V21D/E154V/M156Q	78.8	2.9	4%	0.20	2
Q286R	Q143R	1085.1	320.0	29%	2.76	20
T128N/P129A/Q286R	T[128]N/P[129]A/Q143R	1645.2	440.2	27%	4.18	9
T128N/P129A/Q286R †	T[128]N/P[129]A/Q143R †	1739.2	467.0	27%	3.46	5
S52A/S60A/Q143R	S[52]A/S[60]A/Q143R	1318.0	376.8	29%	3.35	2
S222A	S82A	383.5	84.4	22%	0.97	3
T128N/P129A/S222A	T[128]N/P[129]A/S82A	401.0			1.02	1
H257S	H117S	722.8			1.84	1
Q366V	Q217V	101.1	24.7	24%	0.26	3
Gla 交換 FIX/Q366V	Gla 交換 FIX/Q217V	108.2	5.8	5%	0.27	2
A175S	A39S	1328.0	96.2	7%	3.37	3
K109N/A175S	K[109]N/A39S	2031.8	401.2	20%	5.16	2
S119N/L121S/A175S	S[119]N/L[121]S/A39S	1637.2	171.3	10%	4.16	2
T128N/P129A/A175S	T[128]N/P[129]A/A39S	1392.7	295.3	21%	3.54	2
A122N/G124S/A175S	A[122]N/G[124]S/A39S	1345.8	241.1	18%	3.42	2
Q286R/H257A	Q143R/H117A	2398.7	551.2	23%	6.09	9
Q286R/H257A †	Q143R/H117A †	2800.8	938.4	34%	5.57	5
Q286R/S222A	Q143R/S82A	1203.0	191.2	16%	3.05	2
Gla 交換 FIX/ T128N/P129A/ S222A/Q286R	Gla 交換 FIX/ T[128]N/P[129]A/ S82A/Q143R	1703.2	145.2	9%	4.32	2
Q286R/S222A/H257A	Q143R/S82A/H117A	2592.0	806.5	31%	6.58	4
Q286R/M298Q	Q143R/M156Q	299.3	62.9	21%	0.76	7
Q286R/M298Q †	Q143R/M156Q †	287.3	26.6	9%	0.57	20
Q286R/M298Q §	Q143R/M156Q §	395.1	56.4	14%	0.79	3
Gla 交換 FIX/ Q286R/M298Q	Gla 交換 FIX/ Q143R/M156Q	281.6	43.2	15%	0.72	3
Gla 交換 FIX/ Q286R/M298Q †	Gla 交換 FIX/ Q143R/M156Q †	238.2	21.6	9%	0.47	3
T128N/P129A/Q286R/ M298Q	T[128]N/P[129]A/Q143R/M156Q	283.7	49.4	17%	0.72	13
T128N/P129A/Q286R/ M298Q †	T[128]N/P[129]A/Q143R/M156Q †	283.7	77.6	27%	0.56	3
Gla 交換 FIX /T128N/P129A/Q286R/ M298Q	Gla 交換 FIX /T[128]N/P[129]A/Q143R/ M156Q	508.2	197.0	39%	1.29	3
Gla 交換 FIX /T128N/P129A/Q286R/ M298Q †	Gla 交換 FIX /T[128]N/P[129]A/Q143R/M156Q †	325.2	82.2	25%	0.65	2
{Gla 交換 FIX/E40L}/ Q286R/M298Q	{Gla 交換 FIX/E[40]L}/ Q143R/M156Q	286.7	2.4	1%	0.73	2
{Gla 交換 FIX/K43I}/ Q286R/M298Q	{Gla 交換 FIX/K[43]I}/ Q143R/M156Q	244.3	29.8	12%	0.62	5
{Gla 交換 FIX/K43I}/ Q286R/M298Q †	{Gla 交換 FIX/K[43]I}/ Q143R/M156Q †	219.3	13.7	6%	0.44	2
{Gla 交換 FIX/Q44S}/ Q286R/M298Q	{Gla 交換 FIX/Q[44]S}/ Q143R/M156Q	271.4	12.4	5%	0.69	2
{Gla 交換 FIX/M19K}/ Q286R/M298Q	{Gla 交換 FIX/M[19]K}/ Q143R/M156Q	309.6			0.79	1
Gla 交換 FIX /S52A/S60A/ Q286R/M298Q †	Gla 交換 FIX /S[52]A/S[60]A/Q143R/M156Q †	253.6			0.50	1
{Gla 交換 FIX/M19K/E40L/K43I/Q44S}/ Q286R/M298Q	{Gla 交換 FIX/M[19]K/ E[40]L/ K[43]I/ Q[44]S} /Q143R/M156Q	339.3	100.8	30%	0.86	2

{Gla 交換 FIX/K43I}/T128N/P129A/ Q286R/M298Q †	{Gla 交換 FIX/K[43]I}/ T[128]N/P[129]A/Q143R/M156Q †	222.5	10.7	5%	0.44	2
S222A/H257A/Q286R/ M298Q	S82A/H117A/Q143R/M156Q	313.9			0.80	1
T128N/P129A/S222A/ H257A/Q286R/M298Q	T[128]N/P[129]A/S82A/H117A/Q143R/M156Q	653.0	127.9	20%	1.66	4
T128N/P129A/S222A/ H257A/Q286R/M298Q †	T[128]N/P[129]A/S82A/H117A/Q143R/M156Q †	327.7	23.2	7%	0.65	2
S52A/S60A/S222A/H257A/Q286R/M298Q	S[52]A/S[60]A/S82A/H117A/Q143R/M156Q	447.6	117.6	26%	1.14	3
Q286R/M298Q/Q366N	Q143R/M156Q/Q217N	324.1	77.9	24%	0.82	3
T128N/P129A/Q286R/M298Q/Q366N †	T[129]N/P[129]A/Q143R/M156Q/Q217N †	345.8	24.2	7%	0.69	3
{Gla 交換 FIX/K43I}/Q286R/M298Q/Q366N †	{Gla 交換 FIX/K[43]I}/Q143R/M156/Q217N †	404.4	48.0	12%	0.80	3
{Gla 交換 FIX/K43I} /T[128]N/P[129]A/Q286R/M298Q/Q366N †	{Gla 交換 FIX/K[43]I}/ T[128]N/P[129]A/Q143R/M156Q/Q217N †	319.1	71.8	22%	0.63	2
Q286R/H373F	Q143R/H224F	620.8	133.4	3%	1.58	2
T128N/P129A/ Q286R/H373F	T[128]N/P[129]A/Q143R/H224F	590.4	104.2	18%	1.50	4
Q286R/M298Q/H373F	Q143R/M156Q/H224F	152.1	7.2	5%	0.39	3
T128N/P129A/Q286R/M298Q/H373F	T[128]N/P[129]A/Q143R/M156Q/H224F	182.6	43.2	24%	0.46	5
M298Q/H373F	M156Q/H224F	81.7	10.5	13%	0.21	2
T128N/P129A /M156Q/H224F †	T[128]N/P[129]A /M156Q/H224F †	89.1	3.8	4%	0.18	2
V21D/Q143R/E154V/M156Q	V21D/Q143R/E154V/M156Q	85.0	14.7	17%	0.22	13
S222A/T239V	S82A/T99V	967.3	282.6	29%	2.46	5
Gla 交換 FIX /S222A/T239V/Q286R	Gla 交換 FIX /S82A/T99V/Q143R	2438.4	269.4	11%	6.19	2
Gla 交換 FIX /S222A/T239V/Q286R †	Gla 交換 FIX /S82A/T99V/Q143R †	1343.5	507.1	38%	2.67	3
T239V/Q286R/M298Q	T99V/Q143R/M156Q	3626.9	1465.9	40%	9.21	4
Gla 交換 FIX/ T239V/Q286R/M298Q	Gla 交換 FIX/ T99V/Q143R/M156Q	483.7	65.6	14%	1.23	2
Gla 交換 FIX/ T239V/Q286R/M298Q †	Gla 交換 FIX/ T99V/Q143R/M156Q †	314.3			0.62	1
T128N/P129A/ T239V/Q286R/M298Q †	T[128]N/P[129]A/ T99V/Q143R/M156Q †	266.4	52.1	20%	0.53	2
S222A/T239V/H257A/ Q286R/M298Q	S82A/T99V/H117A/Q143R/ M156Q	469.3	133.2	28%	1.19	6
T128N/P129A/ S222A/T239V/H257A/ Q286R/M298Q †	T[128]N/P[129]A/ S82A/T99V/H117A/Q143R/ M156Q †	326.5	55.3	17%	0.65	2
T239V/Q286R/H373F	T99V/Q143R/H224F	630.6	194.0	31%	1.60	3
T128N/P129A/T239V/Q286R/M298Q/H373F †	T[128N]/P129]A/T99V/Q143R/M156Q/H224F †	121.2	25.8	21%	0.24	4
V158D/T239I/E296V /M298Q	V21D/T99I/E154V /M156Q	179.5	50.5	28%	0.46	5
T239I/Q286R	T99I/Q143R	5823.0	2185.5	38%	14.79	9
S222A/T239I	S82A/T99I	1149.8	12.8	1%	2.92	2
Gla 交換 FIX/S222A/T239I/Q286R	Gla 交換 FIX /S82A/T99I/Q143R	3313.1	130.3	4%	8.41	2
T239I/Q286R/M298Q	T99I/Q143R/M156Q	1611.4	185.9	12%	4.09	2

Gla 交換 FIX / T239I/Q286R/M298Q	Gla 交換 FIX /T99I/Q143R/M156Q	1171.3	104.5	9%	2.97	2
T128N/P129A T239I/Q286R/M298Q †	T[128N]/P129]A T99I/Q143R/M156Q †	917.0	60.5	7%	1.82	3
S222A/T239I/H257A/Q286R/M298Q	S82A/T99I/H117A/Q143R/M156Q	1223.6	18.9	2%	3.11	2
T239I/Q286R/H373F	T99I/Q143R/H224F	1007.6	29.8	3%	2.56	2
V158D/T239V/E296V/M298Q	V21D/T99V/E154V/M156Q	67.7	16.6	24%	0.17	4
V158D/T239V/E296V/M298Q †	V21D/T99V/E154V/M156Q †	67.1			0.13	1
T239V/Q286R	T99V/Q143R	1787.9	106.3	6%	4.54	2
T239I/Q286R/M298Q/H237F	T99I/Q143R/M156Q/H224F	370.4	3.0	1%	0.94	2
T128N/P129AT239I/Q286R/M298Q H237F †	T[128]N/P[129]AT99I/Q143R/M156Q /H224F †	316.6	24.7	8%	0.63	2
S222A/H257S/Q286R/M298Q	S82A/H117S/Q143R/M156Q	526.7			1.34	1
S222A/Q286R/M298Q/H373F	S82A/Q143R/M156Q/H224F	163.2	46.9	29%	0.41	4
Gla 交換 FIX/S222A/Q286R/M298Q/H373F	Gla 交換 FIX S82A/Q143R/M156Q/H224F	163.5	58.2	36%	0.42	4
S222A/Q286R/M298Q	S82A/Q143R/M156Q	308.4	119.9	39%	0.78	4
Gla 交換 FIX S222A/Q286R/M298Q	Gla 交換 FIX S82A/Q143R/M156Q	266.3	104.2	39%	0.68	4
T128N/P129A/A175S/Q366V	T[128]N/P[129]A/A39S/Q217V	332.6	56.2	17%	0.84	3
A122N/G124S/A175S/Q366V	A[122]N/G[124]S/A39S/Q217V	336.1	11.0	3%	0.85	3
T128N/P129A/A175S/S222A	T[128]N/P[129]A/A39S/S82A	1913.4			4.86	1
A122N/G124S/A175S/S222A	A[122]N/G[124]S/A39S/S82A	1548.6	394.1	25%	3.93	2
T128N/P129A/A175S/Q286R	T[128]N/P[129]A/A39S/Q143R	9545.5	2797.3	29%	24.24	2
A122N/G124S/A175S/Q286R	A[122]N/G[124]S/A39S/Q143R	6923.3			17.58	1
Gla 交換 FIX/ S222A/Q286R/H373F	Gla 交換 FIX/ S82A/Q143R/H224F	587.3	5.1	1%	1.49	2
H257A/Q286R/M298Q	H117A/Q143R/M156Q	390.8			0.99	1
Gla 交換 FIX/ T128N/P129A/A175S/ S222A/Q286R	Gla 交換 FIX/ T[128]N/P[129]A/A39S/S82A/Q143R	6486.4	148.2	2%	16.47	2
Gla 交換 FIX/ A122N/G124S/A175S/ S222A/Q286R	Gla 交換 FIX/ A[122]N/G[124]S/A39S/S82A/Q143R	5524.0	1434.1	26%	14.03	2
T128N/P129A/A175S/ Q286R/M298Q	T[128]N/P[129]A/A39S/Q143R/M156Q	2311.8	520.7	23%	5.87	2
A122N/G124S/A175S/ Q286R/M298Q	A[122]N/G[124]S/A39S/Q143R/M156Q	1954.2	450.7	23%	4.96	2
T128N/P129A/A175S/ S222A/H257A/Q286R/M298Q	T[128]N/P[129]A/A39S/S82A/H117A/Q143R/M156Q	3212.9	1140.7	36%	8.16	2
A122N/G124S/A175S/ S222A/H257A/Q286R/M298Q	A[122]N/G[124]S/A39S/S82A/H117A/Q143R/M156Q	2972.8	751.2	25%	7.55	2
T128N/P129A/A175S/ Q286R/M298Q/H373F	T[128]N/P[129]A/A39S/Q143R/M156Q/H224F	1132.4	441.3	39%	2.88	2
A122N/G124S/A175S/ Q286R/M298Q/H373F	A[122]N/G[124]S/A39S/Q143R/M156Q/H224F	1000.1	184.3	18%	2.54	2

V158D/Q286R/E296V/M298Q/H373F	V21D/Q143R/E154V/M156Q/H224F	62.1	10.5	17%	0.16	11
M298Q/Q366N/H373F †	M156Q/Q217N/H224F	90.8	4.8	5%	0.18	2
T239V/M298Q/H373F †	T99V/M156Q/H224F	46.6	7.9	17%	0.09	2
T239I/M298Q/H373F †	T99I/M156Q/H224F	178.7	29.7	17%	0.36	2
T128N/P129A/Q286R/M298Q/Q366N/H373F †	T[128]N/P[129]A/Q143R/M156Q/Q217N/H224F	148.3	12.9	9%	0.29	2
T239V/Q286R/M298Q/Q366N †	Q143R/M156Q/Q217N/T99V	252.2	40.9	16%	0.50	2
T239I/Q286R/M298Q/Q366N †	T99I/Q143R/M156Q/Q217N	813.2	105.1	13%	1.62	2

† 在 CHOX 細胞中產生

§在 CHOX 穩定細胞系純系 52-5F7 中產生

實施例 6

FVIIa 多肽促凝血活性之活體內評估

建立 A 型血友病之小鼠模型以評估 FVIIa 多肽之促凝血活性。在 CD-1 小鼠中藉由腹膜內投予抗 FVIII 抗體誘導 A 型血友病，接著手術移除尾尖以起始出血。亦使用缺乏 FVIII 之小鼠（$FVIII^{-/-}$小鼠），但其未經抗 FVIII 抗體處理。接著以 FVIIa 多肽處理小鼠且量測 20 分鐘內損失之血液量以測定 FVIIa 多肽之促凝血活性。

A. *野生型 FVIIa 促凝血活性之活體內評估*

建立 A 型血友病之小鼠模型以評估 FVIIa 多肽之促凝血活性。在 CD-1 小鼠中藉由投予抗 FVIII 抗體誘導 A 型血友病，接著手術移除尾尖以起始出血。接著，以 FVIIa 多肽處理小鼠且量測停止出血所消耗時間及此時所損失之血液量以測定 FVIIa 多肽之促凝血活性。

藉由腹膜內投予 100 mg/kg 之硫巴比妥鈉（thiobarbital sodium）及 100 mg/kg 之氯胺酮（ketamine）使雄性 CD-1 小鼠麻醉。藉由皮下注射於內側頸中投予利多卡因

（Lidocaine）以降低敏感性。經由頸部之小皮膚切口在氣管及頸動脈中插入導管，以利於無限制呼吸及投予抗因子 VIII 抗體、重組人類因子 VIIa（rhFVIIa）及/或經修飾之 FVII 多肽。

以 40 μL 向插有導管之小鼠投予 3.76 mg 綿羊抗人類 FVIII 抗體（Affinity Biologicals，批號 IG129R4，612 小鼠 BU/ml）。藉由以抗體（使用 0.376、0.94、1.88 及 3.76 mg 抗人類 FVIII）進行初始劑量反應實驗且評估失血及出血時間測定此劑量。20 分鐘後，將小鼠之尾置於含有 39℃ 磷酸鹽緩衝生理食鹽水（PBS）之 15 mL 管中歷時 10 分鐘時期。30 分鐘時，自 PBS 溶液簡單移除尾且切斷最後 5 mm 尾以起始出血。記錄出血開始時間。接著，使尾返回至含有 39℃ PBS 之管中，且使其出血 5 分鐘（預出血）以確保小鼠已對抗 FVIII 抗體作出反應。預出血後，向小鼠投予 FVIIa 多肽或製備及傳遞 FVIIa 蛋白之媒介。在 PBS 或包含 52 mM 氯化鈉、10.2 mM 脫水氯化鈣、9.84 mM 甘胺醯甘胺酸、0.01%聚山梨醇酯 80 及 165 mM 甘露糖醇的緩衝液中稀釋 FVIIa 多肽。經由頸動脈導管以 3 mL/kg 之體積當量投予 1、3 或 10 mg/kg 之 FVIIa 製劑，且將尾置於含有 39℃ PBS 之新管中。監測出血歷時 20 分鐘時期且記錄出血停止時間。總出血時間經計算為預出血期間出血之持續時間與投予 FVIIa 多肽或 PBS 或緩衝液後出血之持續時間的總和。

為測定出血事件期間的失血量，檢定 15 mL 管之內含物的血紅素含量。在無菌水中以 1:4 稀釋曲通 X-100 且將

100 μL 添加至 1 mL 樣品中以引起溶血。接著在 546 nm 之波長下量測樣品之吸光率。為計算失血量，針對藉由量測稀釋於 PBS 中且如上所述以曲通 X100 溶血之已知體積的鼠類血液在 546 nm 下之吸光率產生之標準曲線讀取吸光率。

進行實驗比較如上所述產生之 rhFVIIa 與市售重組人類 FVIIa（NovoSeven®，Novo Nordisk）且在投予 3 mg/kg 劑量之各蛋白質後評估失血。媒劑組（緩衝液，n = 15）之失血為經 20 分鐘時期 671.9 ± 57.89 μl。此值由 Catalyst Biosciences 產生之 rhFVIIa 降低至 264.1 ± 56.59 μl 且由 NovoSeven®降低至 273.7 ± 53.93 μl（n = 14）。此實驗證明兩種蛋白質等效。

B. 對 FVIIa 變異體在患有誘發之 A 型血友病的 CD-1 小鼠中之凝血活性的分析

進行初始實驗以測定當藉由腹膜內途徑給予以在 CD-1 小鼠中誘發血友病時，抗人類 FVIII 抗體之所要求劑量及時間及作用持續時間。對於第一批抗 FVIII（批次 1；Affinity Biologicals，批號 IG129R4），此最初係基於用於上述插入導管實驗之劑量。經測定引起血友病病況（經 20 分鐘檢定時期不受控出血）之劑量為 7.54 mg/小鼠（80 μl 94.25 mg/mL 儲備溶液）。此批具有 612 小鼠 BU/ml 之中和活性。對於第二批抗人類 FVIII（批次 2；Biologicals，批號 IG1577R2，中和活性 474 小鼠 BU/ml），所用劑量為 11.98 mg/小鼠（120 μl 99.8 mg/mL 儲備溶液）且在尾切割 6 小

時之前投予。

為誘發血友病，在實驗之前，對雄性 CD-1 小鼠（25-35 g）腹膜內給予批次 1 或批次 2 之抗 FVIII。藉由腹膜內投予氯胺酮/甲苯噻嗪（xylazine）混合物（於鹽水中分別為 45 mg/mL 及 3.6 mg/mL）使雄性 CD-1 及 $FVIII^{-/-}$ 小鼠麻醉且將其置於經加熱平台（39℃）上以確保不存在體溫下降。將程序室保持在 82°F 之溫度下。尾切割之前 10 分鐘，將尾浸沒於 10 ml 預加熱 PBS（15 ml 離心管；39℃）中。經由尾靜脈以單次注射形式給 8 至 10 隻小鼠注射稀釋於包含 52 mM 氯化鈉、10.2 mM 脫水氯化鈣、9.84 mM 甘胺醯甘胺酸、0.01%聚山梨醇酯 80 及 165 mM 甘露糖醇之緩衝液中的重組人類 FVIIa（Novoseven®，Novo Nordisk）或經修飾之 FVIIa 多肽。亦僅注入媒劑於一組小鼠中作為對照。若未注射，則自研究排除動物。在尾切割 5 分鐘之前進行 FVIIa 多肽或媒劑之注射。使用刀片在距尾末端 5 mm 處進行尾切割且歷時 20 分鐘時期將血液收集於 PBS 中。收集期結束時，評估總失血。混合收集管且取各樣品之 1 ml 等分試樣並檢定血紅素含量。在無菌水中以 1:4 稀釋曲通 X-100 且將 100 μL 添加至 1 mL 樣品中以引起溶血。接著在 546 nm 之波長下量測樣品之吸光率。為計算失血量，針對藉由量測稀釋於 PBS 中且如上所述以曲通 X100 溶血之已知體積的鼠類血液在 546 nm 之吸光率下產生之標準曲線讀取吸光率。

1. 評估野生型 FVIIa 凝血活性之劑量反應研究

亦進行評估 0.3、1 或 3 mg/kg 之野生型 FVIIa 的劑量反應研究。接受媒劑之小鼠在 20 分鐘檢定中損失 1002.3 ± 60.71 μL。此在投予 3 mg/kg 野生型 FVIIa 之小鼠中顯著降低至 415.5 ± 90.85 μL(使用 Kruskal-Wallis 接著 Dunn 事後檢驗，$p < 0.05$)。降低劑量至 1 mg/kg 引起 679.57 ± 83.95 μL 之失血且 0.3 mg/kg 之更低劑量引起 852.42 ± 94.46 μL 之失血。

2. 對 FVIIa 變異體凝血活性之初始分析

僅注射媒劑用作對照。僅接受媒劑之小鼠在 20 分鐘檢定中損失 915.2 ± 105.6 μL，若對小鼠投予重組人類 FVIIa，則其降至 352 ± 99.86μL(平均值± S.E.M)。若對小鼠投予 Q286R-FVIIa，則失血量甚至進一步降至 165.8 ± 48.41 μL，投予 Q286R/M298Q-FVIIa 失血量降至 141.3 ± 43.77 μL 或投予 V158D/E296V/M298Q-FVIIa 失血量降至 129.5 ± 36.64 μL。與投予野生型 FVIIa 之小鼠相比，投予 S222A-FVIIa 之小鼠亦展現降低之失血(至 225.7 ± 62.75 μL)。投予 Gla 交換 FIX-FVIIa、Q366V-FVIIa 或 A122N/G124S-FVIIa 引起與給予重組人類 FVIIa 的小鼠所觀察到大致相同之失血量(分別為 334.6 ± 54.95μL、321.7 ± 102.6 μL 及 329.8 ± 83.91μL)，而投予 H257A-FVIIa、S222A/Q286R-FVIIa 或 H257A-FVIIa 之小鼠似乎具有稍多失血(分別為 390 ± 107 μL、447.3 ± 127.7 μL 及 443.7 ± 139.5 μL)。

3. 評估 FVIIa 變異體凝血活性之劑量反應

向小鼠投予 0.1、0.3、1 或 3 mg/kg 之 Q286R-FVIIa、

S222A-FVIIa、Q286R/M298Q-FVIIa 或 V158D/E296V/M298Q-FVIIa 的劑量反應研究。接受僅媒劑之小鼠在 20 分鐘檢定中損失 915.2 ± 105.6 μL 血液。此損失在投予 3 mg/kg 之 Q286R-FVIIa（141.3 ± 43.77 μL）、S222A-FVIIa（225.7 ± 62.75μL）或 Q286R/M298Q-FVIIa（129.5 ± 36.64 μL）中的任一者之小鼠中顯著降低（使用 Kruskal-Wallis 接著 Dunn 事後檢驗，$p < 0.05$）。降低劑量至 1 mg/kg 在接受 Q286R-FVIIa 之小鼠中引起 641 ± 96.48 μL 之失血且在接受 S222A-FVIIa 之小鼠中引起 487.92 ± 92.07μL 之失血。較低劑量之此 FVIIa 變異體引起與接受媒劑對照之小鼠所觀察到大致相同之失血（對於 Q286R-FVIIa 及 S222A-FVIIa，分別為 817.71 ± 107.94 μL 及 900.34 ± 115.77 μL）。相反，與僅媒劑對照小鼠相比，接受 1 mg/kg 之小鼠具有顯著降低之失血（69.36 ± 15.55 μL）。在 0.3 mg/kg 及 0.1 mg/kg 之較低劑量下，失血分別為 538.3 ± 94.04 μL 及 664 ± 121.6 μL。接受 0.3、1 及 3 mg/kg 之 V158D/E296V/M298Q-FVIIa 的小鼠分別具有 754.49 ± 121.6 μL、481.95 ± 114.22 μL 及 133.25 ± 50.09 μL 之失血。

進行 Q286R-FVIIa、Q286R/M298Q-FVIIa 及 V158D/E296V/M298Q-FVIIa 之其他劑量反應研究且將資料與以上資料組合。在評估 Q286R-FVIIa 之作用的實驗中，接受媒劑之組損失 833.61 ± 73.95 μL 血液。此損失在以 3 mg/kg 之 Q286R-FVIIa 處理之小鼠中顯著降至 196.71 ± 49.18 μL。降低劑量至 1 mg/kg 引起 577.78 ± 66.29 μL 之失

血。當給予小鼠 0.1 及 0.3 mg/kg Q286R-FVIIa 時，產生與媒劑對照值相似之失血（分別為 739.58 ± 104.28 μL 及 806.63 ± 65.17 μL）。在評估 Q286R/M298Q-FVIIa 之作用的實驗中，媒劑組產生 902.42 ± 88.04 μL 之失血，其藉由以 1 與 3 mg/kg Q286R/M298Q-FVIIa 處理使失血顯著降至 145.17 ± 38.89 μL 及 140.76 ± 33.36 μL。降低劑量至 0.1 及 0.3 mg/kg 分別引起 664.03 ± 121.62 μL 及 551.94 ± 67.60 μL 之失血值。在評估 V158D/E296V/M298Q-FVIIa 之實驗中，媒劑對照組顯示 966.64 ± 57.97 μL 之失血，其藉由以 3 mg/kg 之 V158D/E296V/M298Q-FVIIa 處理顯著降低至 128.19 ± 27.73 μL。降低劑量至 1 mg/kg 引起 565.50 ± 65.78 μL 之失血且進一步降低劑量至 0.3 及 0.1 mg/kg 產生與對照組相似的失血（811.16 ± 71.87 μL 及 893.62 ± 106.73 μL）。藉由 Kruskal Wallis 接著 Dunn 事後檢驗進行統計分析且當 $p < 0.05$ 時接受顯著性。

4. 3 mg/kg 劑量之 H216A-FVIIa、H373F-FVIIa、Q366D-FVIIa 及 Q366N-FVIIa 之凝血活性

一組實驗測試 3 mg/kg 劑量之 H216A-FVIIa、H373F-FVIIa、Q366D-FVIIa 及 Q366N-FVIIa。僅注射媒劑用作對照。接受媒劑之小鼠在 20 分鐘檢定中損失 915.2 ± 105.6 μL。若以 H373F-FVIIa 處理小鼠，則此損失甚至進一步降至 211.1 ± 67.70 μL。以 H216A-FVIIa、Q366D-FVIIa 及 Q366N-FVIIa 處理後，失血受到較小影響，其值分別為 558.6 ± 66.22、577.1 ± 151.4 及 477.1 ± 112.6 μL。

4. 3 mg/kg 劑量之 Q286R/M298Q/Gla 交換 FIX-FVIIa、S222A/H257A/Q286R/M158Q-FVIIa、Q286R/M298Q/K341D-FVIIa 及 Q286R/M298Q/H373F-FVIIa 之凝血活性

在 CD-1 血友病小鼠模型中評估 3 mg/kg 劑量之 Q286R/M298Q/Gla 交換 FIX-FVIIa、S222A/H257A/Q286R/M158Q-FVIIa、Q286R/M298Q/K341D-FVIIa 及 Q286R/M298Q/H373F-FVIIa 之凝血活性。僅注射媒劑用作對照。接受媒劑之小鼠在 20 分鐘檢定中損失 803 ± 92.18 μL。此損失藉由以 S222A/H257A/Q286R/M158Q-FVIIa 處理降至 118.6 ± 63.27 μL。與媒劑組相比，以 3 mg/kg 之 Q286R/M298Q/Gla 交換 FIX-FVIIa 處理使失血由 888.89 ± 104.76 μL 降至 171.83 ± 62.06 μL。在評估 Q286R/M298Q/K341D-FVIIa 及 Q286R/M298Q/H373F-FVIIa 之實驗中，媒劑組之失血為 813.1 ± 82.66 μL。以 Q286R/M298Q/H373F-FVIIa 處理後，此損失降至 39.42 ± 5.53 μL 失血。Q286R/M298Q/K341D-FVIIa 似乎在檢定中不太有效，引起 636.7 ± 121.6 μL 之失血。

5. 評估 S222A/H257A/Q286R/M158Q-FVIIa 及 Q286R/M298Q/H373F-FVIIa 的凝血活性之劑量反應研究

評估對 0.3、0.5、1 及 3 mg/kg 之 S222A/H257A/Q286R/M158Q-FVIIa 的劑量反應。接受媒劑之小鼠在 20 分鐘檢定中損失 832.48 ± 71.70 μL。此損失在

投予 3 mg/kg S222A/H257A/Q286R/M158Q-FVIIa 之小鼠中顯著降至 118.63 ± 63.27 μL（使用 Kruskal-Wallis，接著 Dunn 事後檢驗，$p < 0.05$）。降低劑量至 1 及 0.5 mg/kg 引起失血顯著降低（202.69 ± 77.60 μL 及 366.52 ± 106.21 μL）且 0.3 mg/kg 之較低劑量引起比媒劑量多的失血（742.04 ± 112 μL）。亦評估對 0.1、0.3、1 及 3 mg/kg 之 Q286R/M298Q/H373F-FVIIa 的劑量反應，且在此實驗中，接受媒劑之小鼠具有 813.15 ± 82.66 μL 之失血。此損失在以 3 mg/kg Q286R/M298Q/H373F-FVIIa 處理之小鼠中顯著降至 39.42 ± 5.52 μL（使用 Kruskal-Wallis，接著 Dunn 事後檢驗，$p < 0.05$）。降低劑量至 1 及 0.3 mg/kg 分別引起 208.10 ± 105.12 及 508.9 ± 155.8 μL 之失血值。0.1 mg/kg 之最低測試劑量產生接近媒劑對照量之失血（733.5 ± 152.88 μL）。

C. 在 $FVIII^{-/-}$ 小鼠中分析 FVIIa 凝血活性

除小鼠並未以抗 FVIII 抗體處理以外，使用如上所述相同之方案，亦使用缺乏 FVIII 之小鼠（$FVIII^{-/-}$ 小鼠）的 A 型血友病小鼠模型來評估 FVIIa 多肽之凝血活性。

1. 評估野生型 FVIIa 凝血活性之劑量反應研究

進行評估 NovoSeven®及野生型 rhFVIIa 在 $FVIII^{-/-}$ 小鼠中在 0.3、1、3 及 6 mg/kg 下之凝血活性的劑量反應研究。在 NovoSeven® 實驗中，媒劑組之失血為 912.79 ± 38.32μL，其藉由以 6 及 3 mg/kg NovoSeven®處理顯著降低（至 361.74 ± 55.28 μL 及 586.98 ± 60.56 μL，使用

Kruskal-Wallis，接著 Dunn 事後檢驗，$p < 0.05$）。降低劑量至 1 mg/kg 引起 674.84 ± 46.88 μL 之失血且在最低測試劑量下值為 801.08 ± 41.39 μL。在野生型 rhFVIIa 實驗中，媒劑對照組產生 904.08 ± 15.38 μL 之失血。此損失藉由 6 mg/kg 之野生型 rhFVIIa 處理顯著降至 451.04 ± 74.17 μL（使用 Kruskal-Wallis，接著 Dunn 事後測試，$p < 0.05$）。降低劑量至 3 mg/kg 產生 695.75 ± 60.50 μL 之失血值，而進一步降低劑量至 1 及 0.3 mg/kg 引起接近媒劑對照量及與媒劑對照量相同之失血值（分別為 846.08 ± 34.17 μL 及 936.43 ± 31.39 μL）。

2. 評估 Q143R-FVIIa、S222A-FVIIa、Q286R/M298Q-FVIIa 及 V158D/E296V/M298Q-FVIIa 凝血活性之劑量反應

第一組實驗測試 3 mg/kg 之重組人類 FVIIa（NovoSeven®，Novo Nordisk）、V158D/E296V/M298Q-FVIIa、Q143R-FVIIa 及 S222A-FVIIa。僅注射媒劑用作對照。僅接受媒劑之小鼠在 20 分鐘檢定中具有 942.9 ± 27.37 μL 之失血。以 NovoSeven®、V158D/E296V/M298Q-FVIIa、Q143R-FVIIa 及 S222A-FVIIa 處理分別使失血降至 468 ± 55.9 μL、302.38 ± 73.12 μL、697.26 ± 92.22 μL 及 675.07 ± 35.29 μL。當在 $FVIII^{-/-}$ 小鼠中以 3 mg/kg 再次測試時，與媒劑對照組（935.54 ± 51.96 μL）相比，Q143R-FVIIa 顯示 754.84 ± 60.96 μL 之降低之失血。當以 5 mg/kg 評估時，與媒劑對照

組（960.42 ± 24.5μL）相比，Q143R-FVIIa 使失血進一步降至 445.87 ± 79.62 μL。

第二組實驗為劑量反應研究，其中在 0.3、1 及 3 mg/kg 下評估 V158D/E296V/M298Q-FVIIa 及 Q286R/M298Q-FVIIa。與媒劑對照相比（960.42 ± 24.5 μL；使用 Kruskal-Wallis，接著 Dunn 事後測試，$p < 0.05$），以 3 mg/kg 之 V158D/E296V/M298Q-FVIIa 處理使失血明顯降低（375.62 ± 74.22 μL）。降低劑量至 1 及 0.3 mg/kg 引起接近對照量之分別為 834.76 ± 54.38 μL 及 841.62 ± 68.99 μL 的失血值。評估不同批之 V158D/E296V/M298Q-FVIIa 的第二實驗產生 912.79 ± 38.32 μL 之媒劑對照失血值，其在 3 及 1 mg/kg 下顯著受抑制（247.24 ± 35.17 μL 及 628.30 ± 37.36 μL；使用 Kruskal-Wallis，接著 Dunn 事後測試，$p < 0.05$）。以較低劑量之 V158D/E296V/M298Q-FVIIa 處理產生接近對照值之失血（841.85 ± 19.32 μL）。在評估 Q286R/M298Q-FVIIa 在 $FVIII^{-/-}$ 小鼠中之作用的實驗中，媒劑組產生 941.39 ± 35.18 μL 之失血。此在 3 mg/kg 之劑量下顯著受抑制，引起 258.92 ± 59.82 μL 之失血。在 1 及 0.3 mg/kg 之較低劑量下，所產生失血量分別為 616.82 ± 78.43μL 及 924.9 ± 38.01 μL。

D. 使用誘發之血友病模型分析其他 FVIIa 變異體之凝血活性

使用以上實施例 6.B 所述之 CD-1 小鼠之誘發血友病模型（IHM）評估數種 FVIIa 變異體之凝血活性。除評估使用

不同批（分別為第三及第四批）人類抗 FVIII 的 T128N/P129A-FVIIa 變異體及 M156Q/H224F-FVIIa 變異體外，方案與如上所述相同。對於第三批抗人類 FVIII（批次 3；Affinity Biologicals，批號 IG1603R1，中和活性 418 小鼠 BU/ml），所用劑量為 12.17 mg/小鼠（120 μl 101.4 mg/mL 儲備溶液），其在尾切割 18 小時之前投予。對於第四批抗人類 FVIII（批次 4；Affinity Biologicals，批號 IG1639R1，中和活性 875 小鼠 BU/ml），所用劑量為 8.04 mg/小鼠（80 μl 100.45 mg/mL 儲備溶液）。如上所述量測失血且以抑制百分數（使用所關注變異體的平均值且除以媒劑組來計算）及 ED50 值（使用非線性回歸分析確定（使用 GraphPad Prism®軟體，GraphPad Software, Inc））形式呈示於下表 19 中，分別以媒劑處理及正常對照動物所觀察到之失血約束反應曲線之頂部及底部。

表 19

突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	IHM 失血；抑制%（1.5mg/kg）	n	IHM 失血；ED50（mg/kg）	n
WT (NovoSeven®)	WT (NovoSeven®)	61	1	0.7	1
WT	WT	59	1	0.75	1
T128N/P129A	T[128]N/P[129]A	78	1	0.5	1
Gla 交換 FIX	Gla 交換 FIX	63	1		
A122N/G124S	A[122]N/G[124]S	64	1		
V158D/E296V/M298Q	V21D/E154V/M156Q	86	3	0.5	3
Q286R	Q143R	76	2	0.55	2
S222A	S82A	75	1	0.45	1
H257S	H117S	50	1		
H373F	H224F	78	1		
Q366V	Q217V	64	1		
A175S	A39S	58	1		
K109N/A175S	K[109]N/A39S	60	1		
Q286R/H257A	Q143R/H117A	58	1		
Q286R/S222A	Q143R/S82A	50	1		
Q286R/S222A/H257A	Q143R/S82A/H117A	68	1		
Q286R/M298Q	Q143R/M156Q	85	2	0.15	2
Q286R/M298Q †	Q143R/M156Q †	89	1	0.16	2
Gla 交換 FIX/	Gla 交換 FIX/ Q143R/M156Q	83	2	0.13	1

Q286R/M298Q					
S222A/H257A/Q286R/M298Q	S82A/H117A/Q143R/M156Q	85	1	0.2	1
H257S/Q286R/Q366V	H117S/Q143R/Q217V	46	1		
S222A/H257A/Q286R/Q366V	S82A/H117A/Q143R/Q217V	49	1		
Q286R/M298Q/Q366N	Q143R/M156Q/Q217N	88	1		
Q286R/H373F	Q143R/H224F	75	1		
Q286R/M298Q/H373F	Q143R/M156Q/H224F	95	1	0.15	1
M298Q/H373F	M156Q/H224F	95	1	0.21	1
Gla 交換 FIX/S222A/Q286R	Gla 交換 FIX/S82A/Q143R	85	1	0.4	1
V158D/Q286R/E296V/M298Q	V21D/Q143R/E154V/M156Q	95	1		
T128N/P129A/Q286R/H373F	T[128]N/P[129]A/Q143R/H224F/	70	1		

† 自 CHOX 細胞產生之 FVIIa 多肽

E. 使用誘發之血友病模型分析其他 FVIIa 變異體之凝血活性

使用以上實施例 6.B 所述之 CD-1 小鼠之誘發血友病模型（IHM）評估數種 FVIIa 變異體之凝血活性。除對於此等實驗使用第 4 至第 6 批抗 FVIII 以外，方案與如上所述相同。此等批次之詳情如下：批次 4（以上詳述），對於第五批（批次 5；Affinity Biologicals，批號 IG1593R2，中和活性 255 小鼠 BU/ml），所用劑量為 12.25mg/小鼠（120 μl 102.1 mg/mL 儲備溶液），其在尾切割 6 小時之前投予。對於第六批（批次 6；Affinity Biologicals，批號 IG1703R2，中和活性 685 小鼠 BU/ml），所用劑量為 8.02 mg/小鼠（80 μl 100.2 mg/mL 儲備溶液），其在實驗前一天在 4 pm 投予。如上所述量測失血且以抑制百分數（使用所關注變異體的平均值且除以媒劑組來計算）（在各情況下展示所有劑量，其下方具有對應抑制值），及 ED50 值（使用非線性回歸分析確定（使用 GraphPad Prism® 軟體，GraphPad

Software, Inc））形式呈示於下表 20 中，分別以媒劑處理及正常對照動物所觀察到之失血約束反應曲線之頂部及底部。'n/組'係指每組小鼠之量，而關於 ED50 計算之 'n' 係指以變異體進行之實驗的量。

表 20

突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	IHM 失血；各劑量之抑制%（mg/kg）			n/組	IHM 失血；ED50（mg/kg）	n
		劑量（mg/kg）					
		0.1	0.3	1			
H257A/Q286R	H117A/Q143R			53	7-10		
M298Q	M156Q	37	81	87	7-10	0.11	1
M298Q/T128N/P129A	M156Q/T[128]N/P[129]A	39	79	93	7-9	0.1	1
Q286R/T128N/P129A	Q143R/T[128]N/P[129]A	32	42	58	6-8	0.27	1
Gla 交換 FIX/ T128N/P129A /S222A/Q286R	Gla 交換 FIX/ T[128]N/P[129]A /S82A/Q143R	27	45	62	6-8	0.27	
Q286R/M298Q	Q143R/M156Q	33	57	89	9-10	0.15	1
Q286R/M298Q	Q143R/M156Q	35	57	94	8-10	0.13	1
Q286R/M298Q	Q143R/M156Q	32	62	95	8-9	0.14	1
Q286R/M298Q	Q143R/M156Q	44	65	95	9	0.09	1
Gla 交換 FIX /Q286R/M298Q	Gla 交換 FIX /Q143R/M156Q	35,	57	80	7-10	0.14	1
T128N/P129A/Q286R/ M298Q	T[128]N/P[129]A/ Q143R/M156Q	47,	83	91	9-14	0.1	1
Gla 交換 FIX/T128N/P129A /Q286R/M298Q	Gla 交換 FIX/T[128]N/P[129]A /Q143R/M156Q	15	71	96	7-9	0.17	1
{Gla 交換 FIX/K43I}/Q286R/ M298Q	{Gla 交換 FIX/K[43]I}/Q143R/ M156Q	49	65	80	7-9	0.08	1
Gla 交換 FIX/ S52A/S60A/ Q286R/M298Q/	Gla 交換 FIX/ S[52]A/S[60]A/ Q143R/M156Q/	38	71	88 †	9-10	0.11	1
{Gla 交換 FIX/K43I}/T128N/P129A/ Q286R/M298Q	{Gla 交換 FIX/K[43]I}/ T[128]N/ P[129]A/Q143R/M156Q	23	58	84	9	0.17	1
S222A/H257A/Q286R/ M298Q/ T128N/P129A	S82A/H117A/Q143R/M156Q/ T[128]N/P[129]A	24	71	96	7-8	0.15	1
Q286R/M298Q/Q366N	Q143R/M156Q/Q217N	41	79	96	7-8 僅媒劑: n=17	0.1	1
T128N/P129A/ Q286R/M298Q/Q366N	T[128]N/P[129]A/ Q143R/M156Q/Q217N	40	53	84	6-8	0.09	1

{Gla 交換 FIX/K43I}/T128N/P129A/ Q286R/M298Q/Q366N /	{Gla 交換 FIX/K[43]I}/ T[128]N/ P[129]A/Q143R/M156Q /Q217N	39	81	94	8-10	0.1	1
T128N/P129A/Q286R/ H373F	T[128]N/P[129]A/Q143R /H224F		26		7-9		
T128N/P129A/Q286R/ M298Q/ H373F	T[128]N/P[129]A /Q143R/M156Q/H224F	43	42	87	6-13	0.12	1
M298Q/H373F	M156Q/H224F	27	46	82	7-8	0.21	1
T128N/P129A/M298Q/ H373F	T[128]N/P[129]A/M156 Q/ H224F	48	77	85†	8-10	0.09	1
V158D/E296V/M298Q /Q286R	V21D/E154V/M156Q/Q 143R	27,	61	95	7-8	0.16	1
Gla 交換 FIX/S222A/Q286R/ T239V	Gla 交換 FIX/S82A/Q143R/T99V	30,	32	60	8-9	0.36	1
Q286R/M298Q/T239V	Q143R/M156Q/T99V	21	67	92	7	0.16	1
Gla 交換 FIX/Q286R/M298Q/ T239V	Gla 交換 FIX/Q143R/M156Q/ T99V	16	69	90	7-9	0.17	1
T128N/P129A/T239V/ Q286R/M298Q	T[128]N/P[129]A/ T99V/ Q143R/M156Q/	29	63	91	9	0.15	1
S222A/T239V/H257A /Q286R/M298Q	S82A/T99V/H117A/ Q143R/M156Q/	38	63	94	7-8	0.12	1
T128N/P129A/S222A/ T239V/ H257A/Q286R/M298Q	T[128]N/P[129]A/S82A/ T99V/ H117A/Q143R/M156Q	44	75	79	7-9	0.09	1
T128N/P129A/T239V/ Q286R/M298Q/H373F	T[128]N/P[129]A/T99V/ Q143R/M156Q/H224F	51	75	88	8-10	0.08	1
V158D/T239I /E296V/M298Q	V21D/T99I /E154V/M156Q	45	48	85	7-9	0.11	1
T128N/P129A/ T239I/Q286R/M298Q	T[128]N/P[129]A/T99I/ Q143R/M156Q	20	61	82	8-10	0.18	1
V158D/T239V/E296V/ M298Q	V21D/T99V/E154V/M15 6Q	23	52	86	8-9	0.19	1
T128N/P129A/T239I/ Q286R/M298Q/H373F/	T[128]N/P[129]A/T99I/ Q143R/M156Q/H224F	36	67	73	8-10	0.11	1
M298Q/Q366N/H373F	M156Q /Q217N/H224F	33	80	88	8-10	0.11	1
T239V/M298Q/H373F	T99V/M156Q/H224F	50	68	84	7-9 僅媒劑: n=16	0.07	1
T239I/M298Q/H373F	T99I/M156Q/H224F	56	74	96	9-10	0.07	1
T128N/P129A/Q286R/ M298Q/Q366N/H373F	T[128]N/P[129]A/Q143R /M156Q/ Q217N/H224F	51	87	92	7-9	0.1	1
T239V/Q286R/M298Q/ Q366N	T99V/Q143R/M156Q/Q2 17N	45	62	80	7-9	0.08	1
T239I/Q286R/M298Q/ Q366N	T99I/Q143R/M156Q/Q2 17N	8	34	79	8-9	0.34	1

實施例 7

FVIIa 對小分子受質之醯胺水解活性的 Michaelis Menten 動力學常數測定

可藉由量測 FVIIa 多肽對肽基受質 Spectrozyme FVIIa (CH_3SO_2-D-CHA-But-Arg-pNA.AcOH)之 Michaelis Menten 動力學常數來評估 FVII 變異體之醯胺水解活性。該檢定可如下進行。

在檢定中包括脂化人類經純化組織因子(Innovin, Dade Behring, VWR Cat#68100-390) 以提供 FVIIa 之最佳活性。TF-FVIIa 複合物裂解呈高特異性發色受質形式之 Spectrozyme FVIIa，釋放對硝基苯胺發色團（pNA），其可藉由量測在 405 nm 下之吸收監測。藉由作為時間之函數監測所產生的游離 pNA 在 405 nm 下之吸光率測定酶活性。

在三種不同酶濃度下進行反應。對於反應，首先在 1.7 mL 管（來自 ISC Bioexpress 之低黏附微量離心管）中於 1x 直接檢定緩衝液(100 mM Tris pH 8.4，100 mM NaCl，5 mM $CaCl_2$，0.01% BSA) 中將 FVIIa 變異體稀釋至 40 nM。藉由在如下之 12 孔聚丙烯儲集器（Axygen）中稀釋至 2 nM 在 TF (Innovin, Dade Behring) 存在下進一步稀釋 FVIIa：720 μl 5x直接緩衝液（500 mM Tris pH 8.4，500 mM NaCl，25 mM $CaCl_2$，0.05% BSA）、180 μl 40 nM FVIIa 及 2700 μl 2xTF（重構於 10 mL 水中之 6 nM 儲備溶液）。將經稀釋蛋白酶在室溫下培育 5 分鐘。以 2 倍連續稀釋進一步稀釋 FVIIa 之 2 nM 儲備液以亦在 TF 存在下分別提供蛋白酶之 1

nM 及 0.5 nM 儲備液。連續稀釋反應如下：首先將 1800 μl 上述 2 nM FVIIa/TF 儲備液稀釋於 360 μl 5×直接緩衝液、900 μl 2×TF 及 540 μl 水中。將此經稀釋儲備液再次以 1:1 稀釋於直接緩衝液中之 1800 μl 1×TF 中。

產生受質 Spectrozyme FVIIa（American Diagnostica）之稀釋板。藉由在蒸餾水中重構 50 微莫耳小瓶至 10 mM 製備 Spectrozyme FVIIa 之儲備溶液且在 4℃ 下儲存。將 80 μl（10 mM Spectrozyme FVIIa）及 60 μl + 20 μl 水（7.5 mM Spectrozyme FVIIa）之 10 mM Spectrozyme FVIIa 添加至 96 孔聚丙烯檢定板（Costar）之兩個相鄰行之孔中。沿各別行之 8 個孔中的每一者連續 2 倍稀釋兩個孔，以產生範圍為沿第一行之孔 10 mM 至 78 μM 受質及沿第二行之孔 7.5 mM 至 58.6 μM 之一系列 10×受質濃度。

將 5 μl 各 Spectrozyme FVIIa 受質稀釋液添加至 96 孔透明半區域檢定板（Costar）中。將 45 μl 三種 FVIIa/TF 稀釋液之每一者添加至三組受質系列稀釋液之行中。在該步驟期間，謹慎避免在檢定之孔中引入氣泡。若引入鼓泡，則其可藉由在開始各檢定之前以乾淨針刺穿移除。接著，藉由振盪混合板。起始檢定之前，使用 Spectramax Gemini M5 板讀取器分光光度計（Molecular Devices）藉由取終點讀數，且使用 SoftMax Pro 軟體（Molecular Devices）之 Pathcheck 特徵來量測檢定孔之光程。在 37℃ 下每 30 秒量測 405 nm 下吸光率之增加歷時 1 小時。

藉由使用光程及 pNA 脫離基在 405 nm 下之消光係數

9600 $M^{-1}cm^{-1}$，使用 SoftMax Pro 軟體將吸光速率（毫單位/秒）轉化為所釋放 pNA 之濃度（μM/sec）。轉化方程式如下：速率× (1/60 × 1000) × (1/9600 × 光程) × 100000。使用 Graph Pad Prism 軟體以 X 軸上之受質濃度及 Y 軸上之經測定 μM/sec 速率將各濃度之蛋白酶的結果作圖。使用 Graph Pad Prism 4 軟體，藉由擬合資料至如下 Michaelis Menten 方程式測定 Km 及 Ymax：

$$Y = ((k_{cat}K_m/1000000) \times X \times [E])/(1+(X + K_m)$$

其中：X 為受質濃度（μM）

Y 為酶活性（μM/sec）

$k_{cat}K_m$ 為特異性常數（$M^{-1}sec^{-1}$）

K_m 為 Michaelis 常數（μM）

E 為酶濃度（μM）

設定初始值：在 0.5 × Ymax 下，E=1, Km = X，且 $k_{cat}K_m$ = 1000。

實施例 8

評估 FVIIa 變異體與 TFPI 之間的交互作用之效能

可使用一或多種檢定評估諸如彼等本文提供者之 FVIIa 多肽與 TFPI 之間的交互作用之效能。在一實例中，藉由量測各種濃度之 TFPI 對 FVIIa/TF 對受質 Spectrazyme VIIa 的催化活性之抑制程度來評估 TFPI 與 FVIIa/TF 複合物之間的交互作用之效能。在另一實例中，可使用高通量表面電漿共振（SPR）檢定。

A. 測定 FVIIa/TF 之 TFPI 抑制的 IC_{50} 值

藉由量測各種濃度之 TFPI 對 FVIIa/TF 對受質 Spectrazyme VIIa 的催化活性之抑制程度來評估 TFPI 與 FVIIa/TF 複合物之間的交互作用之效能。計算各 FVII 變異體及 FVIIa 標準之 50%抑制所需的 TFPI 之濃度（IC_{50} 值）。

藉由添加 150 微升/孔之 1x板緩衝液（100 mM Tris pH 8.4，100 mM NaCl，0.01% BSA，0.01%吐溫-20）至各孔中且在 37℃下將板培育至少 1 小時，預處理 96 孔透明半區域檢定板（Nunc）。藉由振盪且吸乾板且倒轉離心板以移除剩餘緩衝液來完全移除緩衝液。將板風乾 1 小時且儲存在室溫下（RT）。

在 1.7 ml 微量離心管（來自 ISC Bioexpress 之低黏附微量離心管）中，藉由混合 9 μl 250 nM FVIIa（American Diagnostica，野生型 FVIIa 或待測試各別變異體）與 337.5 μl 2xTF（Innovin；Dade Behring；將凍乾產品再懸浮於 10 mL 蒸餾水中以產生 2xTF，其大致等於 7 nM 脂化 TF）、90 μl 5x檢定緩衝液（500 mM Tris pH 8.4，500 mM NaCl，25 mM $CaCl_2$，0.05% BSA）及 13.5 μl 水，產生含有 5 nM FVIIa 及 5.2 nM TF 之溶液，來製備總體積為 450 μl 的 FVIIa/TF 之混合物。在室溫下培育混合物 5 分鐘以允許組份複合。向經預處理 96 孔透明半區域檢定板中 2 行之各孔中添加 25 μl 各別 FVIIa/sTF 混合物且覆蓋板以防止蒸發。

最初，將人類重組 TFPI（R & D Systems）溶解於 33 μl 50%甘油（v/v）中以製備在-20℃下儲存之 10 μM 儲備液。將 TFPI 儲備液如下在聚丙烯儲存板中於最終 1x緩衝液

（100 mM Tris pH 8.4，100 mM NaCl，5 mM $CaCl_2$，0.01% BSA）中進一步稀釋至 1.5 μM：對於所測試各蛋白酶，藉由混合 13.1 μl 10 μM TFPI 與 17.5 μl 5x檢定緩衝液及 56.9 μl 蒸餾水製備 87.5 μl TFPI 之 1.5 μM 溶液。在 1x檢定緩衝液中藉由混合 27.5 μl TFPI 於 55 μl 1x檢定緩衝液中製備 TFPI 溶液之連續 3 倍稀釋液，以使得產生含有 750 nM、250 nM、83.3 nM、27.8 nM、9.26 nM、3.1 nM 及 1.03 nM TFPI 之溶液。系列之最後一個孔僅含有 1x緩衝液作為對照。

將 25 μl TFPI 之各稀釋液添加至含有 FVIIa/TF 混合物的 96 孔透明半區域檢定板之 2 行中的 2 個孔（亦即一式兩份）中，以使得以各 TFPI 稀釋液一式兩份檢定蛋白酶混合物。亦將無 TFPI 的 1x檢定緩衝液之溶液添加至含有 FVIIa/TF 混合物之 2 個孔中作為陰性對照。簡單攪拌板且隨後在 3000 rpm 下離心 5 分鐘，隨後在 37℃ 下培育 1.5 小時。

藉由在 5 ml 蒸餾水中重構 50 微莫耳至 10 mM 且儲存在 4℃ 下直至使用來製備 Spectrazyme VIIa（American Diagnostica）之儲備溶液。使用前不久，將溶液在蒸餾水中稀釋至 600 μM。培育上述檢定板後，將 10 μl 經稀釋 Spectrazyme VIIa 添加至檢定板之各孔中。混合反應且在 37℃ 下培育板。在 37℃ 下每 30 秒量測 405 nm 下之吸光率之增加歷時 1 小時，且使用 SoftMax Pro 軟體（Molecular Devices）計算吸光率速率。

為測定受 TFPI 抑制之程度，首先將含有 TFPI 的蛋白酶反應之吸光率速率除以不含 TFPI（對照樣品）的反應之吸光率速度，以獲得比活性且測定各 TFPI 濃度之 log_{10}。使用 GraphPad Prism 軟體，將 log_{10} [TFPI]對各蛋白酶之比活性作圖，且以假定活性資料之頂部及底部分別固定為 1 及 0 的曲線擬合產生劑量反應曲線。使用軟體以各蛋白酶的 log IC_{50}（pIC_{50}）值及絕對 IC_{50}（以 nM 計之 TFPI 抑制）形式測定 TFPI 抑制，且測定其平均值及標準偏差。

測定與脂化 TF（Innovin；Dade Behring）之複合物中各 FVIIa 變異體的 TFPI 抑制程度且將其表示為與野生型 FVIIa 相比 TFPI 抗性之增加倍數（表 21）。

表 21. FVIIa 變異體受 TFPI 之抑制

突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	TFPI 抗性之增加倍數
wt	wt	1.0
A292N/A294S	A150N/A152S	2.4
A175S	A39S	1.5
K109N	K[109]N	0.7
A122N/G124S	A[122]N/G[124]S	1.1
A122N/G124S/E394N/P395A/R396S	A[122]N/G[124]S/E245N/P246A/R247S	1.0

B. 關於對 TFPI 之抗性以表面電漿共振（SPR）篩選 FVIIa 變異體

使用高通量表面電漿共振（SPR）檢定以 Biacore T100 儀器評估各種 FVIIa 變異體對人類重組可溶性 TFPI 抑制之相對抗性。藉由在標準化注射時間及蛋白酶濃度後與所結合的野生型 FVIIa 之量相比較，量測結合於固定於 Biacore CM5 傳感器晶片上之可溶性 TFPI 的 FVIIa 變異體之相對量評估 FVIIa 變異體對 TFPI 抑制之相對抗性。

對於各實驗，使用 Biacore T-100 控制軟體（GE Healthcare）內可用之胺偶合方案及胺偶合套組（GE Healthcare）所提供的試劑，將可溶性 TFPI（R & D Systems）固定於新的 4 流量槽 Biacore CM5 Series S 傳感器晶片（GE Healthcare）。使用所有四個可用流量槽固定兩個不同密度之 TFPI 及牛血清白蛋白（BSA），其在參考槽中充當阻斷劑。將 BSA 在乙酸鈉（pH 4.0）中稀釋至 5 μg/ml，且分別以 1000 及 2000 反應單位（RU）固定於流量槽 1 及 3 中。對於 TFPI 固定，將經凍乾可溶性 TFPI（10 μg）再懸浮於 100 μl 1×偶合緩衝液（30 mM Hepes、135 mM NaCl、1 mM EDTA、0.01%吐溫-20，pH 7.4）中至 0.1 mg/mL 之濃度。總計 20 μL 0.1 mg/mL TFPI 經在乙酸鈉 pH 4.0 中稀釋至 10 μg/ml 以便分別以 1000 及 2000 RU 固定於流量槽 2 及 4 中。在固定步驟期間使用偶合緩衝液作為工作緩衝液。

在含有 620 nM sTF（人類凝血因子 III；R & D Systems）之 1×工作緩衝液（20 mM Hepes、150 mM NaCl、5 mM $CaCl_2$、0.1% PEG 8000、0.1% BSA、0.01%吐溫-20，pH 7.4）中以 320 nM 之最終濃度製備 FVIIa 之各樣品。通常，在最終稀釋至 320 nM 之前，將各 FVIIa 變異體 10 倍稀釋於 1×工作緩衝液中。以 120 μL 之最終體積一式兩份製備 FVIIa/sTF 複合物，從而允許多達 48 種獨特 FVIIa 變異體加載於 96 孔儲存板中，且在單次操作中以重複注射對其加以評估。將 FVIIa/sTF 複合物在室溫下培育 10-15 分鐘，隨後起始第一次樣品注射。

在 Biacore 控制軟體（GE Healthcare）中建立標準化結合分析方法，其中經 180 秒之締合時間，接著短暫 60 秒之解離，以 10 μL/min 之流速注射各 FVIIa 重複。解離階段後，以 10 mM 甘胺酸、500 mM NaCl pH 3.0 將傳感器晶片再生 30 秒，且隨後為以相同 10 μL/min 流速以 1x工作緩衝液進行 60 秒穩定期。記錄兩個檢定參考點用於每次操作及後續資料分析，亦即締合階段（結合）結束前之一個 5 秒，及解離階段（解離）結束前第二個所報導之 5 秒。起始全面檢定前，以單次注射 320 nM 野生型 FVIIa/sTF 歷時 180 秒測試傳感器晶片，對於與流量槽 2（1000 RU）及 4（200 RU）之結合其應分別提供約 400-450 RU 及 750-850 RU 之反應。

首先，以 Biacore T100 評估軟體（GE Healthcare）進行資料分析以檢查檢定驗證參數，其包括驗證與參考槽之結合最小，基線漂移及對照空白注射液（工作緩衝液）之結合。在此應用內產生指示在結合報導點及解離報導點所結合 FVIIa 變異體之量（以 RU 計）的資料表。隨後輸出資料表用於在 Microsoft Excel 試算表環境內進一步分析。校正原始資料點（所結合 RU）之對照與感應器晶片之結合，且隨後取各參數的所結合野生型 FVIIa 之量（以 RU 計）與所結合 FVIIa 變異體之量（以 RU 計）的比率且報導為結合（wt/變異體）及解離（wt/變異體）。表 22 呈示研究之結果。以所評估參數中之一或兩者的比率增加形式反映對 TFPI 抑制之抗性。舉例而言，對於特定 FVIIa 變異體，20

之結合（wt/變異體）或解離（wt/變異體）值指示彼變異體對 TFPI 抑制之抗性比野生型 FVIIa 高 20 倍。數種變異體展現增強之對 TFPI 抑制之抗性。舉例而言，諸如 Q286R/M298Q/K341D-FVIIa、Q286R/K341D-FVIIa 及 M298Q/K341D-FVIIa 的含有 K341D 突變（成熟 fvii 編號）之變異體具有指示顯著 TFPI 抗性之比率（高 40-150 倍）。在一些情況下，解離速率比締合速率更易受影響。

表 22. FVIIa 變異體對 TFPI 抑制之抗性

突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	TF-依賴性 TFPI 抗性檢定			
		293-F 細胞		BHK-21 細胞	
		結合（wt/變異體）	解離（wt/變異體）	結合（wt/變異體）	解離（wt/變異體）
WT	WT	1.0	1.0	1.0	1.0
Q286R	Q143R	2.2	1.9	3.7	3.4
A292N/A294S	A150N/A152S	2.6	2.2		
A175S	A39S	1.6	1.4		
K109N	K[109]N	0.8	0.7		
A122N/G124S	A[122]N/G[124]S	1.2	1.1		
A122N/G124S/E394N/P395A/R396S	A[122]N/G[124]S/E245N/P246A/R247S	1.1	1.0		
S119N/L121S	S[119]N/L[121]S			1.2	1.3
T128N/P129A	T[128]N/P[129]A			1.1	1.2
Q286R/S222A/ Gla 交換 FIX	Q143R/S82A/Gla 交換 FIX	1.9	1.7		
Q286R/M298Q	Q143R/M156Q			2.0	1.8
Q286R/M298Q/K341Q	Q143R/M156Q/K192Q	3.1	3.5	3.0	3.5
Q286R/M298Q/K199E	Q143R/M156Q/K60cE	4.6	4.1	2.4	2.1
T239V	T99V	1.4	1.4	1.1	1.1
H257A/M298Q	H117A/M156Q			2.4	2.7
S222A/H257A/Q286R/M298Q	S82A/H117A/Q143R/M156Q			1.6	1.4
A175S/Q286R/Q366V	A39S/Q143R/Q217V	4.2	3.5	3.5	2.9
K109N/A175S	K[109]N/A39S			3.4	3.2
S222A/Q286R/Q366V	S82A/Q143R/Q217V			1.2	1.2
Q366I	Q217I	0.6	0.5		
K197E/M298Q	K60aE/M156Q	2.6	2.3		
Q286R/M298Q/K341D	Q143R/M156Q/K192D	33.6	182.3		
Q286R/K341D	Q143R/K192D	29.8	281.8		
M298Q/K341D	M156Q/K192D	146.8	196.5		
S119N/L121S/A175S	S[119]N/L[121]S/A39S	2.8	2.7		
T128N/P129A/A175S	T[128]N/P[129]A/A39S	2.7	2.6		
A122N/G124S/A175S	A[122]N/G[124]S/A39S	3.0	2.9		

實施例 9

FVIIa 多肽之藥物動力學分析

藉由量測小鼠血漿中人類因子 VIIa 之量評估 FVIIa 多肽之藥物動力學特性。可使用兩個檢定來量化血漿中之 FVIIa。可使用 ELISA 來量化小鼠血漿中之總 FVIIa 蛋白，且使用 FVIIa 依賴性凝結檢定（FVIIa:C）來量化血漿中的 FVIIa 多肽之凝血活性。

A. 向小鼠投予 FVIIa 多肽

在藥物動力學研究中評估經修飾之 FVIIa 多肽及未經修飾之重組人類 FVIIa（rhFVIIa）蛋白（NovoSeven®或 NovoSeven® RT，Novo Nordisk）。對於各研究，給 18 隻雄性 CD-1 小鼠靜脈內快速注射 rFVIIa 之劑量（0.1-3.0 mg/kg，視研究而定）。在注射後 5、15、30、60、120 及 240 分鐘，使用 CO_2 窒息使來自各注射方案之 3 隻小鼠安樂死，且經由經皮心臟穿刺將約 1.0 mL 血液抽入 1.0 mL 注射器中。各注射器預裝載有足量檸檬酸鈉以取得在 1 mL 血液中 3.2%之最終濃度。接著，在 4℃下將血樣在 9000 rpm 下離心 8 min。將血漿移至經標記個別 1.5 ml 管（Eppendorf），快速冷凍於液氮中且在-80℃下儲存。另外，給每個實驗 1 隻小鼠單獨注射媒劑（假治療）且使用此小鼠之血漿用於背景 FVIIa 活性測定。

B. ELISA 檢定

藉由 ELISA 使用市售套組 IMUBIND®因子 VII ELISA（American Diagnostica）偵測血清中之 FVII 蛋白。此套組採用經抗 FVII/FVIIa 抗體預塗佈以捕獲蛋白質之板，及生

物素化抗 FVII 抗體以便經由鏈親合素（steptavidin）標記之辣根過氧化物酶偵測。除以下例外根據製造商之指示使用該套組：第一，使標準曲線縮窄以確保線性範圍在整個濃度範圍內確保且涵蓋 0.88 ng/ml 至 10 ng/ml 之濃度；第二，由於抗體親和力之差異，故使用經純化 FVIIa 變異體本身而非套組提供之 FVII 標準用於標準曲線。實驗指示在 75%之游離蛋白酶含量下偵測到 FVIIa 與抗凝血酶 III（ATIII）（一種 FVIIa 之潛在血漿抑制子）之複合物，此確保該檢定可偵測血漿樣品中之活性及無活性形式的總 FVIIa。

簡言之，在室溫下解凍血漿樣品且 10 倍稀釋於樣品緩衝液（PBS + 0.1%曲通 X-100 + 1.0% BSA）中，接著連續 5.5 倍稀釋四個稀釋液。將四個稀釋樣品 2 倍稀釋於 ELISA 板上用於 20、110、605 及 3327.5 倍之最終樣品稀釋。小鼠血漿之此等四個稀釋液涵蓋 33,000 ng/ml 至 20 ng/ml 之蛋白酶濃度範圍。在兩個獨立檢定板上量測各樣品，且使用彼等在標準曲線範圍內之量測值來計算血漿樣品中 FVIIa 變異體之濃度。

C. 凝結檢定

使用市售套組（STACLOT FVIIa-rTF，Diagnostica Stago, Parsippany, NJ）進行凝結檢定。為測定活性 FVIIa 多肽之凝血活性，使用 FVIIa 依賴性凝結檢定（FVIIa:C）檢定血漿樣品。使用商業套組內提供的試劑及用法說明書進行該檢定，且使用電動機械凝塊偵測儀（STArt4，Diagnostica

Stago, Parsippany, NJ）量測凝結時間。除以下例外根據製造商之指示使用該套組：第一，使用經純化 FVIIa 變異體本身而非套組提供的 rhFVIIa 標準用於標準曲線；第二，使用以下大量商業試劑用於常規藥物動力學篩選研究且提供可比於套組試劑之結果：可溶性組織因子（CalBioChem, La Jolla, Ca）及合成磷脂摻合物（Avanti Polar Lipids, Alabaster, AL）、TBSA 緩衝液（具有 1% BSA 之 Tris-NaCl pH 7.5；DiaPharma, West Chester, Ohio）及 25 μM 氯化鈣溶液（Diagnostica Stago, Parsippany, NJ）。

如下進行凝結檢定。在室溫下解凍冷凍血漿樣品約 45 min 且隨後以 1:5000 稀釋於緩衝液中。將 50 μl 經稀釋血漿與 50 μl 缺乏因子 VII 之人類血漿及 50 μl 重脂化組織因子組合且預培育 180 秒。預培育後，添加 50 μl 氯化鈣溶液（25 μM）以起始凝結。使用電動機械凝塊偵測測定凝結時間。一式兩份檢定各血漿樣品。藉由使用含有已知量之所檢定特定 FVIIa 變異體的緩衝液之連續稀釋液的凝結時間構築標準曲線來校正系統。由 log FVIIa 相對於 Log 凝結時間標準曲線之線性部分計算小鼠血漿樣品中之 FVIIa 濃度。血漿樣品誘導缺乏因子 VII 之血漿凝結的能力經報導為由假治療小鼠減去血漿中內源性野生型 FVIIa 之背景後，每毫升小鼠血漿中 FVIIa 之毫微克數。

藉由使活性之自然對數按常規擬合為直線，且量測 FVIIa 蛋白之活性減少一半所消耗的時間，常規測定各 FVII 蛋白之半衰期。對於具有多指數式衰減之 FVII 蛋白，由 log

血漿對時間分布之末端部分測定半衰期。其他藥物動力學參數如下計算：血漿 AUC_{0-inf}/劑量（計算為[$AUC_{(0-t)}$ + Ct/(ln2/$T_{½}$)]，其中 t 為最後一個時間點 FVIIa 多肽之可量測血漿濃度除以 IV 劑量（mg/kg））；半衰期（血漿 FVIIa 濃度對時間分布之末端階段中 FVIIa 多肽之半衰期；$T_{½}$ 經計算為 -ln2 除以血漿 FVIIa 濃度對時間曲線之 log-線性圖的末端階段中的負斜率）；MRT_{0-last}（FVIIa 多肽停留在體內的平均時間；經計算為 $AUMC_{0-last}/AUC_{0-last}$，其中 $AUMC_{0-last}$ 為第一時刻對時間曲線（moment-versus-time curve）（FVIIa 濃度時間對時間曲線）下的總面積，且藉由線性梯形法則計算）；Cl（全身清除率；計算為劑量/AUC_{0-inf}）；及 V_d（基於終末消除 e 常數（ß）之分布容積；計算為[Cl/(ln2/$T_{½}$)]）。

D. FVIIa 變異體之藥物動力學特性

使用上述 FVIIa:C 方案，基於血漿之凝結活性評估野生型 FVIIa 及 FVIIa 變異體之藥物動力學特性。結果闡明於表 23 中。與野生型 FVIIa 相比，數種 FVIIa 變異體展現改良之藥物動力學參數。

表 23. FVIIa 變異體之小鼠藥物動力學參數

突變（成熟 FVII 編號）	IV 劑量 (mg/kg)	血漿 AUC0-inf (μg.min/mL)/劑量	半衰期 (min)	MRT_0-last (min)	Cl (mL/min/kg)	Vd (mL/kg)	N
NovoSeven® RT FVIIa	0.1	1165	37	50	0.9	46	1
NovoSeven® FVIIa	0.1	741	30	31	1.4	58	1
NovoSeven® FVIIa	1.0	1156	36	41	1.7	89	1
WT	0.1	686	37	37	1.8	92	6
WT	1.0	798	50	57	1.5	118	2
P257 插入 GGGSCSFGRGDIRNVC	0.1	391	32	32	2.3	108	1

T128N/P129A	0.1	1392	57	43	0.8	64	2
S52A	0.1	594	51	58	1.6	118	1
K109N	0.1	951	50	40	1.1	75	1
A51N	0.1	270	33	32	3.7	174	1
S52A/S60A	0.05	460	25	29	2.2	78	1
S52A/S60A	0.1	408	17	34	2.5	61	1
M298Q	0.1	258	76	33	4.9	443	2
T128N/P129A/M298Q	0.1	495	26	28	2.0	75	1
V158D/E296V/M298Q	0.05	72	13	10	13.9	258	1
V158D/E296V/M298Q	0.1	44	16(á), 45(â)	20	22.8	1465	1
V158D/E296V/M298Q	1.0	39	7	13	26.6	979	2
V158D/E296V/M298Q	3.0	22	7.7á	7.9	45.6	506	1
V158D/E296V/M298Q	6.0	48	43	45	20.8	1305	1
T128N/P129A/V158D/E296V/M298Q	0.1	125	11	14	8.0	122	1
S52A/S60A/V158D/E296V/M298Q	0.1	47	15	11	21.4	450	1
Q286R	0.1	181	55	59	5.5	439	1
Q286R	0.3	460	41.7	76	1.8	110	1
Q286R	1.0	1256	67	68	0.8	80	2
T128N/P129A/Q286R	0.1	2443	96	82	0.4	56	1
S52A/S60A/Q286R	0.1	1565	43	60	0.6	55	1
Gla 交換 FIX	0.1	207	20	22	4.9	140	2
K341D	0.1	2817	106	114	0.1	22	1
S222A	0.1	189	32	33	5.3	248	1
S222A	1.0	139	30	33	3.8	293	1
T128N/P129A/S222A	0.1	422	28.4(á), 71(â)	58	2.4	244	1
S52A/S60A/S222A	0.1	270	45	38	3.7	243	1
H257A	0.1	595	31	30	1.7	76	1
H257S	0.1	1015	59	62	1.0	84	1
H257S	0.75	816	50	62	1.2	85	1
Q366V	0.1	19	14	11	51.6	1060	1
Gla 交換 FIX/Q366V	0.1	157	11	7.0	6.4	107	1
A122N/G124S/E394N/P395A/R396S	0.1	1089	63	45	0.9	84	1
G318N	1.0	568	95	56	1.8	242	1
A175S	0.1	2081	111	85	0.5	76	2
K109N/A175S	0.1	1280	183	51	0.8	207	1
S119N/L121S/A175S	0.1	2460	102	50	0.4	60	1
T128N/P129A/A175S	0.1	2770	83	48	0.4	43	1
A122N/G124S/A175S	0.1	3240	91	50	0.3	40	1
A122N/G124S	0.1	679	52.9	42	1.1	87	1
H257A/Q286R	0.1	1848	56.8	73	0.5	44	1
S222A/Q286R	0.1	861	30	38	1.5	97	2
Gla 交換 FIX/S222A/Q286R	1.0	415	39	42	2.4	136	1
Gla 交換 FIX/T128N/P129A /S222A/Q286R	0.1	929	55	59	1.1	86	1
S222A/H257A/Q286R	0.1	976	56	42	1.0	83	1
Q286R/M298Q	0.055	1198	40	44	0.8	49	1
Q286R/M298Q	0.1	605	35	42	1.9	94	6
Q286R/M298Q	1.0	363	29	36	2.8	116	1
Gla 交換 FIX/Q286R/M298Q	0.1	231	26	20	4.9	194	3

T128N/P129A/Q286R/M298Q	0.1	1571	41	60	0.6	38	1
T[128]N/P[129]A/Q286R/M298Q	0.1	1326	42.3	50	0.8	47	1
Gla 交換 FIX /T128N/P129A/Q286R/M298Q	0.1	427	30	32	2.3	101	1
{Gla 交換 FIX/E[40]L}/Q286R/M298Q	0.1	386	53	43	2.6	198	1
{Gla 交換 FIX/K[43]I}/Q286R/M298Q	0.1	439	85	47	2.3	280	1
{Gla 交換 FIX/Q[44]S}/Q286R/M298Q	0.1	291	14	24	3.4	150	1
{Gla 交換 FIX/M[19]K}/Q286R/M298Q	0.1	648	14 (á), 75 (â)	43	1.5	32	1
S52A/S60A/Q286R/M298Q	0.1	374	32	34	2.7	122	1
Gla 交換 FIX/S52A/S60A/Q286R/M298Q	0.1	256	19	18	3.9	107	1
{Gla 交換 FIX/K[43]I}/T128N/P129A/Q286R/M298Q	0.1	154	18	17	6.5	166	1
S222A/M298Q	0.1	72	17	12	13.9	332	1
S222A/H257A/Q286R/M298Q	0.1	93	33	30	10.8	517	1
T128N/P129A/S222A/H257A/Q286R/M2986Q	0.1	770	38	45	1.3	72	1
S52A/S60A/S222A/H257A/Q28R/M2986Q	0.1	469	26	28	2.1	78	1
A175S/Q286R/Q366V	0.1	353	28.9	23	2.8	118	1
Q286R/M298Q/K341D	0.1	219	23	20	4.6	151	1
M298Q/K341D	0.1	2430	78	76	0.4	46	1
Q286R/M298Q/Q366N	0.1	569	29	32	1.8	74	1
T128N/P129A/Q286R/M298Q/Q366N	0.1	1897	50	58	0.5	38	1
{Gla 交換 FIX K[43]I}/Q286R/M298Q/Q366N	0.1	257	10(á), 28(â)	20	3.9	163	1
{Gla 交換 FIX K[43]I}/T128N/P129A/Q286R/M298Q/Q366N	0.1	393	24	27	2.5	89	1
T128N/P129A/Q286R/H373F	0.1	1467	59	62	0.9	74	1
Q286R/M298Q/H373F	0.1	466	28	23	2.2	87	1
T128N/P129A/Q286R/M298Q/H373F	0.1	597	27(á), 67(â)	51	1.6	153	1
T128N/P129A/M298Q/H373F	0.1	307	7(á), 27(â)	23	3.3	126	1
V158D/Q286R/E296V/M298Q	0.1	172	14	36	5.8	535	1
S222A/T239V	0.1	127	47	39	7.9	535	1
Gla 交換 FIX/S222A /T239V/Q286R	0.1	460	34	33	2.2	108	1
T239V/Q286R/M298Q	0.1	398	28(á),71(â)	60	2.5	258	1

Gla 交換 FIX/T239V/ Q286R/M298Q	0.1	365	13(á),56(â)	29	2.7	220	1
T128N/P129A/T239V/ Q286R/M298Q	0.1	914	38	36	1.1	60	1
S222A/T239V/H257A/ Q286R/M298Q	0.1	181	28	31	5.5	225	1
T128N/P129A/S222A/T239V/H257A/ Q286R/M298Q	0.1	564	27	30	1.8	70	1
T239V/Q286R/H373F	0.1	385	72	54	2.6	269	1
T239V/Q286R/M298Q/ H373F	0.1	149	36	23	6.7	353	1
T128N/P129A/T239V/ Q286R/M298Q/H373F	0.1	345	27	27	2.9	113	1
V158D/T239I/E296V/ M298Q	0.1	370	14(á),70(â)	50	2.7	273	1
T239I/Q286R	0.1	1820	85	76	0.6	68	1
S222A/T239I	0.1	1300	6(á), 81(â)	69	0.8	90	1
Gla 交換 FIX /S222A/T239I/Q286R	0.1	1073	70	66	0.9	94	1
T239I/Q286R/M298Q	0.1	1029	27(á),60(â)	62	1.0	84	1
Gla 交換 FIX / T239I/Q286R/M298Q	0.1	1269	54	62	0.8	61	1
T128N/P129A/T239I/Q286R/M298Q	0.1	2105	82	74	0.5	56	1
S222A/T239I/H257A/Q286R/M298Q	0.1	1212	31(á), 79(â)	60	0.8	101	1
T239I/Q286R/H373F	0.1	1841	30(á), 85(â)	69	0.5	62	1
V158D/T239V/E296V/ M296Q	0.1	184	24(á), 134(â)	78	5.4	1053	1
T239V/Q286R	0.1	1522	29(á), 72(â)	68	0.7	68	1
T239V/Q286R/M298Q/ H373F	0.1	950	36	61	1.1	55	1
T239V/Q286R/M298Q/ H373F	0.1	806	32	56	1.3	57	2
T239V/Q286R/M298Q/ H373F	0.1	663	27	52	1.5	59	1
T239V/Q286R/M298Q/ H373F	0.1	1350	53	62	0.7	57	1
S222A/H257S/Q286R/ M298Q	0.1	814	33	31	1.2	59	1
H257S/Q286R/M298Q/ H373F	0.1	297	34	34	3.4	163	1
S222A/Q286R/M298Q/ H373F	0.1	106	35	23	9.4	478	1
Gla 交換 FIX /S222A/ Q286R/M298Q/H373F	0.1	104	9.1(á),17(â)	13	9.7	242	1
S222A/Q286R/M298Q	0.1	347	24	26	2.9	102	1
Gla 交換 FIX / S222A/ Q286R/M298Q	0.1	263	11	13	3.8	62	1
T128N/P129A/A175S/ Q366V	0.1	2196	52(á), 85(â)	78	0.5	56	1
A122N/G124S/A175S/ Q366V	0.1	2148	92	81	0.5	62	1
T128N/P129A/A175S/S222A	0.1	4248	122	88	0.2	41	1

A122N/G124S/A175S/S222A	0.1	3316	102	83	0.3	44	1
T128N/P129A/A175S/Q286R	0.1	6160	151	94	0.2	35	1
A122N/G124S/A175S/Q286R	0.1	4097	139	93	0.2	49	1
Gla 交換 FIX /S222A/Q286R/H373F	0.1	480	26	30	2.1	79	1
V258D/E296V/M298Q/H373F	0.1	90	8.7(á), 20(â)	14	11.1	321	1
H257A/Q286R/M298Q	0.1	1029	42	48	1.0	59	1
Gla 交換 FIX /T128N/P129A/A175S/S222A/Q286R	0.1	2787	38(á), 134(â)	88	0.4	69	1
Gla 交換 FIX /A122N/G124S/A175S/S222A/Q286R	0.1	3492	148	95	0.3	61	1
T128N/P129A/A175S/Q286R/M298Q	0.1	5120	171	96	0.2	48	1
A122N/G124S/A175S/Q286R/M298Q	0.1	3681	154	92	0.3	61	1
T128N/P129A/A175S/S222A/H257A/Q286R/M298Q	0.1	3140	113	87	0.3	52	1
A122N/G124S/A175S/S222A /H257A/Q286R/M298Q	0.1	2659	37.(á),130(â)	85	0.4	70	1
T128N/P129A/A175S/Q286R/M298Q/H373F	0.1	3580	118	88	0.3	48	1
A122N/G124S/A175S/Q286R/M298Q/H373F	0.1	3148	105	84	0.3	48	1
V158D/Q286R/E296V/M298Q/H373F	0.1	124	20	17	8.1	237	1
M298Q/H373F/Q366N	0.1	169	8	8.2	5.9	69	1
T239V/M298Q/H373F	0.1	110	18	16	9.1	235	1
T239I/M298Q/H373F	0.1	562	26	28	1.8	66	1
T128N/P129A/Q286R/M298Q/Q366N/H373F	0.1	607	29	30	1.6	69	1
T239V/Q286R/M298Q/Q366N	0.1	729	29	30	1.4	57	1
T239I/Q286R/M298Q/Q366N	0.1	1548	72	73	0.6	67	1

α = α 半衰期，量測分布半衰期

β = β 半衰期，量測消除半衰期

表 24 使用以下藥物動力學參數闡明研究之結果：回收率%（活體內）（給藥 5 分鐘後（第一個時間點）FVIIa 之經量測血漿濃度除以理論最大 FVIIa 血漿濃度(基於所投予 FVIIa 質量及理論全血體積）乘 100%）；回收率%(試管內）

（加有已知量之FVIIa的血漿中經量測FVIIa濃度除以理論FVIIa血漿濃度(基於加入已知血漿體積的FVIIa質量之量）乘100%）；AUC *活性/劑量（TF依賴性）（血漿AUC/劑量乘以TF依賴性間接活性(參見以上表15))；NovoSeven® FVIIa活性暴露之提高（TF依賴性）（藉由AUC*活性/劑量(TF依賴性)$_{NovoSeven®\ FVIIa}$/AUC*活性/劑量(TF依賴性)$_{突變型\ FVIIa}$計算）；AUC*活性/劑量（TF獨立性）（血漿AUC/劑量乘以TF-獨立性間接活性（參見以上表15）；NovoSeven® FVIIa活性暴露之提高（TF獨立性）（藉由AUC*活性/劑量(TF獨立性)$_{NovoSeven®\ FVIIa}$/AUC*活性/劑量(TF獨立性)$_{突變型\ FVIIa}$計算）。

表 24

突變（成熟FVII編號）	回收率%（活體內）	AUC*活性/劑量（TF-依賴性）	Novo7活性暴露之提高（TF依賴性）	AUC*活性/劑量（TF獨立性）	Novo7活性暴露之提高（TF獨立性）
NovoSeven® FVIIa	60%	2.95E+10	1.0	7.26E+03	1.0
WT	46%	4.71E+10	1.4	1.22E+04	1.5
T239I/Q286R/M298Q/Q366N	52%	1.15E+11	3.9	1.38E+05	18.9
T239V/Q286R/ M298Q/Q366N	66%	1.35E+11	4.6	4.69E+04	6.5
T128N/P129A/Q286R/M298Q/Q366N/ H373F	66%	8.10E+10	2.8	9.77E+04	13.5
T239I/M298Q/H373F	60%	1.95E+10	0.7	7.77E+04	10.7
T239V/M298Q/H373F	17%	4.89E+09	0.2	3.53E+04	4.9
M298Q/H373F/ Q366N	32%	1.19E+10	0.4	2.13E+04	2.9
V158D/Q286R/E296V/M298Q/H373F	21%	2.97E+10	1.0	7.12E+04	9.8
A122N/G124S/A175S/Q286R/M298Q/ H373F	79%	2.64E+11	9.0	ND	ND
T128N/P129A/A175S/Q286R/M298Q/ H373F	85%	2.05E+11	7.0	ND	ND
A122N/G124S/A175S/S222A /H257A/ Q286R/M298Q	76%	2.23E+11	7.6	ND	ND
T128N/P129A/A175S/S222A/H257A/Q286R/M298Q	69%	2.16E+11	7.4	6.36E+04	8.8
A122N/G124S/ A175S/Q286R/M298Q	84%	2.73E+11	9.3	ND	ND
T128N/P129A/A175S/Q286R/M298Q	76%	3.69E+11	12.6	ND	ND
Gla 交換 FIX /A122N/ G124S/ A175S/S222A/Q286R	42%	1.44E+11	4.9	ND	ND
Gla 交換 FIX /T128N/P129A/ A175S/S222A/Q286R	69%	1.08E+11	3.7	8.51E+04	11.7
H257A/Q286R /M298Q	42%	1.16E+11	4.0	6.33E+04	8.7
V258D/E296V/ M298Q/H373F	17%	1.36E+10	0.5	1.17E+05	16.1
Gla 交換 FIX /S222A/Q286R/H373F	42%	5.88E+10	2.0	3.90E+04	5.4
A122N/G124S/A175S/Q286R	78%	1.68E+11	5.8	1.22E+04	1.7

T128N/P129A/A175S/Q286R	34%	2.05E+11	7.0	2.01E+04	2.8
A122N/G124S/A175S/S222A	60%	6.90E+10	2.4	ND	ND
T128N/P129A/A175S/S222A	88%	7.31E+10	2.5	8.00E+03	1.1
A122N/G124S/A175S/Q366V	60%	6.48E+10	2.2	6.42E+03	0.9
T128N/P129A/A175S/Q366V	74%	7.43E+10	2.5	7.39E+03	1.0
Gla 交換 FIX / S222A/Q286R/M298Q	40%	5.52E+10	1.9	1.09E+05	15.0
S222A/Q286R/M298Q	22%	4.46E+10	1.5	8.78E+04	12.1
Gla 交換 FIX/ S222A/Q286R/M298Q/ H373F	16%	2.94E+10	1.0	1.99E+04	2.7
S222A/Q286R/M298Q/H373F	5%	1.57E+10	0.5	4.57E+04	6.3
H257S/Q286R/M298Q/H373F	20%	4.52E+10	1.5	9.01E+03	1.2
S222A/H257S/Q286R/M298Q	72%	1.28E+11	4.4	3.39E+04	4.7
T239I/Q286R/M298Q/H373F	56%	8.73E+10	3.0	1.05E+04	1.5
T239V/Q286R	66%	1.35E+11	4.6	1.79E+04	2.5
V158D/T239V/E296V/ M296Q	8%	4.08E+10	1.4	3.43E+05	47.3
T239I/Q286R/H373F	77%	1.14E+11	3.9	ND	ND
S222A/T239I/H257A/Q286R/M298Q	61%	1.38E+11	4.7	6.26E+04	8.6
T128N/P129A/T239I/Q286R/M298Q	81%	1.72E+11	5.9	1.64E+05	22.6
Gla 交換 FIX / T239I/Q286R/M298Q	56%	1.59E+11	5.4	3.10E+05	42.6
T239I/Q286R/M298Q	54%	1.16E+11	4.0	1.16E+04	1.6
Gla 交換 FIX /S222A/T239I/Q286R	42%	7.27E+10	2.5	2.18E+04	3.0
S222A/T239I	71%	3.97E+10	1.4	2.19E+03	0.3
T239I/Q286R	56%	1.05E+11	3.6	8.34E+03	1.1
V158D/T239I/E296V/M298Q	34%	5.38E+10	1.8	8.01E+04	11.0
T239V/Q286R/M298Q/H373F	10%	2.54E+10	0.9	6.07E+03	0.8
T239V/Q286R/H373F	16%	4.09E+10	1.4	4.69E+03	0.6
T128N/P129A/S222A/T239V/H257A/Q286R/M298Q	49%	6.84E+10	2.3	1.01E+05	13.9
S222A/T239V/H257A/Q286R/M298Q	15%	3.87E+10	1.3	2.59E+04	3.6
T128N/P129A/T239V/Q286R/M298Q	60%	9.47E+10	3.2	2.10E+05	28.9
(Gla 交換 FIX/T239V/ Q286R/M298Q	34%	9.24E+10	3.2	1.01E+05	14.0
T239V/Q286R/ M298Q	21%	6.85E+10	2.3	1.17E+04	1.6
Gla 交換 FIX/S222A /T239V/Q286R	33%	9.32E+10	3.2	7.99E+03	1.1
S222A/T239V	10%	9.52E+09	0.3	3.83E+02	0.1
V158D/Q286R/E296V/M298Q	15%	2.56E+10	0.9	1.76E+05	24.3
T128N/P129A/Q286R/M298Q/H373F	36%	7.92E+10	2.7	1.83E+04	2.5
Q286R/M298Q/H373F	66%	1.39E+11	3.9	1.42E+05	12.1
T128N/P129A/Q286R/H373F	49%	2.03E+11	6.9	1.93E+04	2.7
{Gla 交換 FIX K[43]I}/ T128N/ P129A Q286R/M298Q /Q366N	45%	9.88E+10	3.4	8.58E+04	11.8
{Gla 交換 FIX K[43]I}/Q286R/ M298Q/Q366N	36%	4.35E+10	1.5	2.18E+04	3.0
Q286R/M298Q/ Q366N	41%	1.33E+11	4.5	7.50E+04	10.3
M298Q/K341D	84%	4.26E+10	1.0	1.02E+04	0.6
Q286R/M298Q/ K341D	33%	4.98E+09	0.1	5.24E+03	0.3
A175S/Q286R/Q366V	22%	3.72E+10	0.9	7.31E+03	0.4
S52A/S60A/S222A/ H257A/Q286R/ M298Q	45%	1.17E+11	4.0	5.42E+04	7.5
T128N/P129A/S222A/H257A/Q286R/ M2986Q	53%	1.80E+11	6.1	5.23E+04	7.2
S222A/H257A/Q286R/M298Q	9%	3.04E+10	0.9	4.17E+04	4.9
S222A/M298Q	7%	8.63E+09	0.2	9.51E+04	5.1
{Gla 交換 FIX/K[43]I}/T128N/ P129A/Q286R/M298Q	23%	2.46E+08	0.0	6.00E+04	8.3
Gla 交換 FIX/S52A/S60A/ Q286R/M298Q	32%	4.63E+10	1.6	2.54E+05	34.9
S52A/S60A/ Q286R/M298Q	31%	4.67E+10	1.6	8.11E+04	11.2
{Gla 交換 FIX/M[19]K}/ Q286R/M298Q	69%	9.11E+10	3.1	3.32E+05	45.7
{Gla 交換 FIX/Q[44]S}/ Q286R/M298Q	35%	5.77E+10	2.0	2.12E+05	29.2
{Gla 交換 FIX/K[43]I}/ Q286R/M298Q	28%	1.20E+11	4.1	3.96E+05	54.5
{Gla 交換 FIX/E[40]L}/ Q286R/M298Q	36%	8.04E+10	2.7	3.14E+05	43.3

Gla 交換 FIX /T128N/P129A/ Q286R/M298Q	84%	9.00E+10	3.1	3.58E+04	4.9
T[128]N/P[129]A/ Q286R/M298Q	66%	1.55E+11	5.3	2.20E+05	30.3
T[128]N/P[129]A/ Q286R/M298Q	62%	4.21E+11	14.4	1.84E+05	25.4
Q143R/M156Q/Gla 交換 FIX	21%	8.53E+10	2.7	2.30E+05	29.9
Q286R/M298Q	51%	1.08E+11	3.2	1.03E+05	11.2
S222A/H257A/Q286R	40%	1.55E+11	4.4	2.72E+04	3.2
Gla 交換 FIX/T128N/P129A /S222A/Q286R	44%	1.37E+11	4.7	1.44E+04	2.0
Gla 交換 FIX/S222A/ Q286R	32%	5.95E+10	1.4	2.15E+04	1.2
S222A/Q286R	51%	1.85E+11	5.4	4.61E+04	2.5
H257A/Q286R	63%	3.66E+11	12.5	1.59E+04	2.2
A122N/G124S/A175S	82%	8.70E+10	2.4	2.18E+04	1.2
T128N/P129A/A175S	80%	6.16E+10	1.7	ND	ND
S119N/L121S/A175S	60%	8.68E+10	2.5	ND	ND
K109N/A175S	22%	4.73E+10	1.3	ND	ND
A175S	52%	8.10E+10	2.4	1.40E+04	0.8
G318N	37%	5.22E+10	1.2	0.00E+00	0.0
A122N/G124S/E394N/P395A/R396S	46%	1.07E+11	2.5	ND	ND
Gla 交換 FIX/Q366V	26%	1.43E+10	0.5	1.41E+04	1.9
Q366V	3%	4.09E+09	0.1	1.44E+03	0.1
H257S	39%	1.67E+11	5.1	1.30E+04	0.9
H257A	36%	4.96E+10	1.2	1.18E+04	0.6
S52A/S60A/S222A	11%	1.05E+10	0.4	5.28E+03	0.7
T128N/P129A/S222A	21%	5.28E+10	1.8	4.06E+03	0.6
S222A	10%	1.55E+10	0.4	8.56E+03	0.5
K341D	98%	4.77E+10	1.1	ND	ND
S52A/S60A/Q286R	67%	6.42E+10	2.2	1.59E+04	2.2
T128N/P129A/Q286R	67%	4.13E+11	14.1	4.24E+04	5.8
Q286R	35%	1.31E+11	3.7	3.52E+04	2.6
S52A/S60A/V158D/ E296V/M298Q	7%	9.34E+09	0.3	8.24E+04	11.3
T128N/P129A/V158D/E296V/M298Q	21%	5.03E+10	1.7	3.44E+05	47.4
T128N/P129A/M298Q	58%	3.11E+10	1.1	4.49E+04	6.2
M286Q	18%	1.33E+10	0.4	4.93E+04	3.8
S52A/S60A	51%	5.36E+10	1.4	7.76E+03	0.6
A51N	15%	4.65E+10	1.1	9.39E+03	0.5
A122N/G124S	45%	5.26E+10	1.8	4.61E+03	0.6
A122N/G124S	45%	9.20E+10	2.2	0.00E+00	0.0
K109N	52%	1.05E+11	3.6	ND	ND
K109N	52%	8.43E+10	2.0	ND	ND
S52A	37%	3.50E+10	0.8	0.00E+00	0.0
Gla 交換 FIX	31%	2.63E+10	0.7	1.28E+04	1.4
T128N/P129A	88%	8.25E+10	2.4	25147.5	2.6
P257 插入 GGGSCSFGRGDIRNVC	38%	6.29E+10	1.5	ND	ND

實施例 10

測定因子 VIIa 與可溶性組織因子之結合

使用 Biacore 表面電漿共振評估由 HEK 293 或 BHK 細胞表現的 FVIIa 變異體結合可溶性組織因子（sTF）之能力。

經由使用兩種不同含量的與 Biacore CM5 晶片結合之 sTF，在兩個重複實驗中量測三種蛋白酶濃度之結合特徵來評估 FVIIa 變異體。

使用 Biacore T100 儀器使新 Series S CM5 傳感器晶片（GE Healthcare 目錄號 BR1006-68）與牛血清白蛋白及可溶性組織因子偶合。使用 Biacore 偶合緩衝液（30 mM Na Hepes pH 7.4，135 mM NaCl，1 mM EDTA，0.01%吐溫-20）與胺偶合套組（GE Healthcare 目錄號 BR-1000-50）及 Biacore T100 軟體中之方案範例（protocol wizard）進行偶合。對於固定，使用晶片之所有四個槽。使槽 1 及 3 與稀釋於乙酸鹽緩衝液 pH 4.0 中之 500 反應單位（RU）牛血清白蛋白參考蛋白偶合，且使槽 2 及 4 與稀釋於乙酸鹽緩衝液 pH 4.5 中的 500 及 250 RU 之 sTF（R & D Systems）偶合。

在三種濃度且一式兩份情況下測試各 FVIIa 變異體及野生型 FVIIa 蛋白酶。在 96 孔檢定板中在 100 mL Biacore 檢定緩衝液（20 mM Na Hepes pH 7.4，150 mM NaCl，5 mM $CaCl_2$，0.1% PEG 8000，0.1% BSA，0.01%吐溫-20）中將蛋白酶稀釋至 60 nM、30 nM 及 15 nM。在 Biacore T100 儀器中使用 120 秒之接觸時間，接著 180 秒之解離時間，以 10 mL/min 之流速檢定各樣品。亦檢定緩衝液空白。以 50 mM EDTA pH 7.0 將晶片再生 60 秒，接著再生 30 秒。量測野生型 FVIIa 與 sTF 結合之檢定應產生提供約 8 nM 之 K_d 的三組曲線。

使用 Biacore T100 評估軟體分析資料。具體言之，使用將資料擬合為蘭格繆爾等溫線（Langmuir isotherm）之動力學/親和力 1:1 結合分析，且單獨擬合資料在 2 次反應單元偶合時用於各變異體之兩個重複。求 4 個擬合 K_d 值之平均值且呈示於表 25 中。含有 M298Q 突變之 FVIIa 變異體趨向於展現較低 K_d 結果且因此與 sTF 更緊密地結合。

表 25. FVIIa 變異體與可溶性 TF 之結合

突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	親和力 K_d（nM）	
		293-F 細胞	BHK 細胞
wt	wt	7.9	9.0
Q286N	Q143N	8.9	
Q286E	Q143E	3.8	
Q286D	Q143D	9.8	
Q286S	Q143S	8.2	
Q286T	Q143T	10.6	
Q286R	Q143R	7.6	
Q286K	Q143K	8.2	
Q286A	Q143A	6.3	
Q286V	Q143V	11.9	
S222A	S82A	4.2	
H257S	H117S	4.2	
Q366D	Q217D	3.2	
Q366E	Q217E	5.6	
Q366N	Q217N	3.8	
Q366T	Q217T	7.1	
Q366S	Q217S	9.0	
Q366V	Q217V	7.9	
A175S	A39S	6.5	
V158T/L287T/M298K	V21T/L144T/M156K	8.4	
V158D/L287T/M298K	V21D/L144T/M156K	8.5	
Q286R/S222A	Q143R/S82A		7.3
Q286R/S222A/ Gla 交換 FIX	Q143R/S82A/Gla 交換 FIX	8.4	
Q286R/M298Q	Q143R/M156Q		4.7
Q286R/M298Q/K341Q	Q143R/M156Q/K192Q		11.4
Q286R/M298Q/K199E	Q143R/M156Q/K60cE		4.9
S222A/M298Q	S82A/M156Q		5.1
H257A/M298Q	H117A/M156Q		3.1

S222A/H257A/Q286R/M298Q	S82A/H117A/Q143R/M156Q	2.5	
Q286R/Q366V	Q143R/Q217V	29.3	
A175S/Q286R/Q366V	A39S/Q143R/Q217V		18.3
S222A/Q286R/Q366V	S82A/Q143R/Q217V		8.6
Q286M	Q143M	7.1	
Q286L	Q143L	7.1	
Q286Y	Q143Y	7.5	
Q366I	Q217I	6.7	
Q366L	Q217L	5.2	
Q366M	Q217M	4.7	
H216A/H257A	H76A/H117A	6.0	
Q286R/K341D	Q143R/K192D	3.5	
M298Q/K341D	Q143R/Q217D	7.9	
Q286R/Q366N	Q143R/Q217N	8.0	
Q286R/M298Q/Q366D	Q143R/M156Q/Q217D	4.6	
Q286R/M298Q/Q366N	Q143R/M156Q/Q217N	3.8	

進行另一組實驗以使用與上述相同之檢定，但將 FVIIa 劑量範圍修改為 30 nM、15 nM 及 7.5 nM 及使用資料分析以使得使用兩態模型擬合 SPR 資料，評估 FVIIa 變異體與可溶性 TF 之結合。此兩態模型分析經提供於 Biacore T100 評估套裝軟件中且再現如下。結果提供於下表 26 中。

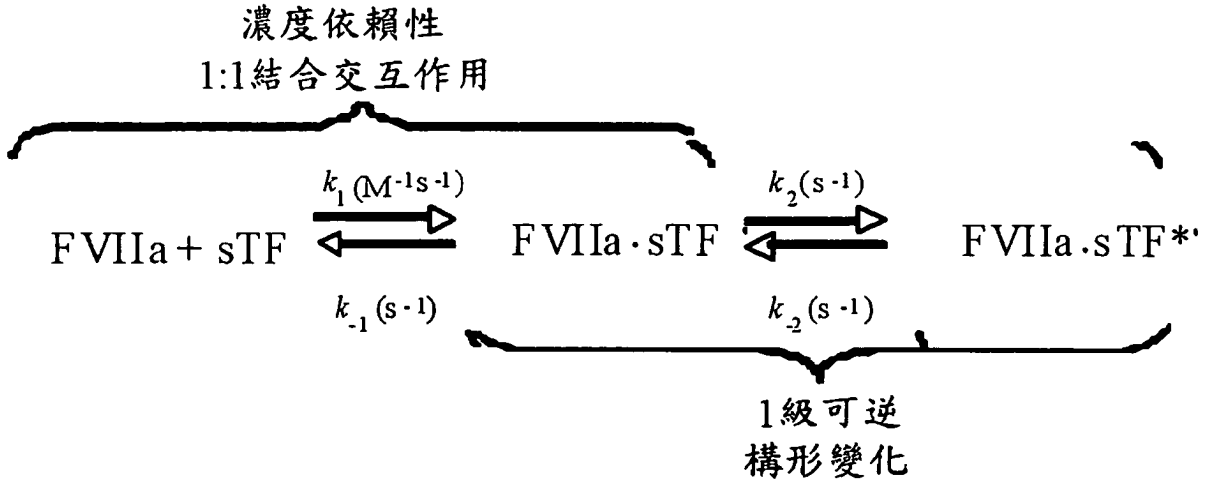

表 26. FVIIa 變異體與可溶性 TF 之結合

突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	親和力 K_d(nM)	SD	%CV	親和力 $K_{d\text{-}WT}/K_{d\text{-}變}$	n
WT (NovoSeven® FVII)	WT (NovoSeven® FVII)	6.5	1.2	19%	1.2	19
WT (NovoSeven-RT® FVII)	WT (NovoSeven-RT® FVII)	6.3	85%	13%	1.2	4
WT	WT	7.6	1.9	24%	1.0	6
WT †	WT †	3.9	0.6	15%	1.0	6
T128N/P129A	T[128]N/P[129]A	6.8	1.2	18%	1.1	7
Gla 交換 FIX	Gla 交換 FIX	36.0	2.6	7%	0.2	3
K109N	K[109]N	10.8	0.2	2%	0.7	2
S52A/S60A	S[52]A/S[60]A	23.2	4.0	17%	0.3	2
M298Q	M156Q	5.9	0.7	11%	1.3	4
M298Q †	M156Q †	1.9	0.1	7%	2.0	2
T128N/P129A/M298Q †	T[128]N/P[129]A/M156Q †	2.4	0.4	16%	1.6	2
V158D/E296V/M298Q	V21D/E154V/M156Q	2.0	0.5	26%	3.9	10
V158D/E296V/M298Q †	V21D/E154V/M156Q †	1.8	0.5	30%	2.2	4
T128N/P129A/V158D/E296V/M298Q	T[128]N/P[129]A/V21D/E154V/M156Q	2.0	0.1	4%	3.9	2
S52A/S60A/V158D/E296V/M1298Q	S[52]A/S[60]A/V21D/E154V/M156Q	14.6	1.3	9%	0.5	2
Q286R	Q143R	6.7	0.4	5%	1.1	2
T128N/P129A/Q286R	T[128]N/P[129]A/Q143R	11.1	4.3	39%	0.7	6
T128N/P129A/Q286R †	T[128]N/P[129]A/Q143R †	10.0	1.6	16%	0.4	4
S52A/S60A/Q286R	S[52]A/S[60]A/Q143R †	51.6	18.4	36%	0.1	5
S222A	S82A	2.6	0.1	4%	3.0	2
T128N/P129A/S222A	T[128]N/P[129]A/S82A	3.6	0.2	7%	2.1	2
S52A/S60A/S222A	S[52]A/S[60]A/S82A	17.2	2.4	14%	0.4	2
H257S	H117S	6.6	1.5	23%	1.2	2
Gla 交換 FIX/Q366V	Gla 交換 FIX/Q217V	56.0	15.1	27%	0.1	3
A175S	A39S	12.3	0.1	1%	0.6	2
K109N/A175S	K[109]N/A39S	9.0	0.0	0%	0.8	2
S119N/L121S/A175S	S[119]N/L[121]S/A39S	6.6	0.1	1%	1.1	2
T128N/P129A/A175S	T[128]N/P[129]A/A39S	10.0	0.1	1%	0.8	2
A122N/G124S/A175S	A[122]N/G[124]S/A39S	12.1	2.2	18%	0.6	2
Q286R/H257A	Q143R/H117A	7.2	1.0	13%	1.1	2
Q286R/H257A †	Q143R/H117A †	5.5	0.1	2%	0.7	2
Q286R/S222A	Q143R/S82A	3.4	0.2	6%	2.3	2
Gla 交換 FIX/ T128N/P129A/ S222A/Q286R	Gla 交換 FIX/ T[128]N/P[129]A/ S82A/Q143R	21.3	5.6	26%	0.4	6
Gla 交換 FIX/ T128N/P129A/ S222A/Q286R †	Gla 交換 FIX/ T[128]N/P[129]A/ S82A/Q143R †	24.6	6.4	26%	0.2	6
Gla 交換 FIX/ S52A/S60A/S222A/Q286R	Gla 交換 FIX/ S[52]A/S[60]A/S82A/Q143R	56.9	8.5	15%	0.1	2
Q286R/S222A/H257A	Q143R/S82A/H117A	6.0	0.5	8%	1.3	2
Q286R/M298Q	Q143R/M156Q	4.1	0.5	11%	1.9	9
Q286R/M298Q	Q143R/M156Q †	3.6	1.1	29%	1.1	13
Q286R/M298Q	Q143R/M156Q §	3.2	0.2	7%	1.2	4
Gla 交換 FIX/ Q286R/M298Q	Gla 交換 FIX/ Q143R/M156Q	30.4	5.4	18%	0.3	3

Gla 交換 FIX/ Q286R/M298Q †	Gla 交換 FIX/ Q143R/M156Q †	22.1	1.5	7%	0.2	8
T128N/P129A/Q286R/ M298Q	T[128]N/P[129]A/Q143R/ M156Q	4.7	1.2	26%	1.6	5
T128N/P129A/Q286R/ M298Q †	T[128]N/P[129]A/Q143R/ M156Q †	3.9	0.4	11%	1.0	8
Gla 交換 FIX /T128N/P129A/Q286R/ M298Q	Gla 交換 FIX /T[128]N/P[129]A/Q143R/ M156Q	20.8	1.4	7%	0.4	5
Gla 交換 FIX /T128N/P129A/Q286R/ M298Q †	Gla 交換 FIX /T[128]N/P[129]A/Q143R/ M156Q †	37.5	12.3	33%	0.1	8
{Gla 交換 FIX/E40L}/ Q286R/M298Q	{Gla 交換 FIX/E[40]L}/ Q143R/M156Q	38.5	7.4	19%	0.2	2
{Gla 交換 FIX/K43I}/ Q286R/M298Q	{Gla 交換 FIX/K[43]I}/ Q143R/M156Q	35.3	3.4	10%	0.2	2
{Gla 交換 FIX/K43I}/ Q286R/M298Q †	{Gla 交換 FIX/K[43]I}/ Q143R/M156Q †	23.7	3.6	15%	0.2	2
{Gla 交換 FIX/Q44S}/ Q286R/M298Q	{Gla 交換 FIX/Q[44]S}/ Q143R/M156Q	40.8	6.4	16%	0.2	3
{Gla 交換 FIX/M19K}/ Q286R/M298Q	{Gla 交換 FIX/M[19]K}/ Q143R/M156Q	16.7	2.4	14%	0.5	2
S52A/S60A/ Q286R/M298Q	S[52]A/S[60]A/Q143R/M1 56Q	25.1	1.7	7%	0.3	3
Gla 交換 FIX /S52A/S60A/Q286R/M298 Q †	Gla 交換 FIX/ S[52]A/S[60]A/Q143R/M1 56Q †	6.0	0.1	1%	0.6	2
{Gla 交換 FIX/ M19K/E40L/K43I/Q44S} /Q286R/M298Q	{Gla 交換 FIX/ M[19]K/E[40]L/K[43]I/Q[44]S}/Q143R/M156Q	4.9	0.1	1%	1.6	2
{Gla 交換 FIX/K43I} /T128N/P129A/ Q286R/M298Q †	{Gla 交換 FIX/K[43]I} /T[128]N/P[129]A/Q143R/ M156Q †	10.5	1.3	13%	0.4	2
T239V	T99V	5.2			1.5	1
T239I	T99I	6.2			1.2	1
T128N/P129A/S222A/ H257A/Q286R/M298Q	T[128]N/P[129]A/S82A/H 117A/Q143R/M156Q	2.6	0.3	11%	3.0	2
T128N/P129A/S222A/ H257A/Q286R/M298Q †	T[128]N/P[129]A/S82A/H 117A/Q143R/M156Q †	4.0	0.2	4%	1.0	2
S52A/S60A/S222A/H257 A/Q286R/M298Q	S[52]A/S[60]A/S82A/H11 7A/Q143R/M156Q	11.1	2.7	24%	0.7	2
T128N/P129A/Q286R/M2 98Q/Q366N †	T[129]N/P[129]A/Q143R/ M156Q/Q217N †	3.2	0.6	18%	1.2	2
{Gla 交換 FIX/K43I}/Q286R /M298Q/Q366N †	{Gla 交換 FIX/K[43]I} /Q143R/M156Q/Q217N †	13.0	0.7	5%	0.3	2
{Gla 交換 FIX/K43I}/T[128]N/P[129]A/Q286R/M298Q/Q366N †	{Gla 交換 FIX/K[43]I} /T[128]N/P[129]A/Q143R/ M156Q/Q217N †	13.1	0.3	2%	0.3	2
T128N/P129A/Q286R/H3 73F	T[128]N/P[129]A/Q143R/ H224F	6.8	0.0	0%	1.1	2
T128N/P129A/Q286R/M2 98Q/H373F	T[128]N/P[129]A/Q143R/ M156Q/H224F	3.1	0.1	4%	2.4	2
S52A/S60A/Q286R/M298 Q/H373F	S[52]A/S[60]A/Q143R/M1 56Q/H224F	23.4	7.5	32%	0.3	3
T128N/P129A/M298Q/H3 73F †	T[128]N/P[129]A/M156Q/ H224F †	1.3	0.5	41%	3.1	2

V21D/Q143R/E154V/M156Q	V21D/Q143R/E154V/M156Q	2.2	0.2	8%	3.5	2
Gla 交換 FIX /S222A/T239V/Q286R	Gla 交換 FIX /S82A/T99V/Q143R	19.1	7.7	40%	0.4	7
Gla 交換 FIX /S222A/T239V/Q286R †	Gla 交換 FIX /S82A/T99V/Q143R †	14.9	0.4	3%	0.3	2
T239V/Q286R/M298Q	T99V/Q143R/M156Q	2.5	0.1	4%	3.1	2
Gla 交換 FIX/ T239V/Q286R/M298Q	Gla 交換 FIX/ T99V/Q143R/M156Q	22.7	6.8	30%	0.3	6
Gla 交換 FIX/ T239V/Q286R/M298Q †	Gla 交換 FIX/ T99V/Q143R/M156Q †	25.7	9.2	36%	0.2	6
T128N/P129A/T239V/Q286R/M298Q †	T[128]N/P[129]A/ T99V/Q143R/M156Q †	7.8	0.6	8%	0.5	2
S222A/T239V/H257A/ Q286R/M298Q	S82A/T99V/H117A/Q143R/M156Q	2.2	0.0	2%	3.4	2
T128N/P129A/S222A/T239V/H257A/Q286R/M298Q †	[T128]N/P[129A]/S82A/T99V/H117A/Q143R/M156Q †	3.6	0.7	18%	1.1	2
T128N/P129A/T239V/Q286R/M298Q/H373F †	T[128N]/P129]A/T99V/Q143R/M156Q/H224F †	3.9	0.1	3%	1.0	2
T239I/Q286R	T99I/Q143R	8.0	0.2	3%	1.0	2
Gla 交換 FIX/S222A/T239I/Q286R	Gla 交換 FIX /S82A/T99I/Q143R	39.6	1.2	3%	0.2	2
Gla 交換 FIX / T239I/Q286R/M298Q	Gla 交換 FIX /T99I/Q143R/M156Q	13.1	2.1	16%	0.6	2
T128N/P129A/T239I/Q286R/M298Q †	[T128]N/P[129A]/ T99I/Q143R/M156Q †	5.1	0.9	18%	0.8	2
T239I/Q286R/H373F	T99I/Q143R/H224F	7.8	0.1	1%	1.0	2
V158D/T239V/E296V/M298Q	V21D/T99V/E154V/M156Q	1.7	0.6	32%	4.4	4
V158D/T239V/E296V/M298Q †	V21D/T99V/E154V/M156Q †	1.9	0.7	36%	2.1	4
T239V/Q286R	T99V/Q143R	2.3	0.0	1%	1.7	2
T128N/P129A/T239I/ Q286R/M298Q/ H237F †	T[128]N/P[129]A/T99I/ Q143R/M156Q/H224F †	3.4	0.0	0%	1.2	2
Gla 交換 FIX/ Q286R/S222A/H257S	Gla 交換 FIX/ Q143R/S82A/H117S	34.3	9.1	27%	0.2	3
S222A/Q286R/M298Q/ H373F	S82A/Q143R/M156Q/H224F	2.1	0.1	6%	3.7	2
Gla 交換 FIX/S222A/ Q286R/M298Q/H373F	Gla 交換 FIX S82A/Q143R/M156Q/H224F	9.5	0.9	9%	0.8	2
T128N/P129A/A175S/ Q366V	T[128]N/P[129]A/A39S/Q217V	6.5	12.0	184%	1.2	2
A122N/G124S/A175S/ Q366V	A[122]N/G[124]S/A39S/Q217V	13.0	0.6	5%	0.6	2
T128N/P129A/A175S/ S222A	T[128]N/P[129]A/A39S/S82A	4.5	0.3	7%	1.7	2
A122N/G124S/A175S/ S222A	A[122]N/G[124]S/A39S/S82A	7.0	0.6	9%	1.1	2
T128N/P129A/A175S/ Q286R	T[128]N/P[129]A/A39S/Q143R	8.6	0.1	1%	0.9	2
A122N/G124S/A175S/ Q286R	A[122]N/G[124]S/A39S/Q143R	8.6	0.0	0%	0.9	2
Gla 交換 FIX/ S222A/Q286R/H373F	Gla 交換 FIX/ S82A/Q143R/H224F	40.9	7.5	18%	0.2	3
Gla 交換 FIX/ A122N/G124S/A175S/ S222A/Q286R	Gla 交換 FIX/ A[122]N/G[124]S/A39S/S82A/Q143R	43.7	14.0	32%	0.2	2

T128N/P129A/A175S/Q286R/M298Q	T[128]N/P[129]A/A39S/Q143R/M156Q	5.5	0.0	0%	1.4	2
A122N/G124S/A175S/Q286R/M298Q	A[122]N/G[124]S/A39S/Q143R/M156Q	5.3	0.1	2%	1.4	2
T128N/P129A/A175S/S222A/H257A/Q286R/M298Q	T[128]N/P[129]A/A39S/S82A/H117A/Q143R/M156Q	6.7	0.8	11%	1.1	2
A122N/G124S/A175S/S222A/H257A/Q286R/M298Q	A[122]N/G[124]S/A39S/S82A/H117A/Q143R/M156Q	7.7	0.6	8%	1.0	2
T128N/P129A/A175S/Q286R/M298Q/H373F	T[128]N/P[129]A/A39S/Q143R/M156Q/H224F	7.4	3.2	43%	1.0	2
A122N/G124S/A175S/Q286R/M298Q/H373F	A[122]N/G[124]S/A39S/Q143R/M156Q/H224F	5.0	0.1	3%	1.5	2
V158D/Q286R/E296V/M298Q/H373F	V21D/Q143R/E154V/M156Q/H224F	1.7	0.5	27%	4.5	3
M298Q/Q366N/H373F †	M156Q/Q217N/H224F †	1.6	0.9	60%	2.5	4
T239V/M298Q/H373F †	T99V/M156Q/H224F †	3.5	0.4	11%	1.1	2
T239I/M298Q/H373F †	T99I/M156Q/H224F	2.3	0.6	24%	1.7	4
T128N/P129A/Q286R/M298Q/Q366N/H373F †	T[128]N/P[129]A/Q143R/M156Q/Q217N/H224F †	2.6	0.6	23%	1.5	2
T239V/Q286R/M298Q/Q366N †	T99V/Q143R/M156Q/Q217N †	4.1	0.3	8%	0.9	2
T239I/Q286R/M298Q/Q366N †	T99I/Q143R/M156Q/Q217N †	2.4	0.6	27%	1.6	2

† 在 CHOX 細胞中產生

§ 在 CHOX 穩定細胞系純系 52-5F7 中產生

實施例 11

Zn^{2+}對 FVIIa 變異體之抑制

在可溶性組織因子存在或不存在情況下檢定由 HEK 293 或 BHK 細胞表現之 FVIIa 變異體的對 Zn^{2+}抑制之抗性。簡言之，在 dH_2O 中將 $ZnCl_2$(Aldrich)稀釋至 20 mM，接著在 1x檢定緩衝液（50 mM Na Hepes pH 7.5，100 mM NaCl，1.5 mM $CaCl_2$，0.01%吐溫-20 及 0.01% PEG-8000）中稀釋至 4 mM。進行連續 2 倍稀釋以在 96 孔板中產生直至 3.9 μM 的 11 個鋅濃度。列中之最後一個孔含有無鋅之緩衝液以量測未受抑制之 FVIIa 蛋白水解活性。將 FVIIa 變異體及野生型蛋白酶稀釋至 500 nM，接著再次 10 倍稀釋至

50 nM。將此 50 nM 儲備溶液用於在無可溶性組織因子（sTF，R & D Systems）情況下進行之檢定。對於具有可溶性組織因子之檢定，將蛋白酶在具有 sTF 之 1×檢定緩衝液中分別再次稀釋至 12.5 nM 及 125 nM 之最終濃度。在室溫下預培育溶液至少 5 分鐘。

為起始抑制反應，將 20 μL FVIIa/sTF 或 FVIIa 溶液與 60 μL 各列 10 個濃度之鋅系列混合。對於僅具有 FVIIa 之抑制反應，使用 2 mM $ZnCl_2$ 起始混合物且對於 FVIIa/sTF，使用 4 mM $ZnCl_2$ 起始。在室溫下將板培育 30 分鐘。為檢定 Zn^{2+} 抑制，將 20 μL FVIIa 受質（甲磺醯基-dFPR-ACC，在 DMSO 中溶解至 20 mM 且在檢定緩衝液中稀釋）添加至孔中至 90 μM 之最終濃度。藉由視情況添加至受質溶液中保持檢定中之 sTF 及鋅濃度。在 30℃ 下在 Spectramax Gemini M5（Molecular Devices）板讀取器上經 60 分鐘量測螢光增強（Ex：380 nm；Em：460 nm）。藉由受抑制之速率除以未受抑制之蛋白酶速率計算每一鋅濃度下之殘餘蛋白水解活性。藉由將鋅濃度對殘餘活性作圖且使用 XLFit4 軟體（IDBS）以雙曲線方程式擬合計算抑制半數蛋白水解活性必需之 Zn^{2+} 濃度（$K_{0.5}$）。在兩個獨立時刻將各蛋白酶檢定兩次以獲得 $K_{0.5}$ 之平均值。

結果提供於表 27 中。H257 及 H216 突變使抗性增強約 3 倍。M268Q 突變亦使對鋅之抗性增強 3 倍。在所有情況下，當與其他突變組合時，保留不同程度之作用。抗性最大變異體為上述突變之組合：H216A/H257A-FVIIa 及

H257A/M298Q-FVIIa。

表 27. FVIIa 變異體受 Zn^{2+}之抑制

突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	$K_{0.5}$(mM)	
		HEK 293	BHK
WT	WT	87.0	42.0
M298Q	M156Q	187.3	
Q286R	Q143R	30.1	22.5
H216S	H76S	231.0	
H216A	H76A	244.5	
H216K	H76K	248.8	
H216R	H76R	316.5	
S222A	S82A	87.5	63.8
S222K	S82K	73.0	
H257A	H117A	217.5	113.0
H257S	H117S	149.7	128.0
K161S	K24S	51.5	
K161A	K24A	73.5	
K161V	K24V	79.5	
Q286R/S222A	S82A/Q143R		24.5
Q286R/S222A/ Gla 交換 FIX	S82A/Q143R/gla 交換 FIX	34.0	
S222A/M298Q	S82A/M156Q	138.0	
H257A/M298Q	H117A/M156Q	481.0	
S222A/H257A/Q286R/M298Q	S82A/H117A/Q143R/M156Q	180.6	
S222A/Q286R/Q366V	S82A/Q143R/Q217V	40.5	
S222V	S82V	86.8	
S222D	S82D	89.5	
S222N	S82N	94.6	
S222E	S82E	110.5	
H216A/H257A	H76A/H117A	407.5	
H216A/S222A	H76A/S82A	226.0	
H257S/Q286R	H117S/Q143R	316.5	
S222A/H373A	S82A/H224A	94.0	

實施例 12

使用活性位點滴定劑香豆素(4)p' 胍基苯甲酸酯（MUGB）測定催化活性蛋白酶之濃度

在一些情況下，藉由以香豆素(4)p'-胍基苯甲酸酯（MUGB），一種發展為胰蛋白酶樣絲胺酸蛋白酶之活性位點的螢光酯受質滴定複合物 FVIIa 及可溶性組織因子（sTF）來測定儲備溶液中催化活性 FVIIa 之濃度。在數個微小修改情況下，基本上如 Payne 等人描述（Biochemistry (1996) 35:7100-7106）進行檢定。MUGB 易於與 FVIIa，而非 FVII 或無活性蛋白酶反應，以在 MUGB 濃度飽和且去醯作用尤其緩慢且為催化之速率限制步驟的條件下形成有效穩定醯基酶中間物。在此等條件下，FVIIa 蛋白酶經歷單次催化轉化以釋放 4-甲基繖形酮（4-methylumbelliferone）螢光團（4-MU）。當將螢光之初始突現校正為 4-MU 螢光之外部濃度標準曲線時，可計算活性位點之濃度。

以分別在 0.4 cm×1 cm 或 1 cm×1 cm 石英比色管中之 1 mL 或 2 mL 反應體積在連續攪拌下進行檢定。各反應在含有 50 mM Hepes、100 mM NaCl、5 mM $CaCl_2$ 及 0.1% PEG 8000 pH 7.6 之檢定緩衝液中含有 0.5 μM sTF（R & D Systems Human）。在 DMSO 中新鮮製備儲備液濃度為 0.5 M 之 4-MU 標準溶液，且使用 19,000 M^{-1} cm^{-1} 之消光係數在 50 mM Tris 緩衝液 pH 9.0 中由 360 nm 下之吸光光譜證實濃度。在 DMSO 中基於乾重製備儲備液濃度為 0.04 M 的 MUGB。藉由添加 4 μL 4 mM MUGB（對於 2.0 mL 反應）或 2 mM MUGB（對於 1.0 mL 反應）（在各情況下 8 μM 最終濃度）至 1×檢定緩衝液中 0.5 μM sTF（20.2 μL 或 10.1 μL 49.4 μM sTF）之溶液，且首先量測 MUGB 之背

景水解歷時約 150-200 秒，隨後添加 FVIIa 或 FVIIa 變異體至約 100-200 nM 之最終濃度，基於初始 ELISA（實施例 1C.1）或 FFR-CMK 活性位點滴定（實施例 3），起始檢定。再追蹤反應突然增強階段中 4 MU 螢光的釋放歷時 1000-1200 秒。藉由以 20 nM 步長將吸光率校正之 4-MU 滴定於含有 0.5 μM sTF 之 1x檢定緩衝液中至 260-300 nM 之最終濃度，作游離 4-MU 之標準曲線。

對於資料分析，將反應迹線（reaction trace）輸入 Graphpad Prism 軟體套件且藉由外推典型地小於總螢光突然增強之 5%的自發 MUGB 水解之初始量測速率，自曲線減去背景水解之貢獻值。將校正曲線擬合為具有形式Δ螢光 = $Amp(1-e^{-kt})+Bt$ 的線性組份(考慮到去醯作用之緩慢速率)的單指數方程式，其中 Amp =以上概括之飽和檢定條件下突然增強階段之幅度，k 為對於醯基酶形成所觀察到之一級速率常數且 B 為與 MUGB 之完全轉化相關的容積速率常數。藉由比較幅度之擬合參數與 4-MU 標準曲線計算活性 FVIIa 蛋白酶之濃度。量測多重檢定之值、求平均值且測定標準偏差。

實施例 13

FVIIa 變異體多肽對甲磺醯基-dFPR-ACC 之比活性

為評估 FVIIa 變異體之活性，測定 FVIIa 多肽在一組標準檢定條件下裂解三肽 ACC 受質（甲磺醯基-dFPR-ACC）之活性（活性/莫耳）。檢定涉及預培育 FVIIa 多肽與飽和量之 sTF，隨後稀釋於甲磺醯基-dFPR-ACC 受質中。隨後藉

由評估 ACC 螢光增強追蹤受質裂解之初始速率。將螢光釋放之初始速率正規化為內部 ACC 標準曲線且將資料報導為 μ mol/sec/μmol FVIIa。

為準備反應，在聚丙烯儲存板中在 1x檢定緩衝液（20 mM Hepes、150 mM NaCl、5 mM $CaCl_2$、0.1% BSA、0.1% PEG-8000，pH 7.5）中將待測試之各 FVIIa 樣品稀釋至 200 nM。必要時，製備儲備液 FVIIa 之 1:10 稀釋液以便最低吸移體積為 5 μL。以考慮到篩選 8 至 32 個蛋白酶/板所必需的適當體積之 1x檢定緩衝液製備最終濃度為 1.0 μM 之儲備液可溶性組織因子（sTF）（R & D Systems）的稀釋液。舉例而言，當檢定 8 個蛋白酶時，要求每個板 1.0 mL 1.0 μM sTF，而對於檢定 32 個蛋白酶而言，要求每個板 2.5 mL sTF。藉由在聚丙烯儲存板中混合 25 μL 200 nM FVIIa 變異體與 25 μL 1.0 μM sTF 使 FVIIa 樣品與 sTF 在 50 μL 檢定體積中以 100 nM FVIIa/500 nM sTF 之最終濃度複合。接著在室溫下將 FVIIa/sTF 複合反應培育 15 分鐘以達到平衡。平衡期後，將 10 μL 各 FVIIa/sTF 複合反應分配於 96 孔半區域黑色檢定板（Costar）之對應列中。一式三份檢定 FVIIa 變異體及對照。考慮到將 FVIIa 多肽以 1:10 稀釋於受質中，製備 1.1x 0.09 mM 之最終濃度的甲磺醯基-dFPR-ACC 受質。對於整個 96 孔半區域板，藉由稀釋儲存於無水 DMSO 中之儲備液受質在 1x檢定緩衝液中製備 20 mL 0.1 mM 甲磺醯基-dFPR-ACC 受質。

在裝備有 96 尖頭（MBP BioRobotix ART® 130 μL 尖

端）之 BioMek® FX 自動工作站（Beckman Coulter）上進行檢定。將檢定板（預分配有 10 μL FVIIa/sTF 反應）置於具有填充有 1.1x甲磺醯基-dFPR-ACC 溶液的單通道儲集器之工作站之平台上。板讀取器之溫度經設置為 37℃。BioMek® FX工作站藉由自填充有 1.1x甲磺醯基-dFPR-ACC 受質的單通道儲集器轉移 90 μL 至含有 10 μL FVIIa/sTF 的黑色檢定板之各孔中起始檢定。檢定中 FVIIa 變異體之最終濃度、sTF 及甲磺醯基-dFPR-ACC 濃度分別為 10 nM、50 nM 及 0.09 mM。接著，工作站將 100 μL 中之 70 μL 樣品混合兩次。將黑色檢定板轉移至 SpectraMax Gemini 板讀取器（Molecular Devices）中且在 37℃下追蹤初始反應速率歷時 10 min。

檢定完成後，在相同 SpectraMax Gemini 板讀取器上讀取含有游離 ACC（100 μL/孔）之標準曲線的板且使用其提供 RFU/sec 至μM/sec 之精確轉化。標準板如下製備。在 96 孔黑色半區域檢定板之頂列的所有「偶數」孔（亦即每隔一個孔）中，在 1x檢定緩衝液中將 1 mM ACC 樣品稀釋至 25 nM，最終體積為 200 μL（195 μL 1x檢定緩衝液中 5 μL 1 mM ACC）。將 100 μL 1x檢定緩衝液吸移入「偶數」行之所有剩餘孔中。沿偶數行連續 1:1 稀釋 ACC 受質，以產生 6 個以上 ACC 濃度。最後一列僅放置 100 μL 1x檢定緩衝液（亦即無 ACC）。使用終點讀取形式之檢定條件量測螢光且作螢光相對於 ACC 濃度之圖。經由此等點之線的斜率提供 RFU 轉化為μM 之轉化係數。

使用 SoftMax Pro 軟體（Molecular Devices）分析板讀取以及標準曲線之資料。保存含有資料之文件且輸出為 ASCII 文本文件，其經輸入 Microsoft Excel 程式中，使用 Microsoft Excel 中產生的模板進行處理及分析。將資料輸入 Microsoft Excel 模板後，由 ACC 標準曲線之斜率計算平均 RFU/μM 轉化值且使用其提供將板資料自 RFU/sec 轉變為以μM/sec 計之活性量測值的轉化係數。評估所有三個重複值的異常值，必要時將其排除。以單位μmol/sec/μmol 表示各 FVIIa 變異體及野生型對照之比活性且藉由以下表達式計算：

平均資料(RFU/sec) * 轉化係數(RFU/μM) = 活性 (以μM/sec 計)

比活性(以 μ mol/sec/ μ mol 計) = [(μM/sec)* (100 μL)*(1/1000000)]/[(10 nM)*(100 μL)*(1/1000000)*(1/1000)]

表 28 闡明所檢定 FVIIa 變異體之比活性，包括相對於野生型 FVIIa 的活性。亦包括標準偏差（SD）及變異係數（以百分數形式；%CV）。與野生型 FVIIa 多肽相比，數種 FVIIa 變異體展現增強之裂解甲磺醯基-dFPR-ACC 的比活性。舉例而言，Q366V-FVIIa 展現比野生型 FVIIa 變異體所觀察到之比活性高 4 倍的裂解甲磺醯基-dFPR-ACC 之比活性。與野生型 FVIIa 多肽相比，含有 H373F 突變之 FVIIa 變異體亦趨向於展現增強之裂解甲磺醯基-dFPR-ACC 之比活性。

表 28. FVIIa 多肽對甲磺醯基-dFPR-ACC 之比活性

突變（成熟 FVII 編號）	突變（胰凝乳蛋白酶編號）	活性 (μmol/sec/μmol)	SD	% CV	活性 (WT%)	n
WT (NovoSeven®)	WT (NovoSeven®)	2.31	0.34	0.15	100%	3
WT	WT	2.40	0.15	0.06	104%	4
T128N/P129A	T[128]N/P[129]A	2.50			108%	1
Gla 交換 FIX	Gla 交換 FIX	1.63			71%	1
A122N/G124S	A[122]N/G[124]S	2.24			97%	1
S52A/S60A	S[52]A/S[60]A	1.95			85%	1
V158D/E296V/M298Q	V21D/E154V/M156Q	3.28			142%	1
T128N/P129A/V158D/ E296V/M298Q	T[128]N/P[129]A/V21D/ E154V/M156Q	3.26			142%	1
S52A/S60A/V158D/ E296V/M1298Q	S[52]A/S[60]A/V21D/ E154V/M156Q	2.56			111%	1
Q286R	Q143R	1.24			54%	1
T128N/P129A/Q286R	T[128]N/P[129]A/Q143R	1.21			52%	1
S52A/S60A/Q286R	S[52]A/S[60]A/Q143R	0.44	0.11	0.25	19%	2
S222A	S82A	2.35			102%	1
T128N/P129A/S222A	T[128]N/P[129]A/S82A	2.70			117%	1
S52A/S60A/S222A	S[52]A/S[60]A/S82A	1.22			53%	1
H257S	H117S	2.64			115%	1
H373F	H224F	1.17			51%	1
Q366V	Q217V	9.29			403%	1
Gla 交換 FIX/Q366V	Gla 交換 FIX/Q217V	2.82			122%	1
K109N/A175S	K[109]N/A39S	3.38			147%	1
Q286R/H257A	Q143R/H117A	1.96			85%	1
Gla 交換 FIX/ T128N/P129A/ S222A/Q286R	Gla 交換 FIX/ T[128]N/P[129]A/ S82A/Q143R	0.53			23%	1
Gla 交換 FIX/ S52A/S60A/S222A/ Q286R	Gla 交換 FIX/ S[52]A/S[60]A/S82A/ Q143R	0.44	0.42	0.96	19%	2
Q286R/M298Q	Q143R/M156Q	1.91	0.11	0.06	83%	5
Gla 交換 FIX/ Q286R/M298Q	Gla 交換 FIX/ Q143R/M156Q	1.53			66%	1
T128N/P129A/Q286R/ M298Q	T[128]N/P[129]A/Q143R / M156Q	1.80			78%	1
Gla 交換 FIX /T128N/P129A/Q286R/ M298Q	Gla 交換 FIX /T[128]N/P[129]A/Q143R/ M156Q	0.78			34%	1
{Gla 交換 FIX/E40L}/ Q286R/M298Q	{Gla 交換 FIX/E[40]L}/ Q143R/M156Q	1.16			50%	1
{Gla 交換 FIX/K43I}/ Q286R/M298Q	{Gla 交換 FIX/K[43]I}/ Q143R/M156Q	1.20			52%	1
{Gla 交換 FIX/Q44S}/ Q286R/M298Q	{Gla 交換 FIX/Q[44]S}/ Q143R/M156Q	1.11			48%	1
{Gla 交換 FIX/M19K}/ Q286R/M298Q	{Gla 交換 FIX/M[19]K}/ Q143R/M156Q	1.26			55%	1
S52A/S60A/	S[52]A/S[60]A/Q143R/	1.08	0.17	0.15	47%	2

Q286R/M298Q	M156Q					
T128N/P129A/S222A/ H257A/Q286R/M298Q	T[128]N/P[129]A/S82A/ H117A/Q143R/M156Q	1.66			72%	1
S52A/S60A/S222A/ H257A/Q286R/M298Q	S[52]A/S[60]A/S82A/H117A/Q143R/M156Q	0.98			42%	1
H257S/Q286R/Q366V	H117S/Q143R/Q217V	2.00	0.17	0.08	87%	2
S222A/H257A/Q286R/ Q366V	S82A/H117A/Q143R/ Q217V	2.43			105%	1
Q286R/M298Q/Q366N	Q143R/M156Q/Q217N	2.35			102%	1
Q286R/H373F	Q143R/H224F	0.78			34%	1
T128N/P129A/ Q286R/H373F	T[128]N/P[129]A/Q143R / H224F	2.31			100%	1
S52A/S60A/ Q286R/H373F	S[52]A/S[60]A/Q143R/ H224F	3.14			136%	1
Q286R/M298Q/H373F	Q143R/M156Q/H224F	4.59			199%	1
T128N/P129A/Q286R/M298Q/H373F	T[128]N/P[129]A/Q143R /M156Q/H224F	2.83			123%	1
S52A/S60A/Q286R/ M298Q/H373F	S[52]A/S[60]A/Q143R/ M156Q/H224F	5.02			218%	1
M298Q/H373F	M156Q/H224F	4.00			174%	1
V21D/Q143R/E154V/M156Q	V21D/Q143R/E154V/ M156Q	1.83			79%	1
S222A/T239V	S82A/T99V	1.91			83%	1
Gla 交換 FIX /S222A/T239V/Q286R	Gla 交換 FIX /S82A/T99V/Q143R	0.66			28%	1
T239V/Q286R/M298Q	T99V/Q143R/M156Q	1.74			75%	1
Gla 交換 FIX/ T239V/Q286R/M298Q	Gla 交換 FIX/ T99V/Q143R/M156Q	1.13			49%	1
S222A/T239V/H257A/ Q286R/M298Q	S82A/T99V/H117A/Q143R/M156Q	1.66			72%	1
T239V/Q286R/H373F	T99V/Q143R/H224F	1.53			66%	1
T239V/Q286R/M298Q/H373F	T99V/Q143R/M156Q/ H224F	3.07			133%	1
V158D/T239I/E296V/M298Q	V21D/T99I/E154V/M156Q	2.24			97%	1
T239I/Q286R	T99I/Q143R	0.88			38%	1
S222A/T239I	S82A/T99I	1.36			59%	1
Gla 交換 FIX/S222A/T239I/Q286R	Gla 交換 FIX /S82A/T99I/Q143R	0.25			11%	1
T239I/Q286R/M298Q	T99I/Q143R/M156Q	1.37			60%	1
Gla 交換 FIX / T239I/Q286R/M298Q	Gla 交換 FIX /T99I/Q143R/M156Q	0.67			29%	1
S222A/T239I/H257A/Q286R/M298Q	S82A/T99I/H117A/Q143R/M156Q	1.41			61%	1
T239I/Q286R/H373F	T99I/Q143R/H224F	1.24			54%	1
V158D/T239V/E296	V21D/T99V/E154V/	2.19	0.15	0.07	95%	3

V/M298Q	M156Q					
T239V/Q286R	T99V/Q143R	1.26	0.14	0.11	55%	2
T239I/Q286R/M298Q/ H237F	T99I/Q143R/M156Q/ H224F	1.59	0.21	0.13	69%	3
H257S/Q286R/M298Q	H117S/Q143R/M156Q	1.85	0.23	0.13	80%	2
Gla 交換 FIX /Q286R/S222A/H257S	Gla 交換 FIX /Q143R/S82A/H117S	0.49	0.04	0.09	21%	2
S222A/H257S/Q286R/ M298Q	S82A/H117S/Q143R/ M156Q	1.77	0.23	0.13	77%	2
H257S/Q286R/M298Q/ H373F	H117S/Q143R/M156Q/ H224F	2.32	0.41	0.18	101%	3
S222A/Q286R/M298Q/ H373F	S82A/Q143R/M156Q/ H224F	2.79	0.39	0.14	121%	2
Gla 交換 FIX/S222A/ Q286R/M298Q/H373F	Gla 交換 FIX/S82A/ Q143R/ M156Q/H224F	1.92			83%	1
S222A/Q286R/M298Q	S82A/Q143R/M156Q	1.90			82%	1
Gla 交換 FIX S222A/Q286R/M298Q	Gla 交換 FIX S82A/Q143R/M156Q	1.12			49%	1
T128N/P129A/A175S/ Q366V	T[128]N/P[129]A/A39S/ Q217V	3.40			148%	1
A122N/G124S/A175S/ Q366V	A[122]N/G[124]S/A39S/ Q217V	2.34	0.22	0.09	101%	2
T128N/P129A/A175S/ S222A	T[128]N/P[129]A/A39S/ S82A	3.19			138%	1
A122N/G124S/A175S/ S222A	A[122]N/G[124]S/A39S/ S82A	2.68	0.30	0.11	116%	2
T128N/P129A/A175S/ Q286R	T[128]N/P[129]A/A39S/ Q143R	1.88			81%	1
A122N/G124S/A175S/ Q286R	A[122]N/G[124]S/A39S/ Q143R	2.16	0.42	0.20	94%	2
Gla 交換 FIX/ S222A/Q286R/H373F	Gla 交換 FIX/ S82A/Q143R/H224F	1.37	0.26	0.19	60%	2
V158D/E296V/M298Q/ H373F	V21D/E154V/M156Q/ H224F	5.60			243%	1
H257A/Q286R/M298Q	H117A/Q143R/M156Q	2.18			95%	1
Gla 交換 FIX/ T128N/P129A/A175S/ S222A/Q286R	Gla 交換 FIX/T[128]N/P[129]A/ A39S/S82A/Q143R	0.75			32%	1
Gla 交換 FIX/ A122N/G124S/A175S/ S222A/Q286R	Gla 交換 FIX/ A[122]N/G[124]S/A39S/ S82A/Q143R	0.89			38%	1
T128N/P129A/A175S/ Q286R/M298Q	T[128]N/P[129]A/A39S/ Q143R/M156Q	2.02			88%	1
A122N/G124S/A175	A[122]N/G[124]S/A39S/	3.03			131%	1

S/ Q286R/M298Q	Q143R/M156Q					
T128N/P129A/A175S/ S222A/H257A/Q286R/ M298Q	T[128]N/P[129]A/A39S/ S82A/H117A/Q143R/M156Q	2.18			95%	1
A122N/G124S/A175S/ S222A/H257A/Q286R/ M298Q	A[122]N/G[124]S/A39S/ S82A/H117A/Q143R/M156Q	1.99			86%	1
T128N/P129A/A175S/ Q286R/M298Q/H373F	T[128]N/P[129]A/A39S/ Q143R/M156Q/H224F	2.78			121%	1
A122N/G124S/A175S/ Q286R/M298Q/H373F	A[122]N/G[124]S/A39S/ Q143R/M156Q/H224F	2.71			118%	1
V158D/Q286R/E296V/M298Q/H373F	V21D/Q143R/E154V/M156Q/H224F	1.89			82%	1

實施例 15

FX 之活化及使用活性位點滴定劑螢光素-單-p'-胍基苯甲酸酯（FMGB）測定催化活性蛋白酶之濃度

藉由以魯塞爾蝰蛇毒（Russell's Viper Venom）（RVV 酶）活化 FX 樣品，接著以螢光素單-p'-胍基苯甲酸酯（FMGB），一種發展為胰蛋白酶樣絲胺酸蛋白酶的活性位點滴定劑之螢光酯受質，滴定活性因子 X（FXa），測定能夠變得具有催化活性之因子 X（FX）在酶原儲備溶液中之濃度。活化後，在數種微小修改情況下，基本上如 Bock 等人（Archives of Biochemistry and Biophysics (1989) 273:375-388）所述進行活性位點滴定檢定。FMGB 易於與 FXa，而非 FX 或無活性蛋白酶反應以在 FMGB 濃度飽和且去醯作用尤其緩慢且為催化之速率限制步驟的條件下形成有效穩定醯基酶中間物。在此等條件下，FXa 蛋白酶經歷單

一催化轉化以釋放螢光素螢光團。當將螢光之初始突然增強校正為螢光素螢光之外部濃度標準曲線時，可計算活性位點之濃度。

以 10 μM FX 之最終濃度（基於 A_{280} 吸光率及 1.16 之消光係數），在含有 100 mM Tris、50 mM NaCl、5mM $CaCl_2$、0.1% PEG 8000 pH 8.1 之反應緩衝液中以 50-100 μL 之最終體積製備 FXa 活化反應。藉由在 37℃下經 45-60 min 之活化時間（藉由每 15 min 收集樣品且測試 Spectrafluor FXa 螢光受質之裂解的增加，預先測定以表示完全活化）添加 RVV 酶至 5 μg/ml（每 100 μL 反應 5 μL 98 μg/ml 稀釋液或每 50 μL 反應 2.5 μL）之最終濃度起始活化。以 1/10 體積之含有 100 mM Tris、50 mM NaCl、5 mM、100 mM EDTA、0.1% PEG 8000 pH 8.1 的中止緩衝液中止反應。

以 0.4 cm×1 cm 石英比色管內之 1 mL 反應體積在連續攪拌下進行檢定。反應在含有 30 mM Hepes、135 mM NaCl、1 mM EDTA 及 0.1% PEG 8000 pH 7.4 之檢定緩衝液中含有 100-400 nM 新活化之 FXa 及 5 μM FMGB。新鮮製備 DMF 中 70 mM 之儲備液濃度的螢光素標準溶液，且在 496 nm 下在標準條件下使用 89,125 M^{-1} cm^{-1} 之消光係數在 0.1 N NaOH 中由吸光光譜證實濃度。在 DMF 中以乾重計製備 0.01 M 儲備液濃度之 FMGB，且使用 19,498 之消光係數在磷酸鹽緩衝生理食鹽水（PBS）pH 7.2 中由 452 nm 下之吸光光譜證實濃度。藉由添加 5 μL 1 mM FMGB（5 μM 最終濃

度）至 1x檢定緩衝液中且首先量測 FMGB 之背景水解歷時約 150-200 秒，隨後添加 FXa 至約 100-400 nM 之最終濃度（基於在藉由 RVV 酶（參見上文）活化前藉由吸光率確定之初始濃度）起始檢定。再追蹤反應突然增強階段螢光素螢光之釋放歷時約 3600 秒。藉由以 20 nM 步長滴定吸光率校正之螢光素標準於 1x檢定緩衝液中至 260-300 nM 之最終濃度作游離螢光素之標準曲線。

對於資料分析，將反應迹線（reaction trace）輸入 Graphpad Prism 軟體套件且藉由外推典型地小於總螢光突然增強之 5%的自發 FMGB 水解之初始量測速率，自曲線減去背景水解之貢獻值。將校正曲線擬合為具有形式Δ螢光 $= Amp(1-e^{-kt})+Bt$ 的線性組份(考慮到去醯作用之緩慢速率）的單指數方程式，其中 Amp =以上概括之飽和檢定條件下突然增強階段之幅度，k 為對於醯基酶形成所觀察到之一級速率常數且 B 為與 FMGB 之完全轉化相關的容積速率常數。藉由比較幅度之擬合參數與螢光素標準曲線計算活性 FXa 蛋白酶之濃度。量測多重檢定之值、求平均值且測定標準偏差。因此，製劑中活性 FXa 之量直接表示可藉由 FVIIa 活化的儲備液製劑中 FX 之濃度。當計算諸如實施例 4 所述的 TF 依賴性及 TF 獨立性檢定之間接檢定中欲使用的 FX 之濃度時，採用此活性位點滴定值。

由於修改對於熟悉此項技術者將顯而易見，因此希望本發明僅由隨附申請專利範圍之範疇限制。

【圖式簡單說明】

圖 1 描繪凝血級聯。該圖展示獨立產生 FXa 之凝血之固有途徑及外在途徑，及該等途徑匯合於共同途徑產生凝血酶及血纖蛋白以供形成凝塊。此等途徑互聯。該圖描繪參與活化級聯的分子之順序，其中酶原經藉由一或多個肽鍵之裂解轉化成經活化蛋白酶。接著，經活化蛋白酶充當級聯中下一酶原分子之活化蛋白酶，最終引起凝塊形成。

圖 2 描繪凝血之基於細胞的模式（參見例如 Hoffman 等人 (2001) Thromb Haemost 85:958-965）。該圖描繪凝血事件被分為三個階段，其中起始凝血藉由在承載 TF 的細胞上 TF/FVIIa 複合物使 FX 活化為 FXa 來實現，使得在藉由 FXa/FVa 活化後產生少量凝血酶。當凝血酶結合且活化血小板時發生擴增，且起始足夠數量之適當凝血因子活化以形成 FVIIIa/FIXa 及 FVa/FXa 複合物。凝血之增長發生在損傷部位大量經活化血小板之表面上，引起凝血酶突然大量產生，其量足夠大以自血纖維蛋白原產生足以在損傷部位形成凝塊的血纖蛋白。

圖 3 描繪 FVIIa 可起始凝血酶形成之機制。該圖說明 FVIIa 凝血酶產生之 TF 依賴性途徑，其在承載 TF 的細胞之表面上起作用且包括在將 FX 活化為 FXa 之前使 FVIIa 與 TF 複合。該圖亦描繪 FVIIa 凝血酶產生之 TF 獨立性途徑，在此期間 FVIIa 結合經活化血小板上之磷脂且將 FX 活化為 FXa，該 FXa 轉而又與 FVa 複合以將凝血酶原裂解為凝血酶。

【主要元件符號說明】

無

序列表

<110> 愛德恩 梅德森
克利斯多福 丹諾斯

<120> 經修飾的因子VII多肽和其用途

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Gln Ser Arg Gln Arg Pro Gly Gly Pro Val Val Thr Asp Asn Met Phe
355 360 365
Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ala Cys Lys Gly Asp Ser
370 375 380
Gly Gly Pro His Ala Thr Arg Phe Arg Gly Thr Trp Phe Leu Thr Gly
385 390 395 400
Val Val Ser Trp Gly Glu Gly Cys Ala Ala Ala Gly His Phe Gly Ile
405 410 415

Tyr Thr Arg Val Ser Arg Tyr Thr Ala Trp Leu Arg Gln Leu Met Gly
420 425 430
His Pro Pro Ser Arg Gln Gly Phe Phe Gln Val Pro Leu Leu Pro
435 440 445

<210> 5
<211> 446
<212> PRT
<213> 家鼷鼠

<220>
<223> 因子VII前趨物

<400> 5
Met Val Pro Gln Ala His Gly Leu Leu Leu Leu Cys Phe Leu Leu Gln
1 5 10 15
Leu Gln Gly Pro Leu Gly Thr Ala Val Phe Ile Thr Gln Glu Glu Ala
20 25 30
His Gly Val Leu His Arg Gln Arg Arg Ala Asn Ser Leu Leu Glu Glu
35 40 45
Leu Trp Pro Gly Ser Leu Glu Arg Glu Cys Asn Glu Glu Gln Cys Ser
50 55 60
Phe Glu Glu Ala Arg Glu Ile Phe Lys Ser Pro Glu Arg Thr Lys Gln
65 70 75 80
Phe Trp Ile Val Tyr Ser Asp Gly Asp Gln Cys Ala Ser Asn Pro Cys
85 90 95
Gln Asn Gly Gly Thr Cys Gln Asp His Leu Lys Ser Tyr Val Cys Phe
100 105 110
Cys Leu Leu Asp Phe Glu Gly Arg Asn Cys Glu Lys Ser Lys Asn Glu
115 120 125
Gln Leu Ile Cys Ala Asn Glu Asn Gly Asp Cys Asp Gln Tyr Cys Arg
130 135 140
Asp His Val Gly Thr Lys Arg Thr Cys Ser Cys His Glu Asp Tyr Thr
145 150 155 160
Leu Gln Pro Asp Glu Val Ser Cys Lys Pro Lys Val Glu Tyr Pro Cys
165 170 175
Gly Arg Ile Pro Val Val Glu Lys Arg Asn Ser Ser Ser Arg Gln Gly
180 185 190
Arg Ile Val Gly Gly Asn Val Cys Pro Lys Gly Glu Cys Pro Trp Gln
195 200 205
Ala Val Leu Lys Ile Asn Gly Leu Leu Leu Cys Gly Ala Val Leu Leu
210 215 220
Asp Ala Arg Trp Ile Val Thr Ala Ala His Cys Phe Asp Asn Ile Arg
225 230 235 240
Tyr Trp Gly Asn Ile Thr Val Val Met Gly Glu His Asp Phe Ser Glu
245 250 255
Lys Asp Gly Asp Glu Gln Val Arg Arg Val Thr Gln Val Ile Met Pro
260 265 270
Asp Lys Tyr Ile Arg Gly Lys Ile Asn His Asp Ile Ala Leu Leu Arg
275 280 285
Leu His Arg Pro Val Thr Phe Thr Asp Tyr Val Val Pro Leu Cys Leu
290 295 300
Pro Glu Lys Ser Phe Ser Glu Asn Thr Leu Ala Arg Ile Arg Phe Ser
305 310 315 320
Arg Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu
325 330 335
Glu Leu Met Ser Ile Glu Val Pro Arg Leu Met Thr Gln Asp Cys Leu
340 345 350
Glu His Ala Lys His Ser Ser Asn Thr Pro Lys Ile Thr Glu Asn Met
355 360 365
Phe Cys Ala Gly Tyr Met Asp Gly Thr Lys Asp Ala Cys Lys Gly Asp
370 375 380
Ser Gly Gly Pro His Ala Thr His Tyr His Gly Thr Trp Tyr Leu Thr
385 390 395 400
Gly Val Val Ser Trp Gly Glu Gly Cys Ala Ala Ile Gly His Ile Gly
405 410 415
Val Tyr Thr Arg Val Ser Gln Tyr Ile Asp Trp Leu Val Arg His Met
420 425 430
Asp Ser Lys Leu Gln Val Gly Val Phe Arg Leu Pro Leu Leu
435 440 445

<210> 6
<211> 466
<212> PRT
<213> 侏儒黑猩猩

<220>
<223> 因子VII前趨物

<220>
<221> 不確定
<222> (0)...(0)
<223> Xaa可爲任何胺基酸

<400> 6
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Glu Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Ile Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Leu Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr Tyr
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Asn Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Xaa Leu Leu Xaa Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Ala Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Ile Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320
Leu Cys Leu Pro Glu Arg Ala Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Ser Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln

435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 7
<211> 466
<212> PRT
<213> 黑猩猩

<220>
<223> 因子VII前趨物

<220>
<221> 不確定
<222> (0)...(0)
<223> Xaa可爲任何胺基酸

<400> 7
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Glu Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Xaa Xaa Trp Lys Pro Gly Pro His Arg Val Phe Ile Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Leu Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr Tyr
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Ile Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320
Leu Cys Leu Pro Glu Arg Ala Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400

Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Ser Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 8
<211> 444
<212> PRT
<213> 穴兔

<220>
<223> 因子VII前趨物

<400> 8
Met Ala Pro Gln Ala Arg Gly Leu Gly Leu Cys Ser Leu Leu Ala Leu
1 5 10 15
Gln Ala Ser Leu Ala Ala Val Phe Ile Thr Gln Glu Glu Ala His Ser
20 25 30
Val Leu Arg Arg Gln Arg Arg Ala Asn Ser Phe Leu Glu Glu Leu Arg
35 40 45
Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu Leu Cys Ser Phe Glu
50 55 60
Glu Ala Arg Glu Val Phe Gln Ser Thr Glu Arg Thr Lys Gln Phe Trp
65 70 75 80
Ile Thr Tyr Asn Asp Gly Asp Gln Cys Ala Ser Asn Pro Cys Gln Asn
85 90 95
Gly Gly Ser Cys Glu Asp Gln Ile Gln Ser Tyr Ile Cys Phe Cys Leu
100 105 110
Ala Asp Phe Glu Gly Arg Asn Cys Glu Lys Asn Lys Asn Asp Gln Leu
115 120 125
Ile Cys Met Tyr Glu Asn Gly Gly Cys Glu Gln Tyr Cys Ser Asp His
130 135 140
Val Gly Ser Gln Arg Ser Cys Arg Cys His Glu Gly Tyr Thr Leu Leu
145 150 155 160
Pro Asn Gly Val Ser Cys Thr Pro Thr Val Asp Tyr Pro Cys Gly Lys
165 170 175
Val Pro Ala Leu Glu Lys Arg Gly Ala Ser Asn Pro Gln Gly Arg Ile
180 185 190
Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Ala Ala
195 200 205
Leu Met Asn Gly Ser Thr Leu Leu Cys Gly Gly Ser Leu Leu Asp Thr
210 215 220
His Trp Val Val Ser Ala Ala His Cys Phe Asp Lys Leu Ser Ser Leu
225 230 235 240
Arg Asn Leu Thr Ile Val Leu Gly Glu His Asp Leu Ser Glu His Glu
245 250 255
Gly Asp Glu Gln Val Arg His Val Ala Gln Leu Ile Met Pro Asp Lys
260 265 270
Tyr Val Pro Gly Lys Thr Asp His Asp Ile Ala Leu Leu Arg Leu Leu
275 280 285
Gln Pro Ala Ala Leu Thr Asn Asn Val Val Pro Leu Cys Leu Pro Glu
290 295 300
Arg Asn Phe Ser Glu Ser Thr Leu Ala Thr Ile Arg Phe Ser Arg Val
305 310 315 320
Ser Gly Trp Gly Gln Leu Leu Tyr Arg Gly Ala Leu Ala Arg Glu Leu
325 330 335
Met Ala Ile Asp Val Pro Arg Leu Met Thr Gln Asp Cys Val Glu Gln
340 345 350
Ser Glu His Lys Pro Gly Ser Pro Glu Val Thr Gly Asn Met Phe Cys
355 360 365
Ala Gly Tyr Leu Asp Gly Ser Lys Asp Ala Cys Lys Gly Asp Ser Gly
370 375 380
Gly Pro His Ala Thr Ser Tyr His Gly Thr Trp Tyr Leu Thr Gly Val
385 390 395 400

Val Ser Trp Gly Glu Gly Cys Ala Ala Val Gly His Val Gly Val Tyr
405 410 415
Thr Arg Val Ser Arg Tyr Thr Glu Trp Leu Ser Arg Leu Met Arg Ser
420 425 430
Lys Leu His His Gly Ile Gln Arg His Pro Phe Pro
435 440

<210> 9
<211> 446
<212> PRT
<213> 挪威大鼠

<220>
<223> 因子VII前趨物

<400> 9
Met Val Pro Gln Thr His Gly Leu Leu Leu Leu Tyr Phe Leu Leu Gln
1 5 10 15
Leu Gln Gly Pro Leu Gly Ala Val Val Phe Ile Thr Gln Glu Glu Ala
20 25 30
His Gly Val Leu His Arg Gln Arg Arg Ala Asn Ser Leu Leu Glu Glu
35 40 45
Leu Trp Ser Ser Ser Leu Glu Arg Glu Cys Asn Glu Glu Arg Cys Ser
50 55 60
Phe Glu Glu Ala Arg Glu Ile Phe Lys Ser Pro Glu Arg Thr Lys Gln
65 70 75 80
Phe Trp Thr Ile Tyr Ser Asp Gly Asp Gln Cys Ala Ser Asn Pro Cys
85 90 95
Gln Asn Gly Gly Thr Cys Gln Asp His Leu Lys Ser Tyr Val Cys Phe
100 105 110
Cys Pro Leu Asp Phe Glu Gly Arg Asn Cys Glu Lys Asn Lys Asn Glu
115 120 125
Gln Leu Ile Cys Ala Asn Glu Asn Gly Asp Cys Asp Gln Tyr Cys Arg
130 135 140
Asp His Val Gly Thr Lys Arg Thr Cys Ser Cys His Glu Asp Tyr Val
145 150 155 160
Leu Gln Pro Asp Glu Val Ser Cys Lys Pro Lys Val Glu Tyr Pro Cys
165 170 175
Gly Arg Ile Pro Val Val Glu Lys Arg Asn Phe Ser Arg Pro Gln Gly
180 185 190
Arg Ile Val Gly Gly Tyr Val Cys Pro Lys Gly Glu Cys Pro Trp Gln
195 200 205
Ala Val Leu Lys Phe Asn Glu Ala Leu Leu Cys Gly Ala Val Leu Leu
210 215 220
Asp Thr Arg Trp Ile Val Thr Ala Ala His Cys Phe Asp Lys Phe Gly
225 230 235 240
Lys Leu Val Asn Ile Thr Val Val Leu Gly Glu His Asp Phe Ser Glu
245 250 255
Lys Glu Gly Thr Glu Gln Val Arg Leu Val Glu Gln Val Ile Met Pro
260 265 270
Asn Lys Tyr Thr Arg Gly Arg Thr Asp His Asp Ile Ala Leu Val Arg
275 280 285
Leu His Arg Pro Val Thr Phe Thr Asp Tyr Val Val Pro Leu Cys Leu
290 295 300
Pro Glu Arg Ala Phe Ser Glu Asn Thr Leu Ala Ser Ile Arg Phe Ser
305 310 315 320
Arg Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu
325 330 335
Glu Leu Met Val Ile Glu Val Pro Arg Leu Met Thr Gln Asp Cys Leu
340 345 350
Glu His Ala Lys His Ser Ala Asn Thr Pro Arg Ile Thr Glu Asn Met
355 360 365
Phe Cys Ala Gly Tyr Met Asp Gly Thr Lys Asp Ala Cys Lys Gly Asp
370 375 380
Ser Gly Gly Pro His Ala Thr His Tyr His Gly Thr Trp Tyr Leu Thr
385 390 395 400
Gly Val Val Ser Trp Gly Glu Gly Cys Ala Ala Ile Gly His Ile Gly
405 410 415
Val Tyr Thr Arg Val Ser Gln Tyr Ile Asp Trp Leu Val Lys Tyr Met
420 425 430

Asp Ser Lys Leu Arg Val Gly Ile Ser Arg Val Ser Leu Leu
435 440 445

<210> 10
<211> 469
<212> PRT
<213> 恆河獼猴

<220>
<223> 因子VII前趨物

<400> 10
Met Val Ser Arg Ala Leu Gly Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Ala Thr Phe Leu Pro Gln Ala Gly Ser Leu Arg
20 25 30
Pro Gln Glu Glu Lys Thr Gln Asp Leu Leu Trp Lys Pro Gly Pro His
35 40 45
Arg Val Phe Val Thr Gln Glu Glu Ala His Gly Val Leu His Arg Gln
50 55 60
Arg Arg Ala Asn Ser Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu
65 70 75 80
Arg Glu Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile
85 90 95
Phe Lys Asp Leu Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp
100 105 110
Gly Asp Gln Cys Ala Ser Asn Pro Cys Gln Asn Gly Gly Ser Cys Lys
115 120 125
Asp Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ser Phe Glu Gly
130 135 140
Arg Asn Tyr Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly
145 150 155 160
Cys Glu Gln Tyr Cys Ser Asp His Ala Gly Ala Lys Arg Ser Cys Trp
165 170 175
Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Met Pro
180 185 190
Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn
195 200 205
Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Arg Val Cys Pro Lys
210 215 220
Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu
225 230 235 240
Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His
245 250 255
Cys Phe Asp Lys Ile Lys Ser Trp Arg Asn Leu Thr Ala Val Leu Gly
260 265 270
Glu His Asp Leu Ser Glu His Glu Gly Asp Glu Gln Ser Arg Arg Val
275 280 285
Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Leu Gly Ala Thr Asn His
290 295 300
Asp Ile Ala Leu Leu Arg Leu Gln Gln Pro Val Val Leu Thr Asp His
305 310 315 320
Val Val Pro Leu Cys Leu Pro Glu Arg Met Phe Ser Glu Arg Thr Leu
325 330 335
Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp
340 345 350
Arg Gly Ala Thr Ala Leu Glu Leu Met Ala Leu Asn Val Pro Arg Leu
355 360 365
Met Thr Gln Asp Cys Leu Gln Gln Ser Gln Lys Ala Glu Ala Ser Pro
370 375 380
Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Arg
385 390 395 400
Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr Arg Tyr Arg
405 410 415
Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala
420 425 430
Ala Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu
435 440 445
Trp Leu Gln Lys Leu Met His Ser Glu Pro Arg Pro Gly Val Leu Leu
450 455 460

Arg Ala Pro Phe Pro
465

<210> 11
<211> 445
<212> PRT
<213> 豬

<220>
<223> 因子VII前趨物(同功型b)

<400> 11
Met Ala Ser Leu Arg Pro Ala Leu Leu Cys Leu Leu Leu Cys Leu Gln
1 5 10 15
Gly Ser Leu Ala Ala Val Phe Val Gly His Glu Glu Ala His Ser Leu
20 25 30
Leu His Arg Phe Arg Arg Ala Asn Ser Phe Leu Glu Glu Leu Trp Pro
35 40 45
Gly Ser Leu Glu Arg Glu Cys Arg Glu Glu Gln Cys Ser Phe Glu Glu
50 55 60
Ala Arg Glu Ile Phe Lys Ser Glu Glu Arg Thr Arg Gln Phe Trp Val
65 70 75 80
Ser Tyr Asn Asp Gly Asp Gln Cys Ala Ser Asn Pro Cys Leu Asn Gly
85 90 95
Gly Ser Cys Glu Asp Gln Leu Gln Ala Tyr Ile Cys Phe Cys Pro Glu
100 105 110
Gly Phe Glu Gly Arg Asn Cys Glu Thr Asn Lys Lys Ser Gln Leu Ile
115 120 125
Cys Met Asn Asp Asn Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Ala
130 135 140
Glu Ala Gly Arg Ser Cys Trp Cys His Glu Gly Tyr Ala Leu Gln Glu
145 150 155 160
Asp Gly Val Ser Cys Glu Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile
165 170 175
Pro Val Leu Glu Lys Arg Asn Asp Ser Asn Pro Gln Gly Arg Ile Val
180 185 190
Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Ala Met Leu
195 200 205
Lys Leu Lys Gly Ala Leu Leu Cys Gly Gly Thr Leu Leu Asn Thr Ser
210 215 220
Trp Val Val Ser Ala Ala His Cys Phe Asp Arg Ile Arg Ser Trp Lys
225 230 235 240
Asp Leu Thr Val Val Leu Gly Glu His Asp Leu Ser Lys Asp Glu Gly
245 250 255
Asp Glu Gln Glu Arg Pro Val Ala Gln Val Phe Val Pro Asp Lys Tyr
260 265 270
Val Pro Gly Lys Thr Asp His Asp Leu Ala Leu Val Arg Leu Ala Arg
275 280 285
Pro Val Ala Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg
290 295 300
Ser Phe Ser Glu Arg Thr Leu Ala Phe Ile Arg Phe Ser Ala Val Ser
305 310 315 320
Gly Trp Gly Arg Leu Leu Asp Arg Gly Ala Lys Ala Arg Val Leu Met
325 330 335
Ala Ile Gln Val Pro Arg Leu Met Thr Gln Asp Cys Leu Glu Gln Ala
340 345 350
Arg Arg Arg Pro Gly Ser Pro Ser Ile Thr Asp Asn Met Phe Cys Ala
355 360 365
Gly Tyr Leu Asp Gly Ser Lys Asp Ala Cys Lys Gly Asp Ser Gly Gly
370 375 380
Pro His Ala Thr Arg Phe Arg Gly Thr Trp Phe Leu Thr Gly Val Val
385 390 395 400
Ser Trp Gly Glu Gly Cys Ala Ala Thr Gly Arg Phe Gly Val Tyr Thr
405 410 415
Arg Val Ser Arg Tyr Thr Ala Trp Leu Leu Gly Leu Met Ser Ala Pro
420 425 430
Pro Pro Pro Ser Glu Gly Leu Leu Arg Ala Pro Leu Pro
435 440 445

<210> 12
<211> 446
<212> PRT
<213> 家犬

<220>
<223> 因子VII前趨物

<400> 12
Met Val Ala Trp Ala Gly Glu Leu Ala Leu Leu Cys Phe Leu Leu Gly
1 5 10 15
Leu Gln Gly Ser Leu Ala Ala Val Phe Leu Thr Gln Glu Glu Ala Gln
20 25 30
Gly Val Leu His Arg Gln Arg Arg Ala Asn Ser Phe Leu Glu Glu Leu
35 40 45
Arg Ala Gly Ser Leu Glu Arg Glu Cys Arg Glu Glu Gln Cys Ser Phe
50 55 60
Glu Glu Ala Arg Glu Ile Phe Gln Asp Val Asp Arg Thr Arg Gln Phe
65 70 75 80
Trp Ile Ser Tyr Lys Asp Gly Asp Gln Cys Ala Ser Asn Pro Cys Gln
85 90 95
Asn Gly Gly Ser Cys Glu Asp Gln Leu Gln Ser Tyr Ile Cys Phe Cys
100 105 110
Pro Asp Asp Phe Gln Gly Arg Asn Cys Glu Thr Asp Lys Lys Asp Gln
115 120 125
Leu Ile Cys Met Asn Glu Asn Gly Gly Cys Gln Gln Tyr Cys Ser Asp
130 135 140
His Ala Glu Ala Arg Arg Ser Cys Trp Cys His Glu Gly Tyr Thr Leu
145 150 155 160
Gln Asp Asp Gly Val Ser Cys Met Pro Ile Val Glu Tyr Pro Cys Gly
165 170 175
Lys Ile Pro Val Leu Glu Lys Arg Ile Gly Ser Asn Pro Gln Gly Arg
180 185 190
Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Ala
195 200 205
Ala Val Lys Val Asp Gly Lys Leu Leu Cys Gly Gly Thr Leu Ile Asp
210 215 220
Ala Ala Trp Val Val Ser Ala Ala His Cys Phe Glu Arg Ile Lys Asn
225 230 235 240
Trp Lys Asn Leu Thr Val Val Leu Gly Glu His Asp Leu Ser Glu Asp
245 250 255
Asp Gly Asp Glu Gln Glu Arg His Val Ala Arg Val Ile Val Pro Asp
260 265 270
Lys Tyr Ile Pro Leu Lys Thr Asn His Asp Ile Ala Leu Leu His Leu
275 280 285
Arg Thr Pro Val Ala Tyr Thr Asp His Val Val Pro Leu Cys Leu Pro
290 295 300
Glu Lys Thr Phe Ser Glu Arg Thr Leu Ala Phe Ile Arg Phe Ser Thr
305 310 315 320
Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Gln
325 330 335
Leu Met Ala Ile Asp Val Pro Arg Val Met Thr Gln Asp Cys Gln Glu
340 345 350
Gln Ser Arg Arg Arg Ser Gly Ser Pro Ala Ile Thr Glu Asn Met Phe
355 360 365
Cys Ala Gly Tyr Leu Asp Gly Ser Lys Asp Ala Cys Gln Gly Asp Ser
370 375 380
Gly Gly Pro His Ala Thr Lys Phe Gln Gly Thr Trp Tyr Leu Thr Gly
385 390 395 400
Val Val Ser Trp Gly Glu Gly Cys Ala Ala Glu Gly His Phe Gly Val
405 410 415
Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Arg Gln Leu Met Val
420 425 430
Ser Ser His Thr Leu Arg Gly Leu Leu Arg Ala Pro Leu Pro
435 440 445

<210> 13
<211> 433
<212> PRT
<213> 斑馬魚(Brachydanio rerio)

<220>
<223> 因子VII前趨物

<400> 13
Met Ser Leu Leu Leu Val Phe Ser Val Leu Trp Ser Leu His Tyr Cys
1 5 10 15
His Ser Ala Ala Val Phe Val His Arg Asp Glu Ala His Glu Val Leu
20 25 30
Ile Arg Ser Lys Arg Ala Asn Ser Gly Trp Phe Glu Glu Leu Lys Thr
35 40 45
Gly Asn Leu Glu Arg Glu Cys Leu Glu Glu Lys Cys Ser Tyr Glu Gly
50 55 60
Ala Arg Glu Val Phe Glu His Thr Glu Ala Thr Asn Glu Phe Trp Lys
65 70 75 80
Ile Tyr Asp Val Lys Asp His Cys Ala Ser Ser Pro Cys Glu His Asp
85 90 95
Gly Leu Cys Thr Thr Gln Asn Ala Asp Ser Tyr Met Cys Leu Cys Ala
100 105 110
Pro Gly Phe Ser Gly Arg His Cys Glu Gln Ser Ile Gly Asp Val Pro
115 120 125
Asp Ser Cys Leu His Asp Asn Gly Gly Cys Glu His Phe Cys Thr Glu
130 135 140
Gln Asp Gly Arg Arg Asn Cys Ser Cys Ala Asp Gly Tyr Tyr Leu Asp
145 150 155 160
Asn Gly Gly Gln Lys Cys Arg Ser His Glu Val Phe Pro Cys Gly Lys
165 170 175
Val Pro Leu Leu Gln Ala Gly Lys Ala Ala Asp His Gln Val Asp Leu
180 185 190
Arg Ser Arg Ile Val Gly Gly Ser Glu Cys Pro Lys Gly His Cys Pro
195 200 205
Trp Gln Val Leu Leu Lys Tyr Gly Glu Lys Gly Phe Cys Gly Gly Val
210 215 220
Ile Tyr Lys Pro Thr Trp Ile Leu Thr Ala Ala His Cys Leu Glu Lys
225 230 235 240
Leu Lys Val Lys Phe Leu Arg Ile Val Ala Gly Glu His Asp Leu Glu
245 250 255
Val Asp Glu Gly Thr Glu Gln Leu Ile Gln Val Asp Gln Met Phe Thr
260 265 270
His Pro Ala Tyr Val Ser Glu Thr Ala Asp Ser Asp Ile Ala Leu Leu
275 280 285
Arg Leu Arg Thr Pro Ile Val Tyr Ser Val Tyr Ala Val Pro Val Cys
290 295 300
Leu Pro Leu Arg Glu Met Ala Glu Arg Glu Leu Trp Ala Val Ser Lys
305 310 315 320
His Thr Val Ser Gly Trp Gly Lys Arg Ser Glu Asp Gly Pro Thr Ser
325 330 335
Arg Leu Leu Arg Arg Leu Leu Val Pro Arg Ile Arg Thr Gln Glu Cys
340 345 350
Val Gln Val Ser Asn Leu Thr Leu Thr Ser Asn Met Phe Cys Ala Gly
355 360 365
Tyr Ile Glu Gly Arg Gln Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro
370 375 380
Leu Val Thr Arg Tyr Arg Asp Thr Ala Phe Leu Leu Gly Ile Val Ser
385 390 395 400
Trp Gly Lys Gly Cys Ala Arg Pro Gly Ser Tyr Gly Ile Tyr Thr Arg
405 410 415
Val Ser Asn Tyr Leu Gln Trp Ile Arg Gln Thr Thr Asn Thr Thr Ile
420 425 430
His

<210> 14
<211> 441
<212> PRT
<213> 河豚(Fugu rubripes)

<220>
<223> 因子VII前趨物

<400> 14
Met Arg Leu Arg Val Phe Phe Thr Leu Val Phe Thr Phe Thr His Cys
1 5 10 15
Arg Ala Ala Ser Val Phe Leu Asp Ala Asp Lys Ala His Asp Val Leu
20 25 30
Val Arg Thr Arg Arg Tyr Asn Ser Gly Trp Leu Glu Glu Leu Gln Lys
35 40 45
Gly Asp Leu Lys Arg Glu Cys Leu Glu Glu Ile Cys Ser Tyr Glu Glu
50 55 60
Ala Arg Glu Val Phe Glu His Thr Lys Thr Thr Asp Glu Phe Trp Lys
65 70 75 80
Ile Tyr Asn Arg Pro Asn Ser Cys Lys Ser Asn Pro Cys Leu Asn Gly
85 90 95
Gly Ser Cys Ser Ala Glu Gly Ser Ser Tyr Thr Cys Phe Cys Leu Pro
100 105 110
Glu Phe Ser Gly Val Asp Cys Glu Leu Glu Tyr Gln Thr Val Pro Asp
115 120 125
Thr Cys Leu Leu Glu Asn Gly Gly Cys Glu His Phe Cys His Glu Asn
130 135 140
Ser Ala Gly Gln Arg Gly Asn Cys Ser Cys Ala Asp Gly Tyr Asp Leu
145 150 155 160
Asp Val Asp Gly Leu Ser Cys Lys Ala Lys Glu Ser Val Ala Cys Gly
165 170 175
Met Val Leu Ser Ala Gln Phe Glu His Asn Gln Leu Asn Pro Arg Ala
180 185 190
Arg Ile Val Gly Gly Asn Glu Cys Pro Lys Gly Glu Cys Pro Trp Gln
195 200 205
Val Leu Leu Val Tyr Lys Gly Lys Gly Phe Cys Gly Gly Val Ile Tyr
210 215 220
Lys Pro Thr Trp Ile Leu Thr Ala Ser His Cys Met Ala Asp Ile Asp
225 230 235 240
Val Gln Phe Leu Lys Val Val Ala Gly Glu His Asn Thr Glu Val Asp
245 250 255
Glu Gly Thr Glu Gln Ile Ile Gln Val Ser Glu Ile Ile Met His Glu
260 265 270
Lys Tyr Val Pro Arg Thr Ala Asp Asn Asp Ile Ala Leu Leu His Leu
275 280 285
Ala Val Pro Ile Thr Tyr Thr Thr Tyr Ala Ile Pro Val Cys Leu Pro
290 295 300
Thr Arg Pro Leu Ala Glu Arg Glu Leu Trp Ala Val Ser Leu His Thr
305 310 315 320
Val Ser Gly Trp Gly Arg Arg Ser Glu Asn Gly Pro Thr Ser His Leu
325 330 335
Leu Arg Gln Leu Lys Val Pro Arg Ile Arg Thr Gln Gln Cys Ile Glu
340 345 350
Glu Ser Gly Val Val Leu Thr Gln Asn Met Phe Cys Ala Gly Tyr Met
355 360 365
Glu Gly Arg Gln Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro Leu Val
370 375 380
Thr Lys Tyr Lys Lys Thr Val Phe Leu Leu Gly Ile Val Ser Trp Gly
385 390 395 400
Lys Gly Cys Ala Arg Pro Gly Asn Tyr Gly Ile Tyr Thr Arg Val Ala
405 410 415
Asn Tyr Leu Glu Trp Ile His Asn Arg Thr Ala Thr Val Asn Gln Pro
420 425 430
Thr Asn Asn Thr Glu Asn Phe Thr Thr
435 440

<210> 15
<211> 425
<212> PRT
<213> 雞

<220>
<223> 因子VII前趨物

<400> 15
Met Val Ser Arg Gln Cys Val Ala Leu Leu Leu Cys Phe Pro Leu Leu
1 5 10 15
Val Pro Pro Ser Leu Glu Ala Val Phe Leu Lys Gln Glu Glu Ala Asn

20 25 30
Ser Ile Phe Gln Arg His Arg Arg Ala Asn Ser Phe Phe Glu Glu Ile
35 40 45
Lys Leu Gly Pro Leu Glu Arg Glu Cys Ile Glu Glu Lys Cys Ser Phe
50 55 60
Glu Glu Ala Arg Glu Ile Tyr Arg Asp Asp Glu Arg Thr Lys Glu Phe
65 70 75 80
Trp His Ile Tyr Ser Asp Pro Asn Gln Cys Asp Ser Ser Pro Cys Gln
85 90 95
Asn Gly Gly Ser Cys Asp Asp Gln Phe Gln Asp Tyr Val Cys Arg Cys
100 105 110
Pro Pro Glu Tyr Glu Gly Lys Ser Cys Glu Thr Ala Val Ala Glu Asn
115 120 125
Leu Lys Cys Ile Tyr Asp Asn Gly Gly Cys Glu Gln Tyr Cys Ala Asp
130 135 140
Glu Gln Ser Glu Lys Arg Val Cys Phe Cys Ala Glu Gly Tyr Ala Leu
145 150 155 160
Ala Ser Asp Gly Val Ser Cys Ile Pro Gln Val Lys Tyr Pro Cys Gly
165 170 175
Thr Ile Pro Val Leu Ala Arg Lys Asn Thr Thr Ala Gln Gly Arg Ile
180 185 190
Val Gly Gly Val Thr Cys Pro Pro Gly Glu Cys Pro Trp Gln Ala Leu
195 200 205
Ile Ile Gln Asp Gln Lys Gly Lys Cys Gly Gly Ser Leu Leu Ser Pro
210 215 220
Glu Trp Val Val Thr Ala Ala His Cys Leu Asp Tyr Ala His Ser Lys
225 230 235 240
Gln Leu Arg Val Arg Leu Gly Glu Tyr Ser Val Lys Val Ala Glu Lys
245 250 255
Thr Glu Gln Glu Ser Gly Val Ser Lys Ile Ile Arg His Glu Glu Tyr
260 265 270
Thr Ile Gly Gln Val Asn His Asp Ile Ala Leu Leu Lys Leu Glu Thr
275 280 285
Pro Val Asn Leu Thr Asp Phe Val Val Pro Ile Cys Leu Pro Glu Lys
290 295 300
Arg Phe Ala Val Tyr Glu Leu Ser Ser Ile Lys Phe Ser Met Val Ser
305 310 315 320
Gly Trp Gly Arg Leu Leu Asp Gly Gly Ala Thr Ser Thr Phe Leu Met
325 330 335
Arg Val His Leu Pro Arg Val Lys Thr Gln Glu Cys Glu Lys Gln Ala
340 345 350
Asn Leu Asn Ile Thr Glu Asn Met Phe Cys Ala Gly Asp Leu Thr Gly
355 360 365
Lys Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr Lys
370 375 380
Tyr Lys Asn Thr Trp Phe Leu Thr Gly Ile Val Ser Trp Gly Lys Gly
385 390 395 400
Cys Ala Val Glu Gly Ser Tyr Gly Val Tyr Thr Arg Val Ser Arg Tyr
405 410 415
Ile Asn Trp Leu Lys Arg His Met Glu
420 425

<210> 16
<211> 444
<212> PRT
<213> 紅毛猩猩

<220>
<223> 因子VII (片段)

<400> 16
Gly Val Ala Glu Ala Ser Gly Gly Glu Thr Arg Asp Met Gln Trp Lys
1 5 10 15
Leu Gly Pro His Arg Val Phe Ile Thr Gln Glu Glu Ala His Gly Val
20 25 30
Leu His Arg Arg Arg Arg Ala Asn Thr Phe Leu Glu Glu Leu Arg Pro
35 40 45
Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu
50 55 60
Ala Arg Glu Ile Phe Lys Asp Leu Glu Arg Thr Lys Leu Phe Trp Ile

65 70 75 80
Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly
85 90 95
Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro
100 105 110
Asp Phe Glu Gly Arg Asn Cys Glu Met Tyr Lys Asp Asp Gln Leu Ile
115 120 125
Cys Val Asn Glu Asn Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Met
130 135 140
Gly Ala Lys Arg Ser Cys Trp Cys His Glu Gly Tyr Ser Leu Leu Ala
145 150 155 160
Asp Gly Val Ser Cys Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile
165 170 175
Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val
180 185 190
Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu
195 200 205
Leu Val Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile
210 215 220
Trp Val Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg
225 230 235 240
Asn Leu Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu Arg Asp Gly
245 250 255
Asp Glu Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr
260 265 270
Val Pro Gly Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His Gln
275 280 285
Pro Val Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg
290 295 300
Thr Phe Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser
305 310 315 320
Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met
325 330 335
Ala Leu Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser
340 345 350
Arg Lys Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala
355 360 365
Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly
370 375 380
Pro His Ala Thr Arg Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val
385 390 395 400
Ser Trp Gly Gln Gly Cys Ala Ala Val Gly His Phe Gly Val Tyr Thr
405 410 415
Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Cys Ser Glu
420 425 430
Pro Arg Pro Gly Val Leu Leu Arg Ala Pro Phe Pro
435 440

<210> 17
<211> 221
<212> PRT
<213> 大猩猩

<220>
<223> 因子VII (片段)

<220>
<221> 不確定
<222> (0)...(0)
<223> Xaa可爲任何胺基酸

<400> 17
Ile Trp Val Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp
1 5 10 15
Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp
20 25 30
Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Met
35 40 45
Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His
50 55 60

Gln Pro Val Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu
65 70 75 80
Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val
85 90 95
Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu
100 105 110
Met Val Leu Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln
115 120 125
Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys
130 135 140
Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly
145 150 155 160
Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp Xaa Leu Thr Gly Ile
165 170 175
Xaa Ser Trp Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr
180 185 190
Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser
195 200 205
Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro Phe Pro
210 215 220

<210> 18
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體L13P

<400> 18
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Pro Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 19
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物F64L)

<400> 19
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Leu
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 20
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物L73Q)

<400> 20
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Gln Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 21
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物E79Q)

<400> 21
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Gln Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 22
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物S120P)

<400> 22
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Pro Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 23
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物C121F)

<400> 23
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Phe Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 24
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物L125P)

<400> 24
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Pro Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 25
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物Y128C)

<400> 25
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Cys
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 26
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物R139K)

<400> 26
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Lys Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 27
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物R139Q)

<400> 27
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Gln Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 28
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體R139W

<400> 28
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Trp Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 29
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物C151S)

<400> 29
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Ser Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 30
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物E154K)

<400> 30
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Lys Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 31
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物G157C)

<400> 31
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Cys Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 32
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物G157S)

<400> 32
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Ser Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 33
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物G157V)

<400> 33
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Val Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 34
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物Q160R)

<400> 34
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Arg
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 35
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物P194T)

<400> 35
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Thr Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 36
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物C195R)

<400> 36
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Arg Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 37
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物K197E)

<400> 37
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Glu Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 38
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物R212Q)

<400> 38
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Gln Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 39
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物G216D)

<400> 39
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Asp Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 40
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物C238Y)

<400> 40
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Tyr Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 41
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物T241N)

<400> 41
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Asn Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 42
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物C254Y)

<400> 42
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Tyr Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 43
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物A266T)

<400> 43
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Thr Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 44
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物R283W)

<400> 44
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Trp Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 45
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物V295D)

<400> 45
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Asp Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 46
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物D302H)

<400> 46
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His His Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 47
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物D302N)

<400> 47
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asn Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 48
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物A304T)

<400> 48
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Thr
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 49
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物A304V)

<400> 49
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Val
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 50
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物R307C)

<400> 50
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Cys Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 51
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物R307H)

<400> 51
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu His Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 52
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物V312M)

<400> 52
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Met Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 53
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物E325K)

<400> 53
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Lys Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 54
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物T332M)

<400> 54
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Met Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 55
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物V341F)

<400> 55
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Phe Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 56
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物A352T)

<400> 56
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Thr
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 57
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物A354V)

<400> 57
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Val Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 58
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物M358I)

<400> 58
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Ile Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 59
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物M358V)

<400> 59
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Val Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 60
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物P363R)

<400> 60
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Arg Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 61
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物R364Q)

<400> 61
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Gln Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 62
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物T367S)

<400> 62
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Ser Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 63
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物C370F)

<400> 63
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Phe Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 64
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物C389G)

<400> 64
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Gly Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 65
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物G391S)

<400> 65
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Ser Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 66
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物G402E)

<400> 66
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Glu Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 67
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物G402R)

<400> 67
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Arg Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 68
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物D403H)

<400> 68
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly His Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 69
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物R413Q)

<400> 69
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Gln Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 70
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物T419M)

<400> 70
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Met Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 71
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物G435E)

<400> 71
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Glu Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 72
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物E445K)

<400> 72
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Lys Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 73
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物R375W)

<400> 73
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Trp Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 74
<211> 466
<212> PRT
<213> 現代人

<220>
<223> FVII變異體(前趨物R375K)

<400> 74
Met Val Ser Gln Ala Leu Arg Leu Leu Cys Leu Leu Leu Gly Leu Gln
1 5 10 15
Gly Cys Leu Ala Ala Gly Gly Val Ala Lys Ala Ser Gly Gly Glu Thr
20 25 30
Arg Asp Met Pro Trp Lys Pro Gly Pro His Arg Val Phe Val Thr Gln
35 40 45
Glu Glu Ala His Gly Val Leu His Arg Arg Arg Arg Ala Asn Ala Phe
50 55 60
Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu Cys Lys Glu Glu
65 70 75 80
Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys Asp Ala Glu Arg
85 90 95
Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp Gln Cys Ala Ser
100 105 110
Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln Leu Gln Ser Tyr
115 120 125
Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn Cys Glu Thr His
130 135 140
Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly Gly Cys Glu Gln
145 150 155 160
Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys Arg Cys His Glu
165 170 175
Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu
180 185 190
Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys
195 200 205
Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys
210 215 220
Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly
225 230 235 240
Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp
245 250 255
Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp
260 265 270
Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val
275 280 285
Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala
290 295 300
Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro
305 310 315 320

Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val
325 330 335
Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala
340 345 350
Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln
355 360 365
Asp Cys Leu Gln Gln Ser Lys Lys Val Gly Asp Ser Pro Asn Ile Thr
370 375 380
Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys
385 390 395 400
Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp
405 410 415
Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly
420 425 430
His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln
435 440 445
Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro
450 455 460
Phe Pro
465

<210> 75
<211> 304
<212> PRT
<213> 現代人

<220>
<223> TFPI同功型a前趨物

<400> 75
Met Ile Tyr Thr Met Lys Lys Val His Ala Leu Trp Ala Ser Val Cys
1 5 10 15
Leu Leu Leu Asn Leu Ala Pro Ala Pro Leu Asn Ala Asp Ser Glu Glu
20 25 30
Asp Glu Glu His Thr Ile Ile Thr Asp Thr Glu Leu Pro Pro Leu Lys
35 40 45
Leu Met His Ser Phe Cys Ala Phe Lys Ala Asp Asp Gly Pro Cys Lys
50 55 60
Ala Ile Met Lys Arg Phe Phe Phe Asn Ile Phe Thr Arg Gln Cys Glu
65 70 75 80
Glu Phe Ile Tyr Gly Gly Cys Glu Gly Asn Gln Asn Arg Phe Glu Ser
85 90 95
Leu Glu Glu Cys Lys Lys Met Cys Thr Arg Asp Asn Ala Asn Arg Ile
100 105 110
Ile Lys Thr Thr Leu Gln Gln Glu Lys Pro Asp Phe Cys Phe Leu Glu
115 120 125
Glu Asp Pro Gly Ile Cys Arg Gly Tyr Ile Thr Arg Tyr Phe Tyr Asn
130 135 140
Asn Gln Thr Lys Gln Cys Glu Arg Phe Lys Tyr Gly Gly Cys Leu Gly
145 150 155 160
Asn Met Asn Asn Phe Glu Thr Leu Glu Glu Cys Lys Asn Ile Cys Glu
165 170 175
Asp Gly Pro Asn Gly Phe Gln Val Asp Asn Tyr Gly Thr Gln Leu Asn
180 185 190
Ala Val Asn Asn Ser Leu Thr Pro Gln Ser Thr Lys Val Pro Ser Leu
195 200 205
Phe Glu Phe His Gly Pro Ser Trp Cys Leu Thr Pro Ala Asp Arg Gly
210 215 220
Leu Cys Arg Ala Asn Glu Asn Arg Phe Tyr Tyr Asn Ser Val Ile Gly
225 230 235 240
Lys Cys Arg Pro Phe Lys Tyr Ser Gly Cys Gly Gly Asn Glu Asn Asn
245 250 255
Phe Thr Ser Lys Gln Glu Cys Leu Arg Ala Cys Lys Lys Gly Phe Ile
260 265 270
Gln Arg Ile Ser Lys Gly Gly Leu Ile Lys Thr Lys Arg Lys Arg Lys
275 280 285
Lys Gln Arg Val Lys Ile Ala Tyr Glu Glu Ile Phe Val Lys Asn Met
290 295 300

<210> 76
<211> 276
<212> PRT
<213> 現代人

<220>
<223> TFPI同功型a成熟的

<400> 76
Asp Ser Glu Glu Asp Glu Glu His Thr Ile Ile Thr Asp Thr Glu Leu
1 5 10 15
Pro Pro Leu Lys Leu Met His Ser Phe Cys Ala Phe Lys Ala Asp Asp
20 25 30
Gly Pro Cys Lys Ala Ile Met Lys Arg Phe Phe Phe Asn Ile Phe Thr
35 40 45
Arg Gln Cys Glu Glu Phe Ile Tyr Gly Gly Cys Glu Gly Asn Gln Asn
50 55 60
Arg Phe Glu Ser Leu Glu Glu Cys Lys Lys Met Cys Thr Arg Asp Asn
65 70 75 80
Ala Asn Arg Ile Ile Lys Thr Thr Leu Gln Gln Glu Lys Pro Asp Phe
85 90 95
Cys Phe Leu Glu Glu Asp Pro Gly Ile Cys Arg Gly Tyr Ile Thr Arg
100 105 110
Tyr Phe Tyr Asn Asn Gln Thr Lys Gln Cys Glu Arg Phe Lys Tyr Gly
115 120 125
Gly Cys Leu Gly Asn Met Asn Asn Phe Glu Thr Leu Glu Glu Cys Lys
130 135 140
Asn Ile Cys Glu Asp Gly Pro Asn Gly Phe Gln Val Asp Asn Tyr Gly
145 150 155 160
Thr Gln Leu Asn Ala Val Asn Asn Ser Leu Thr Pro Gln Ser Thr Lys
165 170 175
Val Pro Ser Leu Phe Glu Phe His Gly Pro Ser Trp Cys Leu Thr Pro
180 185 190
Ala Asp Arg Gly Leu Cys Arg Ala Asn Glu Asn Arg Phe Tyr Tyr Asn
195 200 205
Ser Val Ile Gly Lys Cys Arg Pro Phe Lys Tyr Ser Gly Cys Gly Gly
210 215 220
Asn Glu Asn Asn Phe Thr Ser Lys Gln Glu Cys Leu Arg Ala Cys Lys
225 230 235 240
Lys Gly Phe Ile Gln Arg Ile Ser Lys Gly Gly Leu Ile Lys Thr Lys
245 250 255
Arg Lys Arg Lys Lys Gln Arg Val Lys Ile Ala Tyr Glu Glu Ile Phe
260 265 270
Val Lys Asn Met
275

<210> 77
<211> 251
<212> PRT
<213> 現代人

<220>
<223> TFPI同功型b前趨物

<400> 77
Met Ile Tyr Thr Met Lys Lys Val His Ala Leu Trp Ala Ser Val Cys
1 5 10 15
Leu Leu Leu Asn Leu Ala Pro Ala Pro Leu Asn Ala Asp Ser Glu Glu
20 25 30
Asp Glu Glu His Thr Ile Ile Thr Asp Thr Glu Leu Pro Pro Leu Lys
35 40 45
Leu Met His Ser Phe Cys Ala Phe Lys Ala Asp Asp Gly Pro Cys Lys
50 55 60
Ala Ile Met Lys Arg Phe Phe Phe Asn Ile Phe Thr Arg Gln Cys Glu
65 70 75 80
Glu Phe Ile Tyr Gly Gly Cys Glu Gly Asn Gln Asn Arg Phe Glu Ser
85 90 95
Leu Glu Glu Cys Lys Lys Met Cys Thr Arg Asp Asn Ala Asn Arg Ile
100 105 110
Ile Lys Thr Thr Leu Gln Gln Glu Lys Pro Asp Phe Cys Phe Leu Glu

```
        115                 120                 125
Glu Asp Pro Gly Ile Cys Arg Gly Tyr Ile Thr Arg Tyr Phe Tyr Asn
    130                 135                 140
Asn Gln Thr Lys Gln Cys Glu Arg Phe Lys Tyr Gly Gly Cys Leu Gly
145                 150                 155                 160
Asn Met Asn Asn Phe Glu Thr Leu Glu Glu Cys Lys Asn Ile Cys Glu
                165                 170                 175
Asp Gly Pro Asn Gly Phe Gln Val Asp Asn Tyr Gly Thr Gln Leu Asn
            180                 185                 190
Ala Val Asn Asn Ser Leu Thr Pro Gln Ser Thr Lys Val Pro Ser Leu
        195                 200                 205
Phe Val Thr Lys Glu Gly Thr Asn Asp Gly Trp Lys Asn Ala Ala His
    210                 215                 220
Ile Tyr Gln Val Phe Leu Asn Ala Phe Cys Ile His Ala Ser Met Phe
225                 230                 235                 240
Phe Leu Gly Leu Asp Ser Ile Ser Cys Leu Cys
                245                 250
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<210> 78
<211> 222
<212> PRT
<213> 現代人

<220>
<223> TFPI同功型b成熟的

<400> 78

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Ser Glu Glu Asp Glu Glu His Thr Ile Ile Thr Asp Thr Glu Leu Pro
 1               5                  10                  15
Pro Leu Lys Leu Met His Ser Phe Cys Ala Phe Lys Ala Asp Asp Gly
            20                  25                  30
Pro Cys Lys Ala Ile Met Lys Arg Phe Phe Phe Asn Ile Phe Thr Arg
        35                  40                  45
Gln Cys Glu Glu Phe Ile Tyr Gly Gly Cys Glu Gly Asn Gln Asn Arg
    50                  55                  60
Phe Glu Ser Leu Glu Glu Cys Lys Lys Met Cys Thr Arg Asp Asn Ala
65                  70                  75                  80
Asn Arg Ile Ile Lys Thr Thr Leu Gln Gln Glu Lys Pro Asp Phe Cys
                85                  90                  95
Phe Leu Glu Glu Asp Pro Gly Ile Cys Arg Gly Tyr Ile Thr Arg Tyr
            100                 105                 110
Phe Tyr Asn Asn Gln Thr Lys Gln Cys Glu Arg Phe Lys Tyr Gly Gly
        115                 120                 125
Cys Leu Gly Asn Met Asn Asn Phe Glu Thr Leu Glu Glu Cys Lys Asn
    130                 135                 140
Ile Cys Glu Asp Gly Pro Asn Gly Phe Gln Val Asp Asn Tyr Gly Thr
145                 150                 155                 160
Gln Leu Asn Ala Val Asn Asn Ser Leu Thr Pro Gln Ser Thr Lys Val
                165                 170                 175
Pro Ser Leu Phe Val Thr Lys Glu Gly Thr Asn Asp Gly Trp Lys Asn
            180                 185                 190
Ala Ala His Ile Tyr Gln Val Phe Leu Asn Ala Phe Cys Ile His Ala
        195                 200                 205
Ser Met Phe Phe Leu Gly Leu Asp Ser Ile Ser Cys Leu Cys
    210                 215                 220
```

<210> 79
<211> 213
<212> PRT
<213> 現代人

<220>
<223> TFPI-2成熟的

<400> 79

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Asp Ala Ala Gln Glu Pro Thr Gly Asn Asn Ala Glu Ile Cys Leu Leu
 1               5                  10                  15
Pro Leu Asp Tyr Gly Pro Cys Arg Ala Leu Leu Leu Arg Tyr Tyr Tyr
            20                  25                  30
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Asp Arg Tyr Thr Gln Ser Cys Arg Gln Phe Leu Tyr Gly Gly Cys Glu
35 40 45
Gly Asn Ala Asn Asn Phe Tyr Thr Trp Glu Ala Cys Asp Asp Ala Cys
50 55 60
Trp Arg Ile Glu Lys Val Pro Lys Val Cys Arg Leu Gln Val Ser Val
65 70 75 80
Asp Asp Gln Cys Glu Gly Ser Thr Glu Lys Tyr Phe Phe Asn Leu Ser
85 90 95
Ser Met Thr Cys Glu Lys Phe Phe Ser Gly Gly Cys His Arg Asn Arg
100 105 110
Ile Glu Asn Arg Phe Pro Asp Glu Ala Thr Cys Met Gly Phe Cys Ala
115 120 125
Pro Lys Lys Ile Pro Ser Phe Cys Tyr Ser Pro Lys Asp Glu Gly Leu
130 135 140
Cys Ser Ala Asn Val Thr Arg Tyr Tyr Phe Asn Pro Arg Tyr Arg Thr
145 150 155 160
Cys Asp Ala Phe Thr Tyr Thr Gly Cys Gly Gly Asn Asp Asn Asn Phe
165 170 175
Val Ser Arg Glu Asp Cys Lys Arg Ala Cys Ala Lys Ala Leu Lys Lys
180 185 190
Lys Lys Lys Met Pro Lys Leu Arg Phe Ala Ser Arg Ile Arg Lys Ile
195 200 205
Arg Lys Lys Gln Phe
210

<210> 80
<211> 245
<212> PRT
<213> 現代人

<220>
<223> 胰凝乳蛋白酶原B成熟的

<400> 80
Cys Gly Val Pro Ala Ile His Pro Val Leu Ser Gly Leu Ser Arg Ile
1 5 10 15
Val Asn Gly Glu Asp Ala Val Pro Gly Ser Trp Pro Trp Gln Val Ser
20 25 30
Leu Gln Asp Lys Thr Gly Phe His Phe Cys Gly Gly Ser Leu Ile Ser
35 40 45
Glu Asp Trp Val Val Thr Ala Ala His Cys Gly Val Arg Thr Ser Asp
50 55 60
Val Val Val Ala Gly Glu Phe Asp Gln Gly Ser Asp Glu Glu Asn Ile
65 70 75 80
Gln Val Leu Lys Ile Ala Lys Val Phe Lys Asn Pro Lys Phe Ser Ile
85 90 95
Leu Thr Val Asn Asn Asp Ile Thr Leu Leu Lys Leu Ala Thr Pro Ala
100 105 110
Arg Phe Ser Gln Thr Val Ser Ala Val Cys Leu Pro Ser Ala Asp Asp
115 120 125
Asp Phe Pro Ala Gly Thr Leu Cys Ala Thr Thr Gly Trp Gly Lys Thr
130 135 140
Lys Tyr Asn Ala Asn Lys Thr Pro Asp Lys Leu Gln Gln Ala Ala Leu
145 150 155 160
Pro Leu Leu Ser Asn Ala Glu Cys Lys Lys Ser Trp Gly Arg Arg Ile
165 170 175
Thr Asp Val Met Ile Cys Ala Gly Ala Ser Gly Val Ser Ser Cys Met
180 185 190
Gly Asp Ser Gly Gly Pro Leu Val Cys Gln Lys Asp Gly Ala Trp Thr
195 200 205
Leu Val Gly Ile Val Ser Trp Gly Ser Asp Thr Cys Ser Thr Ser Ser
210 215 220
Pro Gly Val Tyr Ala Arg Val Thr Lys Leu Ile Pro Trp Val Gln Lys
225 230 235 240
Ile Leu Ala Ala Asn
245

<210> 81
<211> 3141

<212> DNA
<213> 現代人

<220>
<223> FVII轉錄物變異體1

<400> 81
agtcccatgg ggaatgtcaa caggcagggg cagcactgca gagatttcat catggtctcc 60
caggccctca ggctcctctg ccttctgctt gggcttcagg gctgcctggc tgcaggcggg 120
gtcgctaagg cctcaggagg agaaacacgg gacatgccgt ggaagccggg gcctcacaga 180
gtcttcgtaa cccaggagga agcccacggc gtcctgcacc ggcgccggcg cgccaacgcg 240
ttcctggagg agctgcggcc gggctccctg gagagggagt gcaaggagga gcagtgctcc 300
ttcgaggagg cccgggagat cttcaaggac gcggagagga cgaagctgtt ctggatttct 360
tacagtgatg gggaccagtg tgcctcaagt ccatgccaga atgggggctc ctgcaaggac 420
cagctccagt cctatatctg cttctgcctc cctgccttcg agggccggaa ctgtgagacg 480
cacaaggatg accagctgat ctgtgtgaac gagaacggcg gctgtgagca gtactgcagt 540
gaccacacgg gcaccaagcg ctcctgtcgg tgccacgagg ggtactctct gctggcagac 600
ggggtgtcct gcacacccac agttgaatat ccatgtggaa aaatacctat tctagaaaaa 660
agaaatgcca gcaaacccca aggccgaatt gtgggggca aggtgtgccc caaaggggag 720
tgtccatggc aggtcctgtt gttggtgaat ggagctcagt tgtgtggggg gaccctgatc 780
aacaccatct gggtggtctc cgcggcccac tgtttcgaca aaatcaagaa ctggaggaac 840
ctgatcgcgg tgctgggcga gcacgacctc agcgagcacg acggggatga gcagagccgg 900
cgggtggcgc aggtcatcat ccccagcacg tacgtcccgg gcaccaccaa ccacgacatc 960
gcgctgctcc gcctgcacca gcccgtggtc ctcactgacc atgtggtgcc cctctgcctg 1020
cccgaacgga cgttctctga gaggacgctg gccttcgtgc gcttctcatt ggtcagcggc 1080
tggggccagc tgctggaccg tggcgccacg gccctggagc tcatggtcct caacgtgccc 1140
cggctgatga cccaggactg cctgcagcag tcacggaagg tgggagactc cccaaatatc 1200
acggagtaca tgttctgtgc cggctactcg gatggcagca aggactcctg caagggggac 1260
agtggaggcc cacatgccac ccactaccgg ggcacgtggt acctgacggg catcgtcagc 1320
tggggccagg gctgcgcaac cgtgggccac tttggggtgt acaccagggt ctcccagtac 1380
atcgagtggc tgcaaaagct catgcgctca gagccacgcc caggagtcct cctgcgagcc 1440
ccatttccct agcccagcag ccctggcctg tggagagaaa gccaaggctg cgtcgaactg 1500
tcctggcacc aaatcccata tattcttctg cagttaatgg ggtagaggag ggcatgggag 1560
ggagggagag gtggggaggg agacagagac agaaacagag agagacagag acagagagag 1620
actgagggag agactctgag gacatggaga gagactcaaa gagactccaa gattcaaaga 1680
gactaataga gacacagaga tggaatagaa aagatgagag gcagaggcag acaggcgctg 1740
gacagagggg caggggagtg ccaaggttgt cctggaggca gacagcccag ctgagcctcc 1800
ttacctccct tcagccaagc ccacctgcac gtgatctgct ggcctcaggc tgctgctctg 1860
ccttcattgc tggagacagt agaggcatga acacacatgg atgcacacac acacacgcca 1920
atgcacacac acagagatat gcacacacac ggatgcacac acagatggtc acacagagat 1980
acgcaaacac accgatgcac acgcacatag agatatgcac acacagatgc acacacagat 2040
atacacatgg atgcacgcac atgccaatgc acgcacacat cagtgcacac ggatgcacag 2100
agatatgcac acaccgatgt gcgcacacac agatatgcac acacatggat gagcacacac 2160
acaccaatgc gcacacacac cgatgtacac acacagatgc acacacagat gcacacacac 2220
cgatgctgac tccatgtgtg ctgtcctctg aaggcggttg tttagctctc acttttctgg 2280
ttcttatcca ttatcatctt cacttcagac aattcagaag catcaccatg catggtggcg 2340
aatgccccca aactctcccc caaatgtatt tctcccttcg ctgggtgccg ggctgcacag 2400
actattcccc acctgcttcc cagcttcaca ataaacggct gcgtctcctc cgcacacctg 2460
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tctgagatgc tcttttcttt cacaattttc aacatcactg aaatgaaccc tcacatggaa 2580
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<210> 82
<211> 3075
<212> DNA
<213> 現代人

<220>
<223> FVII轉錄物變異體2

<400> 82
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aaaaaaaaaa aaaaa                                                  3075
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<210> 83
<211> 46
<212> PRT
<213> 現代人

<220>
<223> 因子IX Gla功能域

<400> 83

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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
        35                  40                  45
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<210> 84
<211> 45

<212> PRT
<213> 現代人

<220>
<223> 因子X Gla功能域

<400> 84
Ala Asn Ser Phe Leu Glu Glu Met Lys Lys Gly His Leu Glu Arg Glu
1 5 10 15
Cys Met Glu Glu Thr Cys Ser Tyr Glu Glu Ala Arg Glu Val Phe Glu
20 25 30
Asp Ser Asp Lys Thr Asn Glu Phe Trp Asn Lys Tyr Lys
35 40 45

<210> 85
<211> 46
<212> PRT
<213> 現代人

<220>
<223> 凝血酶原/凝血酶Gla功能域

<400> 85
Ala Asn Thr Phe Leu Glu Glu Val Arg Lys Gly Asn Leu Glu Arg Glu
1 5 10 15
Cys Val Glu Glu Thr Cys Ser Tyr Glu Glu Ala Phe Glu Ala Leu Glu
20 25 30
Ser Ser Thr Ala Thr Asp Val Phe Trp Ala Lys Tyr Thr Ala
35 40 45

<210> 86
<211> 46
<212> PRT
<213> 現代人

<220>
<223> 蛋白質C Gla功能域

<400> 86
Ala Asn Ser Phe Leu Glu Glu Leu Arg His Ser Ser Leu Glu Arg Glu
1 5 10 15
Cys Ile Glu Glu Ile Cys Asp Phe Glu Glu Ala Lys Glu Ile Phe Gln
20 25 30
Asn Val Asp Asp Thr Leu Ala Phe Trp Ser Lys His Val Asp
35 40 45

<210> 87
<211> 46
<212> PRT
<213> 現代人

<220>
<223> 蛋白質S Gla功能域

<400> 87
Ala Asn Ser Leu Leu Glu Glu Thr Lys Gln Gly Asn Leu Glu Arg Glu
1 5 10 15
Cys Ile Glu Glu Leu Cys Asn Lys Glu Glu Ala Arg Glu Val Phe Glu
20 25 30
Asn Asp Pro Glu Thr Asp Tyr Phe Tyr Pro Lys Tyr Leu Val
35 40 45

<210> 88
<211> 47
<212> PRT
<213> 現代人

<220>
<223> 骨鈣蛋白(骨骼Gla蛋白質) Gla功能域

<400> 88
Tyr Leu Tyr Gln Trp Leu Gly Ala Pro Val Pro Tyr Pro Asp Pro Leu
1 5 10 15
Glu Pro Arg Arg Glu Val Cys Glu Leu Asn Pro Asp Cys Asp Glu Leu
20 25 30
Ala Asp His Ile Gly Phe Gln Glu Ala Tyr Arg Arg Phe Tyr Gly
35 40 45

<210> 89
<211> 47
<212> PRT
<213> 現代人

<220>
<223> 基質Gla 蛋白質Gla功能域

<400> 89
Arg Ala Lys Val Gln Glu Arg Ile Arg Glu Arg Ser Lys Pro Val His
1 5 10 15
Glu Leu Asn Arg Glu Ala Cys Asp Asp Tyr Arg Leu Cys Glu Arg Tyr
20 25 30
Ala Met Val Tyr Gly Tyr Asn Ala Ala Tyr Asn Arg Tyr Phe Arg
35 40 45

<210> 90
<211> 42
<212> PRT
<213> 現代人

<220>
<223> 生長抑止特異性蛋白6 Gla功能域

<400> 90
Phe Glu Glu Ala Lys Gln Gly His Leu Glu Arg Glu Cys Val Glu Glu
1 5 10 15
Leu Cys Ser Arg Glu Glu Ala Arg Glu Val Phe Glu Asn Asp Pro Glu
20 25 30
Thr Asp Tyr Phe Tyr Pro Arg Tyr Leu Asp
35 40

<210> 91
<211> 46
<212> PRT
<213> 現代人

<220>
<223> 蛋白質Z Gla功能域

<400> 91
Ala Gly Ser Tyr Leu Leu Glu Glu Leu Phe Glu Gly Asn Leu Glu Lys
1 5 10 15
Glu Cys Tyr Glu Glu Ile Cys Val Tyr Glu Glu Ala Arg Glu Val Phe
20 25 30
Glu Asn Glu Val Val Thr Asp Glu Phe Trp Arg Arg Tyr Lys
35 40 45

<210> 92
<211> 45
<212> PRT
<213> 現代人

<220>
<223> 因子VII Gla功能域

<400> 92
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser
35 40 45

<210> 93
<211> 40
<212> PRT
<213> 虎蛇(Notechis scutatus scutatus)

<220>
<223> 蛇毒類凝血因子Xa-蛋白酶- Gla功能域

<220>
<221> 不確定
<222> (0)...(0)
<223> Xaa可爲任何胺基酸

<400> 93
Ser Asn Ser Leu Phe Glu Glu Ile Arg Pro Gly Asn Ile Glu Arg Glu
1 5 10 15
Cys Ile Glu Glu Lys Cys Ser Lys Glu Glu Ala Arg Glu Val Phe Glu
20 25 30
Asp Asn Glu Lys Thr Xaa Xaa Phe
35 40

<210> 94
<211> 46
<212> PRT
<213> Tropidechis carinatus

<220>
<223> 蛇毒類凝血因子Xa 蛋白酶- Gla功能域

<400> 94
Ser Asn Ser Leu Phe Glu Glu Ile Arg Pro Gly Asn Ile Glu Arg Glu
1 5 10 15
Cys Ile Glu Glu Lys Cys Ser Lys Glu Glu Ala Arg Glu Val Phe Glu
20 25 30
Asp Asn Glu Lys Thr Glu Thr Phe Trp Asn Val Tyr Val Asp
35 40 45

<210> 95
<211> 464
<212> PRT
<213> 現代人

<220>
<223> 抗凝血酶III前趨物

<400> 95
Met Tyr Ser Asn Val Ile Gly Thr Val Thr Ser Gly Lys Arg Lys Val
1 5 10 15
Tyr Leu Leu Ser Leu Leu Leu Ile Gly Phe Trp Asp Cys Val Thr Cys
20 25 30
His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
35 40 45
Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
50 55 60
Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
65 70 75 80
Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
85 90 95
His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
100 105 110

Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
115 120 125
Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser
130 135 140
Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys
145 150 155 160
Arg Leu Tyr Arg Lys Ala Asn Lys Ser Ser Lys Leu Val Ser Ala Asn
165 170 175
Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp
180 185 190
Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys
195 200 205
Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn
210 215 220
Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn
225 230 235 240
Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu
245 250 255
Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr
260 265 270
Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly
275 280 285
Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu
290 295 300
Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro
305 310 315 320
Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
325 330 335
Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
340 345 350
Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
355 360 365
Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
370 375 380
Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
385 390 395 400
His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
405 410 415
Ser Thr Ala Val Val Ile Ala Gly Arg Ser Leu Asn Pro Asn Arg Val
420 425 430
Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
435 440 445
Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
450 455 460

<210> 96
<211> 432
<212> PRT
<213> 現代人

<220>
<223> 抗凝血酶III成熟的

<400> 96
His Gly Ser Pro Val Asp Ile Cys Thr Ala Lys Pro Arg Asp Ile Pro
1 5 10 15
Met Asn Pro Met Cys Ile Tyr Arg Ser Pro Glu Lys Lys Ala Thr Glu
20 25 30
Asp Glu Gly Ser Glu Gln Lys Ile Pro Glu Ala Thr Asn Arg Arg Val
35 40 45
Trp Glu Leu Ser Lys Ala Asn Ser Arg Phe Ala Thr Thr Phe Tyr Gln
50 55 60
His Leu Ala Asp Ser Lys Asn Asp Asn Asp Asn Ile Phe Leu Ser Pro
65 70 75 80
Leu Ser Ile Ser Thr Ala Phe Ala Met Thr Lys Leu Gly Ala Cys Asn
85 90 95
Asp Thr Leu Gln Gln Leu Met Glu Val Phe Lys Phe Asp Thr Ile Ser
100 105 110
Glu Lys Thr Ser Asp Gln Ile His Phe Phe Phe Ala Lys Leu Asn Cys
115 120 125

Arg Leu Tyr Arg Lys Ala Asn Lys Ser Ser Lys Leu Val Ser Ala Asn
130 135 140
Arg Leu Phe Gly Asp Lys Ser Leu Thr Phe Asn Glu Thr Tyr Gln Asp
145 150 155 160
Ile Ser Glu Leu Val Tyr Gly Ala Lys Leu Gln Pro Leu Asp Phe Lys
165 170 175
Glu Asn Ala Glu Gln Ser Arg Ala Ala Ile Asn Lys Trp Val Ser Asn
180 185 190
Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn
195 200 205
Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu
210 215 220
Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr
225 230 235 240
Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly
245 250 255
Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu
260 265 270
Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro
275 280 285
Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
290 295 300
Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
305 310 315 320
Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
325 330 335
Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
340 345 350
Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
355 360 365
His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
370 375 380
Ser Thr Ala Val Val Ile Ala Gly Arg Ser Leu Asn Pro Asn Arg Val
385 390 395 400
Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
405 410 415
Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
420 425 430

<210> 97
<211> 263
<212> PRT
<213> 現代人

<220>
<221> THIOLEST
<222> (0)...(0)
<223> 成熟的組織因子

<400> 97
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20 25 30
Val Tyr Thr Val Gln Ile Ser Thr Lys Ser Gly Asp Trp Lys Ser Lys
35 40 45
Cys Phe Tyr Thr Thr Asp Thr Glu Cys Asp Leu Thr Asp Glu Ile Val
50 55 60
Lys Asp Val Lys Gln Thr Tyr Leu Ala Arg Val Phe Ser Tyr Pro Ala
65 70 75 80
Gly Asn Val Glu Ser Thr Gly Ser Ala Gly Glu Pro Leu Tyr Glu Asn
85 90 95
Ser Pro Glu Phe Thr Pro Tyr Leu Glu Thr Asn Leu Gly Gln Pro Thr
100 105 110
Ile Gln Ser Phe Glu Gln Val Gly Thr Lys Val Asn Val Thr Val Glu
115 120 125
Asp Glu Arg Thr Leu Val Arg Arg Asn Asn Thr Phe Leu Ser Leu Arg
130 135 140
Asp Val Phe Gly Lys Asp Leu Ile Tyr Thr Leu Tyr Tyr Trp Lys Ser
145 150 155 160

Ser Ser Ser Gly Lys Lys Thr Ala Lys Thr Asn Thr Asn Glu Phe Leu
165 170 175
Ile Asp Val Asp Lys Gly Glu Asn Tyr Cys Phe Ser Val Gln Ala Val
180 185 190
Ile Pro Ser Arg Thr Val Asn Arg Lys Ser Thr Asp Ser Pro Val Glu
195 200 205
Cys Met Gly Gln Glu Lys Gly Glu Phe Arg Glu Ile Phe Tyr Ile Ile
210 215 220
Gly Ala Val Val Phe Val Val Ile Ile Leu Val Ile Ile Leu Ala Ile
225 230 235 240
Ser Leu His Lys Cys Arg Lys Ala Gly Val Gly Gln Ser Trp Lys Glu
245 250 255
Asn Ser Pro Leu Asn Val Ser
260

<210> 98
<211> 406
<212> PRT
<213> 現代人

<220>
<223> 因子VIIa變異體V21D/E154V/M156Q

<400> 98
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Asp Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Val Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365

Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 99
<211> 4278
<212> DNA
<213> 人工序列

<220>
<223> pCMV Script載體

<400> 99
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gttccgcgtt acataactta cggtaaatgg cccgcctggc tgaccgccca acgacccccg 120
cccattgacg tcaataatga cgtatgttcc catagtaacg ccaataggga ctttccattg 180
acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc aagtgtatca 240
tatgccaagt acgcccccta ttgacgtcaa tgacggtaaa tggcccgcct ggcattatgc 300
ccagtacatg accttatggg actttcctac ttggcagtac atctacgtat tagtcatcgc 360
tattaccatg gtgatgcggt tttggcagta catcaatggg cgtggatagc ggtttgactc 420
acggggattt ccaagtctcc accccattga cgtcaatggg agtttgtttt ggcaccaaaa 480
tcaacgggac tttccaaaat gtcgtaacaa ctccgcccca ttgacgcaaa tgggcggtag 540
gcgtgtacgg tgggaggtct atataagcag agctggttta gtgaaccgtc agatccgcta 600
gcgattacgc caagctcgaa attaaccctc actaaaggga acaaaagctg gagctccacc 660
gcggtggcgg ccgctctagc ccgggcggat cccccgggct gcaggaattc gatatcaagc 720
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tggcgaatgg agatccaatt tttaagtgta taatgtgtta aactactgat tctaattgtt 900
tgtgtatttt agattcacag tcccaaggct catttcaggc ccctcagtcc tcacagtctg 960
ttcatgatca taatcagcca taccacattt gtagaggttt tacttgcttt aaaaaacctc 1020
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attgcagctt ataatggtta caaataaagc aatagcatca caaatttcac aaataaagca 1140
ttttttcac tgcattctag ttgtggtttg tccaaactca tcaatgtatc ttaacgcgta 1200
aattgtaagc gttaatattt tgttaaaatt cgcgttaaat ttttgttaaa tcagctcatt 1260
ttttaaccaa taggccgaaa tcggcaaaat cccttataaa tcaaaagaat agaccgagat 1320
agggttgagt gttgttccag tttggaacaa gagtccacta ttaaagaacg tggactccaa 1380
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ccgatttaga gcttgacggg gaaagccggc gaacgtggcg agaaaggaag ggaagaaagc 1560
gaaaggagcg ggcgctaggg cgctggcaag tgtagcggtc acgctgcgcg taaccaccac 1620
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gcgcggaacc cctatttgtt tatttttcta aatacattca aatatgtatc cgctcatgag 1740
acaataaccc tgataaatgc ttcaataata ttgaaaaagg aagaatcctg aggcggaaag 1800
aaccagctgt ggaatgtgtg tcagttaggg tgtggaaagt ccccaggctc cccagcaggc 1860
agaagtatgc aaagcatgca tctcaattag tcagcaacca ggtgtggaaa gtccccaggc 1920
tccccagcag gcagaagtat gcaaagcatg catctcaatt agtcagcaac catagtcccg 1980
cccctaactc cgcccatccc gcccctaact ccgcccagtt ccgcccattc tccgccccat 2040
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cagaagtagt gaggaggctt ttttggaggc ctaggctttt gcaaagatcg atcaagagac 2160
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cggtgccctg aatgaactgc aagacgaggc agcgcggcta tcgtggctgg ccacgacggg 2400
cgttccttgc gcagctgtgc tcgacgttgt cactgaagcg ggaagggact ggctgctatt 2460
gggcgaagtg ccggggcagg atctcctgtc atctcacctt gctcctgccg agaaagtatc 2520
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cgaatgggct gaccgcttcc tcgtgcttta cggtatcgcc gctcccgatt cgcagcgcat 2940
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gaccaagcga cgcccaacct gccatcacga gatttcgatt ccaccgccgc cttctatgaa 3060
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gggtcgtttg ttcataaacg cggggttcgg tcccagggct ggcactctgt cgatacccca 3300
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cactgagcgt cagaccccgt agaaaagatc aaaggatctt cttgagatcc tttttttctg 3600
cgcgtaatct gctgcttgca aacaaaaaaa ccaccgctac cagcggtggt ttgtttgccg 3660
gatcaagagc taccaactct ttttccgaag gtaactggct tcagcagagc gcagatacca 3720
aatactgtcc ttctagtgta gccgtagtta ggccaccact tcaagaactc tgtagcaccg 3780
cctacatacc tcgctctgct aatcctgtta ccagtggctg ctgccagtgg cgataagtcg 3840
tgtcttaccg ggttggactc aagacgatag ttaccggata aggcgcagcg gtcgggctga 3900
acgggggtt cgtgcacaca gcccagcttg gagcgaacga cctacaccga actgagatac 3960
ctacagcgtg agctatgaga aagcgccacg cttcccgaag ggagaaaggc ggacaggtat 4020
ccggtaagcg gcagggtcgg aacaggagag cgcacgaggg agcttccagg gggaaacgcc 4080
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tgctcgtcag gggggcggag cctatggaaa aacgccagca acgcggcctt tttacggttc 4200
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gataaccgta ttaccgcc 4278

<210> 100
<211> 45
<212> DNA
<213> 人工序列

<220>
<223> CBO-125因子VII正向PCR引子

<400> 100
gcatcatgac gtgacggatc cgccaccatg gtctcccagg ccctc 45

<210> 101
<211> 45
<212> DNA
<213> 人工序列

<220>
<223> CBO-126因子VII反向PCR引子

<400> 101
gatcgtacga tacgtgaatt cctagggaaa tggggctcgc aggag 45

<210> 102
<211> 1398
<212> DNA
<213> 現代人

<220>
<223> FVII cDNA (用於PCR的模板)

<400> 102
atggtctccc aggccctcag gctcctctgc cttctgcttg ggcttcaggg ctgcctggct 60
gcaggcgggg tcgctaaggc ctcaggagga gaaacacggg acatgccgtg gaagccgggg 120
cctcacagag tcttcgtaac ccaggaggaa gcccacggcg tcctgcaccg gcgccggcgc 180
gccaacgcgt tcctggagga gctgcggccg ggctccctgg agagggagtg caaggaggag 240
cagtgctcct tcgaggaggc ccgggagatc ttcaaggacg cggagaggac gaagctgttc 300
tggatttctt acagtgatgg ggaccagtgt gcctcaagtc catgccagaa tgggggctcc 360
tgcaaggacc agctccagtc ctatatctgc ttctgcctcc ctgccttcga gggccggaac 420
tgtgagacgc acaaggatga ccagctgatc tgtgtgaacg agaacggcgg ctgtgagcag 480
tactgcagtg accacacggg caccaagcgc tcctgtcggt gccacgaggg gtactctctg 540
ctggcagacg gggtgtcctg cacacccaca gttgaatatc catgtggaaa aatacctatt 600
ctagaaaaaa gaaatgccag caaaccccaa ggccgaattg tgggggcaa ggtgtgcccc 660
aaaggggagt gtccatggca ggtcctgttg ttggtgaatg gagctcagtt gtgtgggggg 720
accctgatca acaccatctg ggtggtctcc gcggcccact gtttcgacaa aatcaagaac 780
tggaggaacc tgatcgcggt gctgggcgag cacgacctca gcgagcacga cggggatgag 840
cagagccggc gggtggcgca ggtcatcatc cccagcacgt acgtcccggg caccaccaac 900
cacgacatcg cgctgctccg cctgcaccag cccgtggtcc tcactgacca tgtggtgccc 960
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aacgtgcccc ggctgatgac ccaggactgc ctgcagcagt cacggaaggt gggagactcc 1140
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aagggggaca gtggaggccc acatgccacc cactaccggg gcacgtggta cctgacgggc 1260

atcgtcagct ggggccaggg ctgcgcaacc gtgggccact ttggggtgta caccagggtc 1320
tcccagtaca tcgagtggct gcaaaagctc atgcgctcag agccacgccc aggagtcctc 1380
ctgcgagccc catttccc 1398

<210> 103
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 血清白蛋白結合序列

<400> 103
Gln Arg Leu Met Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp
1 5 10 15
Glu Asp Asp Phe
20

<210> 104
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 血清白蛋白結合序列

<400> 104
Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu
1 5 10

<210> 105
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 血清白蛋白結合序列

<400> 105
Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu Asp
1 5 10

<210> 106
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 血清白蛋白結合序列

<400> 106
Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp
1 5 10

<210> 107
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 血清白蛋白結合序列

<400> 107
Gly Gly Gly Ser Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu
1 5 10 15
Trp

<210> 108
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 血清白蛋白結合序列

<400> 108
Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu Asp
1 5 10

<210> 109
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 血清白蛋白結合序列

<400> 109
Gly Gly Gly Ser Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu
1 5 10 15
Asp

<210> 110
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 血小板整合素IIb-IIIa結合序列

<400> 110
Ser Phe Gly Arg Gly Asp Ile Arg Asn Val
1 5 10

<210> 111
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 血小板整合素IIb-IIIa結合序列

<400> 111
Cys Ser Phe Gly Arg Gly Asp Ile Arg Asn Val Cys
1 5 10

<210> 112
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 血小板整合素IIb-IIIa結合序列

<400> 112
Gly Gly Gly Ser Cys Ser Phe Gly Arg Gly Asp Ile Arg Asn Val Cys
1 5 10 15

<210> 113
<211> 406

<212> PRT
<213> 現代人

<220>
<223> Q286N

<400> 113
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Asn Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 114
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286E

<400> 114
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu

1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Glu Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 115
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286D

<400> 115
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn

65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Asp Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 116
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286S

<400> 116
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg

130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Ser Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 117
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286T

<400> 117
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu

195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Thr Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 118
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286R

<400> 118
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr

260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 119
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286K

<400> 119
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Lys Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser

325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 120
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286A

<400> 120
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Ala Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu

385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 121
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286V

<400> 121
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Val Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 122
<211> 406
<212> PRT

<213> 現代人

<220>
<223> Q286M

<400> 122
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Met Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 123
<211> 406
<212> PRT
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<220>
<223> Q296L

<400> 123
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Leu Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 124
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286Y

<400> 124
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80

Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Tyr Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 125
<211> 406
<212> PRT
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<220>
<223> Q286G

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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140

Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gly Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 126
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286F

<400> 126
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205

Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Phe Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 127
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286I

<400> 127
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270

Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Ile Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 128
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286P

<400> 128
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Pro Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335

Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 129
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286H

<400> 129
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly His Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400

Leu Arg Ala Pro Phe Pro
405

<210> 130
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286W

<400> 130
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Trp Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 131
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Q286R/Gla交換FIX

<400> 131
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 132
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286R/H257A

<400> 132
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys

20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 133
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286R/S222A

<400> 133
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly

85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 134
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286R/S222A/H257A

<400> 134
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro

145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 135
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Q286R/S222A/Gla交換FIX

<400> 135
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg

210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 136
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Q286R/H257A/Gla交換FIX

<400> 136
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu

275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 137
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Q286R/S222A/H257A/Gla交換FIX

<400> 137
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His

340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 138
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286R/M298Q

<400> 138
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro

<210> 139
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286R/M298Q/K341Q

<400> 139
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 140
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286R/M298Q/K199E

<400> 140
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Glu Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 141
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Q286R/M298Q/Gla交換FIX

<400> 141
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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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 142
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286R/Q366V

<400> 142
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95

Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 143
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286R/A292N/A294S/Q366V

<400> 143
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160

Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Asn Thr Ser Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 144
<211> 406
<212> PRT
<213> 現代人

<220>
<223> A175S/Q286R/Q366V

<400> 144
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220

Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 145
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S222A/Q286R/Q366V

<400> 145
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285

Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 146
<211> 406
<212> PRT
<213> 現代人

<220>
<223> H257S/Q286R

<400> 146
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ser Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350

Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 147
<211> 406
<212> PRT
<213> 現代人

<220>
<223> H257S/Q286R/Q366V

<400> 147
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ser Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 148
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S222A/H257A/Q286R/Q366V

<400> 148
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 149
<211> 406
<212> PRT
<213> 現代人

<220>

<223> Q286R/H373A

<400> 149
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Ala Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 150
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S222A/H257A/Q286R/M158Q

<400> 150
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp

35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 151
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q286R/K341D

<400> 151
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys

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            100                 105                 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
        115                 120                 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
    130                 135                 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145                 150                 155                 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
                165                 170                 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
            180                 185                 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
        195                 200                 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
    210                 215                 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225                 230                 235                 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
                245                 250                 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
            260                 265                 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
        275                 280                 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
    290                 295                 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305                 310                 315                 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
                325                 330                 335
Lys Asp Ser Cys Asp Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
            340                 345                 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
        355                 360                 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
    370                 375                 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385                 390                 395                 400
Leu Arg Ala Pro Phe Pro
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
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Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
        35                  40                  45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
    50                  55                  60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65                  70                  75                  80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
                85                  90                  95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
            100                 105                 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
        115                 120                 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
    130                 135                 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145                 150                 155                 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
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165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Asp Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
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Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn

225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Asn Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
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35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg

290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Asp Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Asn Gly Cys

355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
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35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
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385 390 395 400
Leu Arg Ala Pro Phe Pro
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35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
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Leu Arg Ala Pro Phe Pro
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35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Asp Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Val Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
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Leu Arg Ala Pro Phe Pro
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35 40 45

Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ser Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
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35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110

Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Asn Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175

Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Gln Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<220>
<223> T239V

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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val Asn
225 230 235 240

His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 163
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T239L

<400> 163
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Leu Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300

Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<211> 406
<212> PRT
<213> 現代人

<220>
<223> T239H

<400> 164
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr His Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365

Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
    370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
                405

<210> 165
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T239I

<400> 165
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 1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
            20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
        35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
    50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
                85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
            100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
        115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
    130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
                165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
            180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
        195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
    210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
                245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
            260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
        275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
    290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
                325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
            340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
        355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
    370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
                405

<210> 166
<211> 406
<212> PRT
<213> 現代人

<220>
<223> P321K

<400> 166
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Lys Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 167
<211> 406
<212> PRT
<213> 現代人

<220>
<223> P321E

<400> 167
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Glu Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 168
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<220>
<223> P321Y

<400> 168
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln

50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Tyr Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 169
<211> 406
<212> PRT
<213> 現代人

<220>
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr

115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Ser Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 170
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q366D

<400> 170
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala

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                180                 185                 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
        195                 200                 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
    210                 215                 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225                 230                 235                 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
                245                 250                 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
            260                 265                 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
        275                 280                 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
    290                 295                 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305                 310                 315                 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
                325                 330                 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
            340                 345                 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Asp Gly Cys
        355                 360                 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
    370                 375                 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385                 390                 395                 400
Leu Arg Ala Pro Phe Pro
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<210> 171
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q366E

<400> 171
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
 1               5                  10                  15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
            20                  25                  30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
        35                  40                  45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
    50                  55                  60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65                  70                  75                  80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
                85                  90                  95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
            100                 105                 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
        115                 120                 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
    130                 135                 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145                 150                 155                 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
                165                 170                 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
            180                 185                 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
        195                 200                 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
    210                 215                 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225                 230                 235                 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
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245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Glu Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 172
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q366N

<400> 172
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser

305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Asn Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 173
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q366T

<400> 173
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Thr Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile

370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 174
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q366S

<400> 174
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Ser Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 175

<211> 406
<212> PRT
<213> 現代人

<220>
<221> 不確定
<222> (0)...(0)
<223> Q366V

<400> 175
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 176
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q366I

<400> 176
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Ile Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 177
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q366L

<400> 177
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45

Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Leu Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 178
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q366M

<400> 178
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110

Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Met Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 179
<211> 406
<212> PRT
<213> 現代人

<220>
<223> H373D

<400> 179
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175

Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Asp Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 180
<211> 406
<212> PRT
<213> 現代人

<220>
<223> H373E

<400> 180
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240

His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Glu Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 181
<211> 406
<212> PRT
<213> 現代人

<220>
<223> H373S

<400> 181
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300

Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Ser Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 182
<211> 406
<212> PRT
<213> 現代人

<220>
<223> H373F

<400> 182
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365

Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 183
<211> 406
<212> PRT
<213> 現代人

<220>
<223> H373A

<400> 183
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Ala Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 184
<211> 406
<212> PRT
<213> 現代人

<220>
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<400> 184
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Asp Gly Cys
355 360 365
Ala Thr Val Gly Glu Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly Val Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 186
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln

50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly Leu Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 187
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q366V/H373I

<400> 187
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr

115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly Ile Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 188
<211> 406
<212> PRT
<213> 現代人

<220>
<223> K161S

<400> 188
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Ser Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala

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            180                 185                 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
        195                 200                 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
    210                 215                 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225                 230                 235                 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
                245                 250                 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
            260                 265                 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
        275                 280                 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
    290                 295                 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305                 310                 315                 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
                325                 330                 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
            340                 345                 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
        355                 360                 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
    370                 375                 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385                 390                 395                 400
Leu Arg Ala Pro Phe Pro
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<212> PRT
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<223> K161A

<400> 189

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 1               5                  10                  15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
            20                  25                  30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
        35                  40                  45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
    50                  55                  60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65                  70                  75                  80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
                85                  90                  95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
            100                 105                 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
        115                 120                 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
    130                 135                 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145                 150                 155                 160
Ala Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
                165                 170                 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
            180                 185                 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
        195                 200                 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
    210                 215                 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225                 230                 235                 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
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245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 190
<211> 406
<212> PRT
<213> 現代人

<220>
<223> K161V

<400> 190
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Val Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser

305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<211> 406
<212> PRT
<213> 現代人

<220>
<223> H216S

<400> 191
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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu Ser Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile

370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 192
<211> 406
<212> PRT
<213> 現代人

<220>
<223> H216A

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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu Ala Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 193

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<212> PRT
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<220>
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<400> 193
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu Lys Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 194
<211> 406
<212> PRT
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<220>
<223> H216R

<400> 194

Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu Arg Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
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<220>
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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60

Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125

Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Lys Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190

His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Val Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<220>
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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Asn Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255

His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<212> PRT
<213> 現代人

<220>
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20 25 30
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35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Glu Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320

Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<213> 現代人

<220>
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20 25 30
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35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Asp Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380

Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
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<213> 現代人

<220>
<223> H257A

<400> 201
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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<211> 406

<212> PRT
<213> 現代人

<220>
<223> H257S

<400> 202
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ser Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<211> 406
<212> PRT
<213> 現代人

<220>
<223> S222K/H257A

<400> 203
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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Lys Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
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<212> PRT
<213> 現代人

<220>
<223> H216A/H257A

<400> 204
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn

65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu Ala Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<212> PRT
<213> 現代人

<220>
<223> H216A/S222A

<400> 205
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg

130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu Ala Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 206
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S52A

<400> 206
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ala Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu

195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 207
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S60A

<400> 207
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ala Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr

260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 208
<211> 406
<212> PRT
<213> 現代人

<220>
<223> E394N/P395A/R396S

<400> 208
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser

325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Asn Ala Ser Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 209
<211> 406
<212> PRT
<213> 現代人

<220>
<223> R202S

<400> 209
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Ser Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu

385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 210
<211> 406
<212> PRT
<213> 現代人

<220>
<223> A292N/A294S

<400> 210
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Asn Thr Ser Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 211
<211> 406
<212> PRT

<213> 現代人

<220>
<223> G318N

<400> 211
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Asn Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 212
<211> 406
<212> PRT
<213> 現代人

<220>
<223> A175S

<400> 212
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15

Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 213
<211> 406
<212> PRT
<213> 現代人

<220>
<223> K109N

<400> 213
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80

Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Asn Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 214
<211> 406
<212> PRT
<213> 現代人

<220>
<223> A122N/G124S

<400> 214
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Asn Asp Ser Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140

Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 215
<211> 406
<212> PRT
<213> 現代人

<220>
<223> A51N

<400> 215
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Asn Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205

Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 216
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T130N/E132S

<400> 216
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Asn Val Ser Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270

Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 217
<211> 406
<212> PRT
<213> 現代人

<220>
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Asn Asp Ser Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335

Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Asn Ala Ala Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 218
<211> 406
<212> PRT
<213> 現代人

<220>
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<400> 218
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Asn Asp Ser Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Asn Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Asn Ala Ala Pro Gly Val Leu
385 390 395 400

Leu Arg Ala Pro Phe Pro
405

<210> 219
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S52A/S60A

<400> 219
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ala Ser Pro Cys Gln Asn Gly Gly Ala Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 220
<211> 406
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<213> 現代人

<220>
<223> S52N/P54S

<400> 220
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Asn Ser Ser Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<211> 406
<212> PRT
<213> 現代人

<220>
<223> S119N/L121S

<400> 221
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys

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            20                  25                  30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
        35                  40                  45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
    50                  55                  60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65                  70                  75                  80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
                85                  90                  95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
            100                 105                 110
Arg Cys His Glu Gly Tyr Asn Leu Ser Ala Asp Gly Val Ser Cys Thr
        115                 120                 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
    130                 135                 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145                 150                 155                 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
                165                 170                 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
            180                 185                 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
        195                 200                 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
    210                 215                 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225                 230                 235                 240
His Asp Ile Ala Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
                245                 250                 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
            260                 265                 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
        275                 280                 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
    290                 295                 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305                 310                 315                 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
                325                 330                 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
            340                 345                 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
        355                 360                 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
    370                 375                 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385                 390                 395                 400
Leu Arg Ala Pro Phe Pro
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<210> 222
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A

<400> 222

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Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
 1               5                  10                  15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
            20                  25                  30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
        35                  40                  45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
    50                  55                  60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65                  70                  75                  80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
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85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 223
<211> 406
<212> PRT
<213> 現代人

<220>
<223> Q66N/Y68S

<400> 223
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Asn Ser Ser Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro

145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<211> 406
<212> PRT
<213> 現代人

<220>
<223> S52N/P54S/A122N/G124S/E394N/P395A/R396S

<400> 224
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Asn Ser Ser Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Asn Asp Ser Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg

210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Asn Ala Ser Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 225
<211> 406
<212> PRT
<213> 現代人

<220>
<223> K109N/A292N/A294S

<400> 225
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Asn Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu

275 280 285
Asp Arg Gly Asn Thr Ser Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 226
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<212> PRT
<213> 現代人

<220>
<223> K109N/A175S

<400> 226
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Asn Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr

340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 227
<211> 417
<212> PRT
<213> 現代人

<220>
<223> S103S111缺失插入QRLMEDICLPRWGCLWEDDF

<400> 227
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Gln Arg Leu Met Glu Asp Ile Cys Leu Pro
100 105 110
Arg Trp Gly Cys Leu Trp Glu Asp Asp Phe Cys Arg Cys His Glu Gly
115 120 125
Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu Tyr
130 135 140
Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro
145 150 155 160
Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro
165 170 175
Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly Thr
180 185 190
Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp Lys
195 200 205
Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp Leu
210 215 220
Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val Ile
225 230 235 240
Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala Leu
245 250 255
Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro Leu
260 265 270
Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val Arg
275 280 285
Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr
290 295 300
Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln Asp
305 310 315 320
Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr Glu
325 330 335
Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys
340 345 350
Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp Tyr
355 360 365
Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly His
370 375 380
Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys
385 390 395 400
Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro Phe

405 410 415
Pro

<210> 228
<211> 414
<212> PRT
<213> 現代人

<220>
<223> H115S126缺失插入QRLMEDICLPRWGCLWEDDF

<400> 228
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys Gln Arg Leu Met Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys
115 120 125
Leu Trp Glu Asp Asp Phe Cys Thr Pro Thr Val Glu Tyr Pro Cys Gly
130 135 140
Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg
145 150 155 160
Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val
165 170 175
Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn
180 185 190
Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn
195 200 205
Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His
210 215 220
Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser
225 230 235 240
Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu
245 250 255
His Gln Pro Val Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro
260 265 270
Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu
275 280 285
Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu
290 295 300
Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln
305 310 315 320
Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe
325 330 335
Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser
340 345 350
Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly
355 360 365
Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val
370 375 380
Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg
385 390 395 400
Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro Phe Pro
405 410

<210> 229
<211> 419
<212> PRT

<213> 現代人

<220>
<223> T128P134缺失插入QRLMEDICLPRWGCLWEDDF

<400> 229
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Gln
115 120 125
Arg Leu Met Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu
130 135 140
Asp Asp Phe Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser
145 150 155 160
Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu
165 170 175
Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly
180 185 190
Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe
195 200 205
Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His
210 215 220
Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln
225 230 235 240
Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp Ile
245 250 255
Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val
260 265 270
Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe
275 280 285
Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly
290 295 300
Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr
305 310 315 320
Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile
325 330 335
Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser
340 345 350
Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr
355 360 365
Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val
370 375 380
Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu
385 390 395 400
Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala
405 410 415
Pro Phe Pro

<210> 230
<211> 411
<212> PRT
<213> 現代人

<220>
<223> S103S111缺失插入IEDICLPRWGCLWE

<400> 230

Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly
100 105 110
Cys Leu Trp Glu Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp
115 120 125
Gly Val Ser Cys Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro
130 135 140
Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly
145 150 155 160
Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu
165 170 175
Val Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp
180 185 190
Val Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn
195 200 205
Leu Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp
210 215 220
Glu Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val
225 230 235 240
Pro Gly Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro
245 250 255
Val Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr
260 265 270
Phe Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly
275 280 285
Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val
290 295 300
Leu Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg
305 310 315 320
Lys Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly
325 330 335
Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro
340 345 350
His Ala Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser
355 360 365
Trp Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg
370 375 380
Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro
385 390 395 400
Arg Pro Gly Val Leu Leu Arg Ala Pro Phe Pro
405 410

<210> 231
<211> 408
<212> PRT
<213> 現代人

<220>
<223> H115S126缺失插入IEDICLPRWGCLWE

<400> 231
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60

Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu
115 120 125
Cys Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu
130 135 140
Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val
145 150 155 160
Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly
165 170 175
Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser
180 185 190
Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala
195 200 205
Val Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser
210 215 220
Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr
225 230 235 240
Thr Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu
245 250 255
Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu
260 265 270
Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln
275 280 285
Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val
290 295 300
Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly
305 310 315 320
Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp
325 330 335
Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr
340 345 350
His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln
355 360 365
Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln
370 375 380
Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly
385 390 395 400
Val Leu Leu Arg Ala Pro Phe Pro
405

<210> 232
<211> 413
<212> PRT
<213> 現代人

<220>
<223> 128P134缺失插入IEDICLPRWGCLWE

<400> 232
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Ile
115 120 125

Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu Cys Gly Lys
130 135 140
Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile
145 150 155 160
Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu
165 170 175
Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr
180 185 190
Ile Trp Val Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp
195 200 205
Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp
210 215 220
Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr
225 230 235 240
Tyr Val Pro Gly Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His
245 250 255
Gln Pro Val Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu
260 265 270
Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val
275 280 285
Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu
290 295 300
Met Val Leu Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln
305 310 315 320
Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys
325 330 335
Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly
340 345 350
Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile
355 360 365
Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr
370 375 380
Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser
385 390 395 400
Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro Phe Pro
405 410

<210> 233
<211> 410
<212> PRT
<213> 現代人

<220>
<223> S103S111缺失插入DICLPRWGCLWED

<400> 233
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu
100 105 110
Trp Glu Asp Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly
115 120 125
Val Ser Cys Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile
130 135 140
Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly
145 150 155 160
Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val
165 170 175
Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val
180 185 190

Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu
195 200 205
Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu
210 215 220
Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro
225 230 235 240
Gly Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val
245 250 255
Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe
260 265 270
Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp
275 280 285
Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu
290 295 300
Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys
305 310 315 320
Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr
325 330 335
Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His
340 345 350
Ala Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp
355 360 365
Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val
370 375 380
Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg
385 390 395 400
Pro Gly Val Leu Leu Arg Ala Pro Phe Pro
405 410

<210> 234
<211> 407
<212> PRT
<213> 現代人

<220>
<223> H115S126缺失插入DICLPRWGCLWED

<400> 234
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu Asp Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255

Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 235
<211> 412
<212> PRT
<213> 現代人

<220>
<223> T128P134缺失插入DICLPRWGCLWED

<400> 235
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asp
115 120 125
Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu Asp Cys Gly Lys Ile
130 135 140
Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val
145 150 155 160
Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu
165 170 175
Leu Val Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile
180 185 190
Trp Val Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg
195 200 205
Asn Leu Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp Gly
210 215 220
Asp Glu Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr
225 230 235 240
Val Pro Gly Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His Gln
245 250 255
Pro Val Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg
260 265 270
Thr Phe Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser
275 280 285
Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met
290 295 300
Val Leu Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser
305 310 315 320

Arg Lys Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala
325 330 335
Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly
340 345 350
Pro His Ala Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val
355 360 365
Ser Trp Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr
370 375 380
Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu
385 390 395 400
Pro Arg Pro Gly Val Leu Leu Arg Ala Pro Phe Pro
405 410

<210> 236
<211> 419
<212> PRT
<213> 現代人

<220>
<223> P406插入IEDICLPRWGCLW

<400> 236
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380

Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly
405 410 415
Cys Leu Trp

<210> 237
<211> 423
<212> PRT
<213> 現代人

<220>
<223> P406插入GGGSIEDICLPRWGCLW

<400> 237
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro Gly Gly Gly Ser Ile Glu Asp Ile Cys Leu
405 410 415
Pro Arg Trp Gly Cys Leu Trp
420

<210> 238
<211> 419
<212> PRT
<213> 現代人

<220>
<223> P406插入DICLPRWGCLWED

<400> 238
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu
405 410 415
Trp Glu Asp

<210> 239
<211> 423
<212> PRT
<213> 現代人

<220>
<223> P406插入GGGSDICLPRWGCLWED

<400> 239
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro Gly Gly Gly Ser Asp Ile Cys Leu Pro Arg
405 410 415
Trp Gly Cys Leu Trp Glu Asp
420

<210> 240
<211> 407
<212> PRT
<213> 現代人

<220>
<223> S103S111缺失插入SFGRGDIRNV

<400> 240
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu

1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Phe Gly Arg Gly Asp Ile Arg Asn Val
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 241
<211> 404
<212> PRT
<213> 現代人

<220>
<223> H115S126缺失插入SFGRGDIRNV

<400> 241
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn

65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys Ser Phe Gly Arg Gly Asp Ile Arg Asn Val Cys Thr Pro Thr
115 120 125
Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala
130 135 140
Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly
145 150 155 160
Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys
165 170 175
Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys
180 185 190
Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu
195 200 205
His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala
210 215 220
Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn His Asp
225 230 235 240
Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val
245 250 255
Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala
260 265 270
Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg
275 280 285
Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met
290 295 300
Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn
305 310 315 320
Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp
325 330 335
Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly
340 345 350
Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr
355 360 365
Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp
370 375 380
Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg
385 390 395 400
Ala Pro Phe Pro

<210> 242
<211> 409
<212> PRT
<213> 現代人

<220>
<223> T128P134缺失插入SFGRGDIRNV

<400> 242
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Ser
115 120 125
Phe Gly Arg Gly Asp Ile Arg Asn Val Cys Gly Lys Ile Pro Ile Leu

130 135 140
Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys
145 150 155 160
Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn
165 170 175
Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val
180 185 190
Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile
195 200 205
Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln
210 215 220
Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly
225 230 235 240
Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val
245 250 255
Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser
260 265 270
Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly
275 280 285
Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn
290 295 300
Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val
305 310 315 320
Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser
325 330 335
Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala
340 345 350
Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly
355 360 365
Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser
370 375 380
Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro
385 390 395 400
Gly Val Leu Leu Arg Ala Pro Phe Pro
405

<210> 243
<211> 418
<212> PRT
<213> 現代人

<220>
<223> P406插入CSFGRGDIRNVC

<400> 243
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu

195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro Cys Ser Phe Gly Arg Gly Asp Ile Arg Asn
405 410 415
Val Cys

<210> 244
<211> 422
<212> PRT
<213> 現代人

<220>
<223> P406插入GGGSCSFGRGDIRNVC

<400> 244
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp

245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro Gly Gly Gly Ser Cys Ser Phe Gly Arg Gly
405 410 415
Asp Ile Arg Asn Val Cys
420

<210> 245
<211> 407
<212> PRT
<213> 現代人

<220>
<223> S222A/Gla交換FIX

<400> 245
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro

290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 246
<211> 407
<212> PRT
<213> 現代人

<220>
<223> H257A/Gla交換FIX

<400> 246
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly

355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 247
<211> 407
<212> PRT
<213> 現代人

<220>
<223> S222A/H257A/Gla交換FIX

<400> 247
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 248
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S222A/M298Q

<400> 248
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<211> 406
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<213> 現代人

<220>
<223> H257A/M298Q

<400> 249
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 250
<211> 406
<212> PRT
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<220>
<223> S222A/H257A/M298Q

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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45

Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 251
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S222A/A292N/A294S/Q366V

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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110

Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Asn Thr Ser Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<211> 406
<212> PRT
<213> 現代人

<220>
<223> A175S/S222A/Q366V

<400> 252
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175

Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 253
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S222A/Q366V

<400> 253
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240

His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 254
<211> 406
<212> PRT
<213> 現代人

<220>
<223> H257S/Q366V

<400> 254
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ser Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300

Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 255
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S222A/H373A

<400> 255
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365

Ala Thr Val Gly Ala Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 256
<211> 406
<212> PRT
<213> 現代人

<220>
<223> V158T/L287T/M298K

<400> 256
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Thr Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Thr Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Lys Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 257
<211> 406
<212> PRT
<213> 現代人

<220>
<223> V21D/L287T/M298K

<400> 257
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Asp Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Thr Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Lys Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 258
<211> 411
<212> PRT
<213> 現代人

<220>
<223> S103S111缺失插入IEDICLPRWGCLWE/G237V

<400> 258
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly
100 105 110
Cys Leu Trp Glu Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp
115 120 125
Gly Val Ser Cys Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro
130 135 140
Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly
145 150 155 160
Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu
165 170 175
Val Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp
180 185 190
Val Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn
195 200 205
Leu Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp
210 215 220
Glu Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val
225 230 235 240
Pro Val Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro
245 250 255
Val Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr
260 265 270
Phe Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly
275 280 285
Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val
290 295 300
Leu Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg
305 310 315 320
Lys Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly
325 330 335
Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro
340 345 350
His Ala Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser
355 360 365
Trp Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg
370 375 380
Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro
385 390 395 400
Arg Pro Gly Val Leu Leu Arg Ala Pro Phe Pro
405 410

<210> 259
<211> 410
<212> PRT
<213> 現代人

<220>
<223> S103S111缺失插入DICLPRWGCLWED/G237V

<400> 259
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln

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    50                  55                  60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65                  70                  75                  80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
                85                  90                  95
Gly Cys Glu Gln Tyr Cys Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu
            100                 105                 110
Trp Glu Asp Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly
        115                 120                 125
Val Ser Cys Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile
    130                 135                 140
Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly
145                 150                 155                 160
Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val
                165                 170                 175
Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val
            180                 185                 190
Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu
        195                 200                 205
Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu
    210                 215                 220
Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro
225                 230                 235                 240
Val Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val
                245                 250                 255
Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe
            260                 265                 270
Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp
        275                 280                 285
Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu
    290                 295                 300
Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys
305                 310                 315                 320
Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr
                325                 330                 335
Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His
            340                 345                 350
Ala Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp
        355                 360                 365
Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val
    370                 375                 380
Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg
385                 390                 395                 400
Pro Gly Val Leu Leu Arg Ala Pro Phe Pro
                405                 410
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<210> 260
<211> 414
<212> PRT
<213> 現代人

<220>
<223> H115S126缺失插入QRLMEDICLPRWGCLWEDDF/G237V

<400> 260

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Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
 1               5                  10                  15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
            20                  25                  30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
        35                  40                  45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
    50                  55                  60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65                  70                  75                  80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
                85                  90                  95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
            100                 105                 110
Arg Cys Gln Arg Leu Met Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys
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115 120 125
Leu Trp Glu Asp Asp Phe Cys Thr Pro Thr Val Glu Tyr Pro Cys Gly
130 135 140
Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg
145 150 155 160
Ile Val Gly Gly Lys Val Cys Prc Lys Gly Glu Cys Pro Trp Gln Val
165 170 175
Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn
180 185 190
Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn
195 200 205
Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His
210 215 220
Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser
225 230 235 240
Thr Tyr Val Pro Val Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu
245 250 255
His Gln Pro Val Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro
260 265 270
Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu
275 280 285
Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu
290 295 300
Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln
305 310 315 320
Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe
325 330 335
Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser
340 345 350
Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly
355 360 365
Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val
370 375 380
Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg
385 390 395 400
Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro Phe Pro
405 410

<210> 261
<211> 408
<212> PRT
<213> 現代人

<220>
<223> H115S126缺失插入IEDICLPRWGCLWE/G237V

<400> 261
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys Ile Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu
115 120 125
Cys Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu
130 135 140
Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val
145 150 155 160
Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly
165 170 175
Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser

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            180                 185                 190
Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala
        195                 200                 205
Val Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser
    210                 215                 220
Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Val Thr
225                 230                 235                 240
Thr Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu
                245                 250                 255
Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu
            260                 265                 270
Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln
        275                 280                 285
Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val
    290                 295                 300
Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly
305                 310                 315                 320
Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp
                325                 330                 335
Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr
            340                 345                 350
His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln
        355                 360                 365
Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln
    370                 375                 380
Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly
385                 390                 395                 400
Val Leu Leu Arg Ala Pro Phe Pro
                405


<210> 262
<211> 407
<212> PRT
<213> 現代人

<220>
<223> H115S126缺失插入DICLPRWGCLWED/G237V

<400> 262
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
 1               5                  10                  15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
            20                  25                  30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
        35                  40                  45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
    50                  55                  60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65                  70                  75                  80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
                85                  90                  95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
            100                 105                 110
Arg Cys Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu Asp Cys
        115                 120                 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
    130                 135                 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145                 150                 155                 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
                165                 170                 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
            180                 185                 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
        195                 200                 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
    210                 215                 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Val Thr Thr
225                 230                 235                 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
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245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 263
<211> 419
<212> PRT
<213> 現代人

<220>
<223> T128P134缺失插入QRLMEDICLPRWGCLWEDDF/G237V

<400> 263
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Gln
115 120 125
Arg Leu Met Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu
130 135 140
Asp Asp Phe Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser
145 150 155 160
Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu
165 170 175
Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly
180 185 190
Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe
195 200 205
Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His
210 215 220
Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln
225 230 235 240
Val Ile Ile Pro Ser Thr Tyr Val Pro Val Thr Thr Asn His Asp Ile
245 250 255
Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val
260 265 270
Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe
275 280 285
Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly
290 295 300
Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr

305 310 315 320
Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile
325 330 335
Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser
340 345 350
Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr
355 360 365
Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val
370 375 380
Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu
385 390 395 400
Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala
405 410 415
Pro Phe Pro

<210> 264
<211> 413
<212> PRT
<213> 現代人

<220>
<223> T128P134缺失插入IEDICLPRWGCLWE/G237V

<400> 264
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Ile
115 120 125
Glu Asp Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu Cys Gly Lys
130 135 140
Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile
145 150 155 160
Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu
165 170 175
Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr
180 185 190
Ile Trp Val Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp
195 200 205
Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp
210 215 220
Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr
225 230 235 240
Tyr Val Pro Val Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His
245 250 255
Gln Pro Val Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu
260 265 270
Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val
275 280 285
Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu
290 295 300
Met Val Leu Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln
305 310 315 320
Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys
325 330 335
Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly
340 345 350
Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile

355 360 365
Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr
370 375 380
Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser
385 390 395 400
Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro Phe Pro
405 410

<210> 265
<211> 417
<212> PRT
<213> 現代人

<220>
<223> S103S111缺失插入QRLMEDICLPRWGCLWEDDF/G237V

<400> 265
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Gln Arg Leu Met Glu Asp Ile Cys Leu Pro
100 105 110
Arg Trp Gly Cys Leu Trp Glu Asp Asp Phe Cys Arg Cys His Glu Gly
115 120 125
Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr Pro Thr Val Glu Tyr
130 135 140
Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro
145 150 155 160
Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro
165 170 175
Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys Gly Gly Thr
180 185 190
Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys Phe Asp Lys
195 200 205
Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu His Asp Leu
210 215 220
Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala Gln Val Ile
225 230 235 240
Ile Pro Ser Thr Tyr Val Pro Val Thr Thr Asn His Asp Ile Ala Leu
245 250 255
Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val Val Pro Leu
260 265 270
Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala Phe Val Arg
275 280 285
Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr
290 295 300
Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met Thr Gln Asp
305 310 315 320
Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn Ile Thr Glu
325 330 335
Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys
340 345 350
Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly Thr Trp Tyr
355 360 365
Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr Val Gly His
370 375 380
Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys
385 390 395 400
Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg Ala Pro Phe
405 410 415
Pro

<210> 266
<211> 412
<212> PRT
<213> 現代人

<220>
<223> T128P134缺失插入DICLPRWGCLWED/G237V

<400> 266
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asp
115 120 125
Ile Cys Leu Pro Arg Trp Gly Cys Leu Trp Glu Asp Cys Gly Lys Ile
130 135 140
Pro Ile Leu Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val
145 150 155 160
Gly Gly Lys Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu
165 170 175
Leu Val Asn Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile
180 185 190
Trp Val Val Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg
195 200 205
Asn Leu Ile Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp Gly
210 215 220
Asp Glu Gln Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr
225 230 235 240
Val Pro Val Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His Gln
245 250 255
Pro Val Val Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg
260 265 270
Thr Phe Ser Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser
275 280 285
Gly Trp Gly Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met
290 295 300
Val Leu Asn Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser
305 310 315 320
Arg Lys Val Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala
325 330 335
Gly Tyr Ser Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly
340 345 350
Pro His Ala Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val
355 360 365
Ser Trp Gly Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr
370 375 380
Arg Val Ser Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu
385 390 395 400
Pro Arg Pro Gly Val Leu Leu Arg Ala Pro Phe Pro
405 410

<210> 267
<211> 407
<212> PRT
<213> 現代人

<220>
<223> S103S111缺失插入SFGRGDIRNV/G237V

<400> 267
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Phe Gly Arg Gly Asp Ile Arg Asn Val
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Val Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 268
<211> 404
<212> PRT
<213> 現代人

<220>
<223> H115S126缺失插入SFGRGDIRNV/G237V

<400> 268
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30

Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys Ser Phe Gly Arg Gly Asp Ile Arg Asn Val Cys Thr Pro Thr
115 120 125
Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg Asn Ala
130 135 140
Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro Lys Gly
145 150 155 160
Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln Leu Cys
165 170 175
Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala His Cys
180 185 190
Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu Gly Glu
195 200 205
His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg Val Ala
210 215 220
Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Val Thr Thr Asn His Asp
225 230 235 240
Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp His Val
245 250 255
Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr Leu Ala
260 265 270
Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu Asp Arg
275 280 285
Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg Leu Met
290 295 300
Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser Pro Asn
305 310 315 320
Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser Lys Asp
325 330 335
Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr Arg Gly
340 345 350
Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys Ala Thr
355 360 365
Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile Glu Trp
370 375 380
Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu Leu Arg
385 390 395 400
Ala Pro Phe Pro

<210> 269
<211> 409
<212> PRT
<213> 現代人

<220>
<223> T128P134缺失插入SFGRGDIRNV/G237V

<400> 269
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95

Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Ser
115 120 125
Phe Gly Arg Gly Asp Ile Arg Asn Val Cys Gly Lys Ile Pro Ile Leu
130 135 140
Glu Lys Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys
145 150 155 160
Val Cys Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn
165 170 175
Gly Ala Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val
180 185 190
Ser Ala Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile
195 200 205
Ala Val Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln
210 215 220
Ser Arg Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Val
225 230 235 240
Thr Thr Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val
245 250 255
Leu Thr Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser
260 265 270
Glu Arg Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly
275 280 285
Gln Leu Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn
290 295 300
Val Pro Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val
305 310 315 320
Gly Asp Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser
325 330 335
Asp Gly Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala
340 345 350
Thr His Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly
355 360 365
Gln Gly Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser
370 375 380
Gln Tyr Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro
385 390 395 400
Gly Val Leu Leu Arg Ala Pro Phe Pro
405

<210> 270
<211> 406
<212> PRT
<213> 現代人

<220>
<223> M298Q/H373F

<400> 270
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160

Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 271
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S119N/L121S/A175S

<400> 271
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Asn Leu Ser Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220

Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 272
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A/A175S

<400> 272
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285

Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 273
<211> 406
<212> PRT
<213> 現代人

<220>
<223> A122N/G124S/A175S

<400> 273
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Asn Asp Ser Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350

Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 274
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/E39L/Q286R/M298Q

<400> 274
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 Leu Phe Trp Lys Gln Tyr Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 275
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/K42I/Q286R/M298Q/

<400> 275
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 Ile Gln Tyr Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 276
<211> 407
<212> PRT
<213> 現代人

<220>

<223> Gla交換FIX/Q43S/Q286R/M298Q/

<400> 276
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 Ser Tyr Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 277
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/M18K/Q286R/M298Q/

<400> 277
Tyr Asn Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg
1 5 10 15
Glu Cys Lys 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 Ser Asp Gly

35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 278
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/M18K/E39L/K42I/Q43S/Q286R/M298Q/

<400> 278
Tyr Asn Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg
1 5 10 15
Glu Cys Lys Glu Glu Lys Cys Ser Phe Glu Glu Ala Arg Glu Val Phe
20 25 30
Glu Asn Thr Glu Arg Thr Thr Leu Phe Trp Ile Ser Tyr Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser

```
                100                 105                 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
        115                 120                 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
    130                 135                 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145                 150                 155                 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
                165                 170                 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
            180                 185                 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
        195                 200                 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
    210                 215                 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225                 230                 235                 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
                245                 250                 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
            260                 265                 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
        275                 280                 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
    290                 295                 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305                 310                 315                 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
                325                 330                 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
            340                 345                 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
        355                 360                 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
    370                 375                 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385                 390                 395                 400
Leu Leu Arg Ala Pro Phe Pro
                405
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<210> 279
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A/Q286R

<400> 279

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 1               5                  10                  15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
            20                  25                  30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
        35                  40                  45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
    50                  55                  60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65                  70                  75                  80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
                85                  90                  95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
            100                 105                 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
        115                 120                 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
    130                 135                 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145                 150                 155                 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
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165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 280
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A/Q286R/M298Q

<400> 280
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn

225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 281
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A/Q286R/H373F

<400> 281
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg

290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 282
<211> 406
<212> PRT
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<220>
<223> V158D/Q286R/E296V/M298Q

<400> 282
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Asp Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Val Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys

355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 283
<211> 406
<212> PRT
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<223> T128N/P129A/V158D/E296V/M298Q

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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Asp Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Val Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<212> PRT
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<220>
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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 285
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/T128N/P129A/S222A/Q286R

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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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Asn Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

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<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/T128N/P129A/Q286R/M298Q

<400> 286
Tyr Asn Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg
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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 Ser Asp Gly
35 40 45

Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Asn Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

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<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A/S222A/H257A/Q286R/M298Q

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Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110

Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 288
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A/Q286R/M298Q/H373F

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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175

Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 289
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S52A/S60A/V158D/E296V/M298Q

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Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ala Ser Pro Cys Gln Asn Gly Gly Ala Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Asp Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240

His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Val Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 290
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S52A/S60A/Q286R

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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ala Ser Pro Cys Gln Asn Gly Gly Ala Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300

Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 291
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S52A/S60A/S222A

<400> 291
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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ala Ser Pro Cys Gln Asn Gly Gly Ala Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365

Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 292
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/S52A/S60A/S222A/Q286R

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Tyr Asn Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg
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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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ala Ser Pro Cys Gln Asn Gly Gly Ala Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 293
<211> 406
<212> PRT
<213> 現代人

<400> 293
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ala Ser Pro Cys Gln Asn Gly Gly Ala Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 294
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/S52A/S60A/Q286R/M298Q

<400> 294
Tyr Asn Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg
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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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ala Ser Pro Cys Gln Asn Gly Gly Ala Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 295
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S52A/S60A/S222A/H257A/Q286R/M298Q

<400> 295
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ala Ser Pro Cys Gln Asn Gly Gly Ala Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80

Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 296
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S52A/S60A/Q286R/H373F

<400> 296
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ala Ser Pro Cys Gln Asn Gly Gly Ala Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140

Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 297
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S52A/S60A/Q286R/M298Q/H373F

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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ala Ser Pro Cys Gln Asn Gly Gly Ala Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205

Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 298
<211> 406
<212> PRT
<213> 現代人

<220>
<223> V158D/T239V/E296V/M298Q

<400> 298
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Asp Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270

Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Val Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 299
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T239V/Q286R

<400> 299
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Val Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335

Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 300
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S222A/T239V

<400> 300
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400

Leu Arg Ala Pro Phe Pro
405

<210> 301
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/S222A/T239V/Q286R

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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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 302
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T239V/Q286R/M298Q

<400> 302
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 303
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S222A/T239V/H257A/Q286R/M298Q

<400> 303
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys

20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 304
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/T239V/Q286R/M298Q

<400> 304
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn

85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 305
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T239V/Q286R/H373F

<400> 305
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro

145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 306
<211> 406
<212> PRT
<213> 現代人

<400> 306
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val Asn
225 230 235 240

His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 307
<211> 406
<212> PRT
<213> 現代人

<220>
<223> V158D/T239I/E296V/M298Q

<400> 307
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Asp Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Val Leu Gln Val Leu Asn Val Pro Arg
290 295 300

Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 308
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T239I/Q286R

<400> 308
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365

Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 309
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S222A/T239I

<400> 309
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 310
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/S222A/T239I/Q286R

<400> 310
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 311
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T239I/Q286R/M298Q

<400> 311
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 312
<211> 406
<212> PRT
<213> 現代人

<220>
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln

50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 313
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/T239I/Q286R/M298Q

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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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys

115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 314
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T239I/Q286R/H373F

<400> 314
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala

180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 315
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T239I/Q286R/M298Q/H373F

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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp

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                245                 250                 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
            260                 265                 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
        275                 280                 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
    290                 295                 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305                 310                 315                 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
                325                 330                 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
            340                 345                 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
        355                 360                 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
    370                 375                 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385                 390                 395                 400
Leu Arg Ala Pro Phe Pro
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<210> 316
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/S222A/Q286R/H373F

<400> 316
Tyr Asn Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg
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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 Ser Asp Gly
        35                  40                  45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
    50                  55                  60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65                  70                  75                  80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
                85                  90                  95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
            100                 105                 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
        115                 120                 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
    130                 135                 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145                 150                 155                 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
                165                 170                 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
            180                 185                 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
        195                 200                 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg
    210                 215                 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225                 230                 235                 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
                245                 250                 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
            260                 265                 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
        275                 280                 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
    290                 295                 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
```

305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 317
<211> 407
<212> PRT
<213> 現代人

<220>
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<400> 317
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr

370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 318
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/S222A/Q286R/M298Q/H373F

<400> 318
Tyr Asn Ser Gly Lys Leu Glu Glu Phe Val Gln Gly Asn Leu Glu Arg
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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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

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<213> 現代人

<220>
<223> V158D/E296V/M298Q/H373F

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Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Asp Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Val Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 320
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Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Asp Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Val Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<220>
<223> H257A/Q286R/M298Q

<400> 321
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60

Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 322
<211> 406
<212> PRT
<213> 現代人

<220>
<223> H257S/Q286R/M298Q

<400> 322
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125

Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ser Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 323
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/S222A/H257S/Q286R/

<400> 323
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190

Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp Ser Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 324
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S222A/H257S/Q286R/M298Q

<400> 324
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255

Ser Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 325
<211> 406
<212> PRT
<213> 現代人

<220>
<223> H257S/Q286R/M298Q/H373F

<400> 325
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ser Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320

Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 326
<211> 406
<212> PRT
<213> 現代人

<220>
<223> S222A/Q286R/M298Q/H373F

<400> 326
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380

Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 327
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/Q366V

<400> 327
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 328
<211> 406

<212> PRT
<213> 現代人

<220>
<223> S222A/Q286R/M298Q

<400> 328
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 329
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T28N/P129A/A175S/Q366V

<400> 329
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu

1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 330
<211> 406
<212> PRT
<213> 現代人

<220>
<223> A122N/G124S/A175S/Q366V

<400> 330
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn

65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Asn Asp Ser Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Val Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 331
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A/A175S/S222A

<400> 331
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg

130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 332
<211> 406
<212> PRT
<213> 現代人

<220>
<223> A122N/G124S/A175S/S222A

<400> 332
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Asn Asp Ser Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu

195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 333
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A/A175S/Q286

<400> 333
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr

260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 334
<211> 406
<212> PRT
<213> 現代人

<220>
<223> A122N/G124S/A175S/Q286R

<400> 334
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Asn Asp Ser Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser

325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 335
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/T128N/P129A/A175S/S222A/Q286R

<400> 335
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Asn Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val

385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 336
<211> 407
<212> PRT
<213> 現代人

<220>
<223> Gla交換FIX/A122N/G124S/A175S/S222A/Q286R

<400> 336
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 Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Asn Asp Ser Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 337
<211> 406
<212> PRT

<213> 現代人

<220>
<223> T128N/P129A/A175S/Q286R/M298Q

<400> 337
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 338
<211> 406
<212> PRT
<213> 現代人

<220>
<223> A122N/G124S/A175S/Q286R/M298Q

<400> 338
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15

Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Asn Asp Ser Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 339
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A/A175S/S222A/H257A/Q286R/M298Q

<400> 339
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80

Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 340
<211> 406
<212> PRT
<213> 現代人

<220>
<223> A122N/G124S/A175S/S222A/H257A/Q286R/M298Q

<400> 340
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Asn Asp Ser Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140

Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
Ala Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 341
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A/A175S/Q286R/M298Q/H373F

<400> 341
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205

Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 342
<211> 406
<212> PRT
<213> 現代人

<220>
<223> A122N/G124S/A175S/Q286R/M298Q/H373F

<400> 342
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Asn Asp Ser Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ser Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270

Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 343
<211> 406
<212> PRT
<213> 現代人

<220>
<223> E296V/M298Q

<400> 343
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Val Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335

Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<220>
<223> V158E

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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Glu Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400

Leu Arg Ala Pro Phe Pro
405

<210> 345
<211> 406
<212> PRT
<213> 現代人

<220>
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Arg Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 346
<211> 406
<212> PRT
<213> 現代人

<220>
<223> K337A

<400> 346
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1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Ala Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<211> 406
<212> PRT
<213> 現代人

<220>
<223> V158D/E296V/M298Q/K337A

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Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys

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Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
        35                  40                  45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
    50                  55                  60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65                  70                  75                  80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
                85                  90                  95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
            100                 105                 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
        115                 120                 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
    130                 135                 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Asp Cys Pro
145                 150                 155                 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
                165                 170                 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
            180                 185                 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
        195                 200                 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
    210                 215                 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225                 230                 235                 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
                245                 250                 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
            260                 265                 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
        275                 280                 285
Asp Arg Gly Ala Thr Ala Leu Val Leu Gln Val Leu Asn Val Pro Arg
    290                 295                 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305                 310                 315                 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
                325                 330                 335
Ala Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
            340                 345                 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
        355                 360                 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
    370                 375                 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385                 390                 395                 400
Leu Arg Ala Pro Phe Pro
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<212> PRT
<213> 現代人

<220>
<223> V253N

<400> 348

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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
            20                  25                  30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
        35                  40                  45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
    50                  55                  60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65                  70                  75                  80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
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85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Asn Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<211> 406
<212> PRT
<213> 現代人

<220>
<223> T106N

<400> 349
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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Asn Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro

145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<213> 現代人

<220>
<223> T106N/V253N

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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Asn Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg

210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Asn Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 351
<211> 406
<212> PRT
<213> 現代人

<220>
<223> K143N/N145T

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Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Asn Arg
130 135 140
Thr Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu

275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 352
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<212> PRT
<213> 現代人

<220>
<223> R315N/V317T

<400> 352
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1 5 10 15
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20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Asn Lys Thr Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr

340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

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<211> 406
<212> PRT
<213> 現代人

<220>
<223> K143N/N145T/R315N/V317T

<400> 353
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
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Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Asn Arg
130 135 140
Thr Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Met Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro

<210> 354
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A/M298Q

<400> 354
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 355
<211> 407
<212> PRT
<213> 現代人

<220>
<223> {Gla交換FIX/K43I}/T128N/P129A/Q286R/M298Q

<400> 355
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 Ile Gln Tyr Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Asn Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 356
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A/Q286R/M298Q/Q366N

<400> 356
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30

Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Asn Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 357
<211> 407
<212> PRT
<213> 現代人

<220>
<223> {Gla交換FIX/K43I}/Q286R/M298Q/Q366N

<400> 357
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 Ile Gln Tyr Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95

Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Thr Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160
Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Asn Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 358
<211> 407
<212> PRT
<213> 現代人

<220>
<223> {Gla交換FIX/K43I}/T128N/P129A/Q286R/M298Q/Q366N

<400> 358
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 Ile Gln Tyr Ser Asp Gly
35 40 45
Asp Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp
50 55 60
Gln Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg
65 70 75 80
Asn Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn
85 90 95
Gly Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser
100 105 110
Cys Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys
115 120 125
Asn Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys
130 135 140
Arg Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys
145 150 155 160

Pro Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala
165 170 175
Gln Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala
180 185 190
Ala His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val
195 200 205
Leu Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg
210 215 220
Arg Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr
225 230 235 240
Asn His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr
245 250 255
Asp His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg
260 265 270
Thr Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu
275 280 285
Leu Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro
290 295 300
Arg Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp
305 310 315 320
Ser Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly
325 330 335
Ser Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His
340 345 350
Tyr Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Asn Gly
355 360 365
Cys Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr
370 375 380
Ile Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val
385 390 395 400
Leu Leu Arg Ala Pro Phe Pro
405

<210> 359
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T128N/P129A/M298Q/H373F

<400> 359
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220

Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 360
<211> 406
<212> PRT
<213> 現代人

<220>
<223> V158D/Q286R/E296V/M298Q

<400> 360
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Asp Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285

Asp Arg Gly Ala Thr Ala Leu Val Leu Gln Val Leu Asn Val Pro Arg
    290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
    370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 361
<211> 406
<212> PRT
<213> 現代人

<220>
<223> M298Q/Q366N/H373F

<400> 361
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
    50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
    130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
    210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
    290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350

Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Asn Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 362
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T239V/M298Q/H373F

<400> 362
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
Glu Trp Leu Gln Lys Leu Met Arg Ser Glu Pro Arg Pro Gly Val Leu
385 390 395 400
Leu Arg Ala Pro Phe Pro
405

<210> 363
<211> 406
<212> PRT
<213> 現代人

<220>
<223> T239I/M298Q/H373F

<400> 363
Ala Asn Ala Phe Leu Glu Glu Leu Arg Pro Gly Ser Leu Glu Arg Glu
1 5 10 15
Cys Lys Glu Glu Gln Cys Ser Phe Glu Glu Ala Arg Glu Ile Phe Lys
20 25 30
Asp Ala Glu Arg Thr Lys Leu Phe Trp Ile Ser Tyr Ser Asp Gly Asp
35 40 45
Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
115 120 125
Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Gln Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
370 375 380
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Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
50 55 60
Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
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85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
100 105 110
Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
115 120 125
Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
130 135 140
Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Thr Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
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355 360 365
Ala Thr Val Gly Phe Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
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Pro Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
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145 150 155 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
165 170 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
275 280 285
Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Asn Gly Cys
355 360 365
Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
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Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
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Leu Gln Ser Tyr Ile Cys Phe Cys Leu Pro Ala Phe Glu Gly Arg Asn
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Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
85 90 95
Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys

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Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Thr
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Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
                165                 170                 175
Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
            180                 185                 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
        195                 200                 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
    210                 215                 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile Asn
225                 230                 235                 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
                245                 250                 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
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Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
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Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
    290                 295                 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
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Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
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Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Asn Gly Cys
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Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
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Gln Cys Ala Ser Ser Pro Cys Gln Asn Gly Gly Ser Cys Lys Asp Gln
    50                  55                  60
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Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
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Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
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Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
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Asn Ala Ser Lys Pro Gln Gly Arg Ile Val Gly Gly Lys Val Cys Pro
145                 150                 155                 160
Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
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Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
195 200 205
Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
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290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
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Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
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Ala Thr Val Glu Tyr Pro Cys Gly Lys Ile Pro Ile Leu Glu Lys Arg
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Lys Gly Glu Cys Pro Trp Gln Val Leu Leu Leu Val Asn Gly Ala Gln
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Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
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Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ala Arg Arg
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Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val Asn

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Leu Ala Phe Val Arg Phe Ser Leu Val Ser Gly Trp Gly Arg Leu Leu
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Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
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Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
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Ala Thr Val Gly His Phe Gly Val Tyr Thr Arg Val Ser Gln Tyr Ile
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Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
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Arg Cys His Glu Gly Tyr Ser Leu Leu Ala Asp Gly Val Ser Cys Asn
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180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
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Gly Glu His Asp Leu Ser Glu His Asp Gly Asp Glu Gln Ser Arg Arg
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Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Val Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
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His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
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65 70 75 80
Cys Glu Thr His Lys Asp Asp Gln Leu Ile Cys Val Asn Glu Asn Gly
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Gly Cys Glu Gln Tyr Cys Ser Asp His Thr Gly Thr Lys Arg Ser Cys
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Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
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210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile Asn
225 230 235 240
His Asp Ile Ala Leu Leu Arg Leu His Gln Pro Val Val Leu Thr Asp
245 250 255
His Val Val Pro Leu Cys Leu Pro Glu Arg Thr Phe Ser Glu Arg Thr
260 265 270
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Asp Arg Gly Ala Thr Ala Leu Glu Leu Gln Val Leu Asn Val Pro Arg
290 295 300
Leu Met Thr Gln Asp Cys Leu Gln Gln Ser Arg Lys Val Gly Asp Ser
305 310 315 320
Pro Asn Ile Thr Glu Tyr Met Phe Cys Ala Gly Tyr Ser Asp Gly Ser
325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
340 345 350
Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys

355 360 365
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Leu Cys Gly Gly Thr Leu Ile Asn Thr Ile Trp Val Val Ser Ala Ala
180 185 190
His Cys Phe Asp Lys Ile Lys Asn Trp Arg Asn Leu Ile Ala Val Leu
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210 215 220
Val Ala Gln Val Ile Ile Pro Ser Thr Tyr Val Pro Gly Thr Ile Asn
225 230 235 240
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245 250 255
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325 330 335
Lys Asp Ser Cys Lys Gly Asp Ser Gly Gly Pro His Ala Thr His Tyr
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Arg Gly Thr Trp Tyr Leu Thr Gly Ile Val Ser Trp Gly Gln Gly Cys
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I465247

公告本

發明專利說明書

（本說明書格式、順序，請勿任意更動，※記號部分請勿填寫）

※申請案號：P811171P1　　A61K 38/37 (2006.01)

※申請日：P8.4.P　　※IPC 分類：C07K 14/755 (2006.01)

A61P 7/04 (2006.01)

一、發明名稱：（中文/英文）

經修飾的因子 VII 多肽和其用途

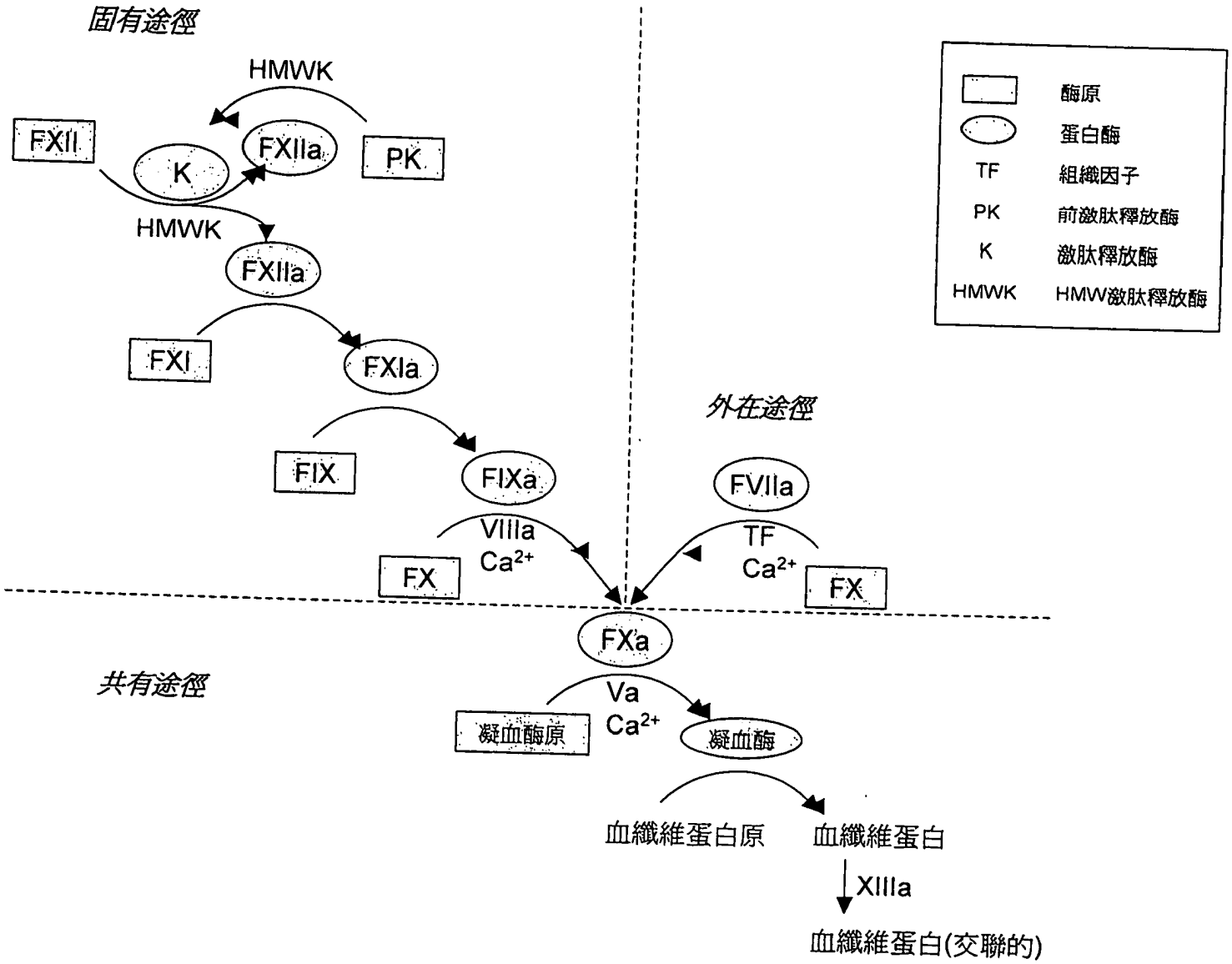
FACTOR VII POLYPEPTIDES THAT ARE MODIFIED AND USES THEREOF

二、中文發明摘要：

本發明提供經修飾的因子 VII 多肽和其用途。該等經修飾的 FVII 多肽包括因子 VIIa 及因子 VII 之其他形式。所提供之經修飾的 FVII 多肽中，有具有經改變之活性（典型地經改變之促凝血活性，包括促凝血活性增強之彼等 FVII 多肽）者。因此，該等經修飾的多肽為治療劑。

三、英文發明摘要：

Modified factor VII polypeptides and uses thereof are provided. Such modified FVII polypeptides include Factor VIIa and other forms of Factor VII. Among modified FVII polypeptides provided are those that have altered activities, typically altered procoagulant activity, including increased procoagulant activities. Hence, such modified polypeptides are therapeutics.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HMWK
FXII
K
FXIIa
PK
HMWK
FXIIa
FXI
FXIa
FIX
FIXa
VIIIa
Ca2+
FX
外在途徑
FVIIa
TF
Ca2+
FX
FXa
共有途徑
Va
Ca2+
凝血酶原
凝血酶
血纖維蛋白原
血纖維蛋白
XIIIa
血纖維蛋白(交聯的)
酶原
蛋白酶
TF 組織因子
PK 前激肽釋放酶
K 激肽釋放酶
HMWK HMW激肽釋放酶

圖1.凝血級聯

四、指定代表圖：

(一)本案指定代表圖為：第（ 1 ）圖。

(二)本代表圖之元件符號簡單說明:

無

五、本案若有化學式時，請揭示最能顯示發明特徵的化學式：

無

103年6月5日修正替換頁 第1-10頁

103 年 6 月 5 日替換頁

七、申請專利範圍：

1.一種經修飾之因子 VII（FVII）多肽，其在 FVII 多肽中包含修飾，其中：

該修飾在對應於具有 SEQ ID NO: 3 中所闡明的胺基酸序列之 FVII 多肽中位置 286 及位置 298 的位置或在 FVII 多肽比對位（aligned loci）之對應位置上；

在位置 286 上的修飾為使用精胺酸（Arg, R）的胺基酸置換；

在位置 298 上的修飾為使用麩醯胺酸（Gln, Q）的胺基酸置換；

未經修飾的 FVII 多肽包含 SEQ ID NO: 1-3 中任一者所闡明的胺基酸序列；

與未經修飾的 FVII 多肽（其不具有在位置 286 上的修飾）相比，經修飾的 FVII 多肽當活化時，展現增強之凝血劑活性。

2.如申請專利範圍第 1 項之經修飾之 FVII 多肽，其包含修飾 Q286R 及 M298Q，其中該未經修飾的 FVII 多肽由 SEQ ID NO: 3 中所闡明的胺基酸序列組成。

3.如申請專利範圍第 1 項之經修飾之 FVII 多肽，其中該未經修飾的多肽是包含 SEQ ID NO: 1 或 2 中所闡明的胺基酸序列的多肽。

4.如申請專利範圍第 1-3 項中任一項之經修飾之 FVII 多肽，其包含選自以下者之一或多個進一步修飾：D196K、D196R、D196A、D196Y、D196F、D196W、D196L、D196I、

K197Y、K197A、K197E、K197D、K197L、K197M、K197I、K197V、K197F、K197W、K199A、K199D、K199E、G237W、G237T、G237I、G237V、T239A、R290A、R290E、R290D、R290N、R290Q、R290K、R290M、R290V、K341E、K341R、K341Q、K341N、K341M、K341D、G237T238 插入 A、G237T238 插入 S、G237T238 插入 V、G237T238 插入 AS、G237T238 插入 SA、D196K197 插入 K、D196K197 插入 R、D196K197 插入 Y、D196K197 插入 W、D196K197 插入 A、D196K197 插入 M、K197I198 插入 E、K197I198 插入 Y、K197I198 插入 A、K197I198 插入 S、T239S、T239N、T239Q、T239V、T239L、T239H、T239I、L287T、P321K、P321E、P321Y、P321S、Q366D、Q366E、Q366N、Q366T、Q366S、Q366V、Q366I、Q366L、Q366M、H373D、H373E、H373S、H373L、H373I、H373F、H373A、K161S、K161A、K161V、H216S、H216A、H216K、H216R、S222A、S222K、S222V、S222N、S222E、S222D、H257A、H257S、Gla 交換 FIX 、{Gla 交換 FIX/E40L}、{Gla 交換 FIX/K43I}、{Gla 交換 FIX/Q44S}、{Gla 交換 FIX/M19K} 、{Gla 交換 FIX/M19K/E40L/K43I/Q44S}、Gla 交換 FX 、Gla 交換蛋白質 C、Gla 交換蛋白質 S、Gla 交換凝血酶、S52A、S60A、E394N、P395A、R396S、R202S、A292N、A294S、G318N、A175S、K109N、A122N、G124S、A51N、T130N、E132S、S52N、P54S、S119N、L121S、T128N、P129A、Q66N、Y68S、S103S111 缺失插入 QRLMEDICLPRWGCLWEDDF 、

H115S126 缺失插入 QRLMEDICLPRWGCLWEDDF、T128P134 缺失插入 QRLMEDICLPRWGCLWEDDF、S103S111 缺失插入 IEDICLPRWGCLWE、H115S126 缺失插入 IEDICLPRWGCLWE、T128P134 缺失插入 IEDICLPRWGCLWE、S103S111 缺失插入 DICLPRWGCLWED、H115S126 缺失插入 DICLPRWGCLWED、T128P134 缺失插入 DICLPRWGCLWED、P406 插入 IEDICLPRWGCLW、P406 插入 GGGSIEDICLPRWGCLW、P406 插入 DICLPRWGCLWED、P406 插入 GGGSDICLPRWGCLWED、S103S111 缺失插入 SFGRGDIRNV、H115S126 缺失插入 SFGRGDIRNV、T127P134 缺失插入 SFGRGDIRNV、P406 插入 CSFGRGDIRNVC、P406 插入 GGGSCSFGRGDIRNVC、V158T、V158D、L287T 及 E296V。

5.如申請專利範圍第 4 項中之經修飾之 FVII 多肽，其包含選自以下者之修飾：Q286R/M298Q/K341Q、Q286R/M298Q/K199E、Q286R/M298Q/Gla 交換 FIX、Q286R/M298Q/Q366D、Q286R/M298Q/Q366N、Q286R/M298Q/H373F、{Gla 交換 FIX/E40L}/Q286R/M298Q、{Gla 交換 FIX/K43I}/Q286R/M298Q、{Gla 交換 FIX/Q44S}/Q286R/M298Q、{Gla 交換 FIX/M19K}/Q286R/M298Q、{Gla 交換 FIX/M19K/E40L/K43I/Q44S}/Q286R/M298Q、

T128N/P129A/Q286R/M298Q、V158D/Q286R/E296V/M298Q、Gla 交換 FIX/T128N/P129A/Q286R/M298Q、T128N/P129A/S222A/H257A/Q286R/M298Q、T128N/P129A/Q286R/M298Q/H373F、S52A/S60A/Q286R/M298Q、Gla 交換 FIX/S52A/S60A/Q286R/M298Q、S52A/S60A/S222A/H257A/Q286R/M298Q、S52A/S60A/Q286R/M298Q/H373F、T239V/Q286R/M298Q、S222A/T239V/H257A/Q286R/M298Q、Gla 交換 FIX/T239V/Q286R/M298Q、T239V/Q286R/M298Q/H373F、T239I/Q286R/M298Q、S222A/T239I/H257A/Q286R/M298Q、Gla 交換 FIX/T239I/Q286R/M298Q、T239I/Q286R/M298Q/H373F、Gla 交換 FIX/S222A/Q286R/M298Q、Gla 交換 FIX/S222A/Q286R/M298Q/H373F、V158D/Q286R/E296V/M298Q/H373F、H257A/Q286R/M298Q、H257S/Q286R/M298Q、S222A/H257S/Q286R/M298Q、H257S/Q286R/M298Q/H373F、S222A/Q286R/M298Q/H373F、S222A/Q286R/M298Q、T128N/P129A/A175S/Q286R/M298Q、A122N/G124S/A175S/Q286R/M298Q、T128N/P129A/A175S/S222A/H257A/Q286R/M298Q、

A122N/G124S/A175S/S222A/H257A/Q286R/M298Q、T128N/P129A/A175S/Q286R/M298Q/H373F、A122N/G124S/A175S/Q286R/M298Q/H373F、{Gla 交換 FIX /K43I}/T128N/P129A/Q286R/M298Q、T128N/P129A/Q286R/M298Q/Q366N、{Gla 交換 FIX /K43I}/Q286R/M298Q/Q366N、{Gla 交換 FIX /K43I}/T128N/P129A/Q286R/M298Q/Q366N、V158D/Q286R/E296V/M298Q、T128N/P129A/Q286R/M298Q/Q366N/H373F、T239V/Q286R/M298Q/Q366N、T239I/Q286R/M298Q/Q366N、T128N/P129A/T239V/Q286R/M298Q、T128N/P129A/S222A/T239V/H257A/Q286R/M298Q、T128N/P129A/T239V/Q286R/M298Q/H373F、T128N/P129A/T239I/Q286R/M298Q 及 T128N/P129A/T239I/Q286R/M298Q/H373F。

6.如申請專利範圍第 4 項中之經修飾之 FVII 多肽，其包含選自以下者之修飾：T128N/P129A/Q286R/M298Q、T239I/Q286R/M298Q/Q366N、T239V/Q286R/M298Q/Q366N、T128N/P129A/Q286R/M298Q/Q366N/H373F、V158D/Q286R/E296V/M298Q/H373F、A122N/G124S/A175S/Q286R/M298Q/H373F、T128N/P129A/A175S/Q286R/M298Q/H373F、

A122N/G124S/A175S/S222A/H257A/ Q286R/M298Q、T128N/P129A/A175S/S222A/H257A/Q286R/M298Q、A122N/G124S/ A175S/Q286R/M298Q、T128N/P129A/A175S/Q286R/M298Q、H257A/Q286R/M298Q、Gla 交換 FIX/S222A/Q286R/M298Q、S222A/Q286R/M298Q、Gla 交換 FIX/ S222A/Q286R/M298Q/H373F、S222A/Q286R/M298Q/H373F、S222A/H257S/Q286R/M298Q、T239I/Q286R/M298Q/H373F、S222A/T239I/H257A/Q286R/M298Q、T128N/P129A/T239I/Q286R/M298Q、Gla 交換 FIX / T239I/Q286R/M298Q、T239I/Q286R/M298Q、T128N/P129A/S222A/T239V/H257A/Q286R/M298Q、S222A/T239V/H257A/Q286R/M298Q、T128N/P129A/T239V/Q286R/M298Q、Gla 交換 FIX/T239V/Q286R/M298Q、V158D/Q286R/E296V/M298Q、T128N/P129A/Q286R/M298Q/H373F、Q286R/M298Q/H373F、{Gla 交換 FIX K[43]I}/ T128N/P129A/Q286R/M298Q /Q366N、{Gla 交換 FIX K[43]I}/Q286R/M298Q/Q366N、Q286R/M298Q/Q366N、S52A/S60A/S222A/H257A/Q286R/M298Q、T128N/P129A/S222A/H257A/Q286R/ M298Q、S222A/H257A/Q286R/M298Q、{Gla 交換

FIX/K[43]I}/T128N/P129A/Q286R/M298Q、Gla交換FIX/S52A/S60A/ Q286R/M298Q、S52A/S60A/ Q286R/M298Q、{Gla交換FIX/M[19]K}/ Q286R/M298Q、{Gla交換FIX/Q[44]S}/ Q286R/M298Q、{Gla交換FIX/K[43]I}/ Q286R/M298Q、{Gla交換FIX/E[40]L}/ Q286R/M298Q及Gla交換FIX /T128N/P129A/Q286R/M298Q。

7.如申請專利範圍第1-3項中任一項之經修飾之FVII多肽，其包含異源Gla域或異源Gla域之至少30個連續胺基酸以實現磷脂結合。

8.如申請專利範圍第1-3項中任一項之經修飾之FVII多肽，其包含由以下任一者所闡述之胺基酸序列：SEQ ID NO: 138-141、150、154、155、157、274-278、280、282、286-288、293-295、297、302-304、306、311-313、317、318、321、322、324-326、328、337-342、355-358、360或364-371。

9.如申請專利範圍第1-3項中任一項之經修飾之FVII多肽，其為FVIIa。

10.如申請專利範圍第1-3項中任一項之經修飾之FVII多肽，其與未經修飾的由SEQ ID NO: 3中所闡明的胺基酸序列所組成多肽相較，包含2、3、4、5、6、7或更多個修飾。

11.如申請專利範圍第7項之經修飾之FVII多肽，其中該異源Gla域係選自因子IX（FIX）、因子X（FX）、凝血酶原、蛋白質C、蛋白質S、骨鈣蛋白（osteocalcin）、

基質 Gla 蛋白、生長抑止特異性蛋白 6（Growth-arrest-specific protein 6，Gas6）及蛋白質 Z 之 Gla 域。

12.如申請專利範圍第 7 項之經修飾之 FVII 多肽，其中該異源 Gla 域具有 SEQ ID NO: 83-91、93 及 94 之任一者中所闡明的胺基酸序列。

13.如申請專利範圍第 1-3 項中任一項之經修飾之 FVII 多肽，其包含修飾 T128N/P129A/Q286R/M298Q。

14.如申請專利範圍第 13 項之經修飾之 FVII 多肽，其胺基酸序列由 SEQ ID NO: 280 中所闡述的序列組成。

15.如申請專利範圍第 14 項之經修飾之 FVII 多肽，其中該多肽是由胺基酸 Arg152 及 Ile153 間的裂解所造成的經活化雙鏈形式，以雙硫鍵彼此相連的第一鏈及第二鏈分別由 SEQ ID NO: 280 之胺基酸 1-152 及 153-406 組成。

16.如申請專利範圍第 1-3 項中任一項之經修飾之 FVII 多肽，其為成熟多肽。

17.如申請專利範圍第 1-3 項中任一項之經修飾之 FVII 多肽，其為單鏈多肽或雙鏈多肽。

18.如申請專利範圍第 1-3 項中任一項之經修飾之 FVII 多肽，其包含轉譯後修飾。

19.如申請專利範圍第 18 項之經修飾之 FVII 多肽，其中該轉譯後修飾包含糖苷化(glycosylation)。

20.一種經活化之雙鏈形式的如申請專利範圍第 1-15 項中任一項之經修飾之 FVII 多肽。

21.一種核酸分子，其包含編碼如申請專利範圍第 1-17 項中任一項之經修飾之 FVII 多肽的核苷酸序列。

22.一種載體，其包含如申請專利範圍第 21 項之核酸分子。

23.一種細胞，其包含如申請專利範圍第 22 項之載體。

24.一種用於治療藉由投予 FVII 或促凝血劑來治療之疾病或病狀之如申請專利範圍第 1-20 項中任一項之經修飾之 FVII 多肽。

25.如申請專利範圍第 24 項之經修飾之 FVII 多肽，其中該疾病或病狀係藉由投予酶原或活化形式的 FVII 來治療。

26.如申請專利範圍第 24 或 25 項之經修飾之 FVII 多肽，其中欲治療的疾病或病狀係選自凝血病症、血液學病症、出血性病症、血友病、因子 VII 缺乏、出血病症、手術出血、或由創傷造成之出血。

27.如申請專利範圍第 24 項之經修飾之 FVII 多肽，其中該疾病或病狀為血友病且該血友病為血友病 A 型或血友病 B 型或血友病 C 型。

28.一種用於治療患有具抑制劑之血友病 A 型或具抑制劑之血友病 B 型的患者之如申請專利範圍第 20 項之經活化之雙鏈形式的經修飾之 FVII 多肽。

29.一種醫藥組成物，其在醫藥上可接受之媒劑中包含如申請專利範圍第 1-20 項中任一項之經修飾之 FVII 多肽。

30.一種醫藥組成物，其包含經活化之雙鏈形式的如申

請專利範圍第 1-20 項中任一項之經修飾之 FVII 多肽及醫藥上可接受之載劑。

31.如申請專利範圍第 29 或 30 項之醫藥組成物，其係經調配以用於單劑量投予。

32.如申請專利範圍第 29 或 30 項之醫藥組成物，其係經調配以用於靜脈內、非經腸、肌肉內或皮下投予。

33.如申請專利範圍第 29 或 30 項之醫藥組成物，其係經凍乾。

34.一種用於製造經修飾之因子 VII（FVII）多肽的方法，其包含讓包含如申請專利範圍第 21 項之核酸分子或如申請專利範圍第 22 項之載體的細胞在使編碼的經修飾之 FVII 多肽表現的條件下生長。

35.如申請專利範圍第 34 項之方法，其進一步包含回收所表現的經修飾之 FVII 多肽。

36.如申請專利範圍第 34 或 35 項之方法，其中該細胞為哺乳動物細胞。

37.如申請專利範圍第 36 項之方法，其中該細胞為 CHO 細胞。

八、圖式：

（如次頁）