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(54)名稱

使用 FGF 23 融合多肽之方法及組合物

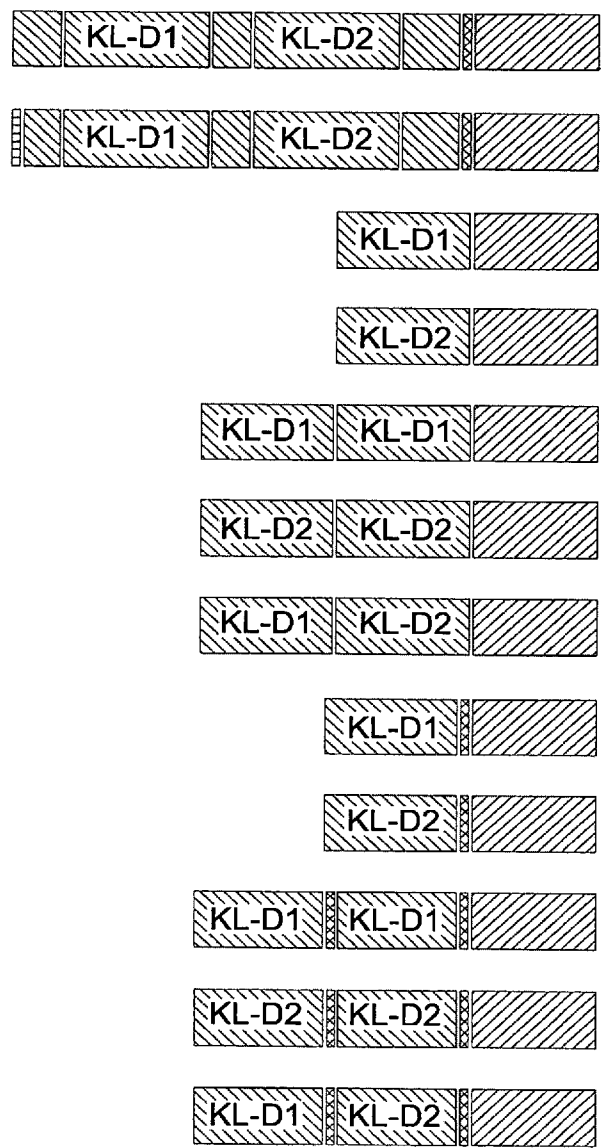
METHODS AND COMPOSITIONS USING FGF23 FUSION POLYPEPTIDES

(57)摘要

本發明係關於預防或治療年齡相關之病狀或代謝障礙的方法、套組及組合物。本發明之融合多肽包括 FGF23 或其活性片段。在一實施例中，該融合多肽包含(a)包含纖維母細胞生長因子 23 (FGF23)的多肽，或其功能活性變異體或衍生物，其中 FGF23 在 Q156、C206 及 C244 處中一或多個位置具有突變；及(b)具有降低對 Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之 Fc 片段，或包含 Klotho 蛋白質之至少一個細胞外子域的多肽，或其功能活性變異體或衍生物；及視情況存在之(c)連接子。Klotho 融合蛋白質適用於治療及預防多種年齡相關之病狀及代謝障礙。在另一實施例中，該融合多肽包含 FGF(諸如 FGF23)或其功能活性變異體或衍生物；及經修飾之 Fc 片段或其功能活性變異體或衍生物。在該融合多肽之多個實施例中，FGF23 具有可減少聚集及蛋白酶介導之裂解的突變。

The present disclosure is directed to methods, kits and compositions for preventing or treating age-related conditions or metabolic disorders. The fusion polypeptides of the disclosure include FGF23 or an active fragment thereof. In one embodiment, the fusion polypeptide comprises (a) a polypeptide comprising fibroblast growth factor 23 (FGF23), or a functionally active variant or derivative thereof, wherein FGF23 has a mutation at one or more of the positions Q156, C206 and C244; and (b) either a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life, or a polypeptide comprising at least one extracellular subdomain of a Klotho protein, or a functionally active variant or derivative thereof; and, optionally (c) a linker. The Klotho fusion proteins are useful in the treatment and prevention of a variety of age-related conditions and metabolic disorders. In another embodiment, the fusion polypeptide comprises a FGF (such as FGF23), or a functionally active variant or derivative thereof; and a modified Fc fragment, or a functionally active variant or derivative thereof. In various embodiments of the fusion polypeptides, FGF23 has mutations which decrease aggregation and protease-mediated cleavage.

指定代表圖：



 :Klotho (細胞外域) 或Klotho活性片段;
 : FGF23(R179Q)、FGF23、FGF19、FGF21 ;  : 連接子 ;  :IgG信號肽。

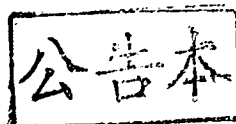
圖 1



 : Klotho (細胞外域) 或Klotho活性片段
 : FGF23(R179Q)、FGF23、FGF19、FGF21； : 連接子； : IgG信號肽

圖 1 (續)

發明摘要



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使用FGF23融合多肽之方法及組合物

METHODS AND COMPOSITIONS USING FGF23 FUSION

POLYPEPTIDES

【中文】

本發明係關於預防或治療年齡相關之病狀或代謝障礙的方法、套組及組合物。本發明之融合多肽包括FGF23或其活性片段。在一實施例中，該融合多肽包含(a)包含纖維母細胞生長因子23(FGF23)的多肽，或其功能活性變異體或衍生物，其中FGF23在Q156、C206及C244處中一或多個位置具有突變；及(b)具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段，或包含Klotho蛋白質之至少一個細胞外子域的多肽，或其功能活性變異體或衍生物；及視情況存在之(c)連接子。Klotho融合蛋白質適用於治療及預防多種年齡相關之病狀及代謝障礙。在另一實施例中，該融合多肽包含FGF(諸如FGF23)或其功能活性變異體或衍生物；及經修飾之Fc片段或其功能活性變異體或衍生物。在該融合多肽之多個實施例中，FGF23具有可減少聚集及蛋白酶介導之裂解的突變。

【英文】

The present disclosure is directed to methods, kits and compositions for preventing or treating age-related conditions or metabolic disorders. The fusion polypeptides of the disclosure include FGF23 or an active fragment thereof. In one embodiment, the fusion polypeptide comprises (a) a polypeptide comprising fibroblast growth factor 23 (FGF23), or a functionally active variant or derivative thereof, wherein FGF23 has a mutation at one or more of the positions Q156, C206 and C244; and (b) either a modified Fc fragment having decreased affinity for Fc-gamma-receptor and/or increased serum half-life, or a polypeptide comprising at least one extracellular subdomain of a Klotho protein, or a functionally active variant or derivative thereof; and, optionally (c) a linker. The Klotho fusion proteins are useful in the treatment and prevention of a variety of age-related conditions and metabolic disorders. In another embodiment, the fusion polypeptide comprises a FGF (such as FGF23), or a functionally active variant or derivative thereof; and a modified Fc fragment, or a functionally active variant or derivative thereof. In various embodiments of the fusion polypeptides, FGF23 has mutations which decrease aggregation and protease-mediated cleavage.

【代表圖】

【本案指定代表圖】：第（ 1 ）圖。

【本代表圖之符號簡單說明】：

（無）

【本案若有化學式時，請揭示最能顯示發明特徵的化學式】：

（無）

發明專利說明書

(本說明書格式、順序，請勿任意更動)

【發明名稱】

使用FGF23融合多肽之方法及組合物

METHODS AND COMPOSITIONS USING FGF23 FUSION
POLYPEPTIDES

本申請案主張2010年1月29日申請之美國申請案第12/696693號之優先權，該申請案之內容係以全文引用的方式併入本文中。

【技術領域】

纖維母細胞生長因子(FGF)組成表現於許多生物體中之同源多肽生長因子家族(Ornitz及Itoh, Genome Biol. 2: reviews, 3005.1-3005.12 (2001))。在脊椎動物物種中，FGF在基因結構與胺基酸序列方面高度保留，彼此間具有13%至71%之胺基酸一致性。在人類中，有22個已知的FGF家族成員(FGF15為人類FGF19之小鼠直系同源物，因此不存在人類FGF15)。雖然在發育早期，FGF調控細胞增殖、遷移及分化，但在成年生物體中，FGF維持體內平衡，起組織修復作用且對損傷作出反應。

FGF藉由結合並藉此活化細胞表面FGF受體來執行作為生長因子之功能。FGF受體(FGFR)為酪胺酸激酶受體，其藉由FGFR自磷酸化、FRS2(FGF受體受質2)及ERK1/2(細胞外信號調控蛋白質激酶1/2)之磷酸化以及活化Egr-1(早期生長反應-1)來活化信號轉導。FGF亦對硫酸肝素蛋白聚糖具有高親和力。當結合至FGF時，硫酸肝素增強FGFR之活化。

α -Klotho基因編碼具有細胞外域及短細胞質域之130 kDa單次跨膜I型跨膜蛋白。 α -Klotho蛋白質之細胞外域包含兩個子域，稱為KL-

D1及KL-D2。此兩個子域與細菌及植物之 β -葡糖苷酶享有序列同源性。 α -Klotho蛋白質之細胞外域可藉由跨膜域結合至細胞表面，或可裂解並釋放至細胞外環境中。局部低細胞外 Ca^{2+} 濃度似乎有助於細胞外域之裂解。

除 α -Klotho以外，亦已鑑別 α -Klotho之同源物 β -Klotho (Ito等人, *Mech. Dev.* 98:115-9 (2000))。 β -Klotho亦為具有細胞外KL-D1及KL-D2子域之單次跨膜I型跨膜蛋白。

α -Klotho表現之調節已顯示在哺乳動物中產生與老化相關之特徵。經同種接合以喪失 α -Klotho基因之功能突變的小鼠發展類似於人類老化之特徵，包括壽命縮短、皮膚萎縮、肌肉萎縮、動脈硬化、肺氣腫及骨質疏鬆症(Kuro-o等人, *Nature*, 390:45-51 (1997))。相反， α -Klotho基因在小鼠中過度表現相對於野生型小鼠可延長壽命並增加對氧化性應力之抗性(Kurosaki等人, *Science* 309:1829-1833 (2005)；Yamamoto等人, *J. Biol. Chem.* 280:38029-38034 (2005))。

最近研究已顯示FGF23缺乏型小鼠與 α -Klotho缺乏型小鼠之生物學特徵驚人地相似(Shimada等人, *J. Clin. Invest.* 113:561-568(2004)；Yoshida等人, *Endocrinology* 143:683-689(2002))，表明FGF23與 α -Klotho之間存在功能串擾。此等研究致使在經同源FGF受體進行結合與信號傳導方面，將 α -Klotho鑑別為FGF23專性搭配物(Urakawa等人, *Nature* 22:1524-6 (2007))。 α -Klotho基因主要表現於腎臟、副甲狀腺及脈絡叢中。假定 α -Klotho之組織特異性表現限制向彼等組織傳導信號之FGF23之活化。

與FGF23/ α -Klotho相似， β -Klotho在經其各別同源FGF受體進行結合與信號傳導方面為FGF19及FGF21之專性搭配物(Ogawa等人, *Proc. Natl. Acad. Sci. USA* 104:7432-7 (2007)；Lin等人, *J. Biol. Chem.* 282:27227-84 (2007)；及Wu等人, *J. Biol. Chem.* 282:29069-72

(2007))。該等研究亦已顯示， β -Klotho涉及調控組織特異性代謝活性。 β -Klotho最初顯示與FGF21一起充當調控脂肪組織中之碳水化合物及脂質代謝之輔因子。 β -Klotho連同FGF19一起調控肝臟中之膽汁酸代謝，因而可解釋 β -Klotho缺乏型小鼠中之膽汁合成升高(Ito等人, J Clin Invest. 2005年8月; 115(8):2202-8)。

美國專利第6,579,850號描述包含 α -Klotho多肽之多肽及組合物。揭示人類及小鼠 α -Klotho多肽。該專利亦揭示包含該等多肽之組合物適用於治療類似於過早老化之症候群、治療成人疾病及抑制老化。

美國專利第7,223,563號描述編碼FGF23多肽序列之分離之核酸或包含該分離之核酸的重組細胞。該專利進一步關於診斷及治療低磷酸鹽血性病徵及高磷酸鹽血性病徵、骨質疏鬆症、皮膚肌炎及冠狀動脈病的方法。

美國專利第7,259,248號描述編碼FGF21多肽序列之分離之核酸。該專利進一步關於診斷及治療肝臟疾病、與胸腺功能相關之病狀的方法，以及治療睪丸病狀之方法。

【發明內容】

本發明係關於用融合多肽或可溶性多肽預防或治療年齡相關之病狀或代謝障礙的方法、用途、套組及組合物。本發明之融合多肽係由以下形成：FGF(例如FGF23)；及Klotho蛋白質或其活性片段(例如sKlotho)及/或Fc片段(例如FcLALA)；及視情況存在之連接子。在一些實施例中，FGF23經突變。在一些實施例中，本發明提供Klotho融合多肽，其包含Klotho蛋白質或其活性片段及纖維母細胞生長因子或其活性片段。在一些實施例中，該融合多肽包含Klotho多肽、FGF(諸如FGF23)及經修飾之Fc片段。該Fc片段可例如具有降低與Fc- γ 受體之結合及增加之血清半衰期。包含sKlotho、FGF23及FcLALA(具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段)之融

合蛋白質描述於SEQ ID NO. 46、47、48及49中。在一些實施例中，該融合多肽或蛋白質包含FGF(例如FGF23)或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)；及經修飾之Fc片段或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)。包含FGF23及FcLALA之融合蛋白質描述於SEQ ID NO. 50、51、52及53中。在一些實施例中，該融合多肽在FGF23中具有一或多個減少聚集及/或蛋白酶介導之裂解的突變。

在第一態樣中，本發明提供一種融合多肽，其具有Klotho蛋白質之至少一個細胞外子域及纖維母細胞生長因子或其活性片段。在一些實施例中，該融合物進一步包含具有降低對之Fc- γ 受體之親和力(例如降低之 K_a 或增加之 K_d)及/或增加之血清半衰期的經修飾之Fc片段。Klotho細胞外域可源自 α 或 β Klotho同功異型物。此外，雖然主要參考纖維母細胞生長因子19、纖維母細胞生長因子21及纖維母細胞生長因子23描述Klotho融合多肽之FGF組分，但涵蓋23種已知FGF中之任一者均可用於實施本發明。本申請案之讀者可假定個別且特定地涵蓋 α 或 β 細胞外域與各人類FGF蛋白質或其活性片段之每一組合中之每一者。

根據本發明，Klotho蛋白質之細胞外域可包括Klotho蛋白質之KL-D1及KL-D2域中之一者或兩者，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)。在一些實施例中，本發明之Klotho融合多肽具有Klotho蛋白質之至少兩個細胞外子域或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)。舉例而言，該至少兩個細胞外子域可為呈串聯重複形式之至少兩個KL-D1域、呈串聯重複形式之至少兩個KL-D2域，或至少一個KL-D1域及至少一個KL-D2

域。在多個實施例中，本發明之融合多肽包含全長 α Klotho蛋白質之胺基酸28-292，或胺基酸28-982(SEQ ID NO:7)。在另一實施例中，本發明之融合多肽包含全長 β Klotho蛋白質之胺基酸52-997。

在本發明之一實施例中，融合多肽之組分包含：(a)包含纖維母細胞生長因子23(FGF23)之多肽或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)，其中FGF23在Q156、C206及C244處中一或多個位置具有突變；及(b)具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段，或包含Klotho蛋白質之至少一個細胞外子域之多肽，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)；及視情況存在之(c)連接子。該等組分可例如由肽鍵化學連接或同框融合。其亦可經由連接子連接。多肽連接子之非限制性實例為SEQ ID NO: 11、12、13、14、15、16、17及18。該等連接子可包含至少一個且至多約30個SEQ ID NO: 11、12、13、14、15、16、17及18之重複單元。在另一非限制性實施例中，融合物包含(2)FGF或其活性片段及(3)經修飾之Fc片段。該融合物之各種組分可以任何順序以操作方式連接；多肽(1)可以操作方式連接至(2)或(3)之多肽的N末端；(2)之多肽可以操作方式連接至(1)或(3)之多肽的N末端；(3)之多肽可以操作方式連接至(1)或(2)之多肽的N末端。

根據本發明，Klotho蛋白質之細胞外子域、纖維母細胞生長因子及(視情況存在之)具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段可以多種定向及方式彼此以操作方式連接。舉例而言，Klotho蛋白質之細胞外子域可以操作方式連接至纖維母細胞生長因子之N末端，或者纖維母細胞生長因子可以操作方式連接至Klotho蛋白質之細胞外子域之N末端。

在一實施例中，本發明提供一種融合多肽，其包含Klotho蛋白質

之sKlotho及連接子。在另一實施例中，本發明提供一種融合多肽，其包含 α Klotho蛋白質之sKlotho及連接子。在另一實施例中，本發明提供一種融合多肽，其包含 β Klotho蛋白質之sKlotho及連接子。在又一實施例中，本發明提供一種人類FGF蛋白質或其活性片段(例如無信號肽)及連接子。在一實施例中，本發明提供融合蛋白質、核酸分子或醫藥組合物，其係用於療法中或用作用於治療病理性病症的藥物。本發明亦涵蓋包含本發明之融合蛋白質之醫藥組合物及其用於治療或預防年齡相關之病狀或代謝障礙的用途。在一些實施例中，該融合蛋白質進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

在一實施例中，本發明提供一種融合多肽，其包含具有信號肽之 α Klotho蛋白質之sKlotho(直接或經由連接子間接)與FGF-23融合。在另一實施例中，本發明提供一種融合多肽，其包含無信號肽之 α Klotho蛋白質之sKlotho(直接或經由連接子間接)與FGF-23融合。在另一實施例中，本發明提供具有信號肽之 α Klotho蛋白質之sKlotho(直接或經由連接子間接)與無信號之FGF-23融合。在另一實施例中，本發明提供一種融合多肽，其包含無信號肽之 α Klotho蛋白質之sKlotho(直接或經由連接子間接)與無信號肽之FGF-23融合。在一些實施例中，該融合蛋白質進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

在一實施例中，本發明提供一種融合多肽，其包含具有信號肽之 α Klotho蛋白質之sKlotho(直接或經由連接子間接)與FGF-23(R179Q)變異體融合。在另一實施例中，本發明提供一種融合多肽，其包含無信號肽之 α Klotho蛋白質之sKlotho(直接或經由連接子間接)與FGF-23(R179Q)變異體融合。在另一實施例中，本發明提供具有信號肽之 α Klotho蛋白質之sKlotho(直接或經由連接子間接)與無信

號肽之FGF-23(R179Q)變異體融合。在另一實施例中，本發明提供一種融合多肽，其包含無信號肽之 α Klotho蛋白質之sKlotho(直接或經由連接子間接)與無信號肽之FGF-23(R179Q)變異體融合。在一些實施例中，該融合蛋白質進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

在一實施例中，本發明提供一種融合多肽，其包含：(a)包含纖維母細胞生長因子23(FGF23)之多肽或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)，其中FGF23在Q156、C206及C244處中一或多個位置具有突變；及(b)具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段，或包含Klotho蛋白質之至少一個細胞外子域的多肽，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)；及視情況存在之(c)連接子。該等融合多肽揭示於SEQ ID NO: 54、55、56、57、58、59、60、61、62、63、64、65、66、67及68中。

在一實施例中，本發明提供一種融合多肽，其包含(1)具有信號肽之 α Klotho蛋白質之sKlotho，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)；(2)連接子；及(3)無信號肽之FGF-23(R179Q)變異體，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)。在另一實施例中，本發明提供一種融合多肽，其包含(1)無信號肽之 α Klotho蛋白質之sKlotho，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)；(2)連接子；及(3)無信號肽之FGF-23(R179Q)變異體，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)。在一些實施例中，本發明之融合多肽經糖基

化。在一些實施例中，該融合蛋白質進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

在一實施例中，本發明提供一種融合多肽，其包含(1)具有信號肽之 α Klotho蛋白質之sKlotho(SEQ ID NO: 44或SEQ ID NO: 45)或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)；(2)包含SEQ ID NO: 11之連接子；及(3)無信號肽之FGF-23 (R179Q)變異體(SEQ ID NO: 43)，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)。在另一實施例中，本發明提供一種融合多肽，其包含(1)無信號肽之 α Klotho蛋白質之sKlotho(SEQ ID NO: 7)，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)；(2)包含SEQ ID NO: 11之連接子；及(3)無信號肽之FGF-23(R179Q)變異體(SEQ ID NO: 43)，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)。在一實施例中，本發明提供一種融合多肽，其包含SEQ ID NO: 19、20、40或41之胺基酸序列。在一些實施例中，本發明之融合多肽經糖基化。

在一實施例中，本發明提供一種融合多肽，其包含具有信號肽之 α Klotho蛋白質之sKlotho(SEQ ID NO: 44或SEQ ID NO: 45)，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)；及包含SEQ ID NO: 11之連接子。在另一實施例中，本發明提供一種融合多肽，其包含無信號肽之 α Klotho蛋白質之sKlotho(SEQ ID NO: 7)；及包含SEQ ID NO: 11之連接子。在一些實施例中，本發明之融合多肽經糖基化。在一些實施例中，該融合蛋白質進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

在一實施例中，本發明提供一種融合多肽，其包含人類FGF蛋白質或其活性片段(例如無信號肽)；及包含SEQ ID NO: 11之連接子。在一些實施例中，本發明之融合多肽經糖基化。在一些實施例中，該融合蛋白質進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

在一實施例中，本發明提供一種融合多肽，其包含人類FGF蛋白質(例如FGF23)或其活性片段(例如無信號肽)；連接子(例如包含SEQ ID NO: 11之連接子)；及sKlotho(具有信號肽或無信號肽)，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)，或Fc- γ 受體(例如FcLALA)；其中該FGF(例如FGF23)具有一或多個處於以下殘基處之突變：R179、Q156、C206及/或C244。在多個實施例中，該等突變為R179Q、Q156A、C206S及/或C244S。即使此等突變在人類、恆河猴(rhesus)、牛、小鼠及大鼠FGF23中為保留性突變，使其突變亦不妨礙FGF23活性。相反，使此等胺基酸突變因減少聚集、減少不想要之蛋白酶誘導之裂解及增加自細胞之蛋白質產生而出乎意料地增強蛋白質之品質。在多個實施例中，該包含一或多個FGF23突變之融合蛋白質經糖基化。

在一實施例中，本發明提供一種醫藥組合物(例如呈肌肉內投藥形式)，其包含(例如作為唯一醫藥學活性成分)融合多肽(例如經糖基化或未糖基化)，該融合多肽包含(1)無信號肽之FGF-23(R179Q)變異體(SEQ ID NO: 43)或包含減少聚集及/或蛋白酶介導之裂解之其他突變的變異體，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)；(2)視情況存在之連接子，其包含SEQ ID NO: 11；及(3)具有信號肽之 α Klotho蛋白質之sKlotho(SEQ ID NO: 44或SEQ ID NO: 45)，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變

異體)，或具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段；及該醫藥組合物用於治療病理性病症之療法或藥物的用途，例如治療及/或預防年齡相關之病狀(諸如肌肉萎縮)。在另一實施例中，本發明提供一種醫藥組合物(例如呈肌肉內投藥形式)，其包含(例如作為唯一醫藥學活性成分)融合多肽(例如經糖基化或未糖基化)，該融合多肽包含(1)無信號肽之FGF-23(R179Q)變異體(SEQ ID NO: 43)或包含減少聚集及/或蛋白酶介導之裂解之其他突變的變異體，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)；(2)連接子，其包含SEQ ID NO: 11；及(3)無信號肽之 α Klotho蛋白質之sKlotho(SEQ ID NO: 7)，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)，或具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)；及該醫藥組合物用於治療病理性病症之療法或藥物的用途，例如治療及/或預防年齡相關之病狀(諸如肌肉萎縮)。在一實施例中，本發明提供一種醫藥組合物(例如呈肌肉內投藥形式)，其包含(例如作為唯一醫藥學活性成分)融合多肽(例如經糖基化或未糖基化)，該融合多肽包含SEQ ID NO: 19、20、40或41之胺基酸序列；及該醫藥組合物用於治療病理性病症之療法或藥物的用途，例如治療及/或預防年齡相關之病狀(諸如肌肉萎縮)。

在一實施例中，本發明提供一種醫藥組合物(例如呈肌肉內投藥形式)，其包含(例如作為唯一醫藥學活性成分)融合多肽(例如經糖基化或未糖基化)，該融合多肽包含具有信號肽之 α Klotho蛋白質之sKlotho(SEQ ID NO: 44或SEQ ID NO: 45)；及包含SEQ ID NO: 11之連接子；及該醫藥組合物用於治療及/或預防年齡相關之病狀(諸如肌

肉萎縮)的用途。在另一實施例中，本發明提供一種醫藥組合物(例如呈肌肉內投藥形式)，其包含(例如作為唯一醫藥學活性成分)融合多肽(例如經糖基化或未經糖基化)，該融合多肽包含無信號肽之 α Klotho蛋白質之sKlotho(SEQ ID NO: 7)；及包含SEQ ID NO: 11之連接子；及該醫藥組合物用於治療病理性病症之療法或藥物的用途，例如治療及/或預防年齡相關之病狀(諸如肌肉萎縮)。在一些實施例中，該融合蛋白質進一步包含經修飾之Fc片段。

在一實施例中，本發明提供一種醫藥組合物，其包含(例如作為唯一醫藥學活性成分)融合多肽(例如經糖基化或未經糖基化)，該融合多肽包含人類FGF蛋白質或其活性片段(例如無信號肽)；及包含SEQ ID NO: 11之連接子。

本發明亦涵蓋包含本發明之融合蛋白質之醫藥組合物及其用於治療病理性病症之療法或藥物的用途，例如治療或預防年齡相關之病狀(例如肌肉萎縮)或代謝障礙(例如糖尿病)。

在一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 19之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%。在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 20之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%。

在一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 40之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%。在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 41之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%。

在一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 46之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 47之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 48之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 49之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 50之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 51之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 52之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 53之一致性為至少85%、至少90%、至少91%、至少92%、至少

93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 54之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 55之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 56之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 57之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 58之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 59之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 60之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 61之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 62之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 63之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 64之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 65之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 66之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、

至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 67之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在另一實施例中，本發明提供一種融合多肽，其與SEQ ID NO: 68之一致性為至少85%、至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%、至少99%或100%。

在一實施例中，本發明提供一種融合多肽，其包含具有信號肽之 β Klotho蛋白質之sKlotho(直接或經由連接子間接)與FGF-19或其活性片段融合。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。在另一實施例中，本發明提供一種融合多肽，其包含無信號肽之 β Klotho蛋白質之sKlotho(直接或經由連接子間接)與FGF-19或其活性片段融合。在另一實施例中，本發明提供一種融合多肽，其包含具有信號肽之 β Klotho蛋白質之sKlotho(直接或經由連接子間接)與FGF-21或其活性片段融合。在另一實施例中，本發明提供一種融合多肽，其包含無信號肽之 β Klotho蛋白質之sKlotho(直接或經由連接子間接)與FGF-21或其活性片段融合。

本發明提供編碼本文所述之任何Klotho融合多肽之核酸序列及含有該等核酸之宿主細胞。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

本發明亦提供具有本文所涵蓋之任何Klotho融合多肽的組合物。本發明之組合物可進一步包括肝素。在一些實施例中，該融合物進一

步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

本發明亦提供一種治療或預防個體之年齡相關之病狀的方法。向個體(例如人類)投與治療有效劑量之醫藥組合物以治療或預防年齡相關之病狀，該醫藥組合物含有具有Klotho蛋白質(例如 α Klotho蛋白質)之至少一個細胞外子域及纖維母細胞生長因子或其活性片段的Klotho融合多肽。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。詳言之，本發明提供一種治療或預防肌肉萎縮之方法，該方法包含向個體(例如人類)投與治療有效量之具有 α Klotho蛋白質之至少一個細胞外子域及纖維母細胞生長因子(或其活性片段)的融合多肽。

另外，本發明亦提供一種治療或預防個體之代謝障礙的方法。向個體投與治療有效劑量之醫藥組合物以治療代謝障礙，該醫藥組合物含有具有Klotho蛋白質之至少一個細胞外子域及纖維母細胞生長因子(或其活性片段)的本發明之融合多肽。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。詳言之，具有 β -Klotho蛋白質之至少一個細胞外子域及纖維母細胞生長因子21的本發明之融合多肽適用於治療代謝障礙。

本發明之Klotho-FGF23融合多肽可用於治療或預防個體之高磷酸鹽血症或鈣質沉著。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。投與藥理學有效劑量之含有本發明Klotho融合多肽之醫藥組合物以治療或預防高磷酸鹽血症或鈣質沉著，該融合多肽具有Klotho蛋白質之至少一個細胞外子域及纖維母細胞生長因子。詳言之，具有 α Klotho蛋白質之至少一個細胞外子域及纖維母細胞生長因子23之本發明Klotho融合多肽適用於治療高磷酸鹽血症或鈣質沉著。

本發明之Klotho-FGF23融合多肽可用於治療或預防個體之慢性腎病或慢性腎衰竭。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。投與治療有效劑量之含有本發明Klotho融合多肽之醫藥組合物以治療或預防慢性腎病或慢性腎衰竭，該融合多肽具有Klotho蛋白質(例如 α Klotho蛋白質)之至少一個細胞外子域及纖維母細胞生長因子。

本發明之Klotho-FGF23融合多肽可用於治療或預防個體之癌症(例如乳癌)。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。投與治療有效劑量之含有本發明Klotho融合多肽之醫藥組合物以治療或預防癌症或乳癌，該融合多肽具有Klotho蛋白質(例如 α Klotho蛋白質)之至少一個細胞外子域及纖維母細胞生長因子。

本發明提供包含Klotho蛋白質之至少一個細胞外子域及FGF或其活性片段之融合多肽，其用於醫學中。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。在一實施例中，本發明提供包含Klotho蛋白質之至少一個細胞外子域及FGF或其活性片段之融合多肽，其用於治療或預防肌肉萎縮。本發明亦提供一種治療或預防年齡相關之病狀(例如肌肉萎縮)的方法，該方法包含投與有需要之個體治療有效劑量之包含可溶性Klotho蛋白質之醫藥組合物。

此外，本發明提供上述肽及融合多肽或包含該等肽之醫藥組合物，其用於療法中、用作藥物或用於治療個體之病理性病症，例如年齡相關之病狀、代謝障礙、高磷酸鹽血症或鈣質沉著、慢性腎病或慢性腎衰竭，或用於預防癌症或乳癌。另外，本發明進一步提供本發明之多肽、核酸或醫藥組合物之用途，其用於製造治療病理性病症、尤其治療上述病症，較佳如肌肉萎縮之年齡相關之病狀的藥物。

本發明亦包括治療或預防個體之年齡相關之病症或代謝障礙的套組。該套組包括使用說明書及具有Klotho蛋白質之至少一個細胞外子域及纖維母細胞生長因子的純化Klotho融合多肽。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

本發明亦提供一種用於產生本發明之Klotho融合多肽的套組。本發明之套組包括使用說明書及編碼具有Klotho蛋白質之至少一個細胞外子域及纖維母細胞生長因子之Klotho融合多肽的核酸。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

在本發明之一實施例中，該融合多肽包含：(a)包含纖維母細胞生長因子的多肽，或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)；及(b)具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段或其功能活性變異體或衍生物(例如包含至少一個保留性胺基酸取代及/或一個胺基酸缺失之變異體)。

在本發明之一實施例中，(a)之多肽及(b)之多肽由多肽連接子連接。該連接子可重複1至30次或30次以上。

在本發明之一實施例中，該多肽連接子包含選自由以下組成之群的胺基酸序列：SEQ ID NO: 11、SEQ ID NO: 12、SEQ ID NO: 13、SEQ ID NO: 14、SEQ ID NO: 15、SEQ ID NO: 16、SEQ ID NO: 17及SEQ ID NO: 18。

在本發明之一實施例中，(a)之多肽由肽鍵連接至該多肽連接子之N末端，且(b)之多肽由肽鍵連接至該多肽連接子之C末端。

在本發明之一實施例中，該融合多肽進一步包含信號肽。

在本發明之一實施例中，該信號肽為IgG信號肽。

在本發明之一實施例中，該纖維母細胞生長因子為纖維母細胞生長因子-23或纖維母細胞生長因子-23變異體(R179Q)。

在本發明之一實施例中，該纖維母細胞生長因子為纖維母細胞生長因子-19或纖維母細胞生長因子-21。

在本發明之一實施例中，融合多肽包含與SEQ ID NO: 51或SEQ ID NO: 53之胺基酸序列之一致性為95%或95%以上的胺基酸序列。

在本發明之一實施例中，融合多肽包含SEQ ID NO: 51或SEQ ID NO: 53之胺基酸序列。

在本發明之一實施例中，融合多肽包含FcLALA。

【圖式簡單說明】

圖1說明本發明之Klotho融合多肽之若干不同實施例。所提供之融合多肽包括一或多個以操作方式連接至纖維母細胞生長因子之Klotho細胞外子域。含有一或多個Klotho細胞外子域之多肽包括例如Klotho之細胞外域(例如人類Klotho之aa 1至982)或Klotho之活性片段。

圖2說明本發明之若干Klotho融合多肽及其組分(例如Klotho細胞外域、FGF)之胺基酸序列及核酸序列。包含sKlotho、FGF23及FcLALA(具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段)之融合蛋白質描述於SEQ ID NO. 46、47、48及49中。包含FGF23及FcLALA之融合蛋白質描述於SEQ ID NO. 50、51、52及53中。

圖3A至圖3C描述sKlotho-FGF23融合蛋白質之蛋白質表現。圖3A展示在條件培養基中由西方墨點法以抗FGF23抗體偵測sKlotho-FGF23融合蛋白質。圖3B展示在條件培養基中由SDS-PAGE及庫馬斯藍染色偵測sKlotho-FGF23融合蛋白質。圖3C展示由SDS-PAGE及庫馬斯藍染色分析之經高度純化之sKlotho-FGF23-6 $\times$ His融合蛋白質。

圖4說明比較在不存在或存在肝素(20 $\mu\text{g/ml}$)之情況下經含有Klotho融合多肽、僅FGF23多肽、僅可溶性Klotho (sKlotho)多肽及可溶性Klotho多肽與FGF23多肽之組合的條件培養基處理之細胞中之Egr-1活化量的Egr-1螢光素酶檢定之結果。

圖5A至圖5B描述比較在不存在或存在肝素之情況下經純化Klotho融合多肽、FGF23多肽或可溶性Klotho多肽處理之細胞中之Egr-1活化量的Egr-1螢光素酶檢定之結果。圖5A展示在不存在或存在肝素(20 $\mu\text{g/ml}$)之情況下經單獨FGF23、sKlotho-His(10 nM或20 nM)及FGF23與sKlotho-His(10 nM或20 nM)之組合處理之細胞中之Egr-1活化量之實驗的結果。圖5B展示經sKlotho-FGF23-His融合物(0 nM、0.6 nM、1.21 nM、2.41 nM、4.83 nM、9.65 nM及19.3 nM)處理之細胞中的Egr-1螢光素酶報導子活性。

圖6A至圖6B說明用純化sKlotho融合多肽處理對C2C12肌細胞之效應。圖6A展示在不存在或存在地塞米松(100 μM)之情況下經IGF-1(10 nM)、FGF2(20 ng/ml)或純化Klotho融合多肽(20 nM)處理之C2C12肌細胞中之肌管直徑的量測值。圖6B展示在不存在或存在雷帕黴素(40 nM)之情況下C2C12肌細胞中由IGF-1(10 nM)、FGF2(20 ng/ml)或純化Klotho融合多肽(20 nM)所致之信號傳導路徑蛋白質的磷酸化。

圖7展示由sKlotho-FGF23(R179Q)-FcLALA融合蛋白質所致之EGR-1-luc報導子基因的活化。

圖8展示由FGF23(R179Q)-FcLALA蛋白質所致之EGR-1-luc報導子基因的活化。

圖9展示FGF23(R179Q)對FGF23(R179Q)-FcLALAv2之藥物動力學概況。

圖10A及圖10B展示sKlotho-FGF23融合物在地塞米松誘導之肌肉

萎縮後增強肌肉生長方面的活體內效力。

圖 11. 此圖展示由 FGF23(R179Q)-FcLALA 及 Q156A、C206S、C244S 及 C206S/C244S 突變體所致之 EGR-1-luc 報導子基因的活化。

圖 12 展示 FGF23(R179Q)-FcLaLa 之 WT(野生型)、Q156A、C206S、C244S 及 C206S/C244S 突變體之蛋白質品質及二聚。

【實施方式】

本發明係關於預防或治療年齡相關之病狀及代謝障礙之方法、套組及組合物；及該等組合物在治療病理性病症之療法、藥物或使用中之用途。本發明之融合多肽包括 Klotho 蛋白質或其活性片段。在一些實施例中，本發明之融合多肽包括 Klotho 蛋白質或其活性片段以操作方式連接至纖維母細胞生長因子多肽或其活性片段。在一些實施例中，該融合物進一步包含具有降低結合 FcRn 之能力及/或增加之血清穩定性的經修飾之 Fc 片段。在另一實施例中，該融合多肽包含 FGF(例如 FGF23)及具有降低結合 FcRn 之能力及/或增加之血清穩定性的經修飾之 Fc 片段。

本發明之融合蛋白質或 sKlotho 適用於治療及預防各種年齡相關之病狀，包括肌肉減少症、皮膚萎縮、肌肉萎縮、腦萎縮、動脈粥樣硬化、動脈硬化、肺氣腫、骨質疏鬆症、骨關節炎、免疫機能不全、高血壓、癡呆症、亨廷頓氏病(Huntington's disease)、阿茲海默氏病(Alzheimer's disease)、白內障、年齡相關之黃斑部變性、前列腺癌、中風、預期壽命縮短、記憶損失、皺紋、腎功能損傷及年齡相關之聽力損失；及代謝障礙，包括 II 型糖尿病、代謝症候群、高血糖症及肥胖症。

本發明至少部分基於如下發現結果：儘管存在物理約束(例如 Klotho 與 FGF 多肽之尺寸較大)，但 Klotho-FGF 融合多肽在活化 FGF 受體方面高度有效。此發現結果出乎意料，此係因為此兩種蛋白質之融

合可能會干擾異源二聚且因而干擾蛋白質之活性之故；舉例而言，若該等蛋白質之結合域呈「順式」結構，則其可能受融合擾亂或該等蛋白質可能在空間上誤定向。

本文所述之融合多肽為有利的，此係因為相較於單獨投與或以獨立之多肽形式一起投與的Klotho或FGF，其投與具有增強之活性的單一治療性蛋白質之故。使用呈單一融合多肽而非兩種獨立之多肽(亦即Klotho多肽及獨立之FGF多肽)形式的Klotho及FGF在活化FGF受體方面更有效。

定義

如本文所使用之「Klotho多肽」、「Klotho蛋白質」或「Klotho」包括野生型「Klotho」之活性片段、衍生物、模擬物、變異體及經化學修飾之化合物或其雜交物。Klotho活性片段能夠結合FGF多肽。一般而言，Klotho活性多肽含有至少一個Klotho子域(例如KL-D1及KL-D2)。野生型Klotho具有自然界中所發現之胺基酸序列。適用於本發明之實例Klotho多肽包括 α -Klotho(SEQ ID NO: 2)及 β -Klotho(SEQ ID NO: 4)。 α -Klotho及 β -Klotho之核苷酸及胺基酸序列可分別以寄存編號NM_004795；NP_004786及NM_175737；NP_783864於GenBank資料庫中獲得。Klotho多肽包括美國專利第6,579,850號中所述之多肽，該專利之內容係以全文引用的方式併入本文中。Klotho多肽包括來自除人類以外之其他物種的多肽，包括來自小鼠(NP_038851)、大鼠(NP_112626)、兔(NP_001075692)之 α -Klotho及來自小鼠之 β -Klotho(NP_112457)。預計具有 α -Klotho之物種包括黑猩猩(XP_522655)、獼猴(XP_001101127)、馬(XP_001495662)、乳牛(XP_001252500)、鴨嘴獸(XP_001510981)及雞(XP_417105)。預計具有 β -Klotho之物種包括黑猩猩(XP_526550)、獼猴(XP_001091413)、馬(XP_001495248)、狗(XP_536257)、大鼠(XP_001078178)、鴨嘴獸

(XP_001512722)及雞(XP_423224)。Klotho多肽具有與SEQ ID NO: 2或SEQ ID NO: 4之胺基酸序列實質上一致的胺基酸序列；亦即，與SEQ ID NO: 2或SEQ ID NO: 4之胺基酸序列或其活性片段之一致性為至少70%、75%、80%、85%、90%、95%、96%、97%、98%、99%或99%以上。

如本文所使用之「融合多肽」或「融合蛋白質」應意謂包含不天然存在於同一多肽中之兩種或兩種以上不同多肽或其活性片段的多肽。在一些實施例中，該兩種或兩種以上不同多肽以操作方式共價連接在一起，例如由肽鍵化學連接或同框融合。如本文所使用之「Klotho融合多肽」為包括來自Klotho多肽或其活性片段之胺基酸序列的融合多肽。作為非限制性實例，融合多肽可包含Klotho(例如sKlotho)、FGF(例如FG23)及(視情況存在之)經修飾之Fc片段(例如具有降低對FC- γ 受體之結合親和力及/或增加之血清半衰期的經修飾之Fc片段)。此類型融合多肽之實例提供於SEQ ID NO. 46至49中。在另一實施例中，融合蛋白質包含FGF(例如FGF23)及經修飾之Fc(例如FcLALA)。包含FGF23及FcLALA之融合蛋白質描述於SEQ ID NO. 50、51、52及53中。FcLALA為具有LALA突變(L234A、L235A)之Fc片段，其以較低效率引發ADCC且以較弱程度結合並活化人類補體。Hessell等人, 2007 Nature 449:101-104。

「纖維母細胞生長引子」及「FGF」在本文中可互換使用，且應指在動物(包括人類個體)中調控細胞增殖、遷移、分化、體內平衡、組織修復及對損傷之反應的多肽。FGF能夠結合纖維母細胞生長因子受體且調控其活性，包括FGFR自磷酸化、FRS2(FGF受體受質2)及ERK1/2(細胞外信號調控蛋白質激酶1/2)之磷酸化及活化Egr-1(早期生長反應-1)。術語「FGF」包括野生型「FGF」之活性片段、衍生物、模擬物、變異體及經化學修飾之化合物或其雜交物，例如如此項技術

中已知且如美國專利第7,223,563號及美國專利第7,259,248號中所述，該等專利之內容係以全文引用的方式併入本文中。野生型FGF具有自然界中所發現之胺基酸序列。適用於本發明之實例纖維母細胞生長因子包括纖維母細胞生長因子-19(FGF19；SEQ ID NO: 31)、纖維母細胞生長因子-21(FGF21；SEQ ID NO: 33)及纖維母細胞生長因子-23(FGF23；SEQ ID NO: 35)。FGF多肽包括來自除人類以外之其他物種之多肽，包括鼠類FGF。一般而言，FGF多肽具有與SEQ ID NO: 31、SEQ ID NO: 33或SEQ ID NO: 35之胺基酸序列實質上一致的胺基酸序列；亦即具有與SEQ ID NO: 31、SEQ ID NO: 33或SEQ ID NO: 35或其活性片段之胺基酸序列之一致性為至少70%、75%、80%、85%、90%、95%、96%、97%、98%、99%或99%以上或100%的胺基酸序列。FGF、尤其FGF23之其他非限制性實例提供於SEQ ID NO: 47之aa 1002-1228；SEQ ID NO: 49之aa 1002-1228；SEQ ID NO: 51之aa 1-251；及SEQ ID NO: 53之aa 1-251；及與此等序列之一致性為至少70%、75%、80%、85%、90%、95%、96%、97%、98%、99%或99%以上或100%的序列。編碼此等序列之核苷酸提供於SEQ ID NO: 46、48、50及52中。

術語「FGF」包括全長多肽之活性片段。能夠結合相應FGF受體之活性FGF片段在此項技術中為已知的且亦涵蓋用於本發明中。基於本文所揭示之序列，熟習此項技術者將瞭解，可使用標準重組技術產生FGF之重疊片段，該技術如例如Sambrook等人(1989, Molecular Cloning : A Laboratory Manual, Cold Spring Harbor Laboratory Press, New York)及 Ausubel 等人 (1997, Current Protocols in Molecular Biology, Green & Wiley, New York)中所述。基於本文所提供之揭示內容，熟習此項技術者將瞭解，可利用此項技術中熟知及本文所述之方法來測試FGF片段之生物活性，包括結合FGF受體。類似地，可用

FGF片段轉染具有必需的FGF信號轉導機構(亦即FGF受體)之細胞培養模型，隨後測試FGF信號傳導相對於野生型FGF之變化。

基於FGF核心同源性域(長約120個胺基酸)之同源性，FGF分成7個子族，該域側接有在長度與初級序列方面高度可變之N末端及C末端序列，尤其在FGF子族中(Goetz等人, *Molecular and Cellular Biology*, 2007, 第27卷, 3417-3428)。FGF活性多肽一般含有至少一個FGF核心同源性域。在一些實施例中，除FGF核心同源性域以外，FGF活性多肽亦可含有側接序列，該等側接序列可能賦予額外的FGF受體結合特異性。FGF19、FGF21及FGF23分在FGF19子族中，此係因為此等配位體之核心區相對於其他FGF享有較高序列一致性(FGF19相對於FGF21：38%一致性；FGF19相對於FGF23：36%一致性)之故。FGF19子族成員類似於內分泌系統之信號傳導分子起作用且調控對經典FGF罕見之多樣性生理學過程(例如FGF19：能量及膽汁酸體內平衡；FGF21：葡萄糖及脂質代謝；及FGF23：磷酸鹽及維生素D體內平衡)。

如本文所使用之「纖維母細胞生長因子受體」及「FGFR」係指此項技術中已知之FGFR1-4中之任一者，或其剪接變異體(例如FGFR1c)。適用於本發明之實例纖維母細胞生長因子受體包括纖維母細胞生長因子受體-19(例如FGFR4- β Klotho)、纖維母細胞生長因子受體-21(例如FGFR1c- α Klotho)及纖維母細胞生長因子受體-23(例如FGFR1c- α Klotho、FGFR3- α Klotho、FGFR4- α Klotho)。

如本文所使用之「細胞外域」係指跨膜蛋白質之存在於細胞外之片段(例如不包括細胞內或跨膜區)。「Klotho蛋白質之細胞外域」、「可溶性Klotho」或「sKlotho」(例如SEQ ID NO: 7；SEQ ID NO: 39)係指能夠結合纖維母細胞生長因子及/或能夠藉由結合纖維母細胞生長因子而使纖維母細胞生長因子結合纖維母細胞生長因子受體

的Klotho多肽之細胞外域。Klotho細胞外域對應於全長 α Klotho序列 (SEQ ID NO: 2)之胺基酸殘基28-982及全長 β Klotho序列(SEQ ID NO: 4)之胺基酸殘基52-997。

「Klotho蛋白質之細胞外子域」及「Klotho蛋白質之細胞外子域」在本文中可互換使用，且應指能夠結合纖維母細胞生長因子及/或能夠藉由結合纖維母細胞生長因子而使纖維母細胞生長因子結合纖維母細胞生長因子受體的Klotho多肽之細胞外域中之區。在多個實施例中，該融合物包含：包含Klotho蛋白質之至少一個細胞外子域的多肽；包含纖維母細胞生長因子之多肽；及視情況存在之具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。Klotho細胞外域具有兩個重複之同源子域，亦即KL-D1(SEQ ID NO: 5)及KL-D2(SEQ ID NO: 6)。KL-D1及KL-D2分別對應於全長 α Klotho多肽 (SEQ ID NO: 2)之胺基酸殘基58-506及517-953，且分別對應於全長 β Klotho多肽(SEQ ID NO: 4)之胺基酸殘基77-508及571-967，且適用於本發明。一般而言，含有至少一個Klotho子域之多肽為Klotho活性多肽。用於本發明多肽之Klotho細胞外子域可為分別具有與SEQ ID NO: 5或SEQ ID NO: 37之胺基酸序列實質上一致之胺基酸序列的 α Klotho或 β Klotho K-D1域。此外，Klotho KL-D1域可具有與SEQ ID NO: 5或SEQ ID NO: 37之胺基酸序列之一致性為至少70%、75%、80%、85%、90%、95%、96%、97%、98%、99%或99%以上的胺基酸序列。Klotho細胞外子域亦可為分別與SEQ ID NO: 6或SEQ ID NO: 38之胺基酸序列實質上一致的 α 或 β Klotho多肽KL-D2域。在另一實施例中，KL-D2域具有與SEQ ID NO: 6或SEQ ID NO: 38之胺基酸序列之一致性為至少70%、76%、80%、85%、90%、95%、96%、97%、98%、99%或99%以上的胺基酸序列。在一些實施例中，該融合物包含Klotho蛋白質之至少兩個細胞外子域(例如KL-D1及KL-D2；呈串聯

重複形式之KL-D1及KL-D1；呈串聯重複形式之KL-D2及KL-D2等)。

如本文所使用之「經修飾之Fc片段」應意謂包含經修飾之序列之抗體之Fc片段。Fc片段為包含CH2、CH3及部分鉸鏈區之抗體之一部分。經修飾之Fc片段可源自例如IgG1、IgG2、IgG3或IgG4。FcLALA為具有LALA突變(L234A、L235A)之經修飾之Fc片段，其以較低效率引發ADCC且以較弱程度結合並活化人類補體。Hessell等人，2007 Nature 449:101-104。Fc片段之其他修飾描述於例如美國專利第7,217,798號中。舉例而言，在各種經修飾之Fc片段中：(a)胺基酸殘基250為麩胺酸且胺基酸殘基428為苯丙胺酸；或(b)胺基酸殘基250為麩醯胺酸且胺基酸殘基428為苯丙胺酸；或(c)胺基酸殘基250為麩醯胺酸且胺基酸殘基428為白胺酸。在一些實施例中，胺基酸殘基250及428與存在於未經修飾之Fc融合蛋白質中之殘基的不同之處在於胺基酸殘基250為麩胺酸或麩醯胺酸且胺基酸殘基428為白胺酸或苯丙胺酸，且其中胺基酸殘基以EU編號系統編號，如美國專利第7,217,798號中所述。在一些實施例中，經修飾之Fc融合蛋白質對FcRn之親和力在pH 6.0下高於在pH 8.0下。經修飾之Fc片段較佳具有降低對FcRn之親和力及/或增加之血清半衰期。經修飾之Fc片段之非限制性實例包括SEQ ID NO: 47之aa(胺基酸)1234-1459；SEQ ID NO: 49之aa 1234至1450；SEQ ID NO: 51之aa 257至482；及SEQ ID NO: 53之aa 257至473；及與此等序列之一致性為至少70%、75%、80%、85%、90%、95%、96%、97%、98%、99%或99%以上或100%的序列。編碼此等序列之核苷酸提供於SEQ ID NO: 46、48、50及52中。

如本文所使用之「信號肽」應意謂將蛋白質之轉譯後轉運導向內質網且可裂解脫除之肽鏈(3-60個胺基酸長)。適用於本發明之實例信號肽包括Klotho信號肽(SEQ ID NO: 19)及IgG信號肽(SEQ ID NO: 20)。應注意：在由生產細胞株分泌及裂解後，信號肽(例如對應於

SEQ ID NO: 19及SEQ ID NO: 20之肽的信號肽)裂解脫除。因而，信號肽由生產細胞株分泌及裂解後，SEQ ID NO: 19之肽將產生SEQ ID NO: 41之肽。

如本文所使用之「連接子」應意謂共價連接兩個或兩個以上多肽或核酸以使其彼此連接的官能基(例如化合物或多肽)。如本文所使用之「肽連接子」係指用於將兩個蛋白質偶合在一起(例如偶合Klotho之細胞外域與纖維母細胞生長因子-23)之一或多個胺基酸。適用於本發明之肽連接子包括但不限於具有由SEQ ID NO: 8、SEQ ID NO: 9、SEQ ID NO: 10、SEQ ID NO: 11、SEQ ID NO: 12、SEQ ID NO: 13、SEQ ID NO: 14、SEQ ID NO: 15、SEQ ID NO: 16、SEQ ID NO: 17及SEQ ID NO: 18表示之胺基酸序列的多肽。多肽連接子可包含至少1個且至多約30個任何此等胺基酸序列之重複單元。

如本文所使用之「以操作方式連接」應意謂連接兩個或兩個以上生物分子以至少保留與該等生物分子相關之生物功能、活性及/或結構。在提及多肽時，該術語意謂兩個或兩個以上多肽之連接產生保留各多肽組分之至少一些各別個別活性的融合多肽。該兩個或兩個以上多肽可直接或經由連接子連接。在提及核酸時，該術語意謂第一聚核苷酸經置放鄰接第二聚核苷酸，當適當分子(例如轉錄活化蛋白質)結合該第二聚核苷酸時，第二聚核苷酸引導第一聚核苷酸之轉錄。

如本文所使用之「特異性結合」應指第一分子在其可能曝露之許多不同類型分子中結合標靶分子的能力，此係因為該第一分子能夠採納有助於在其自身與該另一靶分子之間形成非共價相互作用的特定結構之故。第一分子結合標靶而形成穩定複合物，而該第一分子與任何其他非特異性分子之識別、接觸或複合物形成實質上較少。

如本文所使用之「多肽變異體」或「蛋白質變異體」係指一或多個胺基酸已經來自參考序列之不同胺基酸取代的多肽。此項技術中

已充分瞭解，一些胺基酸可經具有廣泛相似特性之其他胺基酸取代而不改變多肽之活性性質(保留性取代)，如下文中所述。此等術語亦涵蓋一或多個胺基酸已經添加或缺失、或經不同胺基酸置換之多肽，例如蛋白質同功異型物。適用於本發明之纖維母細胞生長因子-23之實例變異體為纖維母細胞生長因子-23變異體(R179Q)。

如本文所使用之「醫藥組合物」應意謂含有可投與個體以治療或預防疾病或病症之化合物(例如本發明之融合多肽)的組合物。

如本文所使用之「個體(Individual或subject)」應指哺乳動物，包括但不限於人類或非人類哺乳動物，諸如牛、馬、犬、綿羊或貓。

如本文所使用之「治療」應意謂降低、抑制、減輕、減弱、阻滯或穩定疾病之發展或進程。在本發明之情況下，投與本發明之多肽可用於治療年齡相關之病狀，包括肌肉減少症、皮膚萎縮、肌肉萎縮、腦萎縮、動脈粥樣硬化、動脈硬化、肺氣腫、骨質疏鬆症、骨關節炎、免疫機能不全、高血壓、癡呆症、亨廷頓氏病、阿茲海默氏病、白內障、年齡相關之黃斑部變性、前列腺癌、中風、預期壽命縮短、記憶損失、皺紋、腎功能損傷及年齡相關之聽力損失；及代謝障礙，包括II型糖尿病、代謝症候群、高血糖症及肥胖症。

如本文所使用之「預防」應指降低病症之發生率或降低個體罹患病症或其相關症狀之風險。在本發明之情況下，投與本發明之多肽可用於預防年齡相關之病狀，包括肌肉減少症、皮膚萎縮、肌肉萎縮、腦萎縮、動脈粥樣硬化、動脈硬化、肺氣腫、骨質疏鬆症、骨關節炎、免疫機能不全、高血壓、癡呆症、亨廷頓氏病、阿茲海默氏病、白內障、年齡相關之黃斑部變性、前列腺癌、中風、預期壽命縮短、記憶損失、皺紋、腎功能損傷及年齡相關之聽力損失；及代謝障礙，包括II型糖尿病、代謝症候群、高血糖症及肥胖症。預防可為完全預防，例如完全不存在年齡相關之病狀或代謝障礙。預防亦可為部

分預防，從而使個體中發生年齡相關之病狀或代謝障礙的可能性與未接受本發明之個體相比發生可能性較小。

如本文所使用之「疾病」應意謂損傷或干擾細胞、組織或器官之正常功能的任何病狀或病症。

如本文所使用之「年齡相關之病狀」應意謂在群體中之發病率或在個體中之嚴重程度與年齡進程有關的任何疾病或病症。在一實施例中，年齡相關之病狀為在100,000名以上個體之所選群體中，60歲以上之人類個體中之發病率相對於介於30-40歲之間的人類個體至少高1.5倍的疾病或病症。與本發明相關之年齡相關之病狀包括但不限於肌肉減少症、皮膚萎縮、肌肉萎縮、腦萎縮、動脈粥樣硬化、動脈硬化、肺氣腫、骨質疏鬆症、骨關節炎、免疫機能不全、高血壓、癡呆症、亨廷頓氏病、阿茲海默氏病、白內障、年齡相關之黃斑部變性、前列腺癌、中風、預期壽命縮短、記憶損失、皺紋、腎功能損傷及年齡相關之聽力損失。

如本文所使用之「代謝障礙」應意謂藉由影響細胞中之能量產生或細胞、組織、器官或個體中之毒素積聚而損傷或干擾細胞、組織或器官之正常功能的任何疾病或病症。與本發明相關之代謝障礙包括但不限於II型糖尿病、代謝症候群、高血糖症及肥胖症。

「有效劑量」或「有效量」為足以實現有利或所要之臨床結果的量。在本發明之情況下，其為有效產生預定藥理學治療性或預防性結果的Klotho融合多肽或sKlotho之量。治療有效劑量可預防或改善病症或病症之一或多種症狀(例如年齡相關之病狀或代謝障礙)。治療有效劑量將視所治療之個體及疾病病狀、個體之體重及年齡、疾病病狀之嚴重程度、投藥方式及其類似物而變化，該劑量可由一般熟習此項技術者容易地確定。

如本文所使用之「Klotho核酸分子」為編碼Klotho蛋白質之基

因。實例人類Klotho基因提供為GenBank寄存編號NM_004795(SEQ ID NO: 1)。Klotho之其他非限制性實例提供為SEQ ID NO: 47之aa 1-982及SEQ ID NO: 49之aa 1-982；及與此等序列之一致性為至少70%、75%、80%、85%、90%、95%、96%、97%、98%、99%或99%以上或100%的序列。

如本文所使用之「片段」係指多肽或核酸分子之一部分。此部分較佳含有參考核酸分子或多肽之完整長度之至少10%、20%、30%、40%、50%、60%、70%、80%、90%或90%以上。片段可含有10、20、30、40、50、60、70、80、90或100、200、300、400、500、600、700、800、900、1000或多達3000個核苷酸或胺基酸。

術語「實質上一致」係指多肽或核酸分子與參考胺基酸序列(例如本文所述之胺基酸序列中之任一者)或核酸序列(例如本文所述之核酸序列中之任一者)展現至少50%之一致性。該序列在胺基酸層面或核酸層面上較佳與用於比較之序列之一致性為至少60%、70%、75%、80%或85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或99%以上。

本發明係關於預防或治療年齡相關之病狀及代謝障礙之方法、套組及組合物；及該等組合物在治療病理性病症之療法、藥物或使用中之用途。在一些實施例中，本發明提供一種融合多肽，其具有Klotho蛋白質之至少一個細胞外子域。在一些實施例中，該融合多肽進一步包含纖維母細胞生長因子或其活性片段。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。在其他實施例中，該融合物包含FGF(例如FGF19、FGF21、FGF23或FGF23變異體R179Q)融合至經修飾之Fc(例如FcLALA)。FcLALA為具有LALA突變(L234A、L235A)之Fc片段，其以較低效率引發ADCC且以較弱程度結合並活化人類補體。Klotho

細胞外域可源自 α 或 β Klotho同功異型物。此外，雖然主要參考纖維母細胞生長因子-19、纖維母細胞生長因子-21及纖維母細胞生長因子-23描述Klotho融合多肽之FGF組分，但涵蓋23種已知FGF或其活性片段中任一者均可用於實施本發明。

Klotho蛋白質之細胞外域可包括Klotho蛋白質之KL-D1域及KL-D2域中之一者或兩者。在一些實施例中，Klotho融合多肽具有Klotho蛋白質之至少兩個細胞外子域。舉例而言，該至少兩個細胞外子域可為呈串聯重複形式之至少兩個KL-D1域、呈串聯重複形式之至少兩個KL-D2域，或至少一個KL-D1域及至少一個KL-D2域。

Klotho蛋白質之細胞外子域及纖維母細胞生長因子(或其活性片段)可以各種定向及方式彼此以操作方式連接。舉例而言，Klotho蛋白質之細胞外子域可以操作方式連接至纖維母細胞生長因子之N末端，或者纖維母細胞生長因子可以操作方式連接至Klotho蛋白質之至少一個細胞外子域之N末端。

本發明之融合多肽可包括Klotho細胞外域中之一者或兩者，亦即KL-D1(SEQ ID NO: 5)及KL-D2(SEQ ID NO: 6)。KL-D1及KL-D2分別對應於全長 α Klotho多肽(SEQ ID NO: 2)之胺基酸殘基58-506及517-953以及全長 β Klotho多肽(SEQ ID NO: 4)之胺基酸殘基77-508及571-967，且適用於本發明。Klotho融合多肽可具有胺基酸序列與SEQ ID NO: 5之胺基酸序列實質上一致之 α Klotho多肽之KL-D1域，或胺基酸序列與SEQ ID NO: 37之胺基酸序列實質上一致之 β Klotho多肽之KL-D1域。特定言之，Klotho融合多肽可具有與SEQ ID NO: 5或SEQ ID NO: 37之胺基酸序列之一致性為至少70%、75%、80%、85%、90%、95%、96%、97%、98%、99%或99%以上的胺基酸序列。Klotho融合多肽可具有胺基酸序列與SEQ ID NO: 6之胺基酸序列實質上一致之 α Klotho多肽之KL-D2域，或胺基酸序列與SEQ ID NO: 38之胺基酸序列

實質上一致之 β Klotho多肽之KL-D2域。特定言之，Klotho融合多肽可具有分別與SEQ ID NO: 6或SEQ ID NO: 38之胺基酸序列之一致性為至少70%、75%、80%、85%、90%、95%、96%、97%、98%、99%或99%以上的胺基酸序列。

在一些實施例中，本發明之Klotho融合多肽為可溶的，且能夠結合FGF受體。

本發明之Klotho融合多肽可含有多肽連接子，其連接具有Klotho蛋白質之至少一個細胞外子域的多肽及纖維母細胞生長因子及(視情況存在之)經修飾之Fc片段。適合的連接子在此項技術中為熟知的，且一般含有若干Gly及若干Ser殘基，例如(Gly₄ Ser)₃(SEQ ID NO: 11)、Gly₄ Ser多肽(SEQ ID NO: 12)、Gly(SEQ ID NO: 13)、Gly Gly(SEQ ID NO: 14)、Gly Ser(SEQ ID NO: 15)、Gly₂ Ser(SEQ ID NO: 16)、Ala(SEQ ID NO: 17)及Ala Ala(SEQ ID NO: 18)。在一些實施例中，連接子將具有至少2個且至多約30個由SEQ ID NO: 12、SEQ ID NO: 13、SEQ ID NO: 14、SEQ ID NO: 15、SEQ ID NO: 16、SEQ ID NO: 17或SEQ ID NO: 18中之任一者所表示之胺基酸序列的重複單元。

當多肽連接子存在於本發明之Klotho融合多肽中時，具有Klotho蛋白質之至少一個細胞外子域的多肽可由肽鍵連接至連接子多肽之N末端，而FGF係由肽鍵連接至多肽連接子之C末端。或者，FGF可由肽鍵連接至連接子多肽之N末端，而具有Klotho之至少一個細胞外子域的多肽係由肽鍵連接至多肽連接子之C末端。化學連接子亦可用於連接該兩個多肽。

本發明之Klotho融合多肽可包括信號肽。用於Klotho融合多肽之實例信號肽包括但不限於Klotho信號肽(SEQ ID NO: 8)及IgG信號肽(SEQ ID NO: 9)。

在一些實施例中，本發明提供一種FGF(例如FGF19、FGF21、FGF23或FGF23變異體R179Q)與經修飾之Fc(例如FcLALA)之融合物。該融合物亦可視情況包含位於FGF與Fc部分之間的連接子。該融合物亦可視情況包含信號肽。在多個實施例中，本發明涵蓋編碼此等融合多肽之核酸、包含此等核酸之載體，及含有此等核酸之宿主細胞。

Klotho及纖維母細胞生長因子多肽

預期本發明之Klotho融合多肽展現可比於自然界中之FGF之生物活性，諸如結合FGF受體及誘導FGF受體、FRS2(FGF受體受質2)及ERK1/2(細胞外信號調控蛋白質激酶1/2)之磷酸化及活化Egr-1(早期生長反應-1)基因。FGF為結合FGF受體之分泌之肽生長因子。熟習此項技術者可容易地獲得FGF之胺基酸及核酸序列。舉例而言，FGF19、FGF21及FGF23之實例核苷酸序列可分別以寄存編號NM_005117、NM_019113及NM_020638於GenBank資料庫中獲得，且在本文中分別稱為SEQ ID NO: 30、32及34。FGF19、FGF21及FGF23之實例胺基序列可分別以寄存編號NP_005108、NP_061986及NP_065689於GenBank資料庫中獲得，且在本文中分別稱為SEQ ID NO: 31、35及35。另外，FGF可包括一或多個有助於表現蛋白質之變化，例如FGF23(R179Q)變異體(SEQ ID NO: 36)。

Klotho蛋白質為具有細胞外域及短細胞質域之130 kDa單次跨膜I型跨膜蛋白。熟習此項技術者可容易地獲得Klotho之胺基酸及核酸序列。舉例而言， α -Klotho及 β -Klotho之實例核苷酸序列可分別以寄存編號NM_004795及NM_175737於GenBank資料庫中獲得，且在本文中分別稱為SEQ ID NO: 7及8。 α -Klotho及 β -Klotho之實例胺基酸序列可分別以寄存編號NP_004786及NP_783864於GenBank資料庫中獲得，且在本文中分別稱為SEQ ID NO: 2及4。

本發明之Klotho融合多肽可結合纖維母細胞生長因子受體，且具

有以操作方式連接至纖維母細胞生長因子-19 (SEQ ID NO: 31)、纖維母細胞生長因子-21(SEQ ID NO: 33)、纖維母細胞生長因子-23(SEQ ID NO: 35)或其變異體(包括纖維母細胞生長因子-23變異體(R179Q)(SEQ ID NO: 36))之 α -Klotho或 β -Klotho細胞外域。

特定言之，本發明之Klotho融合多肽可包括以操作方式偶合至纖維母細胞生長因子-23(SEQ ID NO: 35)或纖維母細胞生長因子-23變異體(R179Q)(SEQ ID NO: 36)之 α -Klotho(SEQ ID NO: 2)。另外，本發明之Klotho融合多肽可具有以操作方式偶合至纖維母細胞生長因子-19(SEQ ID NO: 31)之 β -Klotho(SEQ ID NO: 4)。本發明之Klotho融合多肽可包括以操作方式偶合至纖維母細胞生長因子-21(SEQ ID NO: 33)之 β -Klotho(SEQ ID NO: 4)。

本發明包括各種Klotho及FGF基因以及彼等基因所編碼之蛋白質的同源物。在提及基因時，「同源物」係指與該基因之至少一部分或者其互補股或其部分實質上一致的核苷酸序列，其限制條件為該核苷酸序列編碼與同源物所屬基因所編碼之蛋白質具有實質上相同之活性/功能的蛋白質。本文所述之基因之同源物可由假定同源物之胺基酸或核苷酸序列與基因或其所編碼之蛋白質之序列(例如編碼Klotho及FGF之基因或其互補股的核苷酸序列)之間的一致性百分比來鑑別。一致性百分比可藉由例如目視檢查或藉由使用此項技術中已知或如本文所述之各種電腦程式來確定。序列一致性通常使用序列分析軟體(例如Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wis. 53705; BLAST、BESTFIT、GAP或PILEUP/PRETTYBOX程式)來量測。該軟體係藉由給各種取代、缺失及/或其他修飾分配同源性程度來匹配一致或相似之序列。保留性胺基酸取代通常包括以下各組中之取代：

甘胺酸及丙胺酸；

纈胺酸、異白胺酸及白胺酸；

天冬胺酸、麩胺酸、天冬醯胺及麩醯胺酸；

絲胺酸及蘇胺酸；

離胺酸及精胺酸；及

苯丙胺酸及酪胺酸。

因而，甘胺酸突變成丙胺酸為保留性胺基酸取代，丙胺酸突變成甘胺酸亦然；纈胺酸突變成異白胺酸或白胺酸為保留性胺基酸取代，以纈胺酸或白胺酸置換異白胺酸亦然，以纈胺酸或異白胺酸置換白胺酸亦然，等等。本發明提供具有至少一個保留性胺基酸取代之本文所揭示之所有胺基酸序列的變異體。

在確定一致性程度之一種實例方法中，可使用BLAST程式，可能性得分介於 e^{-3} 與 e^{-100} 之間指示密切相關之序列。

在一實施例中，本發明提供SEQ ID NO: 19之融合多肽。

在另一實施例中，本發明提供SEQ ID NO: 20之融合多肽。

在一實施例中，本發明提供SEQ ID NO: 40之融合多肽。

在另一實施例中，本發明提供SEQ ID NO: 41之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在一實施例中，本發明提供SEQ ID NO: 46之融合多肽。

在另一實施例中，本發明提供SEQ ID NO: 47之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 48之融合多肽。

在另一實施例中，本發明提供SEQ ID NO: 49之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在一實施例中，本發明提供SEQ ID NO: 50之融合多肽。

在另一實施例中，本發明提供SEQ ID NO: 51之融合多肽，或其

包含至少一個保留性胺基酸取代之變異體。

在一實施例中，本發明提供SEQ ID NO: 52之融合多肽。

在另一實施例中，本發明提供SEQ ID NO: 53之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 54之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 55之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 56之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 57之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 58之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 59之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 60之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 61之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 62之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 63之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 64之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 65之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 66之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 67之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

在另一實施例中，本發明提供SEQ ID NO: 68之融合多肽，或其包含至少一個保留性胺基酸取代之變異體。

如本文所使用之術語「同源性」及「同源」不限於具有理論性共同基因祖先之指定蛋白質，而是包括基因上可能無關但已經演化能執行類似功能及/或具有類似結構的蛋白質。本文所述之各種蛋白質之功能同源性亦涵蓋具有同源物所屬之相應蛋白質之活性的蛋白質。關於具有功能同源性之蛋白質，不需要其在胺基酸序列方面具有顯著一致性，而是因具有相似或一致活性而定義為具有功能同源性之蛋白質。舉例而言，關於Klotho分子，該多肽應具有結合FGF多肽且使FGF能夠結合FGFR之功能特徵。關於FGF分子，該多肽應具有結合FGFR且引起FGFR活化(例如磷酸化)之功能特徵。評定FGF與FGF受體之結合及/或FGF信號傳導路徑之活化的檢定在此項技術中為已知的且描述於本文中(參見實例2)。評定Klotho活性之檢定在此項技術中亦為已知的且描述於本文中(例如結合FGF多肽)。具有結構同源性之蛋白質定義為具有類似的三級(或四級)結構且未必需要與其編碼基因具有胺基酸一致性或核酸一致性。在某些情況下，結構同源物可包括僅在蛋白質之活性位點或結合位點處維持結構同源性的蛋白質。

除結構及功能同源性以外，本發明進一步涵蓋與本文所述之各種Klotho及FGF胺基酸序列具有胺基酸一致性的蛋白質。為了測定兩個胺基酸序列之一致性/同源性百分比，出於最佳比較目的，比對該

等序列(例如可在一個蛋白質之胺基酸序列中引入間隙以與另一蛋白質之胺基酸序列最佳比對)。接著比較相應胺基酸位置之胺基酸殘基。當一個序列中之位置被與另一序列中相應位置相同之胺基酸殘基佔據時，則該等分子在該位置處為一致的。兩個序列之一致性百分比為該等序列所享有之一致位置之數目的函數(亦即一致性%=一致位置數/總位置數×100)。

本文所述之本發明分子之胺基酸序列具有與本文所述之胺基酸序列之一致性或同源性為至少約60%、70%、80%、90%、95%、96%、97%、98%、99%或99%以上的胺基酸序列。

本文所述之本發明分子之核酸序列具有與本文所述之核苷酸序列雜交或與其之一致性或同源性為至少約60%、70%、80%、90%、95%、96%、97%、98%、99%或99%以上的核苷酸序列。

適合用於本發明之融合多肽中的核酸分子可具有Klotho或FGF核苷酸序列，其在嚴格條件下分別與編碼Klotho或FGF之核酸分子之補體雜交。如本文所使用之術語「在嚴格條件下雜交」意欲描述彼此間之同源性為至少約70%、80%、85%、90%或90%以上之核苷酸序列通常仍彼此雜交的雜交及洗滌條件。該等嚴格條件為熟習此項技術者所知，且可在Ausubel等人，*Current Protocols in Molecular Biology*, Wiley Interscience, New York (2001), 6.3.1-6.3.6中獲得。嚴格雜交條件之特定非限制性實例為在6×氯化鈉/檸檬酸鈉(SSC)中在約45°C下雜交，接著在0.2×SSC、0.1% SDS中在50-65°C下洗滌一或多次。

本發明之Klotho-FGF融合多肽

在本發明之一些實施例中，Klotho融合多肽具有多肽鏈，該多肽鏈具有Klotho多肽或其活性片段之第一多肽序列及編碼FGF或其活性片段之第二多肽序列。在一些實施例中，該融合物進一步包含具有降低對Fc-γ受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

本發明包括與SEQ ID NO: 19-28中所示之胺基酸序列之同源性為至少約95%或95%以上之融合多肽。SEQ ID NO: 19之胺基酸序列編碼具有連接至FGF23(R179Q)變異體(SEQ ID NO: 36)之N末端之Klotho細胞外域的Klotho融合多肽。SEQ ID NO: 20之胺基酸序列編碼具有連接至Klotho細胞外域之N末端之IgG信號肽且缺乏連接至FGF23(R179Q)變異體之N末端之信號肽的Klotho融合多肽。SEQ ID NO: 21之胺基酸序列編碼具有連接至FGF23(R179Q)變異體之N末端之KL-D1細胞外子域的Klotho融合多肽。SEQ ID NO: 22之胺基酸序列編碼具有連接至FGF23(R179Q)變異體之N末端之KL-D2細胞外子域的Klotho融合多肽。SEQ ID NO: 23之胺基酸序列編碼具有連接至FGF23(R179Q)變異體之N末端之兩個KL-D1細胞外子域的Klotho融合多肽。SEQ ID NO: 24之胺基酸序列編碼具有連接至FGF23(R179Q)變異體之N末端之兩個KL-D2細胞外子域的Klotho融合多肽。SEQ ID NO: 25之胺基酸序列編碼具有連接至Klotho細胞外域之N末端之FGF23(R179Q)變異體的Klotho融合多肽。SEQ ID NO: 26之胺基酸序列編碼具有連接至KL-D1細胞外子域之N末端之FGF23(R179Q)變異體的Klotho融合多肽。SEQ ID NO: 27之胺基酸序列編碼具有連接至KL-D2細胞外子域之N末端之FGF23(R179Q)變異體的Klotho融合多肽。SEQ ID NO: 28之胺基酸序列編碼具有連接至兩個KL-D1細胞外子域之N末端之FGF23(R179Q)變異體的Klotho融合多肽。SEQ ID NO: 29之胺基酸序列編碼具有連接至兩個KL-D2細胞外子域之N末端之FGF23(R179Q)變異體的Klotho融合多肽。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

本發明之Klotho融合多肽可包括與SEQ ID NO: 7中所述之胺基酸序列之一致性為至少約95%的胺基酸序列。SEQ ID NO: 7之胺基酸序

列編碼缺乏信號肽之Klotho細胞外域。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

標的融合蛋白質描述於本文中且可使用此項技術中已知之方法製造。舉例而言，可如美國專利第6,194,177號中所述構築本發明之融合多肽。Klotho多肽之用途描述於美國專利第6,579,850號中。FGF核酸分子之用途描述於美國專利第7,223,563號中。

在一些實施例中，利用PCR選殖編碼Klotho之核酸分子且與編碼FGF之核酸分子同框連接。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。使編碼該融合多肽之核酸以操作方式連接至啟動子以進行表現。隨後將編碼該融合多肽之核酸分子轉染於宿主細胞中來表現。可藉由定序來證實最終構築體之序列。

當製備本發明之融合蛋白質時，編碼Klotho之細胞外子域之核酸分子將同框融合至編碼FGF之核酸分子及(視情況存在之)編碼經修飾之Fc片段之核酸。所得核酸分子之表現使得Klotho之細胞外子域融合至FGF多肽之N末端。亦可能存在Klotho之細胞外子域融合至FGF多肽之C末端的融合物。製造融合蛋白質之方法在此項技術中為熟知的。

本發明之融合多肽具有至少兩個共價連接之多肽，其中一個多肽來自一個蛋白質序列或域，例如Klotho，而另一多肽來自另一蛋白質序列或域，例如FGF。在一些實施例中，該融合物進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。在另一實施例中，本發明包含FGF融合至經修飾之Fc片段。本發明融合多肽之Klotho及/或FGF及/或(視情況存在之)經修飾之Fc片段可由熟習此項技術者所熟知之方法接合。此等方法包括化學法與重組法。

編碼欲併入本發明融合多肽中之域的核酸可使用重組遺傳學領

域中之常規技術獲得。揭示用於本發明中之一般方法的基礎教科書包括Sambrook及Russell, *Molecular Cloning, A Laboratory Manual* (第3版, 2001); Kriegler, *Gene Transfer and Expression: A Laboratory Manual* (1990); 及Current Protocols in Molecular Biology (Ausubel等人編, 1994-1999)。在編碼本發明之Klotho融合多肽之核酸中, 可使用分別由SEQ ID NO: 1及SEQ ID NO: 3表示之編碼 α -Klotho或 β -Klotho之核酸序列。在編碼Klotho融合多肽之核酸中, 可使用分別由SEQ ID NO: 30、SEQ ID NO: 32及SEQ ID NO: 34表示之編碼FGF19、FGF21或FGF23之核酸序列。本文所述之本發明分子之核酸序列包含與SEQ ID NO: 1、SEQ ID NO: 3、SEQ ID NO: 30、SEQ ID NO: 32或SEQ ID NO: 34雜交或與其之一致性或同源性為至少約60%、70%、80%、90%、95%、96%、97%、98%、99%或99%以上的核苷酸序列。

編碼融合物之各種組分[Klotho及/或FGF肽及/或(視情況存在之)經修飾之Fc片段]之核酸序列可使用多種方法中之任一種獲得。舉例而言, 可藉由與探針雜交自cDNA及基因體DNA庫選殖編碼多肽之核酸序列, 或使用擴增技術用寡核苷酸引子分離編碼多肽之核酸序列。更通常, 藉由使用DNA或RNA模板, 使用擴增技術來擴增並分離Klotho及FGF序列(參見例如Dieffenbach及Dveksler, *PCR Primers: A Laboratory Manual* (1995))。或者, 可合成產生重疊寡核苷酸並接合以產生一或多個域。亦可使用抗體作為探針自表現庫中分離編碼Klotho或FGF之核酸。

根據本發明, 融合物之各種組分[Klotho及/或FGF及/或(視情況存在之)經修飾之Fc片段]可直接或經由共價連接子連接, 包括胺基酸連接子, 諸如聚甘胺酸連接子, 或另一類型之化學連接子, 包括碳水化合物連接子、脂質連接子、脂肪酸連接子、聚醚連接子, 諸如PEG等(參見例如Hermanson, *Bioconjugate techniques* (1996))。形成融合物/

融合多肽之多肽通常為C末端連接至N末端，但其亦可為C末端連接至C末端、N末端連接至N末端或N末端連接至C末端。一或多個多肽域可插入本發明融合多肽內之內部位置。融合蛋白質之多肽可呈任何順序。融合多肽可如下產生：藉由將來自一個蛋白質序列之胺基酸鏈(例如Klotho之細胞外子域)共價連接至來自另一蛋白質序列之胺基酸鏈(例如FGF)，藉由製備連續編碼融合蛋白質之重組聚核苷酸。融合蛋白質中之不同胺基酸鏈可直接剪接在一起，或可經由化學連接基團或胺基酸連接基團間接剪接在一起。胺基酸連接基團之長度可為約200個胺基酸或200個胺基酸以上，或一般為1至100個胺基酸。在一些實施例中，將脯胺酸殘基併入連接子中以防止由連接子形成顯著的二級結構元件。連接子通常可為合成作為重組融合蛋白質之一部分的可撓性胺基酸子序列。該等可撓性連接子為熟習此項技術者所知。

根據本發明，融合物之胺基酸序列[Klotho之細胞外子域及/或FGF及/或(視情況存在之)經修飾之Fc片段]可經由肽連接子連接。實例肽連接子在此項技術中為熟知的且描述於本文中。舉例而言，肽連接子一般包括若干Gly及若干Ser殘基，諸如：(Gly₄ Ser)₃(SEQ ID NO: 11)、Gly₄ Ser多肽(SEQ ID NO: 12)、Gly(SEQ ID NO: 13)、Gly Gly(SEQ ID NO: 14)、Gly Ser(SEQ ID NO: 15)、Gly₂ Ser(SEQ ID NO: 16)、Ala(SEQ ID NO: 17)及Ala Ala(SEQ ID NO: 18)。特定言之，用於本發明之融合蛋白質中之肽連接子可充當可撓性鉸鏈。

在Klotho併入本發明融合蛋白質中之前，可排除Klotho或FGF之信號序列。融合蛋白質之Klotho或FGF之信號序列可包括例如由SEQ ID NO: 19表示之多肽。然而，亦可省去該等序列，或以不同蛋白質之信號序列置換，例如IgG信號序列(SEQ ID NO: 9)。一般而言，本發明之醫藥組合物將含有Klotho及FGF之成熟形式。

一般而言，在Klotho或FGF部分併入融合多肽中之前，自其中之

一者或兩者中排除內含子。

本發明之融合多肽可包括一或多個聚合物共價連接至一或多個反應性胺基酸側鏈。舉例而言，該等聚合物包括但不限於聚乙二醇(PEG)，其可連接至一或多個游離半胱胺酸硫氫基殘基，藉此在蛋白質曝露於氧化條件時阻斷雙硫鍵之形成及聚集。此外，預期本發明融合多肽之聚乙二醇化將提供諸如增加之半衰期、溶解性及蛋白酶抗性之改良特性。或者，本發明之融合多肽可藉由共價加成聚合物與游離胺基(諸如離胺酸 ϵ 或N末端胺基)來修飾。用於共價修飾之特定特異性半胱胺酸及離胺酸將為不涉及受體結合、肝素結合或呈適當蛋白質摺疊的半胱胺酸及離胺酸。熟習此項技術者將顯而易知，可採用檢定融合多肽之生物化學活性及/或生物活性之方法來確定特定胺基酸殘基之修飾是否依照要求影響蛋白質活性。涵蓋其他類似之適合修飾，且其在此項技術中為已知的。

本發明亦關於與SEQ ID NO: 19-28中所示之胺基酸序列之同源性為至少約95%或95%以上的融合多肽的表現。

本發明涵蓋一種融合多肽，其包含：(a)包含Klotho蛋白質之至少一個細胞外子域或其功能活性變異體或衍生物的多肽；(b)包含纖維母細胞生長因子或其功能活性變異體或衍生物之多肽；及(c)具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

「其功能活性變異體或衍生物」意謂與相應野生型多肽相比，包含較長、較短或改變之胺基酸序列同時保留生物活性的變異體或衍生物。因而，Klotho蛋白質之細胞外子域或纖維母細胞生長因子之「功能活性變異體或衍生物」與野生型Klotho蛋白質之細胞外子域或纖維母細胞生長因子相比，包含較少、較多或改變之胺基酸序列，但仍保留野生型多肽序列之至少一種生物活性。本文所揭示之多肽之功能活性變異體或衍生物亦可包含本文所揭示之多肽之相同胺基酸序列，但在轉

譯後修飾(例如聚乙二醇化、甲基化及/或糖基化)方面不同或具有添加之其他部分或元件。在多個實施例中，FGF23之變異體或衍生物包含R179Q或不包含R179Q。

在一實施例中，功能活性變異體或衍生物多肽包括與本文所揭示之序列(例如Klotho蛋白質之至少一個細胞外域或纖維母細胞生長因子)之一致性為至少約60%的胺基酸序列。該多肽較佳與本文所揭示之序列之一致性為至少55%、60%、65%、70%、75%、80%、85%、90%、95%、98%、99%或99%以上。

如本文所使用，使用 Karlin 及 Altschul 之算法(PNAS USA 87:2264-2268, 1990，在Karlin及Altschul, PNAS USA 90:5873-5877, 1993中加以改進)確定兩個胺基酸序列(或兩個核酸序列)之一致性百分比。將該算法併入Altschul等人(J. Mol. Biol. 215:403-410, 1990)之NBLAST及XBLAST程式中。用NBLAST程式、得分=100、字長=12來執行BLAST核苷酸搜尋。用XBLAST程式、得分=50、字長=3來執行BLAST蛋白質搜尋。比較時，為獲得間隙比對，利用GappedBLAST，如Altschul等人(Nucleic Acids Res. 25:3389-3402, 1997)中所述。當利用BLAST及GappedBLAST程式時，使用各別程式(例如XBLAST及NBLAST)之缺省參數獲得與本發明核酸分子同源之核苷酸序列。

一致性或一致意謂胺基酸序列(或核酸序列)相似性且具有技術領域中所公認之含義。具有一致性之序列享有一致或類似之胺基酸(或核酸)。因而，與參考序列享有85%胺基酸序列一致性之候選序列要求在該候選序列與參考序列比對之後，該候選序列中85%之胺基酸與參考序列中之相應胺基酸一致，及/或構成保留性胺基酸變化。

本文所揭示之多肽之功能活性變異體保留與原始多肽或片段實質上相同之功能活性。本發明包括天然存在之功能活性變異體(諸如

對偶基因變異體及物種變異體)及非天然存在之功能活性變異體，且其可由例如突變誘發技術或由直接合成來產生。

功能活性變異體或衍生物與本文所揭示之多肽的不同之處在於約或至少例如1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、25、30、35、40、45、50、55、60或60個以上胺基酸殘基。若此比較需要比對，則比對該等序列以獲得最大同源性。變異位點可存在於多肽中之任何位置，只要活性與本文所揭示之多肽實質上相似即可。

關於如何用表現型沉默之胺基酸取代製造變異體及衍生物的指導提供於Bowie等人, *Science*, 247:1306-1310 (1990)中，該文獻教示研究胺基酸序列對改變之容許度的兩種主要策略。

第一種策略採用在演化過程期間自然選擇對胺基酸取代之容許度。藉由比較不同物種之胺基酸序列，可鑑別物種間之保留之胺基酸位置。參見例如圖5。此等保留性胺基酸對蛋白質功能而言可能較為重要。相反，取代能為自然選擇所容許之胺基酸位置指示對蛋白質功能而言不重要之位置。因而，容許胺基酸取代之位置可經修飾，而仍維持多肽之特異性結合活性。

第二種策略使用基因工程改造在經選殖之基因的特定位置處引入胺基酸變化以鑑別對蛋白質功能而言重要之區。舉例而言，可使用定點突變誘發或丙胺酸掃描突變誘發(在分子中之每個殘基處引入單一丙胺酸突變)(Cunningham等人, *Science*, 244:1081-1085 (1989))。

向蛋白質之胺基酸中引入突變之方法為熟習此項技術者所熟知。參見例如Ausubel(編), *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. (1994)；T. Maniatis, E. F. Fritsch及J. Sambrook, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor laboratory, Cold Spring Harbor, N.Y. (1989)。亦可使用諸如

「QuikChange. TM. Site-Directed Mutagenesis Kit」(Stratagene)之市售套組引入突變。熟習此項技術者可藉由置換不影響多肽功能之胺基酸來產生多肽之多肽功能活性變異體或衍生物。

變異體或衍生物可具有例如一或多個保留性取代而仍保留至少一種生物活性。保留性取代為胺基酸被具有類似特性之另一胺基酸取代，如此熟習肽化學技術者將預期多肽之二級結構及親水性質實質上不變化。一般而言，以下各組胺基酸表示保留性變化：(1)ala、pro、gly、glu、asp、gln、asn、ser、thr；(2)cys、ser、tyr、thr；(3)val、ile、leu、met、ala、phe；(4)lys、arg、his；及(5)phe、tyr、trp、his。

特定實例變異體及衍生物包括但不限於包含Klotho蛋白質之至少一個細胞外子域之多肽的功能活性變異體及衍生物，例如包含Klotho之細胞外域(例如SEQ ID NO: 5或6)之至少約100、150、200、250、300、350、375、400或425個連續胺基酸且與野生型序列(如SEQ ID NO: 5或6中所揭示)相比具有不超過約1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、25、30、35、40、45、50、55、60或60個以上胺基酸殘基差異同時保留該野生型多肽之至少一種生物活性的多肽。舉例而言，包含Klotho蛋白質之至少一個細胞外子域之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 5或6之至少約400個連續胺基酸且具有不超過約100個胺基酸殘基差異的多肽。舉例而言，包含Klotho蛋白質之至少一個細胞外子域之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 5或6之至少約400個連續胺基酸且具有不超過約50個胺基酸殘基差異的多肽。舉例而言，包含Klotho蛋白質之至少一個細胞外子域之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 5或6之至少約425個連續胺基酸且具有不超過約25個胺基酸殘基差異的多肽。舉例而言，包含

Klotho蛋白質之至少一個細胞外子域之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 5或6之至少約425個連續胺基酸且具有不超過約10個胺基酸殘基差異的多肽。在另一實例中，包含Klotho蛋白質之至少一個細胞外子域之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 7之至少約100、150、200、250、300、350、400、450、500、550、600、650、700、750、800、850、900、925、950或982個連續胺基酸且與野生型序列相比具有不超過約1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、25、30、35、40、45、50、55、60、70、75、80、85、90、95、100、110、120、140、150、160、170、180、190或200個胺基酸殘基差異的多肽。舉例而言，包含Klotho蛋白質之至少一個細胞外子域之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 7之至少約500個連續胺基酸且具有不超過約100個胺基酸殘基差異的多肽。舉例而言，包含Klotho蛋白質之至少一個細胞外子域之多肽的功能活性變異體或衍生物包含包含SEQ ID NO: 7之至少約600個連續胺基酸且具有不超過約100個胺基酸殘基差異的多肽。舉例而言，包含Klotho蛋白質之至少一個細胞外子域之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 7之至少約700個連續胺基酸且具有不超過約100個胺基酸殘基差異的多肽。舉例而言，包含Klotho蛋白質之至少一個細胞外子域之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 7之至少約800個連續胺基酸且具有不超過約100個胺基酸殘基差異的多肽。舉例而言，包含Klotho蛋白質之至少一個細胞外子域之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 7之至少約900個連續胺基酸且具有不超過約100個胺基酸殘基差異的多肽。舉例而言，包含Klotho蛋白質之至少一個細胞外子域之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 7之至少約900個連續胺基酸且具有不超過

約50個胺基酸殘基差異的多肽。

特定實例變異體及衍生物包括但不限於包含纖維母細胞生長因子之多肽的功能活性變異體及衍生物，例如包含纖維母細胞生長因子(例如FGF19(SEQ ID NO: 31)、FGF21(SEQ ID NO: 33)或FGF23(SEQ ID NO: 35))之至少約100、125、150、150、175、200、225或250個連續胺基酸且與野生型序列(如SEQ ID NO: 31、33或35中所揭示)相比具有不超過約1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、25、30、35、40、45、50、55、60或60個以上胺基酸殘基差異，同時保留該野生型多肽之至少一種生物活性的多肽。在多個實施例中，變異體或衍生物可包含R179Q變異或不包含R179Q變異。舉例而言，包含纖維母細胞生長因子之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 31、33或35之至少約150個連續胺基酸且具有不超過約25個胺基酸殘基差異的多肽。舉例而言，包含纖維母細胞生長因子之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 31、33或35之至少約175個連續胺基酸且具有不超過約25個胺基酸殘基差異的多肽。舉例而言，包含纖維母細胞生長因子之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 31、33或35之至少約200個連續胺基酸且具有不超過約25個胺基酸殘基差異的多肽。舉例而言，包含纖維母細胞生長因子之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 35之至少約225個連續胺基酸且具有不超過約50個胺基酸殘基差異的多肽。舉例而言，包含纖維母細胞生長因子之多肽的功能活性變異體或衍生物包含：包含SEQ ID NO: 35之至少約225個連續胺基酸且具有不超過約25個胺基酸殘基差異的多肽。

本發明融合多肽之表現

爲了表現本發明之融合蛋白質，可利用此項技術中熟知之技術

將由本文所述或此項技術中已知之任何方法所獲得之DNA分子插入適當表現載體中。舉例而言，可由均聚加尾反應(homopolymeric tailing)或由涉及使用合成DNA連接子之限制酶連接反應或由鈍端連接反應，將雙股cDNA選殖於適合載體中。通常使用DNA連接酶來連接DNA分子，且可藉由用鹼性磷酸酶處理，來避免不合需要之接合。

因此，本發明包括載體(例如重組質體及噬菌體)，該等載體包括如本文所述之核酸分子(例如基因或編碼基因之重組核酸分子)。術語「重組載體」包括已經過改變、修飾或工程改造，其與獲得該重組載體之原生或天然核酸分子中所包括之核酸序列相比含有較多、較少或不同核酸序列的載體(例如質體、噬菌體、噬菌粒、病毒、黏質體、F-質粒(fosmid)或其他純化之核酸載體)。舉例而言，重組載體可包括編碼以操作方式連接至如本文所定義之調控序列(例如啟動子序列、終止子序列及/或人工核糖體結合位點(RBS))之Klotho-FGF23融合物的核苷酸序列。允許表現其中所包括之基因或核酸之重組載體稱為「表現載體」。

對於真核宿主，視宿主之性質，可利用不同轉錄及轉譯調控序列。其可源自病毒來源，諸如腺病毒、牛乳頭狀瘤病毒、猴病毒(Simian virus)或其類似物，其中該調控信號與具有高表現量之特定基因相關。實例包括但不限於疱疹病毒(Herpes virus)之TK啟動子、SV40早期啟動子、酵母gal4基因啟動子等。可選擇允許壓制或活化之轉錄起始調控信號，從而可調節基因表現。

在本文所述之一些本發明分子中，由具有編碼融合多肽之一或多個多肽鏈之核苷酸序列的一或多個DNA分子以操作方式連接至一或多個調控序列，該等調控序列能夠將所要DNA分子整合於宿主細胞中。可選擇已經過所引入之DNA穩定轉型之細胞，舉例而言，藉由引入一或多個允許選擇含有表現載體之宿主細胞的標記物。可選擇之標

記基因可直接連接至欲表現之核酸序列，或藉由共同轉染引入同一細胞中。亦可能需要其他元件，以便最佳合成本文所述之蛋白質。一般熟習此項技術者將顯而易知其他可使用元件。

在選擇特定質體或病毒載體時，重要之因素包括但不限於與不含載體之接受者細胞區別以便識別且選擇含有載體之接受者細胞的簡易性；特定宿主中所要之載體的複本數；及是否需要使載體能夠在不同物種之宿主細胞之間「穿梭(shuttle)」。

構築包括用於表現之DNA序列的載體後，即可藉由此項技術中已知之各種適合方法中之一或多種將其引入適當宿主細胞中，包括但不限於例如轉型、轉染、結合、原生質體融合、電穿孔、磷酸鈣沈澱、直接顯微注射等。

宿主細胞可為原核或真核。真核宿主細胞之實例包括例如哺乳動物細胞，諸如人類細胞、猴細胞、小鼠細胞及中國倉鼠卵巢(CHO)細胞。該等細胞有助於蛋白質之轉譯後修飾，包括例如正確摺疊或糖基化。另外，亦可使用酵母細胞表現本發明之融合多肽。類似於大部分哺乳動物細胞，酵母細胞亦能夠進行蛋白質之轉譯後修飾，包括例如糖基化。存在許多重組DNA策略，該等策略利用可用於在酵母中產生蛋白質之強啟動子序列及高複本數質體。酵母轉錄及轉譯機制可識別所選殖之哺乳動物基因產物上之前導序列，從而能夠分泌帶有前導序列之肽(亦即前肽(pre-peptide))。以高產率產生本發明融合多肽之特定方法為藉由在DHFR缺乏型CHO細胞中使用二氫葉酸還原酶(DHFR)擴增，藉由使用連續遞增量之甲胺喋呤，如美國專利第4,889,803號中所述。所獲得之多肽可呈糖基化形式。

在宿主細胞中引入一或多種載體後，宿主細胞通常在選擇性培養基中生長，該培養基選擇生長含載體之細胞。可藉由此項技術中已知或本文所述之任何方法進行重組蛋白質之純化，例如任何習知程

序，涉及萃取、沈澱、層析及電泳。可用於純化蛋白質之另一純化程序為親和層析法，其使用結合標靶蛋白質之單株抗體。一般而言，使含有重組蛋白質之粗製劑穿過固定有適合單株抗體之管柱。蛋白質通常經由特異性抗體結合管柱，而雜質則穿過管柱。洗滌管柱後，藉由例如改變pH值或離子濃度使蛋白質自凝膠中溶離。

評定融合多肽活性之檢定

本文所述之檢定(參見實例2)及此項技術中已知之檢定可用於偵測本發明融合多肽之Klotho或FGF活性。適合的活性檢定包括受體結合檢定、細胞增殖檢定及細胞信號傳導檢定。舉例而言，可用於確定融合多肽是否具有Klotho或FGF活性之結合檢定包括檢定融合多肽與FGF受體之結合。FGF受體結合檢定包括但不限於競爭性與非競爭性檢定。舉例而言，可藉由使表現FGF受體之細胞與經標記之FGF(例如放射性標記)接觸並增加未標記之Klotho-FGF融合多肽之濃度來偵測FGF受體結合。向含有該細胞之反應混合物中添加競爭以結合同一受體之兩種配位體。隨後洗滌該等細胞且量測經標記之FGF。在存在未標記之融合多肽的情況下經標記之FGF之量相對於其受體降低，指示Klotho-FGF融合多肽結合該受體。或者，可標記Klotho-FGF融合多肽，且偵測融合多肽與細胞之直接結合。

亦可藉由確定融合多肽是否誘導細胞反應來量測Klotho或FGF活性。舉例而言，在一些實施例中，偵測Klotho-FGF融合多肽之生物活性的檢定涉及使表現FGF受體之細胞與融合多肽接觸，檢定細胞反應，諸如C2C12細胞中之細胞增殖或Egr-1活化、肌管直徑，並比較在存在及不存在融合多肽之情況下的細胞反應。在存在融合多肽複合物之情況下的細胞反應相對於不存在融合多肽複合物之情況有所增加，指示融合多肽具有生物活性。又，亦可量測來自受體之下游信號傳導事件增加作為生物活性之指標(例如FGFR、FRS2、ERK1/2、p70S6K

等之磷酸化)。

醫藥組合物及治療方法

本發明亦關於醫藥組合物，其含有一或多種本發明融合多肽及醫藥學上可接受之稀釋劑或載劑。該等醫藥組合物可進一步包括醫藥學有效劑量之肝素。該等醫藥組合物可包括於套組或容器中。該套組或容器可與關於融合多肽之延長活體內半衰期或活體外存放期的說明書一起封裝。該套組或容器可視情況隨附呈政府機構指定之形式的規定醫藥或生物產品之製造、使用或銷售的通知，該通知反映機構批准可用於人類投藥製造、使用或銷售。該等組合物可用於治療、預防或改善患者、較佳哺乳動物且最佳人類之疾病或疾病症狀(例如年齡相關之病狀或代謝障礙)之方法中，其係藉由將醫藥組合物投與患者來使用。

一般而言，本發明醫藥組合物之治療有效量為每公斤體重約0.0001 mg至0.001 mg；0.001 mg至約10 mg或約0.02 mg至約5 mg。融合多肽之治療有效量通常為例如約0.001 mg至約0.01 mg、約0.01 mg至約100 mg或約100 mg至約1000 mg。融合多肽之治療有效量較佳為約0.001 mg/kg至2 mg/kg。

融合多肽之最佳醫藥調配物可由熟習此項技術者視投藥途徑及所要劑量來確定。(參見例如Remington's Pharmaceutical Sciences，第18版(1990), Mack Publishing Co., Easton, Pa.，該文獻之全部揭示內容係以引用方式併入本文中)。

本發明之融合多肽可以可呈固體、液體或氣體(氣霧劑)形式之醫藥組合物形式投藥。典型投藥途徑可包括但不限於經口、表面(topical)、非經腸、舌下、直腸、陰道、皮內及鼻內。非經腸投藥包括皮下注射、靜脈內、肌肉內、腹膜內、胸膜內、胸骨內注射或輸注技術。較佳非經腸投與該等組合物。更佳靜脈內投與該等組合物。本

發明之醫藥組合物可經調配以使本發明之多肽在組合物投與個體後具生物可用性。組合物可呈一或多個劑量單位形式，例如其中錠劑可為單一劑量單位，而呈氣霧劑形式之本發明多肽的容器可容納複數個劑量單位。

製備醫藥組合物時所使用之物質在所使用之量下可無毒的。熟習此項技術者將顯而易知，醫藥組合物中之活性成分之最佳劑量將視多種因素而定。相關因素包括但不限於個體類型(例如人類)、個體之總體健康狀況、個體需要治療之年齡相關之病狀或代謝障礙的類型、組合物作為多藥物療程之一部分的使用、本發明多肽之特定形式、投藥方式及所採用之組合物。

醫藥學上可接受之載劑或媒劑可為微粒，以致組合物呈例如錠劑或散劑形式。載劑可為液體，而組合物為例如口服糖漿或可注射液體。此外，載劑可為氣體，以致提供適用於例如吸入投藥之氣霧劑組合物。

術語「載劑」係指與本發明多肽一起投藥之稀釋劑、佐劑或賦形劑。該等醫藥載劑可為液體，諸如水及油，包括石油、動物油、植物油或合成來源之油，諸如花生油、大豆油、礦物油、芝麻油及其類似物。載劑可為鹽水、阿拉伯膠、明膠、澱粉糊、滑石、角蛋白、膠狀二氧化矽、尿素及其類似物。此外，可使用助劑、穩定劑、增稠劑、潤滑劑及著色劑。在一實施例中，當投與個體時，本發明多肽及醫藥學上可接受之載劑為無菌的。當本發明多肽經靜脈內投藥時，水為特定載劑。鹽水溶液及右旋糖水溶液及甘油溶液亦可用作液體載劑，尤其用於可注射溶液。適合的醫藥載劑亦包括賦形劑，諸如澱粉、葡萄糖、乳糖、蔗糖、明膠、麥芽糖、稻米、麵粉、白堊、矽膠、硬脂酸鈉、單硬脂酸甘油酯、滑石、氯化鈉、脫脂奶粉、甘油、丙烯、乙二醇、水、乙醇及其類似物。本發明組合物需要時亦可含有

微量潤濕劑或乳化劑或pH值緩衝劑。

組合物可預定用於經口投藥，且若如此，則組合物較佳呈固體或液體形式，其中半固體、半液體、懸浮液及凝膠形式包括在本文所認為之固體或液體形式內。

作為供經口投藥之固體組合物，組合物可調配成散劑、顆粒劑、壓製錠劑、丸劑、膠囊、口香糖、粉片(wafer)或其類似形式。該固體組合物通常含有一或多種惰性稀釋劑。此外，可存在一或多種以下物質：黏合劑，諸如乙基纖維素、羧甲基纖維素、微晶纖維素或明膠；賦形劑，諸如澱粉、乳糖或糊精；崩解劑，諸如海藻酸、海藻酸鈉、澱粉羥基乙酸鈉(Primogel)、玉米澱粉及其類似物；潤滑劑，諸如硬脂酸鎂或史提若特(Sterotex)；助流劑，諸如膠體二氧化矽；甜味劑，諸如蔗糖或糖精；調味劑，諸如胡椒薄荷、柳酸甲酯或橙味劑；及著色劑。

當醫藥組合物呈膠囊、例如明膠膠囊形式時，除以上類型之物質以外，其亦可含有液體載劑，諸如聚乙二醇、環糊精或脂肪油。

醫藥組合物可呈液體形式，例如酏劑、糖漿、溶液、乳液或懸浮液。液體可適用於經口投藥或藉由注射遞送。當預定用於經口投藥時，組合物可含有一或多種甜味劑、防腐劑、染料/著色劑及口味增強劑。在用於注射投藥之組合物中，亦可包括一或多種界面活性劑、防腐劑、潤濕劑、分散劑、懸浮劑、緩衝劑、穩定劑及等張劑。

本發明之液體組合物不論是溶液、懸浮液還是其他類似形式，亦可包括一或多種以下物質：無菌稀釋劑，諸如注射用水、鹽水溶液(較佳為生理鹽水)、林格氏溶液(Ringer's solution)、等張氯化鈉；固定油，諸如可充當溶劑或懸浮介質之合成單酸甘油酯或二酸甘油酯、聚乙二醇、丙三醇、環糊精、丙二醇或其他溶劑；抗細菌劑，諸如苯甲醇或對羥基苯甲酸甲酯；抗氧化劑，諸如抗壞血酸或亞硫酸氫鈉；

螯合劑，諸如乙二胺四乙酸；緩衝劑，諸如乙酸鹽、檸檬酸鹽或磷酸鹽；及張力調節劑，諸如氯化鈉或右旋糖。非經腸組合物可密封於安瓿、拋棄式注射器或由玻璃、塑膠或其他材料製成之多劑量小瓶中。生理鹽水為特定的具體佐劑。可注射組合物較佳為無菌的。

醫藥組合物含有有效量之本發明化合物(例如融合多肽)以便獲得適合的劑量。醫藥組合物可能含有已知有效量之化合物，如目前針對各別病症所開具之處方。

本發明多肽用於將有效預防、治療及/或管理年齡相關之病狀或代謝障礙的預防性及/或治療性療程中之投藥途徑可基於目前此項技術中已知之其他治療劑之規定的投藥途徑。本發明之多肽可經任何適宜途徑投與，例如藉由輸注或快速注射、藉由經上皮或皮膚黏膜內皮(例如口腔黏膜、直腸及腸黏膜等)吸收。投藥可為全身性的或局部的。各種遞送系統為已知的，例如微粒、微膠囊、膠囊等，且可適用於投與本發明之多肽。可向個體投與超過一種本發明多肽。投藥方法可包括但不限於經口投藥及非經腸投藥；非經腸投藥包括但不限於皮內、肌肉內、靜脈內、皮下、鼻內、硬膜外、舌下、鼻內、腦內、心室內、鞘內、陰道內、經皮、直腸、藉由吸入，或表面投與耳、鼻、眼或皮膚。

本發明之多肽可以非經腸方式投與。特定言之，本發明之多肽可經靜脈內投與。

亦可採用經肺投藥，例如藉由使用吸入器或噴霧器，及與霧化劑一起調配，或經由於氟碳化合物或合成肺用界面活性劑中灌注。本發明多肽亦可與慣用黏合劑及載劑(諸如三酸甘油酯)一起調配成栓劑。

本發明之多肽可於控制釋放系統中遞送。舉例而言，可使用泵(參見Sefton, *CRC Crit. Ref. Biomed. Eng.* 1987, 14, 201; Buchwald等

人, *Surgery* 1980, 88: 507 ; Saudek等人, *N. Engl. J. Med.* 1989, 321: 574)。聚合材料亦可用於本發明多肽之控制釋放(參見 *Medical Applications of Controlled Release*, Langer及Wise (編), CRC Pres., Boca Raton, FL, 1974 ; *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen及Ball (編), Wiley, New York, 1984 ; Ranger及Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 1983, 23, 61 ; 亦參見Levy等人, *Science* 1985, 228, 190 ; During等人, *Ann. Neurol.*, 1989, 25, 351 ; Howard等人, *J. Neurosurg.*, 1989, 71, 105)。特定言之, 控制釋放系統可置於本發明多肽之標靶(例如腦)附近, 因而僅需要全身性劑量之一部分(參見例如 Goodson, *Medical Applications of Controlled Release*, 同上文, 第2卷, 1984, 第115-138頁)。可使用Langer(*Science* 1990, 249, 1527-1533)之綜述中所論述之其他控制釋放系統。

用於達成控制或持續釋放本發明多肽之聚合材料揭示於例如美國專利第5,679,377號、美國專利第5,916,597號、美國專利第5,912,015號、美國專利第5,989,463號、美國專利第5,128,326號、PCT公開案第WO 99/15154號及PCT公開案第WO 99/20253號中。用於持續釋放調配物中之聚合物之實例包括但不限於聚(2-羥基甲基丙烯酸乙酯)、聚(甲基丙烯酸甲酯)、聚(丙烯酸)、聚(乙烯-共-乙酸乙烯酯)、聚(甲基丙烯酸)、聚乙交酯(PLG)、聚酸酐、聚(N-乙基吡咯啉酮)、聚(乙烯醇)、聚丙基醯胺、聚(乙二醇)、聚乳酸交酯(PLA)、聚(丙交酯-共-乙交酯)(PLGA)及聚原酸酯。用於持續釋放調配物中之聚合物較佳為惰性的、不含可浸出雜質、儲存穩定、無菌且生物可降解。

一般而言, 本發明醫藥組合物之治療有效量為每公斤體重約0.0001 mg至0.001 mg ; 0.001 mg至約10 mg或約0.02 mg至約5 mg。

在其他實施例中，預防性及/或治療性療程涉及投與患者一或多次劑量的有效量之本發明多肽，其中該有效量之劑量達成至少0.01 $\mu\text{g/mL}$ 至至少400 $\mu\text{g/mL}$ 之本發明多肽之血漿含量。

預防性及/或治療性療程可涉及投與患者複數個劑量的有效量之本發明多肽，其中該複數個劑量維持至少0.01 $\mu\text{g/mL}$ 至400 $\mu\text{g/mL}$ 之本發明多肽之血漿含量。可投與預防性及/或治療性療程至少1天、1個月、2個月、3個月、4個月、5個月、6個月、7個月、8個月或9個月。

預防性及/或治療性療程可涉及投與本發明多肽與一或多種其他治療劑組合。目前用於預防、治療及/或管理年齡相關之病狀或代謝障礙之一或多種治療劑的推薦劑量可自此項技術中之任何參考文獻獲得，包括但不限於Hardman等人編，*Goodman & Gilman's The Pharmacological Basis Of Basis Of Therapeutics*，第10版，McGraw-Hill, New York, 2001；*Physician's Desk Reference* (第60版, 2006)，該等文獻係以全文引用的方式併入本文中。

本發明包括治療需要Klotho蛋白質及FGF之促效活性之病症的方法。此外，本發明包括所揭示之蛋白質、融合蛋白質、核酸分子或醫藥組合物之用途，其係用於治療需要Klotho蛋白質及FGF之促效活性之病理性病症的療法或藥物中。本發明之該等方法或用途之實例包括但不限於年齡相關之病狀或代謝障礙。

本發明包括治療或預防個體之年齡相關之病狀的方法；及所揭示之蛋白質、融合蛋白質、核酸分子或醫藥組合物在用於治療或預防個體之年齡相關之病狀之療法或藥物中的用途。向需要治療之個體投與藥理學有效劑量之醫藥組合物以便治療或預防年齡相關之病狀，該醫藥組合物含有具有Klotho蛋白質之至少一個細胞外子域及纖維母細胞生長因子及(視情況存在之)經修飾之Fc片段的Klotho融合多肽。在

一些實施例中，Klotho融合多肽與藥理學有效劑量之肝素共同投藥。年齡相關之病狀包括肌肉減少症、皮膚萎縮、肌肉萎縮、腦萎縮、動脈粥樣硬化、動脈硬化、肺氣腫、骨質疏鬆症、骨關節炎、免疫機能不全、高血壓、癡呆症、亨廷頓氏病、阿茲海默氏病、白內障、年齡相關之黃斑部變性、前列腺癌、中風、預期壽命縮短、記憶損失、皺紋、腎功能損傷及年齡相關之聽力損失。在一些實施例中，Klotho融合多肽含有 α Klotho蛋白質之至少一個細胞外域。在一特定實施例中，向需要治療肌肉萎縮之個體投與含有 α Klotho蛋白質之至少一個細胞外域及纖維母細胞生長因子23之Klotho融合蛋白質。

本發明亦關於一種治療或預防個體之代謝障礙的方法；及所揭示之蛋白質、融合蛋白質、核酸分子或醫藥組合物在用於治療或預防個體之代謝障礙之療法或藥物中的用途。向需要治療之個體投與藥理學有效劑量之醫藥組合物，該醫藥組合物含有可治療代謝障礙之Klotho融合多肽，其具有Klotho蛋白質之至少一個細胞外子域及纖維母細胞生長因子，且可視情況含有具有降低對FcRn之結合及/或增加之血清半衰期及/或穩定性的經修飾之Fc片段。在一些實施例中，Klotho融合多肽與藥理學有效劑量之肝素共同投藥。該方法可用於治療或預防II型糖尿病、代謝症候群、高血糖症及肥胖症。在一特定實施例中，向需要治療代謝障礙之個體投與含有 β -Klotho蛋白質之至少一個細胞外域及纖維母細胞生長因子21的Klotho融合蛋白質。

本發明亦提供治療或預防個體之高磷酸鹽血症或鈣質沉著的方法，及所揭示之蛋白質、融合蛋白質、核酸分子或醫藥組合物在用於治療或預防個體之高磷酸鹽血症或鈣質沉著之療法或藥物中的用途。向需要治療之個體投與藥理學有效劑量之醫藥組合物以治療高磷酸鹽血症或鈣質沉著，該醫藥組合物含有具有Klotho蛋白質之至少一個細胞外子域、纖維母細胞生長因子及(視情況存在之)經修飾之Fc片段的

Klotho融合多肽。在一些實施例中，Klotho融合多肽與藥理學上有效劑量之肝素共同投藥。在一特定實施例中，向需要治療高磷酸鹽血症或鈣質沉著之個體投與含有 α Klotho蛋白質之至少一個細胞外域及纖維母細胞生長因子23及(視情況存在之)經修飾之Fc片段的Klotho融合蛋白質。

本發明亦關於一種治療或預防個體之慢性腎病或慢性腎衰竭的方法，及所揭示之蛋白質、融合蛋白質、核酸分子或醫藥組合物在用於治療或預防個體之慢性腎病或慢性腎衰竭之療法或藥物中的用途。向需要治療之個體投與藥理學有效劑量之醫藥組合物以治療慢性腎病或慢性腎衰竭，該醫藥組合物含有具有Klotho蛋白質之至少一個細胞外子域、纖維母細胞生長因子及(視情況存在之)經修飾之Fc片段的Klotho融合多肽。在一些實施例中，Klotho融合多肽與藥理學有效劑量之肝素共同投藥。在一些實施例中，向需要治療慢性腎病或慢性腎衰竭之個體投與含有 α Klotho蛋白質之至少一個細胞外域的Klotho融合蛋白質。

本發明亦包括治療或預防個體之癌症的方法，及所揭示之蛋白質、融合蛋白質、核酸分子或醫藥組合物在用於治療或預防個體之癌症之療法或藥物中的用途。向需要治療之個體投與藥理學有效劑量之醫藥組合物以治療癌症，該醫藥組合物含有具有Klotho蛋白質之至少一個細胞外子域、纖維母細胞生長因子及(視情況存在之)經修飾之Fc片段的Klotho融合多肽。該方法可用於治療或預防乳癌。在一些實施例中，Klotho融合多肽與藥理學有效劑量之肝素共同投藥。在一些實施例中，向需要治療癌症之個體投與含有 α Klotho蛋白質之至少一個細胞外域的Klotho融合蛋白質。

在藉由投與含有Klotho融合多肽之醫藥組合物來治療病症之方法中；或當在治療中使用含有Klotho融合多肽之醫藥組合物時，Klotho

融合多肽及(視情況存在之)經修飾之Fc片段具有Klotho蛋白質之至少一個細胞外子域及纖維母細胞生長因子。在一特定實施例中，Klotho融合蛋白質含有 β Klotho蛋白質之至少一個細胞外域及纖維母細胞生長因子21。

在另一實施例中，該融合物包含FGF(例如FGF19、FGF21、FGF23或FGF23變異體)及具有降低對FcRn之結合及/或增加之血清穩定性的經修飾之Fc片段。此類型之融合物可用於如上文所述之各種疾病中，或用於治療或預防此項技術中已知之任何FGF相關之疾病。該融合物可投與有需要之個體。

該等融合多肽組合物可根據熟習此項技術者已知及本文所述之任何投藥方法進行投藥。特定的具體投藥方法包括皮下或靜脈內。本文中描述其他有效的投藥模式。

治療方法及評定效力之檢定

提供向個體投與本文所述之融合多肽的本發明方法或用途可用於治療多種病症，包括年齡相關之病症或代謝障礙。不受任何特定理論限制，融合多肽可用於治療存在Klotho或FGF失調之病症。實例病症包括代謝障礙及年齡相關之病症。舉例而言，FGF23或Klotho剔除小鼠顯示多種類似表現型，包括低身體活性、生長停滯、肌肉萎縮、皮膚萎縮、動脈粥樣硬化、壽命較短等。(參見Razzaque及Lanske, *J. of Endocrinology*, 194:1-10(2007)，其係以引用的方式併入本文中)。

詳言之，本發明之融合多肽尤其適用於治療老化相關之病症，包括肌肉萎縮。不受理論限制，Klotho及FGF23控制礦物質(例如磷酸鹽及鈣)及維生素D體內平衡之能力可為此等蛋白質調節老化及肌肉萎縮之方法。

另一方面，本發明之融合多肽可用於治療代謝障礙。舉例而言， β -Klotho及FGF19已顯示藉由調控膽固醇7- α -羥化酶(CYP7A1)來

控制膽汁酸體內平衡。膽汁體內平衡障礙之非限制性實例為膽汁淤滯。 β -Klotho及FGF21已顯示誘導脂肪細胞中之脂肪分解，且因此減少脂肪儲存並增加葡萄糖攝取。脂肪分解/脂肪儲存障礙之非限制性實例為肥胖症以及相關代謝及心血管疾病。

至少部分基於FGF23能夠刺激尿中之磷酸鹽分泌且藉此降低血清中之磷酸鹽含量的發現結果，本發明之Klotho-FGF23融合多肽可用於治療或預防個體之高磷酸鹽血症或鈣質沉著。舉例而言，已顯示導致患者之Klotho缺乏症的Klotho中之同種接合錯義突變可能引起嚴重腫瘤樣鈣質沉著及動脈鈣化(Ichikawa等人, *J. Clin. Invest.* 117:2684-2691(2007)，其係以引用的方式併入本文中)。向個體投與藥理學有效劑量之醫藥組合物以治療或預防高磷酸鹽血症或鈣質沉著，該醫藥組合物含有具有Klotho蛋白質之至少一個細胞外子域、纖維母細胞生長因子及(視情況存在之)經修飾之Fc片段的Klotho融合多肽。詳言之，含有 α Klotho蛋白質之至少一個細胞外域、纖維母細胞生長因子及(視情況存在之)經修飾之Fc片段的Klotho融合多肽適用於治療高磷酸鹽血症或鈣質沉著。

本發明之Klotho融合多肽亦可用於治療或預防個體之慢性腎病或慢性腎衰竭。舉例而言，已顯示與未受影響之腎臟相比，患有慢性腎衰竭之患者之腎臟中Klotho表現降低(Koh等人, *Biochem. Biophys. Res. Comm.* 280:1015-1020 (2001)，其係以引用的方式併入本文中)。向個體投與藥理學有效劑量之醫藥組合物以治療或預防慢性腎病或慢性腎衰竭，該醫藥組合物含有具有Klotho蛋白質之至少一個細胞外子域、纖維母細胞生長因子及(視情況存在之)經修飾之Fc片段的Klotho融合多肽。詳言之，含有 α Klotho蛋白質之至少一個細胞外域的Klotho融合多肽適用於治療慢性腎病或慢性腎衰竭。

本發明之Klotho融合多肽亦可用於治療或預防個體之癌症。舉例

而言，已顯示與正常乳癌組織相比，乳癌組織中Klotho表現降低(Wolf等人, *Oncogene* (2008)提前線上出版，其係以引用的方式併入本文中)。向個體投與藥理學有效劑量之醫藥組合物以治療或預防癌症或乳癌，該醫藥組合物含有具有Klotho蛋白質之至少一個細胞外子域、纖維母細胞生長因子及(視情況存在之)經修飾之Fc片段的Klotho融合多肽。詳言之，含有 α Klotho蛋白質之至少一個細胞外域的Klotho融合蛋白質適用於治療癌症或乳癌。

評估本發明Klotho融合多肽對年齡相關之病症或代謝障礙之效力及/或確定其有效劑量的方法包括基於生物體之檢定，例如使用哺乳動物(例如小鼠、大鼠、靈長類動物或一些其他非人類)或其他動物(例如爪蟾屬(*Xenopus*)、斑馬魚(*zebrafish*)或無脊椎動物，諸如蠅類或線蟲)。Klotho融合多肽可投與生物體一次或以療程(規律或不規律)投與。接著評估生物體之參數，例如年齡相關之參數。相關Klotho融合多肽使得參數相對於參考值(例如對照生物體之參數)發生變化。亦可評估其他參數(例如與毒性、清除率及藥物動力學相關之參數)。

可使用患有特定病症之動物評估本發明之Klotho融合多肽，例如本文所述之病症，例如年齡相關之病症、代謝障礙。此等病症亦可提供可觀察測試多肽對生理機能之效應的敏感系統。實例病症包括：去神經性、不用性萎縮；代謝障礙(例如肥胖及/或糖尿病動物之障礙，諸如db/db小鼠及ob/ob小鼠)；大腦、肝臟缺血；順鉑/紫杉醇/長春新鹼模型；各種組織(異種移植)移植物；轉殖基因骨模型；疼痛症候群(包括發炎性及神經性病症)；巴拉劑(Paraquat)、致基因毒性及氧化性應力模型；及腫瘤I模型。

為了量測年齡相關之病症，動物模型可為在熱量受限制時具有改變之表現型的動物。舉例而言，F344大鼠提供評估Klotho融合多肽之適用檢定系統。當熱量受限制時，F344大鼠之腎病發病率為0%至

10%。然而當隨意餵食時，其腎病發病率為60%至100%。

爲了評估本發明之Klotho融合多肽，將其投與動物(例如F344大鼠或其他適合的動物)且在例如一段時間後，評估該動物之參數。該動物可隨意或正常餵食(例如無熱量限制，但一些參數可在該等條件下評估)。通常，一群該等動物用於該檢定。一般而言，若測試多肽在經受熱量限制之類似動物之表現型方向上影響該參數，則可指出該測試多肽有利地改變該動物之壽命調節。該等測試多肽可產生熱量限制之至少一些壽命調節效應，例如該等效應之子集，而不必剝奪生物體之熱量攝取。

待測試之參數可爲年齡相關或疾病相關之參數，例如與動物模型相關之病症之症狀。舉例而言，測試多肽可投與SH大鼠，且監測血壓。相對於未經多肽處理之類似參考動物，有利地指示之測試多肽可改善症狀。與病症或老化相關之其他參數可包括：抗氧化劑含量(例如抗氧化酶含量或活性)、應力抗性(例如巴拉劑抗性)、核心體溫、葡萄糖含量、胰島素含量、促甲狀腺激素含量、促乳素含量及黃體生成激素含量。

爲了量測本發明多肽治療年齡相關之病症的有效性，可使用具有降低之Klotho表現的動物，例如具有突變Klotho之小鼠；參見Kuroo等人, *Nature*, 390; 45 (1997)及美國公開案第2003/0119910號，兩者係以全文引用的方式併入本文中。舉例而言，將測試多肽投與突變型小鼠且監測年齡相關之參數。相對於未經多肽處理之類似參考動物，有利地指示之測試多肽可改善症狀。可藉由量測體重、檢查生殖能力之獲取、量測血糖含量、觀察壽命、觀察皮膚、觀察運動功能(諸如行走)及其類似方式來評定與代謝障礙或老化相關之參數。亦可藉由量測胸腺重量、觀察胸腔內表面上所形成之鈣化節結之大小及其類似方式來評定。此外，Klotho基因或Klotho蛋白質之mRNA之定量

測定亦適用於該評定。

又其他活體內模型及生物體檢定包括評估動物之代謝參數，例如與胰島素病症II型糖尿病相關之參數。實例代謝參數包括：葡萄糖濃度、胰島素濃度及胰島素敏感性。

另一實例系統提供例如於動物模型中之腫瘤。腫瘤可為自發腫瘤或誘導之腫瘤。舉例而言，腫瘤可由具有多種基因組成之細胞發展而來，例如其可為p53+或p53-。亦可能使用具有自體免疫障礙之生物體，例如易患SLE之NZB小鼠。為了評估骨疾病之特徵，可能例如使用進行卵巢切除術之動物作為模型，例如用於骨質疏鬆症。類似地，對於關節病，模型可基於佐劑關節炎(例如可用軟骨蛋白聚糖、高遷移率族蛋白質、鏈球菌細胞壁物質或膠原蛋白使小鼠免疫)；對於腎病，可使用kd/kd小鼠。亦可利用認知(尤其學習及記憶)動物模型。亦可利用糖尿病及其併發症之動物模型，例如鏈脲佐菌素模型。可使用犬科動物模型，例如用於評估中風及局部缺血。

在評定測試多肽是否能夠改變壽命調節時，可監測或評估許多年齡相關之參數或生物標記物。實例年齡相關之參數包括：(i)細胞或生物體之壽命；(ii)具有生物學年齡依賴性表現模式之細胞或生物體中之基因轉錄物或基因產物之存在或豐度；(iii)細胞或生物體對應力之抗性；(iv)細胞或生物體之一或多個代謝參數(實例參數包括循環胰島素含量、血糖含量；脂肪含量；核心體溫等)；(v)生物體中所存在之細胞或一組細胞之增殖能力；及(vi)細胞或生物體之身體外觀或行為。

術語「平均壽命」係指一群生物體死亡年齡之平均值。在一些情況下，在受控環境條件下使用一群基因一致生物體評定「平均壽命」。排除由災禍所致之死亡。若在受控環境條件下無法確定平均壽命(例如對人類而言)，則可使用足夠大群體之可靠統計資訊(例如來自

保險統計表)作為平均壽命。

表徵兩個該等生物體(例如一個參考生物體與一個經Klotho融合多肽處理之生物體)之間的分子差異可揭示生物體之生理狀態的差異。參考生物體及經處理之生物體通常具有相同的實足年齡。如本文所使用之術語「實足年齡」係指自諸如妊娠、所定義之胚胎或胎兒階段，或更佳為出生之預選事件起所經過之時間。多種準則可用於確定生物體是否具有「相同」實足年齡以用於比較分析。通常所需的精確度為野生型生物體之平均壽命的函數。舉例而言，對於線蟲秀麗隱桿線蟲(*C. elegans*)，在一些受控條件下，其實驗室野生型品系N2平均存活約16天，具有相同年齡之生物體可能已存活相同天數。對於小鼠，具有相同年齡之生物體可能已存活相同週數或月數；對於靈長類動物或人類，為相同年數(或在2、3或5年內)等。一般而言，具有相同實足年齡之生物體可能已存活該物種野生型生物體之平均壽命之15%、10%、5%、3%、2%或1%以內之時間。生物體較佳為成年生物體，例如生物體已存活至少平均野生型生物體已成熟達到勝任繁殖之年齡的時間。

可在生物體展現明顯老化的身體特徵之前執行生物體篩選檢定。舉例而言，生物體可為僅存活相同物種野生型生物體之平均壽命之10%、30%、40%、50%、60%或70%的成年生物體。已報導，代謝、免疫能力及染色體結構中之年齡相關之變化。可評估測試個體(例如對於基於生物體之檢定)或患者(例如在用本文所述之治療劑治療之前、期間或之後)之任何此等變化。

亦可評估篩選檢定之個體生物體(或經治療個體)之與熱量限制相關之標記物。雖然此等標記物可能不與年齡相關，但其可指示當調節Klotho路徑時所改變之生理狀態。該標記物可為豐度在熱量受限制之動物中改變之mRNA或蛋白質。WO 01/12851及美國專利第6,406,853

號描述實例標記物。來源於本文所述之動物之細胞或類似於本文所述之動物模型的細胞模型可用於基於細胞之檢定。

用於評估測試多肽對肌肉萎縮之影響的模型包括：1)由去神經(例如藉由切斷大腿中部之右坐骨神經)所致之大鼠內側腓腸肌肌肉質量損失；2)由固定(例如藉由以90度彎曲固定右踝關節)所致之大鼠內側腓腸肌肌肉質量損失；3)由後肢懸置所致之大鼠內側腓腸肌肌肉質量損失；(參見例如U.S. 2003-0129686)；4)由用惡病質細胞激素介白素-1(IL-1)處理所致之骨骼肌萎縮(R. N. Cooney, S. R. Kimball, T. C. Vary, *Shock* 7, 1-16 (1997))；及5)由用糖皮質激素地塞米松(dexamethasone)處理所致之骨骼肌萎縮(A. L. Goldberg, *J. Biol. Chem.* 244, 3223-9 (1969))。

AMD之實例動物模型包括：雷射誘導之模擬滲出性(濕潤)黃斑部變性之小鼠模型(Bora等人, *Proc. Natl. Acad. Sci. U S A.*, 100:2679-84 (2003))；表現組織蛋白酶D之突變形式從而產生與AMD之「區域性萎縮(geographic atrophy)」形式相關之特徵的轉殖基因小鼠(Rakoczy等人, *Am. J. Pathol.*, 161:1515-24 (2002))；及在視網膜色素上皮中過度表現VEGF從而產生CNV之轉殖基因小鼠。Schwesinger等人, *Am. J. Pathol.* 158:1161-72 (2001)。

帕金森氏病(Parkinson's disease)之實例動物模型包括藉由用多巴胺激導性神經毒素(dopaminergic neurotoxin)1-甲基-4-苯基-1,2,3,6-四氫吡啶(MPTP)處理而導致似帕金森氏病(Parkinsonian)的靈長類動物(參見例如美國專利公開案第20030055231號及Wichmann等人, *Ann. N.Y. Acad. Sci.*, 991:199-213 (2003))；6-羥基多巴胺病變大鼠(例如Lab. Anim. Sci., 49:363-71 (1999))；及轉殖基因無脊椎動物模型(例如Lakso等人, *J. Neurochem.* 86:165-72 (2003)及Link, *Mech. Ageing Dev.*, 122:1639-49 (2001))。

II型糖尿病之實例分子模型包括：具有缺陷性Nkx-2.2或Nkx-6.1之轉殖基因小鼠(美國專利第6,127,598號)；Zucker糖尿病性肥胖fa/fa(ZDF)大鼠(美國專利第6,569,832號)；及恆河猴(Rhesus monkey)，其自發罹患肥胖症且隨後往往發展成明顯2型糖尿病(Hotta等人, *Diabetes*, 50:1126-33 (2001))；及具有顯性負IGF-I受體(KR-IGF-IR)之患有2型糖尿病樣抗胰島素症的轉殖基因小鼠。

神經病之實例動物及細胞模型包括：長春新鹼(vincristine)誘導之感覺運動神經病小鼠(美國專利第5,420,112號)或兔(Ogawa等人, *Neurotoxicology*, 21:501-11 (2000))；用於自主神經病研究之鏈脲佐菌素(STZ)-糖尿病性大鼠(Schmidt等人, *Am. J. Pathol.*, 163:21-8 (2003))；及進行性運動神經病(pmn)小鼠(Martin等人, *Genomics*, 75:9-16 (2001))。

高磷酸鹽血症或腫瘤樣鈣質沉著之實例動物模型包括Klotho剔除小鼠及FGF23剔除小鼠(Yoshida等人, *Endocrinology* 143:683-689 (2002))。

慢性腎病或慢性腎衰竭之實例動物模型包括COL4A3+/-小鼠(Beirowski等人, *J. Am. Soc. Nephrol.* 17:1986-1994 (2006))。

癌症之實例動物模型包括向裸小鼠中移植或植入癌細胞或癌組織，如此項技術中已知(Giovanella等人, *Adv. Cancer Res.* 44:69-120 (1985))。舉例而言，乳癌之動物模型包括移植或植入乳癌細胞或組織之裸小鼠(例如Yue等人, *Cancer Res.* 54:5092-5095 (1994))；Glinsky等人, *Cancer Res.* 56:5319-5324 (1996)；Visonneau *Am. J. Pathol.* 152:1299-1311 (1998))。

組合物可投與個體，例如成年個體，尤其健康成年個體或患有年齡相關之疾病的個體。在後一種情況下，該方法可包括評估個體例如以表徵年齡相關之疾病之症狀或其他疾病標記物，且藉此將個體鑑

別為患有神經退化性疾病(例如阿茲海默氏病)或年齡相關之疾病或鑑別為易患該疾病。

骨骼肌萎縮

提供向個體投與Klotho融合多肽之本發明方法或用途可用於治療骨骼肌萎縮。肌肉萎縮包括許多神經肌肉性、代謝性、免疫性及神經性病徵及疾病以及饑餓、營養缺乏、代謝應力、糖尿病、老化、肌肉萎縮症或肌病。肌肉萎縮在老化過程期間發生。肌肉萎縮亦由肌肉之使用減少或不用所致。症狀包括骨骼肌組織質量下降。在人類男性中，肌肉質量在50歲與80歲之間下降三分之一。肌肉萎縮之一些分子特徵包括泛素連接酶調升及肌原纖維蛋白質損失(Furuno等人, *J. Biol. Chem.*, 265:8550-8557, 1990)。可例如藉由量測3-甲基-組胺酸產生來追蹤此等蛋白質之分解，3-甲基-組胺酸為肌動蛋白之特定組分且在某些肌肉中為肌球蛋白之組分(Goodman, *Biochem. J.* 241:121-12, 1987及Lowell等人, *Metabolism*, 35:1121-112, 1986；Stein及Schluter, *Am. J. Physiol. Endocrinol. Metab.* 272: E688-E696, 1997)。亦可指示肌酸激酶(細胞損壞標記物)之釋放(Jackson等人, *Neurology*, 41: 101-104, 1991)。

非胰島素依賴性糖尿病

提供向個體投與Klotho融合多肽之本發明方法或用途可用於治療非胰島素依賴性糖尿病。非胰島素依賴性糖尿病亦稱為「成年發作」糖尿病及2型糖尿病。2型糖尿病亦包括「非肥胖2型」及「肥胖2型」。II型糖尿病之特徵可在於(1)胰島素之胰臟 β -胰島細胞分泌降低以致產生小於保持血糖含量平衡所必需之量的胰島素，及/或(2)「胰島素抗性」，其中身體不能正常應答胰島素。(美國專利第5,266,561號及美國專利第6,518,069號)。舉例而言，葡萄糖刺激之胰島素含量通常不能上升至高於4.0 nmol/L。(美國專利第5,266,561號)。II型糖尿

病之實例症狀包括：空腹高血糖症(美國專利第5,266,561號)；疲勞；極度善渴；尿頻；視力障礙；及感染率增加。II型糖尿病之分子適應症包括胰臟中之胰島類澱粉沈積。

神經病

神經病可包括由全身性疾病、遺傳病症或影響運動神經、感覺神經、感覺運動神經或自主神經之毒性劑所致之中樞及/或周圍神經功能障礙。(參見例如美國專利申請案第20030013771號)。症狀可視神經損傷之誘因及受影響神經之特定類型而變化。舉例而言，運動神經病之症狀包括執行身體任務時或如同肌肉虛弱般笨拙、微量勞力後筋疲力盡、站立或行走困難，及神經肌肉反射衰減或不存在。(美國專利申請案第20030013771號)自主神經病之症狀包括便秘、心臟紊亂及姿勢性低血壓反射衰減。(美國專利申請案第20030013771號)，感覺神經病之症狀包括疼痛及麻木；手、腿或足顫動；及對觸摸極度敏感，且視網膜病症狀包括視力障礙、暴盲、黑點及閃光。

阿茲海默氏病

提供向個體投與Klotho融合多肽之本發明方法或用途可用於治療阿茲海默氏病(AD)。阿茲海默氏病為造成神經元之不可逆損失之複合型神經退化性疾病。僅提供亦為年齡相關之病狀的神經退化性疾病之一個實例。阿茲海默氏病之臨床標誌包括記憶、判斷、實體環境定向及語言之進行性損傷。AD之神經病理學標誌包括區域特異性神經元損失、類澱粉斑塊及神經原纖維纏結。類澱粉斑塊為含有類澱粉肽(亦稱為Ap或Ap42)之細胞外斑塊，該類澱粉肽為8-類澱粉前驅蛋白質(亦稱為APP)之裂解產物。神經原纖維纏結為由異常過度磷酸化之微管相關蛋白質之長絲構成的不可溶細胞內聚集體，拉緊之類澱粉斑塊及神經原纖維纏結可能造成導致由細胞凋亡所致之神經元損失的繼發性事件(Clark及Karlavish, *Ann. Intern. Med.* 138(5):400-410 (2003))。

舉例而言，p-類澱粉在所培養之神經元中誘導卡斯蛋白酶-2(caspase-2)依賴性細胞凋亡(Troy等人, *J Neurosci.* 20(4):1386-1392)。活體內斑塊沈積可以類似方式引發近端神經元之細胞凋亡。

可使用多種準則來評估個體之AD，包括遺傳準則、生物化學準則、生理學準則及認識準則。AD之症狀及診斷為醫學從業者所知。下文提供AD之一些實例症狀及標記物。關於此等適應症及與AD相關之其他已知適應症之資訊可用作「AD相關參數」。AD相關參數可包括定性或定量資訊。定量資訊之一個實例為一或多個尺度之數值，例如蛋白質之濃度或斷層攝影圖。定性資訊可包括評定，例如醫師之註解或二元評定(「是」/「否」)等。AD相關參數包括指示個體經診斷未患AD或未患AD之特定適應症的資訊，例如AD之不典型認識測試結果或與AD無關之遺傳APOE多形現象。

進行性認識損傷為AD之標誌。此損傷可呈現為記憶、判斷、決策、實體環境定向及語言之衰退(Nussbaum及Ellis, *New Eng J. Med.* 348(14):1356 35 1364 (2003))。排除癡呆症之其他形式可有助於進行AD診斷。神經元死亡在AD患者中造成進行性大腦萎縮。成像技術(例如磁共振成像或電腦輔助斷層攝影)可用於偵測腦中之AD相關病變及/或腦萎縮。

AD患者可展現由疾病之病變所致的生物化學異常。舉例而言，AD患者之腦脊液中之tan蛋白質含量升高(Andreasen, N.等人, *Arch Neurol.* 58:349-350 (2001))。

在AD患者之CSF中，類澱粉 β 42(A β 42)肽之含量可能降低。在AD患者之血漿中，A β 42含量可能增加(Ertekekin-Taner, N.等人, *Science* 290:2303 2304 (2000))。用於偵測來自個體之樣品中之生物化學異常的技術包括此項技術中已知之細胞法、免疫法及其他生物學方法。關於一般性指導，參見例如以下文獻中所述之技術：Sambrook及

Russell, *Molecular Cloning: A Laboratory Manual*, 第3版, Cold Spring Harbor Laboratory, N.Y. (2001) ; Ausubel等人, *Current Protocols in Molecular Biology*(Greene Publishing Associates and Wiley Interscience, N.Y. (1989)) ; Harrow E.及Lane, D. (1988) *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY及其更新版本。

舉例而言，抗體、其他免疫球蛋白及其他特異性結合配位體可用於偵測生物分子，例如與AD相關之蛋白質或其他抗原。舉例而言，一或多種特異性抗體可用於探測樣品。可能採用各種格式，例如ELISA、基於螢光之檢定、西方墨點法及蛋白質陣列。此項技術中描述產生多肽陣列之方法，例如De Wildt等人, (2000). *Nature Biotech.* 18, 989-994 ; Lucking等人, (1999). *Anal. Biochem.* 270, 103-111 ; Ge, H. (2000). *Nucleic Acids Res.* 28, e3, I-VII ; MacBeath, G.及Schreiber, S.L. (2000). *Science* 289, 1760至1763 ; 及WO 99/51773A1。

在一個檢定中，使用AD之非人類動物模型(例如小鼠模型)例如來評估多肽或治療療程。舉例而言，美國專利第6,509,515號描述一個天然能夠用於學習及記憶測試之該類模型動物。該動物在腦組織中以使該動物自出生起在短時間內(一般為自出生起一年內，較佳為自出生起2至6個月內)發展進行性神經病症之含量表現類澱粉前驅蛋白質(APP)序列。將APP蛋白質序列引入處於胚胎期、較佳單細胞期或受精卵母細胞期且一般不晚於約8個細胞之期的動物或動物祖先中。受精卵或胚胎接著在作為養育雌性之假懷孕動物體內發育至產期。將類澱粉前驅蛋白質基因引入動物胚胎中以便以引起類澱粉前驅體蛋白質之超內源性表現及在腦皮質邊緣區域(在諸如AD之進行性神經病病況中顯著影響的腦區域)中發展進行性神經學疾病的狀態在染色體層面上併入。受影響之轉殖基因動物模型中之神經膠樣變性及臨床表現為

神經病。神經病之進行性態樣之特徵在於探索性及/或運動性行為減少及去氧葡萄糖攝取/利用減少及腦皮質邊緣區域中肥厚性神經膠樣變性。此外，所見變化與在一些老化動物中所見者類似。US 5,387,742；5,877,399；6,358,752及6,187,992中亦描述其他動物模型。

帕金森氏病

提供向個體投與Klotho融合多肽之本發明方法或用途可用於治療帕金森氏病。帕金森氏病包括黑質中之多巴胺激導性神經元之神經退化，其造成調控運動功能之黑質紋狀體多巴胺系統退化。此病變又造成運動功能障礙(參見例如Lotharius等人, *Nat. Rev. Neurosci.*, 3:932-42 (2002))。實例運動症狀包括：運動不能、駝背姿勢(stooped posture)、步履艱難、姿勢不穩定、強直症、肌肉僵硬及顫抖。實例非運動症狀包括：抑鬱症、缺乏動機、被動、癡呆症及胃腸功能失調(參見例如Fahn, *Ann. N.Y. Acad. Sci.*, 991:1-14 (2003)及Pfeiffer, *Lancet Neurol.*, 2:107-16 (2003))。在0.5%至1%之65至69歲之人士及1%至3%之80歲及80歲以上之人士中觀察到帕金森氏病。(參見例如Nussbaum等人, *N. Engl. J. Med.*, 348:1356-64 (2003))。帕金森氏病之分子標記物包括芳族L胺基酸去羧基酶(AADC)減少(參見例如美國申請案第20020172664號)；及黑質紋狀體神經元中之多巴胺含量損失(參見例如Fahn, *Ann. N.Y. Acad. Sci.*, 991:1-14(2003)及Lotharius等人, *Nat. Rev. Neurosci.*, 3:932-42 (2002))。在一些家族性情況下，PD與編碼 α -突觸核蛋白及parkin(E3泛素連接酶)蛋白質之單一基因中的突變相關。(例如Riess等人, *J. Neurol.* 250 增刊1:I3 10 (2003)及Nussbaum等人, *N. Engl. J. Med.*, 348:1356-64 (2003))。神經元特異性C末端泛素水解酶基因中之錯義突變亦與帕金森氏病相關。(例如Nussbaum等人, *N. Engl. J. Med.*, 348:1356-64 (2003))

亨廷頓氏病

提供向個體投與Klotho融合多肽之本發明方法或用途可用於治療亨廷頓氏病。評估本發明Klotho融合多肽對亨廷頓氏病之效力及/或確定其有效劑量的方法包括基於生物體之檢定，例如使用哺乳動物(例如小鼠、大鼠、靈長類動物或一些其他非人類)或其他動物(例如爪蟾屬、斑馬魚或無脊椎動物，諸如蠅類或線蟲)。可利用許多亨廷頓氏病動物模型系統。參見例如Brouillet, *Functional Neurology* 15(4): 239-251 (2000)；Ona等人, *Nature* 399: 263-267 (1999)；Bates等人 *Hum Mol Genet.* 6(10):1633-7 (1997)；Hansson等人, *J. of Neurochemistry* 78: 694-703；及Rubinsztein, D. C., *Trends in Genetics*, 第1S卷, 第4期, 第202-209頁(關於HD之各種動物及非人類模型之綜述)。

該類動物模型之一個實例為轉殖基因小鼠品系 R6/2 細胞株 (Mangiarini等人, *Cell* 87: 493-506 (1996))。R6/2小鼠為轉殖基因亨廷頓氏病小鼠，其過度表現人類HD基因之外顯子1(在內源性啟動子控制下)。R6/2人類HD基因之外顯子1具有擴增之CAG/聚麩醯胺酸重複單元長度(平均150個CAG重複單元)。此等小鼠發展具有人類亨廷頓氏病之許多特徵的進行性最終致死性神經病。在R6/2小鼠中，在細胞質及細胞核中均觀察到部分由亨廷頓蛋白(Huntingtin)之N末端部分(由HD外顯子1編碼)組成的異常聚集體(Davies等人, *Cell* 90: 537-548 (1997))。舉例而言，轉殖基因動物中之人類亨廷頓蛋白係由包括至少55個CAG重複單元且更佳約150個CAG重複單元之基因編碼。此等轉殖基因動物可發展亨廷頓氏病樣表現型。

此等轉殖基因小鼠之特徵在於自出生後8至10週起體重增加減少、壽命縮短及以步履異常為特徵之運動損傷、靜止時震顫、後肢把握及過動症(例如R6/2品系；參見Mangiarini等人, *Cell* 87: 493-506 (1996))。該表現型進行性向運動功能減退惡化。此等轉殖基因小鼠之

腦亦顯示神經化學及組織學異常，諸如神經傳遞質受體(麩胺酸鹽、多巴胺激導性)之變化、N-乙醯基天冬胺酸(神經元完整性之標記物)之濃度降低，以及紋狀體及腦之大小減小。因此，評估可包括評定與神經傳遞質含量、神經傳遞質受體含量、腦大小及紋狀體大小相關之參數。此外，含有全長人類亨廷頓蛋白或其轉殖基因部分之異常聚集體存在於此等動物(例如R6/2轉殖基因小鼠品系)之腦組織中。參見例如 Mangiarini等人, *Cell* 87: 493-506 (1996)；Davies等人, *Cell* 90: 537-548 (1997)；Brouillet, *Functional Neurology* 15(4): 239-251 (2000)；及 Cha等人, *Proc. Natl. Acad. Sci. USA* 95: 6480-6485 (1998)。

爲了測試本申請案中所述之測試多肽或已知多肽在動物模型中之效應，將不同濃度之測試多肽投與轉殖基因動物，例如藉由將測試多肽注射至動物之循環中。可評估動物之亨廷頓氏病樣症狀。接著，監測如上文關於小鼠模型所述之亨廷頓氏病樣症狀之進展，以確定用測試多肽處理是否減少或延遲症狀。在另一檢定中，監測此等動物中之亨廷頓蛋白聚集體之去聚集。接著可處死動物並獲得腦切片。接著分析腦切片中含有轉殖基因人類亨廷頓蛋白、其部分或包含人類亨廷頓蛋白或其部分之融合蛋白質之聚集體的存在。此分析可包括例如用抗亨廷頓蛋白抗體對腦組織切片進行染色，及添加與識別抗亨廷頓蛋白抗體之FITC結合的二次抗體(例如該抗亨廷頓蛋白抗體爲小鼠抗人類抗體且該二次抗體對人類抗體具特異性)，及藉由螢光顯微術目測蛋白質聚集體。

多種方法可用於評估及/或監測亨廷頓氏病。該疾病之多種臨床症狀及指標爲已知的。亨廷頓氏病造成運動障礙、精神問題及認識變化。此等症狀之程度、發作年齡及表現可變化。運動障礙可包括稱爲舞蹈病之快速、隨機、舞蹈樣運動。

實例運動評估包括：眼追蹤、眼急動起始(saccade initiation)、眼

急動速度、發音困難、舌突起、手指輕敲能力、俯臥/仰臥、握拳-伸手-翻掌順序(a lo fist-hand-palm sequence)、手臂僵硬、運動徐緩、最大程度之肌張力不全(軀幹、上肢及下肢)、最大程度之舞蹈病(例如軀幹、面部、上肢及下肢)、步態、縱列行走及後退。實例治療可引起UHDRS之子量表總運動得分4(TMS-4)之變化，例如經一年的時間。

癌症

提供向個體投與Klotho融合多肽的本發明方法或用途可用於治療癌症。癌症包括由不適當之高細胞分裂量、不適當之低細胞凋亡量或兩者所造成或引起的任何疾病。癌症之實例包括但不限於白血病(例如急性白血病、急性淋巴細胞性白血病、急性髓細胞性白血病、急性髓母細胞性白血病、急性早幼粒細胞白血病、急性髓單核細胞白血病、急性單核細胞性白血病、急性紅白血病、慢性白血病、慢性髓細胞性白血病、慢性淋巴細胞性白血病)、真性紅血球過多症、淋巴瘤(霍奇金氏病(Hodgkin's disease)、非霍奇金氏病)、瓦爾登斯特倫巨球蛋白血症(Waldenstrom's macroglobulinemia)、重鏈病及實體腫瘤，諸如肉瘤及癌瘤(例如纖維肉瘤、黏液肉瘤、脂肉瘤、軟骨肉瘤、骨原性肉瘤、脊索瘤、血管肉瘤、內皮肉瘤、淋巴管肉瘤、淋巴內皮肉瘤、滑膜瘤、間皮瘤、尤因氏瘤(Ewing's tumor)、平滑肌肉瘤、橫紋肌肉瘤、結腸癌瘤、胰臟癌、乳癌、卵巢癌、前列腺癌、鱗狀細胞癌、基底細胞癌、腺癌、汗腺癌、皮脂腺癌、乳頭狀癌、乳頭狀腺癌、囊腺癌、髓性癌、支氣管癌、腎細胞癌、肝癌、膽管癌、絨膜癌、精原細胞瘤、胚胎癌、威姆氏腫瘤(Wilm's tumor)、子宮頸癌、子宮癌、睪丸癌、肺癌瘤、小細胞肺癌、膀胱癌、上皮癌、神經膠質瘤、星形細胞瘤、髓母細胞瘤、顱咽管瘤、室管膜瘤、松果腺瘤、血管母細胞瘤、聽神經瘤、寡樹突神經膠質瘤(oligodendroglioma)、神經鞘瘤、腦膜瘤、黑素瘤、神經母細胞瘤及視網膜胚細胞瘤)。淋巴組

織增殖障礙亦被視為增殖性疾病。

本文所引用之所有專利、專利申請案及公開的參考文獻係以全文引用的方式併入本文中。雖然已參考本發明之實施例特別展示並描述本發明，但熟習此項技術者應理解，在不背離隨附申請專利範圍所涵蓋之本發明範疇的情況下，可對其形式及細節進行各種改變。

實例

實例1. Klotho融合多肽之表現及純化

Klotho融合多肽之表現

藉由用編碼具有 α Klotho之細胞外域及FGF23(R179Q)變異體之Klotho融合多肽的表現載體短暫轉染HEK293T細胞來製備本發明多肽。藉由短暫轉染Klotho、FGF23及Klotho-FGF23(R179Q)融合蛋白質之各別表現質體來產生含有經表現之多肽的條件培養基。在6孔板中使用Lipofectamine 2000(Invitrogen，目錄號11668-019)執行轉染。轉染後5小時，用3 ml DMEM+1% FBS更換轉染混合物。添加3 ml DMEM+1% FBS後72小時，收集條件培養基。由SDS-聚丙烯醯胺凝膠電泳(SDS-PAGE)分離各種經短暫轉染之HEK293T細胞的條件培養基樣品，且由西方墨點法(Western blot)進行分析(圖3A)或用庫馬斯藍染色(Coomassie blue)(圖3B)。

對各種樣品執行SDS-聚丙烯醯胺凝膠電泳(泳道1，對照；泳道2，FGF23；泳道3，sKlotho；泳道4至6，sKlotho-FGF23)。庫馬斯藍染色顯示在含有未經編碼Klotho融合多肽之載體轉染之樣品的泳道1-3中不存在>180 kDa之高條帶表現(圖3B，由右邊的箭頭指示)。由西方墨點法評估分泌於培養基中之Klotho融合多肽之品質(圖3A)。使用抗FGF23大鼠單株IgG2A(R&D Systems，目錄號MAB26291)作為一次抗體來由西方墨點法偵測Klotho融合多肽。西方墨點法證實，庫馬斯藍染色凝膠中所觀察到之其他條帶為Klotho融合多肽。西方墨點法證

實，Klotho融合多肽具有針對Klotho融合多肽所預期之分子量。此分析展示Klotho-FGF23(R179Q)融合蛋白質之表現。

Klotho融合多肽之純化

自來自經編碼具有 α Klotho之細胞外域及FGF23 R179Q變異體之Klotho融合多肽之表現載體短暫轉染之HEK293T細胞之培養物的條件培養基中純化本發明之多肽。爲了產生條件培養基，將編碼sKlotho-FGF23-6 $\times$ His之表現載體(於18 ml OptiMEM 1(GIBCO，目錄號11058)中之500 μ g DNA與18 ml 2 μ g/ml聚伸乙基亞胺(PEI)混合)轉染至於表現培養基之懸浮液中生長的HEK293細胞(464 ml HEK293T細胞，以 10^6 個細胞/毫升處於Freestyle 293表現培養基(GIBCO，目錄號12338)中)中。轉染後，使培養物生長(120小時；37 $^{\circ}$ C，於5% CO₂培育箱中；在125 rpm下搖動)。在培育結束時，藉由離心(1000 rpm，5分鐘)收集條件培養基。接著將條件培養基施加於鎳-瓊脂糖管柱。sKlotho-FGF23-6 $\times$ His緊密結合至管柱，且用50 mM咪唑溶離。接著在PBS中透析所得純化之物質以移除咪唑。由SDS-PAGE(泳道1，純化之sKlotho-FGF23-6 $\times$ His；泳道2，分子量標記物)分離純化之sKlotho-FGF23-6 $\times$ His之樣品，且藉由用庫馬斯藍染色加以分析(圖3C)。染色之SDS-PAGE凝膠證實，純化之sKlotho-FGF23-6 $\times$ His具有預期的分子量。在裝載有純化之物質之泳道中不能偵測到對應於除全長sKlotho-FGF23-6 $\times$ His以外之蛋白質的條帶亦顯示，sKlotho-FGF23-6 $\times$ His已經純化。

實例2. 評定Klotho融合多肽之活性的活體外檢定

Egr-1-螢光素酶

在Egr-1-螢光素酶報導子檢定中，測試經表現之 α Klotho融合多肽之生物活性。Klotho融合多肽結合FGF23受體可活化下游Egr-1及在Egr-1啟動子調控下表現螢光素酶報導子。基於Urakawa等人(Nature,

2006, 第444卷, 770-774)所報導, 構築Egr-1-螢光素酶報導子基因。用Egr-1-螢光素酶報導子基因以及轉染正規化報導子基因(海腎螢光素酶)轉染接種於48孔聚-D-離胺酸板中之HEK293T細胞。Egr-1-螢光素酶報導子基因轉染後5小時, 用3 ml DMEM+1% FBS更換轉染混合物。添加3 ml DMEM+1% FBS後72小時, 收集條件培養基。5小時後, 用欲測試活性之樣品更換轉染混合物。在初始實驗中, 在Egr-1-螢光素酶報導子檢定中, 在存在或不存在20 µg/ml肝素(Sigma, 目錄號H8537; 溶解於DMEM中的2 mg/ml儲備液)的情況下, 測試50%條件培養基(單獨或含有Klotho、FGF23、Klotho與FGF23、及Klotho-FGF23(R179Q)融合蛋白質)及含1% FBS之50% DMEM(圖4)。其他實驗使用所規定量之純化之多肽(圖5A及5B)。20小時後將細胞溶解於被動溶解緩衝劑(Promega, 目錄號E194A)中, 且使用Dual-Glo Luciferase Assay System(Promega, 目錄號E2940)測定螢光素酶活性。

在初始實驗中, 在未分化條件培養基中顯示Klotho融合多肽活性。藉由使用Egr-1-螢光素酶報導子基因(圖4), 此等實驗定量螢光素酶報導子之表現的倍數變化。雖然含有FGF23與Klotho蛋白質之細胞外域之組合的條件培養基活化Egr-1-螢光素酶, 但僅含有FGF23之條件培養基或僅含有Klotho之細胞外域之條件培養基不活化Egr-1-螢光素酶。與含有單獨FGF23或Klotho之條件培養基相反, 含有融合蛋白質sKlotho-FGF23(R179Q)之條件培養基活化Egr-1-螢光素酶報導子基因。在此等實驗中, 與含有FGF23與Klotho之組合的條件培養基相比, 含有融合蛋白質sKlotho-FGF23(R179Q)之條件培養基顯著更佳地活化Egr-1-螢光素酶報導子基因。在存在肝素的情況下, 含有融合蛋白質sKlotho-FGF23(R179Q)之條件培養基及含有FGF23與Klotho之組合的條件培養基之誘導顯著增強。表1列出在Egr-1-螢光素酶報導子

檢定中，各種FGF-Klotho融合多肽在條件培養基中之相對表現及對應於各種FGF-Klotho融合多肽之未分化條件培養基之相對活性。

表1. sKlotho-FGF23融合變異體之表現及活性

	sKlotho-FGF23融合構築體	表現	在Egr-1-luc報導子基因中之活性
1	sKlotho-FGF23	良好	是
2	IgG sp-sKlotho-FGF23	良好	是
3	sKL-D1-FGF23	良好	否
4	sKL-D2-FGF23	無	n.a.
5	s(KL-D1)2-FGF23	良好	否
6	sKL-D1/D2-FGF23	無	n.a.
7	ssKlotho(Δ N-26)-FGF23	差	否*
8	sKLD1-D2(Δ 692-965)-FGF23	差	否*
9	sKL-D1-D2(Δ 507-798)-FGF23	差	否*
10	FGF23-sKlotho	差	否*

*缺乏活性可能為低表現之結果。

亦使用規定量之蛋白質執行Egr-1-螢光素酶報導子檢定，該等蛋白質係使用如實例1中所述之純化程序自條件培養基中純化而來。與使用含有經表現之多肽的未分化條件培養基之先前結果一致，用純化之FGF23與sKlotho之組合處理產生螢光素酶報導子活性，但用單獨純化之FGF23處理則不產生(圖5A)。由純化之FGF23與sKlotho之組合所產生之螢光素酶報導子活性進一步視純化之sKlotho之劑量而定，且該效應可因存在肝素(20 μ g/ml)而增強。在Egr-1-螢光素酶報導子檢定中，可在低達約1.21 nM(1.2倍數變化)及至少多達約19.3 nM(2.4倍數變化)之濃度下偵測sKlotho-FGF23-6 $\times$ His融合多肽對螢光素酶活性之效應(圖5B)。sKlotho-FGF23-6 $\times$ His融合多肽對螢光素酶活性之活性在存在肝素(20 μ g/ml)的情況下顯著增強。在存在肝素的情況下，可在

低達約0.6 nM(2.0倍數變化)之濃度下偵測sKlotho-FGF23-6×His融合多肽對螢光素酶活性之效應。結果展示純化之sKlotho-FGF23-6×His劑量依賴性地誘導EGR-1-luc報導子基因，且用sKlotho-FGF23-6×His處理。

實例3. 評定Klotho融合多肽對肌細胞之效應的活體外檢定

測試表現之Klotho融合多肽對C2C12肌母細胞之生物效應。用IGF-1、FGF2或sKlotho-FGF23處理C2C12肌母細胞引起肌管生長及信號傳導蛋白質之磷酸化。將C2C12肌母細胞於生長培養基(3份DMEM及1份F12)、10% FBS、1% Glut；1% P/S；1%亞油酸；0.1% ITS[胰島素(10 mg/ml)、轉鐵蛋白(5.5 mg/ml)及硒(5 ng/ml)]中接種於經聚-D-離胺酸及纖維結合蛋白塗佈之6孔板中，密度為40,000個細胞/孔。在肌母細胞達到匯合後(3天)，將培養基更換成分化培養基(DMED，含2%馬血清；1% Glut；1% P/S)。

對於肌管直徑實驗，匯合後3天，將培養基更換成分化培養基，在分化培養基中，在不存在或存在地塞米松(100 μ M)之情況下，用IGF-1(10 nM)、FGF2(20 ng/ml)或sKlotho-FGF23(20 nM)處理細胞24小時。處理結束時，用戊二醛(5%於PBS中)固定細胞，且收集多個螢光影像。使用Pipeline Pilot程式量測肌管直徑以確定肥大或萎縮。

對於信號傳導蛋白質磷酸化實驗，匯合後3天，將培養基更換成分化培養基，用不含FBS之DMEM使細胞挨餓4小時，接著在不存在或存在雷帕黴素(Rapamycin)(40 nM)的情況下，用IGF-1(10 nM)、FGF2(20 ng/ml)或sKlotho-FGF23(20 nM)處理30分鐘。在存在蛋白酶及磷酸酶抑制劑的情況下，將細胞溶解於RIPA緩衝液中。進行西方墨點分析，且用如圖中所指示之不同抗體探測膜，且顯影於X射線底片上，掃描該等底片。

此研究之結果展示，與對照相比，sKlotho-FGF23使肌管直徑增

加，且與IGF-1及FGF2之結果類似，其誘導C2C12肌管肥大(圖5A)。此外，基於肌管直徑之量測值，用sKlotho-FGF23、IGF-1及FGF2處理可部分逆轉由地塞米松誘導之肌管萎縮。在不存在或存在地塞米松的情況下，在肌管形態方面，在sKlotho-FGF23與FGF2之間未觀察到差異(以肌管厚度度量)。sKlotho-FGF23、IGF-1及FGF2之營養效應為在統計上顯著的。

與對C2C12肌管之效應一致，sKlotho-FGF23融合蛋白質信號傳導在C2C12肌管中引起p70S6K及ERK之磷酸化，而不引起AKT或FoxO之磷酸化(圖5B)。sKlotho-FGF23對信號傳導之效應類似於FGF2，但不同於IGF-1。據觀察，由sKlotho-FGF23所產生之ERK磷酸化之程度小於IGF-1或FGF2。由sKlotho-FGF23所產生之p70S6K之磷酸化對雷帕黴素敏感。在涉及C2C12細胞之實驗中，不需要肝素來活化信號傳導。此等結果展示sKlotho-FGF23融合多肽在C2C12肌管中活化信號傳導。

實例4. 包含sKlotho、FGF23及FcLALA之融合多肽

使用sKlotho、FGF23及抗體之經修飾之Fc片段構築各種融合多肽。此等經修飾之Fc分子與FcRn之結合已改變(降低)，且因而血清半衰期增加。其生物可用性亦經改良且向黏膜表面及體內之其他標靶之轉運亦改變。在此實例中，FGF23及sKlotho融合至FcLALA，此描述於美國專利第7,217,798號及Hessell等人, 2007 Nature 449:101-104中。此等融合多肽之各種組分之間插有連接子，如Lode等人, 1998 Proc. Natl. Acad. Sci. USA 95: 2475-2480中所述。此等融合物插入例如pcDNA3.1(Invitrogen, Carlsbad, CA)之構築體中，且表現於HEK293細胞中。

A. sKlotho-FGF23-FcLALA v1

構築包含sKlotho、連接子、FGF23、另一連接子及FcLALA的融

合物。此實施例，命名為sKlotho-FGF23-FcLALA v1，提供於下文之SEQ ID NO: 46及47中。

sKlotho-FGF23-FcLALA v1之核苷酸序列(其中起始ATG為1)以SEQ ID NO: 46提供。

sKlotho-FGF23-FcLALA v1之胺基酸序列以SEQ ID NO: 47提供於下文中。

在此序列中，融合物之各種組分如下：

sKlotho：1-982；連接子1：983-1001；FGF23：1002-1228；連接子2：1229-1233；FcLALA：1234-1459。

B. sKlotho-FGF23-FcLALA v2

構築包含sKlotho、連接子、FGF23、另一連接子及FcLALA之融合物。此實施例命名為sKlotho-FGF23-FcLALA v2且以SEQ ID NO: 48及49提供於下文中。

sKlotho-FGF23-FcLALA v2之核苷酸序列(其中起始ATG為1)以SEQ ID NO: 48提供。

sKlotho-FGF23-FcLALA v2之胺基酸序列以SEQ ID NO: 49提供於下文中。

在此序列中，融合物之各種組分如下：

sKlotho：(aa或胺基酸)1-982；連接子1：983-1001；FGF23：1002-1228；連接子2：1229-1233；FcLALA：1234-1450。

可如本文所述或此項技術中已知，藉由以各種組合來組合FGF、Klotho、經修飾之Fc片段及(視情況存在之)連接子序列及其變異體及衍生物來構築其他融合多肽。

實例5. 包含FGF23及FcLALA之融合多肽

使用FGF23及抗體之經修飾之Fc片段來構築各種融合多肽，如美國專利第7,217,798號中所述。此等經修飾之Fc分子與FcRn之結合已

改變(降低)，且因而血清半衰期增加。其生物可用性亦經改良且向黏膜表面及體內之其他標靶之轉運亦改變。在此實例中，FGF23融合至FcLALA，此等融合多肽之各種組分之間插有連接子，如Lode等人，1998 Proc. Natl. Acad. Sci. USA 95: 2475-2480中所述。此等融合物插入例如pcDNA3.1(Invitrogen, Carlsbad, CA)之構築體中，且表現於HEK293細胞中。

C. FGF23-FcLALA v1

構築包含FGF23、連接子及FcLALA之融合物。此構築體命名為FGF23-FcLALA v1且以SEQ ID NO: 50及51提供於下文中。

FGF23-FcLALA v1之核苷酸序列(其中起始ATG為1)以SEQ ID NO: 50提供於下文中。

FGF23(R179Q)-FcLALA v1之胺基酸序列以SEQ ID NO: 51提供於下文中。

在此序列中，融合物之各種組分如下：

FGF23：(aa) 1-251；連接子：252-256；FcLALA：257-482。

D. FGF23-FcLALA v2

構築包含FGF23-FcLALA v2之融合物，FGF23-FcLALA v2包含FGF23及FcLALA。

FGF23-FcLALA v2之核苷酸序列(其中起始ATG為1)以SEQ ID NO: 52提供於下文中。

FGF23(R179Q)-FcLALA v2之胺基酸序列以SEQ ID NO: 53提供於下文中。

在此序列中，融合物之各種組分如下：

FGF23：1-251；連接子：252-256；FcLALA：257-473。

可如本文所述或此項技術中已知，藉由以各種組合來組合FGF序列、經修飾之Fc片段及(視情況存在之)連接子及其變異體及衍生物來

構築其他融合多肽。

E.測定由sKlotho-FGF23(R179Q)-FcLALA融合蛋白質所致之Egr-1-luc報導子基因的活化；由FGF23(R179Q)-FcLALA蛋白質所致之Egr-1-luc報導子基因的活化；及FGF23(R179Q)對FGF23(R179Q)-FcLaLav2之藥物動力學概況。

圖7展示由sKlotho-FGF23(R179Q)-FcLALA融合蛋白質所致之Egr-1-luc報導子基因的活化。用Egr-1-luc報導子基因短暫轉染HEK293T細胞，且在不存在或存在20 µg/ml肝素的情況下，與所指示之條件培養基一起培育。接著在18小時後，測定螢光素酶活性。結果展示sklotho-FGF23-FcLALA融合蛋白質誘導報導子基因活性。此等誘導在肝素存在下顯著增強。sKF-Fcv1：sKlotho-FGF23-FcLALAv1；sKF-Fcv2：sKlotho-FGF23-FcLALAv2。

圖8展示由FGF23(R179Q)-FcLALA蛋白質所致之Egr-1-luc報導子基因的活化。用Egr-1-luc報導子基因以及Klotho之全長跨膜形式短暫轉染HEK293T細胞，且與所指示之30%條件培養基一起培育。接著在18小時後，測定螢光素酶活性。結果展示FGF23-FcLALA融合蛋白質以與FGF23類似之方式誘導報導子基因活性。

圖9展示FGF23(R179Q)對FGF23(R179Q)-FcLALAv2之藥物動力學概況。每組4隻小鼠經皮下注射2 mg/kg的FGF23 (R179Q)-6×His或FGF23(R179Q)-FcLALAv2。在所指示之時間，收集血清樣品，且由ELISA分析FGF23。血清中之FGF23(R179Q)-FcLALA濃度在24小時時間點時仍升高，而FGF23(R179Q)-6×His回到基礎含量。此結果指示在添加FcLALA時，FGF23(R179Q)之活體內半衰期顯著改良。

實例6. sKlotho-FGF23融合物在地塞米松誘導之肌肉萎縮後增強肌肉生長方面之活體內效力

實驗資料展示在地塞米松誘導之肌肉萎縮後，肌肉內注射

sKlotho-FGF23顯著增強肌肉質量生長。在此實驗中，使用對應於SEQ ID NO: 41之肽。

圖10展示腓腸肌-比目魚肌-蹠肌(GSP)肌肉之絕對重量(A)及重量改變百分比(B)，展示與肌肉內注射sKlotho(sKLO)或磷酸鹽緩衝鹽水(PBS)相比，肌肉內注射sKlotho-FGF23(KLOFGF)在地塞米松(DEX)誘導之肌肉萎縮後顯著增強肌肉質量之再生長。

將80隻15週齡雄性C57BL/6小鼠根據體重隨機分成8組，每組10隻小鼠。4組接受無DEX之水(W21d)，而另外4組接受每天2.4 mg/kg之於飲用水中之DEX，持續3週(D21d)。3週後，停止DEX處理，且立即處死一組W21d及一組D21d以確定由DEX處理所誘導之肌肉萎縮的程度。使其餘3組W21d或D21d小鼠再恢復14天(R14d)，期間其分別接受每隔一天向右腓腸肌-比目魚肌-蹠肌複合物中肌肉內注射2×50 μ l PBS、sKlotho-FGF23(KLOFGF；1.6 mg/ml)或sKlotho(sKLO；1.6 mg/ml)。最後一次肌肉內注射後24小時，處死小鼠，且測定肌肉重量並以絕對重量(A)或與W21d+PBS組相比之變化百分比表示。

此等資料展示sKlotho-FGF23融合物在地塞米松誘導之肌肉萎縮後增強肌肉生長方面的活體內效力。

實例7. 融合蛋白質之FGF23部分中之可減少聚集、減少不想要之蛋白酶誘導之裂解且增加產量之其他突變

研究sKlotho-FGF23及FGF23-FcLaLa融合多肽之FGF23部分內的若干突變。此等突變包括Q156、C206及C244(其中數字係基於FGF23胺基酸序列)。實例個別突變包括Q156A、C206S及C244S，且任何此等位點處之突變均可與R179處之突變(例如R179Q)組合。實例序列提供於圖2之SEQ ID NO: 54至68中。

C206及C244疑似涉及二聚作用；且Q156為發明者鑑別為蛋白酶敏感位點的位點。此等胺基酸突變成任何其他胺基酸均因可在不干擾

FGF23活性的情況下減少聚集、減少不想要之蛋白酶誘導之裂解及增加細胞之蛋白質產生而增強蛋白質之品質。此結果為出乎意料之結果，因為此三個位置在人類、恆河猴、牛、小鼠及大鼠中所發現之FGF23蛋白質中為保留性位置。此保留性藉由比較SEQ ID NO: 69、70、71、72及73展示於下文中，其中Q156、C206及C244加粗並加下劃線。

hFGF23	MLGARLRLWVCALCSVCSMSVLRAYPNASPLLGS ^W GGLIHL ^Y TATARN ^S YHLQIHKNGH
恒河猴	MLGARLRLWVCALCSVCSMSVIRAYPNASPLLGS ^W GGLIHL ^Y TATARN ^S YHLQIHKNGH
牛	MLGARLGLWVCTLSCV-----VQAYPNSSPLLGS ^W GGLTHL ^Y TATARN ^S YHLQIHGDGH
小鼠	MLGTCLRLLVGLCTVCSLGTARAYPDTSPLLGS ^N WGS ^L THL ^Y TATART ^S YHLQIHRDGH
大鼠	MLGACRLRLVGLACTVCSLGTARAYS ^D TSPLLGS ^N WGS ^L THL ^Y TATARN ^S YHLQIHRDGH
hFGF23	VDGAPHQTIYSALMIRSEDAGFVVITGVMSRRYL ^C MDFRGNI ^F GSHYFDPENCRFQHQT ^L
恒河猴	VDGAPHQTIYSALMIRSEDAGFVVITGVMSRRYL ^C MDFRGNI ^F GSHYFNPENCRFRHW ^T L
牛	VDGSPQQTIVYSALMIRSEDAGFVVITGVMSRRYL ^C MDFTGNI ^F GSHH ^F SPESCRFRQRT ^L
小鼠	VDGTPHQTIYSALMITSEDAGSVVITGAMTRRFL ^C MDLHGNI ^F GS ^L H ^F SPENCKFRQW ^T L
大鼠	VDGTPHQTIYSALMITSEDAGSVVIIGAMTRRFL ^C MDLRGNI ^F GS ^Y H ^F SPENCRFRQW ^T L
hFGF23	ENGYDVYHSPQYHFLVSLGRAKRAFLPGMNPPPY ^S QFLSRRNEIPLIHFN ^T PI-PRRH ^T R
恒河猴	ENGYDVYHSPQHHLVSLGRAKRAFLPGMNPPPY ^S QFLSRRNEIPLIHFN ^T TPR-PRRH ^T R
牛	ENGYDVYHSPQHRFLVSLGRAKRAFLPGTNPPPY ^A QFLSRRNEIPLPHFAATARPRRH ^T R
小鼠	ENGYDVYLSQKH ^H YLVSLGRAKRI ^F QPGTNPPPF ^S QFLARRNEVPLLHFYT ^V R-PRRH ^T R
大鼠	ENGYDVYLSPK ^H HYLVSLGRSKRI ^F QPGTNPPPF ^S QFLARRNEVPLLHFYT ^A R-PRRH ^T R
hFGF23	SAEDDSERDPLNLVKPRARMTAPASCSQELPSAEDNSPMASDPLGVVRGGRVNT ^H AGGT
恒河猴	SAEDDSERDPLNLVKPRARMTAPASCSQELPSAEDNSPVASDPLGVVRGGRVNT ^H AGGT
牛	SAHDSG--DPLSVLKPRARATPVPAAC ^S QELPSAEDSGPAASDPLGVLRGHR ^L DVRAG ^S A
小鼠	SAEDPPERDPLNLVKPRPRATPVVPVSC ^S RELPSAEEGGPAASDPLGVLRRGGRGDARGG ^A G
大鼠	SAEDPPERDPLNLVKPRPRATPIPVSC ^S RELPSAEEGGPAASDPLGVLRRGGRGDARRG ^A G
hFGF23	GPEG ^C RPFAKFI (SEQ ID NO: 69)
恒河猴	GPEA ^C RPFPKFI (SEQ ID NO: 70)
牛	GAER ^C RPFPGF ^A (SEQ ID NO: 71)
小鼠	GADR ^C RPFP ^R RFV (SEQ ID NO: 72)
大鼠	GTDR ^C RPFP ^R RFV (SEQ ID NO: 73)

此三個突變不防礙FGF23活性之事實展示於圖11中。此圖展示由FGF23(R179Q)-FcLALA及Q156A、C206S、C244S及C206S/C244S突變體所致之EGR-1-luc報導子基因的活化。

用Egr-1-luc報導子基因以及Klotho之全長跨膜形式及所指示之FGF23-FcLaLa突變體短暫轉染HEK293T細胞。接著在18小時後，測定螢光素酶活性。結果展示在活化EGR-1-Luc報導子基因活性方面，C206S、C244S、C206S/C244S (3個獨立純系)及Q156A(3個獨立純系)突變體與FGF23-FcLALA融合蛋白質同等有效。

展示突變C244及C206會改變FGF23之二聚及聚集的資料展示於圖12中。此圖展示FGF23(R179Q)-FcLaLa之WT、Q156A、C206S、

C244S及C206S/C244S突變體之蛋白質品質。由西方墨點法，使用FGF23抗體分析來自經所指示之FGF23-FcLaLa表現載體短暫轉染之HEK293T細胞的條件培養基。結果展示C206S/C244S突變防礙蛋白質二聚且Q156A突變具有減少之蛋白水解片段。

因而，令人驚訝的是，儘管此等Q156、C206及C244殘基在各物種中為保留性，但其可突變而不降低FGF23活性，且可藉由減少聚集及裂解且藉由改良產量來增強蛋白質之品質。

除非另外定義，否則本文所用之技術及科學術語具有與熟悉本發明所屬領域之專家通常所理解相同之含義。

除非另外指示，否則如熟習此項技術者顯而易知，未特定詳細描述之所有方法、步驟、技術及操作可以本身已知之方式執行且已經以本身已知之方式加以執行。再例如參考標準手冊及本文提及之一般背景技術，及其中所引用之其他參考文獻。

本發明之申請專利範圍為非限制性的且提供於下文中。

儘管本文已詳細揭示特定實施例及申請專利範圍，但此揭示僅以實例方式出於說明之目的進行，且不意欲限制隨附申請專利範圍之範疇，或任何相應未來申請案之申請專利範圍之標的物的範疇。詳言之，發明者涵蓋在不背離如申請專利範圍所界定之本發明之精神及範疇的情況下，可對本發明進行各種替代、改變及修改。咸信，相關核酸起始物質或純系之選擇為瞭解本文所述實施例之熟習此項技術者所常見之問題。認為其他態樣、優勢及修改均在隨附申請專利範圍之範疇內。隨後申請之相應申請案中申請專利範圍之範疇的改寫可歸因於不同國家或地區之專利法之限制且不應解釋為放棄申請專利範圍之標的物。

序列表(圖2)

人類Klotho核酸序列(NM_004795)(SEQ ID NO: 1)

蛋白質編碼區：9-3047

```

1  cgcgagcat gccgcccagc gcccgcgcg gccgcccgcg gccgcccgcg
cgtcgctgt
61  cgctgctgct ggtgctgctg ggcctgggcg gccgcccct gcgtgcggag
ccgggagcag
121  gcgagcagac ctgggcccgt ttctgcggc ctctgcccc cgaggccgcg
ggcctcttcc
181  agggcacctt cccgagcggc ttctctggg ccgtgggcag cgccgcctac
cagaccgagg
241  gcggctggca gcagcacggc aagggtgctg ccatctggga tacgttcacc
caccacccc
301  tggcaccccc gggagactcc cggaacgcca gtctgccgtt gggcgccccg
tcgccgctgc
361  agccgcgcac cggggacgta gccagcgaca gctacaacaa cgtcttccgc
gacacggagg
421  cgctgcgca gctcggggtc actcactacc gcttctccat ctcgtagggc
cgagtgtcc
481  ccaatggcag cgcgggcgtc cccaaccgcg aggggctgcg ctactaccg
cgctgctgg
541  agcggtgcg ggagctgggc gtgcagcccg tggtcaccct gtaccactgg
gacctgccc
601  agcgctgca ggacgcctac ggcggctggg ccaaccgcg cctggccgac
cacttcagg
661  attacgcgga gctctgttc cgccacttcg gcggtcaggt caagtactgg
atcaccatcg
721  acaacccta cgtggtggcc tggcacggct acgccaccgg gcgcctggcc
ccggcatcc
781  ggggcagccc gcggctcggg tacctggtgg cgcacaacct cctcctggct
catgccaaag
841  tctggcatct ctacaatact tctttccgtc ccactcaggg aggtcaggtg
tccattgccc
901  taagctctca ctggatcaat cctcgaagaa tgaccgacca cagcatcaaa
gaatgtcaaa
961  aatctctgga ctttgtaact gggtgggttg ccaaaccgt atttattgat
ggtgactatc
1021  ccgagagcat gaagaataac ctttcatcta ttctgctga ttttactgaa
tctgagaaaa
1081  agttcatcaa aggaactgct gacttttttg ctctttgctt tggaccacc
ttgagttttc
1141  aacttttgga ccctcacatg aagttccgcc aattggaatc tcccaacctg
aggcaactgc
1201  tttcctggat tgaccttgaa ttttaaccatc ctcaaataat tattgtggaa
aatggctgg
1261  ttgtctcagg gaccaccaag agagatgatg ccaaataat gtattacctc
aaaaagttca
1321  tcatggaaac cttaaaagcc atcaagctgg atggggtgga tgtcatcggg
tataccgcat
1381  ggtccctcat ggatgggttc gagtggcaca gaggttacag catcaggcgt
ggactcttct
1441  atgttgactt tctaagccag gacaagatgt tgttgccaaa gtcttcagcc
ttgttctacc
1501  aaaagctgat agagaaaaat ggcttccctc ctttacctga aaatcagccc
ctagaaggga
1561  catttccctg tgactttgct tggggagttg ttgacaacta cattcaagta
gataccactc

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1621 tgtctcagtt taccgacctg aatgtttacc tgtgggatgt ccaccacagt
 aaaaggctta
 1681 ttaaagtgga tggggttgtg accaagaaga ggaaatccta ctgtgttgac
 tttgctgcca
 1741 tccagcccca gatcgcttta ctccaggaaa tgcacgttac acattttcgc
 ttctccctgg
 1801 actggggccct gattctccct ctgggtaacc agtcccaggt gaaccacacc
 atcctgcagt
 1861 actatcgctg catggccagc gagcttgtcc gtgtcaacat caccacagtg
 gtggccctgt
 1921 ggcagcctat ggccccgaac caaggactgc cgcgcctcct ggccaggcag
 ggcgcctggg
 1981 agaacccta cactgccctg gcctttgcag agtatgccg actgtgcttt
 caagagctcg
 2041 gccatcacgt caagctttgg ataacgatga atgagccgta tacaaggaat
 atgacataca
 2101 gtgctggcca caaccttctg aaggcccatg ccctggcttg gcatgtgtac
 aatgaaaagt
 2161 ttaggcatgc tcagaatggg aaaatatcca tagccttgca ggctgattgg
 atagaacctg
 2221 cctgcccttt ctcccaaaag gacaaagagg tggccgagag agttttggaa
 tttgacattg
 2281 gctggctggc tgagccatt ttccgctctg gagattatcc atgggtgatg
 agggactggc
 2341 tgaaccaaag aaacaatttt cttcttctt atttactga agatgaaaaa
 aagctaatec
 2401 agggtaacct tgactttttg gctttaagcc attataccac catccttgta
 gactcagaaa
 2461 aagaagatcc aataaaatac aatgattacc tagaagtgc agaaatgacc
 gacatcacgt
 2521 ggctcaactc cccagtcag gtggcggtag tgccctgggg gttgcgcaaa
 gtgctgaact
 2581 ggctgaagtt caagtacgga gacctccca tgtacataat atccaacgga
 atcgatgacg
 2641 ggctgcatgc tgaggacgac cagctgaggg tgtattatat gcagaattac
 ataaacgaag
 2701 ctctcaaagc ccacatactg gatggatatca atctttgcgg atactttgct
 tttcgttta
 2761 acgaccgcac agctccgagg tttggcctct atcgttatgc tgcagatcag
 tttgagccca
 2821 aggcattccat gaaacattac aggaaaatta ttgacagcaa tggtttcccg
 ggcccagaaa
 2881 ctctggaaag attttgtcca gaagaattca ccgtgtgtac tgagtgcagt
 ttttttcaca
 2941 cccgaaagtc tttactggct ttcatagctt ttctattttt tgcttctatt
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 3001 ccttatatt ttactactcg aagaaaggca gaagaagta caaatagttc
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 3061 tctattcatt catthttgaaa taattatgca gacacatcag ctgttaacca
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 3121 taagtgttgt gaaactgtaa atttcataca tttgacttct agaaaacatt
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 3181 atgacagagg ttttgaaatg ggcataggtg atcgtaaaat attgaataat
 gcgaatagtg
 3241 cctgaatttg ttctcttttt ggggtgattaa aaaactgaca ggcactataa
 tttctgtaac
 3301 acactaacia aagcatgaaa aataggaacc acaccaatgc aacatttggtg
 cagaaatttg
 3361 aatgacaaga ttaggaatat tttcttctgc acccatttct aaatttaatg
 tttttctgga
 3421 agtagtaatt gcaagagttc gaatagaaag ttatgtacca agtaaccatt
 tctcagctgc

3481 cataataatg cctagtggtt tccccctctgt caaatctagt ttcctatgga
 aaagaagatg
 3541 gcagatacag gagagacgac agaggggtcct aggctggaat gttcctttcg
 aaagcaatgc
 3601 ttctatcaaa tactagtatt aatttatgta tctgggtaat gacatacttg
 gagagcaaat
 3661 tatggaaatg tgtattttat atgatttttg aggtcctgtc taaaccctgt
 gtccttgagg
 3721 gatctgtctc actggcatct tgttgagggc cttgcacata ggaaactttt
 gataagtatc
 3781 tgcggaaaaa caaacatgaa tcctgtgata ttgggctctt caggaagcat
 aaagcaattg
 3841 tgaaatacag tataccgcag tggctctagg tggaggaaag gagggaaaaag
 tgcttattat
 3901 gtgcaacatt atgattaatc tgattatata ccatttttga gcagatcttg
 gaatgaatga
 3961 catgaccttt ccctagagaa taaggatgaa ataactactc attctatgaa
 cagtgcactc
 4021 actttctatt ctttagctgt actgtaattt ctttgagttg atagttttac
 aaattcttaa
 4081 taggttcaaa agcaatctgg tctgaataac actggatttg tttctgtgat
 ctctgaggtc
 4141 tattttatgt ttttgctgct acttctgtgg aagtagcttt gaactagttt
 tactttgaac
 4201 tttcacgtg aaacatgcta gtgatata gaaagggcta attaggtctc
 atcctttaat
 4261 gcccttaaa taagtcttgc tgattttcag acaggggaagt ctctctatta
 cactggagct
 4321 gttttataga taagtcaata ttgtatcagg caagataaac caatgtcata
 acaggcattg
 4381 ccaacctcac tgacacaggg tcatagtgtg taataatata ctgtactata
 taatatatca
 4441 tcttttagagg tatgattttt tcatgaaaga taagcttttg gtaatatcca
 ttttaaagtg
 4501 gacttattaa aattggatgc tagagaatca agttttttt atgtatatat
 ttttctgatt
 4561 ataagagtaa tatatgttca ttgtaaaaat ttttaaaaca cagaaactat
 atgcaaagaa
 4621 aaaataaaaa ttatctataa tctcagaacc cagaaatagc cactattaac
 atttctacg
 4681 tattttattt tacatagatc atattgtata tagttagtat ctttattaat
 ttttattatg
 4741 aaactttcct ttgtcattat tagtcttcaa aagcatgatt tttaatagtt
 gttgagtatt
 4801 ccaccacagg aatgtatcac aacttaaccg ttcccgtttg ttagactagt
 ttcttattaa
 4861 tgttgatgaa tgttgtttaa aaataatttt gttgctacat ttactttaat
 ttccttgact
 4921 gtaaagagaa gtaattttgc tccttgataa agtattatat taataataaa
 tctgcctgca
 4981 actttttgcc ttctttcata atc

Klotho氨基酸序列(NP_004786)(SEQ ID NO: 2)

1 MPASAPRRP RPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA PEAAGLFQGT
 61 FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTTHPLAP PGDSRNASLP LGAPSPLQPA
 121 TGDVASDSYN NVFRDTEALR ELGVTHYRFS ISWARVLPNG SAGVPNREGL RYYRRLRLERL
 181 RELGVQPVVT LYHWDLPQRL QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP
 241 YVVAWHGYAT GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP DFTESEKKFI
 361 KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW IDLEFNHPQI FIVENGWFVS

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421 GTTKRDDAKY MYLKKFIME TLKAIKLDGV DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD
481 FLSQDKMLLP KSSALFYQKL IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTSLQ
541 FTDNLVYLWD VHHSKRLIKV DGVVTKRKS YCVDFAAIQP QIALLOEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL LARQGAWENP
661 YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG HNLLKAHALA WHVYNEKFRH
721 AQNGKISIAL QADWIEPACP FSQKDKEVAE RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ
781 RNNFLLPYFT EDEKKLIQGT FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN
841 SPSQVAVVPW GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFLYRY AADQFEPKAS MKHYRKIDS NGFPGPETLE
961 RCPPEEFTVC TECSFFHTRK SLLAFIAFLF FASIISLSLI FYYSKKGRRS YK

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β-Klotho核酸序列(NM_175737)(SEQ ID NO: 3)

蛋白質編碼區：98-3232

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1 atcctcagtc tcccagttca agctaatacat tgacagagct ttacaatacac aagctttttac
61 tgaagctttg ataagacagt ccagcagttg gtggcaaagt aagccaggct gtgcggcagg
121 atctccaggg aatgaatgga ttttcttcag cactgatgaa ataaccacac gctataggaa
181 tacaatgtcc aacgggggat tgcaaagatc tgtcatcctg tcagcactta ttctgtctacg
241 agctgttact ggattctctg gagatggaag agctatatgg tctaaaaatc ctaattttac
301 tccggtaaaat gaaagtcagc tgtttctcta tgacactttc cctaaaaact tttctgggg
361 tattgggact ggagcattgc aagtgggaag gaggatggaa aaggaccttc
421 tatatgggat catttcatcc acacacacct taaaaatgtc agcagcacga atggttccag
481 tgacagttaa atttttctgg aaaaagactt atcagccctg gattttatag gaggttcttt
541 ttatcaattt tcaatttctt ggccaaggct tttcccgat ggaatagtaa cagttgcaa
601 cgaaaagggt ctgcagtact acagtactct tctggacgct ctagtgttta gaaacattga
661 acctatagtt actttatacc actgggattt gcctttggca ctacaagaaa aatatggggg
721 gtggaaaaat gataccataa tagatatctt caatgactat gccacatact gtttccagat
781 gtttggggac cgtgtcaaat attggattac aattcacaac ccatatctag tggcttgga
841 tgggtatggg acaggtatgc atgcccctgg agagaaggga aatttagcag ctgtctacac
901 tgtgggacac aacttgatca aggtcactc gaaagtttgg cataactaca acacacattt
961 ccgcccacat cagaagggtt gggtatcgat cacgttggga tctcattgga tcgagccaaa
1021 ccggtcggaa aacacgatgg atatatccaa atgtcaacaa tccatggttt ctgtgcttgg
1081 atggtttgcc aaccctatcc atggggatgg cgactatcca gaggggatga gaaagaagtt
1141 gttctccgtt ctacccattt tctctgaagc agagaagcat gagatgagag gcacagctga
1201 tttctttgcc ttttcttttg gacccaacaa cttcaagccc ctaaacacca tggctaaaat
1261 gggacaaaat gtttcaacta atttaagaga agcgctgaac tggattaaac tggaaataca
1321 caaccctcga atcttgattg ctgagaatgg ctggttcaca gacagtcgtg tgaaaacaga
1381 agacaccacg gccatctaca tgatgaagaa tttcctcagc cagggtgctt aagcaataag
1441 gttagatgaa atacgagtggt ttggttatac tgctgtgtct ctcttggtat gctttgaatg
1501 gcaggatgct tacaccatcc gccgaggatt attttatgtg gattttaaca gtaaacagaa
1561 agagcggaaa cctaagtctt cagcacacta ctacaaacag atcatagcag aaaatgggtt
1621 ttcttttaaa gagtccacgc cagatgtgca gggccagttt ccctgtgact tctcctgggg
1681 tgtcactgaa tctgttctta agcccagatc tgtggcttcg tccccacagt tcagcgatcc
1741 tcatctgtac gtgtggaacg ccaactggca cagactgttg caccgagtgg aaggggtgag
1801 gctgaaaaca cgaccgcctc aatgcacaga ttttgtaaac atcaaaaaaac aacttgagat
1861 gttggcaaga atgaaagtca cccactaccg gtttgctctg gattgggcct cggtccttcc
1921 cactggcaac ctgtccgcgg tgaaccgaca ggccctgagg tactacaggt gcgtggtcag
1981 tgaggggctg aagcttgcca tctccgcgat ggccaccctg tattatccga cccacgccc
2041 cctaggcctc cccgagcctc tgttgcatgc cgacgggtgg ctgaacccat cgacggccga
2101 ggccttccag gcctacgctg ggctgtgctt ccaggagctg ggggacctgg tgaagctctg
2161 gatcaccatc aacgagccta accggctaag tgacatctac aaccgctctg gcaacgacac
2221 ctacggggcg gcgcacaacc tgctggtggc ccacgccttg gcctggcgcc tctacgaccg
2281 gcagttcagg ccctcacagc gcggggccgt gtcgctgtcg ctgcacgcgg actgggcgga
2341 acccgccaac ccctatgctg actcgcactg gaggcgggcc gagcgcttcc tgcagttcga
2401 gatcgctggg ttcgcccagc cgctcttcaa gaccggggac taccgcggcg ccatgaggga
2461 atacattgcc tccaagcacc gacgggggct ttccagctcg gccctgccgc gcctcaccga
2521 ggccgaaagg aggtctgtca agggcacggt cgacttctgc gcgctcaacc acttcaccac
2581 taggttcgtg atgcacgagc agctggccgg cagccgctac gactcggaca gggacatcca
2641 gtttctgcag gacatcaccg gcctgagctc cccacgcgc ctggctgtga ttccctgggg
2701 ggtgcgcaag ctgctgcggt ggtccggag gaactacggc gacatggaca ttacatcac
2761 cgccagtggc atcgacgacc aggtctctgga ggatgaccgg ctccggaagt actacctagg

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2821 gaagtacctt caggaggtgc tgaagcagata cctgattgat aaagtcagaa tcaaaggcta
 2881 ttatgcattc aaactggctg aagagaaatc taaaccagaa tttggattct tcacatctga
 2941 ttttaagct aaatcctcaa tacaatttta caacaaagtg atcagcagca ggggcttccc
 3001 ttttgagaac agtagttcta gatgcagtca gacccaagaa aatacagagt gcactgtctg
 3061 cttattcctt gtgcagaaga aaccactgat attcctgggt tgttgcttct tctccaccct
 3121 gggttctactc ttatcaattg ccatttttca aaggcagaag agaagaaagt tttggaaagc
 3181 aaaaaactta caacacatac cattaagaa aggcaagaga gttgttagct aaactgatct
 3241 gtctgcatga tagacagttt aaaaattcat cccagttcc

β-Klotho胺基酸序列(NP_783864)(SEQ ID NO: 4)

1 mkpgcaagsp gnewiffstd eittryrntm sngglqrsvi lsalillrav tgfsgdgrai
 61 wsknpnftpv nesqlflydt fpknffwgig tgalqvegsw kkdgkgsiw dhfihthlkn
 121 vsstngssds yiflekdlsa ldfigvsfyq fsiswprlfp dgivtvanak glgyystlld
 181 alvlrniepi vtlyhwdlpl alqekyggwk ndtiidifnd yatycfmgf drvkywiti
 241 npylvawhgy gtgmhapsek gnlaavytvn hnlikahskv whnynthfrp hqkgwlsitl
 301 gshwiepnrs entmdifkq qsmvsvlgwf anpihgddgy pegmrkklfs vlpifseae
 361 hemrgtadff afsfgpnnfk plntmakmgq nvslnlreal nwikleymp riliaengwf
 421 tdsrvktedt taiymknfl sqvlqairld eirvfgytaw slldgfewqd aytirrglgy
 481 vdfnsqker kpkssahyyk qiirengfsl kestpdvqgg fpcdfswgvt esvlkpesva
 541 sspqfsdphl yvwnatgnrl lhrvegvrllk trpaqctdfv nikkqlemla rmkvthyrfa
 601 ldwasvlptg nlsavnrqal ryrvcvsvseg lklgisamvt lypthahlg lpepllhadd
 661 wlnpstaeaf qayaglcfe lgdlvklwit inepnrlsdi ynrsngndtyg aahnlhvaha
 721 lawrlydrqf rpsqrgavsl slhadwaepa npyadshwra aerflqfeia wfaeplfktg
 781 dypaamreyi askhrrglss salprlteae rrlkgtvdf calnhfttrf vmheqlagsr
 841 ydsdrdiqfl qditrlsspt rlavipwgvv kllrwvrmy gdmdiyitas giddqaledd
 901 rlrkyylgky lqevlkayli dkvrkgyya fklaeekskp rfgfftsdfk akssiqlfynk
 961 vissrgfpfe nsssrscstg entectvcif lvqkkplifl gccffstlvi llsiaifqrq
 1021 krrkfwkkn lqhiplkkgk rvvs

人類Klotho域1(KL-D1)胺基酸序列(SEQ ID NO: 5)

58 qgt
 61 fpdgflwavg saayqteggw qhgkgasiw dtfthhplap pgdsrnaslp lgapsplqpa
 121 tgdvasdsyn nvfrdtealr elgvthyrfs iswarvlpng sagvpnregl ryyrrllerl
 181 relvgpvvt lyhwdlpqrl qdayggwanr aladhfrdya elcfrhfagg vkywitidnp
 241 yvawhgyat grlapgirgs prlgylvahn lllahakvwh lyntsfrptq ggqvsialss
 301 hwinprmt d hsiqecqksl dfvlwgafak vfidgdypes mknllsilp dfteseckfi
 361 kgtadffalc fgptlsqll dphmkfrgle spnlrqllsw idlefnpqi fivengwfv
 421 gttkrddaky myylkkfime tlkaikldgv dvigytawsl mdgfewhrgy sirrglgyvd
 481 flsqdkmllp kssalfyqkl iekngf

人類Klotho域2(KL-D2)胺基酸序列(SEQ ID NO: 6)

517 gtfp cdfawgvvdn yiqvdtllsq
 541 ftdlnvylwd vhskrlikv dgvttkrks ycvdfaaiqp qiallgemhv thfrfsldwa
 601 lilplngsq vnhtilqyyr cmaselvrn itpvvalwqp mapnqglprl larggawenp
 661 ytalafaeya rlcfeqelghh vclwitmneq ytrnmtysag hnllkahala whvynekfrh
 721 aqngkisial qadwiepacp fsqkdkevae rvlfdigwl aepifgsgdy pwvmrdwlnq
 781 rnnfllpyft edekliqgt fdflalshyt tilvdseked pikyndylev qemtditwln
 841 spsqvavpw glrkvlwkl fkygdipmyi isngiddglh aeddqlrvy mqnyninealk
 901 ahildginlc gyfaysfndr taprfglyry aadqfepkas mkhyrkiids ngf

Klotho細胞外域(無信號肽)胺基酸序列(SEQ ID NO: 7)

28 epgdgaq twarfsrppa peaaglfqgt
 61 fpdgflwavg saayqteggw qhgkgasiw dtfthhplap pgdsrnaslp lgapsplqpa
 121 tgdvasdsyn nvfrdtealr elgvthyrfs iswarvlpng sagvpnregl ryyrrllerl

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181 relgvqpvt lyhwdlpqrl qdayggwanr aladhfrdya elcfrhfggq vkywitidnp
241 yvvawhgyat grlapgirgs prlgylvahn lllahakvwh lyntsfrptq ggqvsialss
301 hwinprmttd hsiyecqksl dfvlgwafak vfidgdypes mknnlssilp dftesekkfi
361 kgtadffalc fgptlsfql dphmkfrqle spnlrqllsw idlfnhpgi fivengwfv
421 gttkrddaky myylkkfime tlkaikldgv dvigytawsl mdgfewhrgy sirrglfyvd
481 flsqdkmlp kssalfyqkl iekngfpplp enqplegtfp cdfawgvvdn yiqvdttsq
541 ftdlnvylwd vhhskrlikv dgvvtkkrks ycvdfaaiqp qiallqemhv thfrfsldwa
601 lilplgnqsq vnhtilqyyr cmaselvrn itpvvalwqp mapngglprl larqgawenp
661 ytalafaeya rlcfcgelghh vklwitmneq ytrnmtysag hnllkahala whvynekfrh
721 aqngkisial qadwiepacp fsqkdkevae rvlefdigwl aepifgsgdy pwvmrdwlnq
781 rnnflipyft edekkliqgt fdfalshyt tilvdseked pikyndylev qemtditwln
841 spsqvavvpw glrkvlwlnk fkygdipmyi isngiddglh aeddqlrvyy mqnyinealk
901 ahildginlc gyfaysfndr taprfglyry aadqfepkas mkhyrkiids ngfpgpetle
961 rfcpeeftvc tecsffhtrk sl

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Klotho信號肽胺基酸序列(SEQ ID NO: 8)

```

1 mpasapprp rpppslsll lvllglgrr lra

```

IgG信號肽胺基酸序列(SEQ ID NO: 9)

```

1 msvltqvlal lllwltgtrc rrlra

```

(Gly₄ Ser)₃多肽連接子核酸序列(SEQ ID NO: 10)

```

1 ggaggtggag gttcaggagg tggaggttca ggaggtggag gttca

```

(Gly₄ Ser)₃多肽連接子胺基酸序列(SEQ ID NO: 11)

```

1 GGGGSGGGGS GGGGS

```

(Gly₄ Ser)多肽連接子胺基酸序列(SEQ ID NO: 12)

```

1 GGGGS

```

(Gly)多肽連接子胺基酸序列(SEQ ID NO: 13)

```

1 G

```

(Gly Gly)多肽連接子胺基酸序列(SEQ ID NO: 14)

```

1 GG

```

(Gly Ser)多肽連接子胺基酸序列(SEQ ID NO: 15)

```

1 GS

```

(Gly₂ Ser)多肽連接子胺基酸序列(SEQ ID NO: 16)

```

1 GGS

```

(Ala)多肽連接子胺基酸序列(SEQ ID NO: 17)

```

1 A

```

(Ala Ala)多肽連接子胺基酸序列(SEQ ID NO: 18)

1 AA

Klotho信號肽-Klotho細胞外域-FGF23 (R179Q)胺基酸序列(SEQ ID NO: 19)

```

1 MPASAPRRRP RPPPPSLSL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTTHPLAP
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYRRLLELRL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADGFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
351 DFTSEKKFI KGTAFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTSLQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLOEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTAFAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWVMDWLNQ RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYI MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLIY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSADAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPFP YSQFLSRRNE IPLIHFNTPPI
1151 PRRHTQSAED DSERDPLNVL KPRARMTAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*

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IgG信號肽-Klotho細胞外域-FGF23(R179Q)胺基酸序列(SEQ ID NO: 20)

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1 MSVLTQVLAL LLLWLTGLGG RRLRAEPGDG AQTWARFSRP PAPEAAGLFQ
51 GTFPDGFLLA VGSAAYQTEG GWQQHGKGAS IWDFTTHHPL APPGDSRNAS
101 LPLGAPSPLQ PATGDVASDS YNNVFRDTEA LRELGVTHYR FSIWARVLP
151 NGSAGVPNRE GLRYRRLLE RLRELGVQPV VTLYHWDLPQ RLQDAYGGWA
201 NRALADHFRD YAELEFRHFG QQVKYWITID NPYVVAWHGY ATGRLAPGIR
251 GSPRLGYLVA HNLLLAHAKV WHLYNTSFRP TQGGQVSIAL SSHWINPRRM
301 TDHSIKECQK SLDFVLGWFA KPVFIDGDYP ESMKNNLSSI LPDFTSEKK
351 FIKGTADFFA LCFGPTLSFQ LLDPHMKFRQ LESPCLRQLL SWIDLEFNHP
401 QIFIVENGWF VSGTTKRDDA KYMYLKKFI METLKAIKLD GVDVIGYTAW
451 SLMDGFEWHR GYSIRRGLFY VDLSQDKML LPKSSALFYQ KLIKNGFPP
501 LPENQPLEGT FPCDFAWGVV DNYIQVDTTL SQFTDLNVYL WDVHHSKRLI
551 KVDGVVTKKR KSYCVDFAAI QPQIALLOEM HVTHFRFSLD WALILPLGNQ
601 SQVNHTILQY YRCMASELVR VNITPVVALW QPMAPNQGLP RLLARQGAWE
651 NPYTALAFAY YARLCFQELG HHVKLWITMN EPYTRNMTYS AGHNLLKAHA
701 LAHWVYNEKF RHAQNGKISI ALQADWIEPA CPFSQKDKEV AERVLEFDIG
751 WLAEPFSGSG DYPVWMDWL NQRNNFLLPY FTEDEKKLIQ GTFDFLALSH
801 YTTILVDSEK EDPIKYNDYL EVQEMTDITW LNPSQVAVV PWGLRKVLNW
851 LKFKYGDLPY YIISNGIDDG LHAEDDQLRV YMQNYINEA LKAHILDGIN
901 LCGYFAYSFN DRTAPRFGLY RYAADQFEPK ASMKHYRKII DSNGFPGPET
951 LERFCPEEFT VCTECSFFHT RKSLGSGGGG SGGGGSGGGG SLKYPNASPL

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1001 LGSSWGGLIH LYTATARN SY HLQIHKNGHV DGAPHQTIYS ALMIRSEDAG
 1051 FVVITGVMSR RYL CMDFRGN IFGSHYFDPE NCRFQHQTLE NGYDVYHSPQ
 1101 YHFLVSLGRA KRAFLPGMNP PPYSQFLSRR NEIPLIHFT PIPRRHTQSA
 1151 EDDSERDPLN VLKPRARMTP APASCSQELP SAEDNSPMAS DPLGVVRGGR
 1201 VNTHAGGTGP EGCRPFAPFI *

KL-D1-FGF23(R179Q)氨基酸序列(SEQ ID NO: 21)

1 MPASAPRRRP RPPPPSLSL LVLGLGGR LRAEPGDGAQ TWARFSRPPA
 51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGFLYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGSGG GSGGGGSGG GGS LKYPNAS PLLGSSWGGL
 551 IHLYTATARN SYHLQIHKNG HVDGAPHQTI YSALMIRSED AGFVVITGVM
 601 SRRYLCMDFR GNIFGSHYFD PENC RFQHQT LENG YDVYHS PQYHFLVSLG
 651 RAKRAFLPGM NPPPY SQFLS RRNEIPLIHF NTP IPRRHTQ SAEDDSERDP
 701 LNVLKPRARM TPAPASCSQE LPSAEDNSPM ASDPLGVVRG GRVNTHAGGT
 751 GPEGCRPFAK FI*

KL-D2-FGF23(R179Q)氨基酸序列(SEQ ID NO: 22)

1 MPASAPRRRP RPPPPSLSL LVLGLGGR LPLPENQPLE GTFPCDFAWG
 51 VVDNYIQVDT TLSQFTDLNV YLWDVHHSKR LIKVDGVVTK KRKSYCVDF
 101 AIQPQIALQ EMHVTHFRFS LDWALILPLG NQSQVNHTIL QYRCMASEL
 151 VRVNITPVVA LWQPMAPNQG LPRLLARQGA WENPYTALAF AEYARLCFQE
 201 LGHHVKLWIT MNEPYTRNMT YSAGHNLKA HALAWHVYNE KFRHAQNGKI
 251 SIALQADWIE PACPFSQKDK EVAERVLEFD IGWLAEPFIG SGDYPWVMRD
 301 WLNQRNNFLL PYFTEDEKKL IQGTFDFLAL SHYTILVDS EKEDPIKYND
 351 YLEVQEMTDI TWLNSPSQVA VVPWGLRKVL NWLKFYKGD PMYIISNGID
 401 DGLHAEDDQL RVYYMQNYIN EALKAHILDG INLCGYFAYS FNDRTAPRFG
 451 LYRYAADQFE PKASMKHYRK IIDSNGFPGP ETLE RFCEP FTVCTECSFF
 501 HTRKSLGSGG GSGGGGSGG GGS LKYPNAS PLLGSSWGGL IHLYTATARN
 551 SYHLQIHKNG HVDGAPHQTI YSALMIRSED AGFVVITGVM SRRYLCMDFR
 601 GNIFGSHYFD PENC RFQHQT LENG YDVYHS PQYHFLVSLG RAKRAFLPGM
 651 NPPPY SQFLS RRNEIPLIHF NTP IPRRHTQ SAEDDSERDP LNVLKPRARM
 701 TPAPASCSQE LPSAEDNSPM ASDPLGVVRG GRVNTHAGGT GPEGCRPFAK
 751 FI*

(KL-D1)₂-FGF23(R179Q)氨基酸序列(SEQ ID NO: 23)

1 MPASAPRRRP RPPPPSLSL LVLGLGGR LRAEPGDGAQ TWARFSRPPA
 51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGFLYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGSGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW
 551 DTFTHHPLAP PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR
 601 ELGVTHYRFS ISWARVLPNG SAGVPNREGL RYYRLLERL RELGVQPVVT
 651 LYHWDLPQRL QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP

701 YVVAWHGYAT GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ
 751 GGQVSIALSS HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES
 801 MKNNLSSILP DFTSEKKFI KGTAFFALC FGPTLSFQLL DPHMKFRQLE
 851 SPNLRQLLSW IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYYLKKFIME
 901 TLKAIKLDGV DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP
 951 KSSALFYQKL IEKNGFPEFG SGGGSGGGG SGGGSLKYP NASPLLGSW
 1001 GGLIHLTYAT ARNSYHLQIH KNGHVDGAPH QTIYSALMIR SEDAGFVVIT
 1051 GVMSRRYLCM DFRGNIFGSH YFDPENCRFQ HQTLENGYDV YHSPQYHFLV
 1101 SLGRAKRAFL PGMNPPYSQ FLSRRNEIPL IHFNTPIPRR HTQSAEDDSE
 1151 RDPLNLKPR ARMTAPASC SQELPSAEDN SPMASDPLGV VRGGRVNTHA
 1201 GGTGPEGCRP FAKFI*

(KL-D2)₂-FGF23(R179Q)氨基酸序列(SEQ ID NO: 24)

1 MPASAPRRP RPPPPSLSL LVLLGLGRR LPLPENQPLE GTFPCDFAWG
 51 VVDNYIQVDT TLSQFTDLNV YLWDVHHSKR LIKVDGVVTK KRKSYCVDF
 101 AIQPQIALLO EMHVTHFRFS LDWALILPLG NQSQVNHTIL QYYRCMASEL
 151 VRVNITPVVA LWQPMAPNQG LPRLLARQGA WENPYTALAF AEYARLCFQE
 201 LGHHVKLWIT MNEPYTRNMT YSAGHNLLKA HALAWHVYNE KFRHAQNGKI
 251 SIALQADWIE PACPFSQKDK EVAERVLEFD IGWLAEPIFG SGDYPWVMRD
 301 WLNQRNFFL PYFTEDEKKL IQGTFDFLAL SHYTTLVDS EKEDPIKYND
 351 YLEVQEMTDI TWLNSPSQVA VVPWGLRKVL NWLKFYKGD PMYIISNGID
 401 DGLHAEDDQL RVYMQNYIN EALKAHILDG INLCGYFAYS FNDRTAPRFG
 451 LYRYAADQFE PKASMKHYRK IIDSNGFPGP ETLERFCPEE FTVCTECSFF
 501 HTRKSLGTFP CDFAWGVVDN YIQVDTLSQ FTDLNVYLWD VHHSKRLIKV
 551 DGVVTKRKS YCVDFAAIQF QIALQEMHV THFRFSLDWA LILPLGNQSQ
 601 VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL LARQGAWENP
 651 YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG HNLLKAHALA
 701 WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE RVLEFDIGWL
 751 AEPIFGSGDY PWVMDWLNQ RNNFLLPYFT EDEKKLIQGT FDFLALSHYT
 801 TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW GLRKVLNWLK
 851 FKYGDLPMYI ISNGIDDGLH AEDDQLRVYI MQNYINEALK AHILDGINLC
 901 GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS NGFGSGGGGS
 951 GGGSGGGGS LKYPNASPLL GSSWGGLIHL YTATARNYSY LQIHKNGHVD
 1001 GAPHQTIYSA LMIRSEDAGF VVITGVMSRR YLCMDFRGNI FGSHYFDPEN
 1051 CRFQHQTLN GYDVYHSPQY HFLVSLGRAK RAFLPGMNPP PYSQFLSRRN
 1101 EIPLIHFNTP IPRRHTQSAE DDSERDPLNV LKPRARMTA PASCSELPS
 1151 AEDNSPMASD PLGVVRGGRV NTHAGGTGPE GCRPFAKFI*

FGF23(R179Q)-Klotho細胞外域氨基酸序列(SEQ ID NO: 25)

1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARN
 51 YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGVDVYHSP QYHFLVSLGR AKRAFLPGMN
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IGSGGGGSGG GSGGGGSLK EPGDGAQTWA RFSRPPAPEA AGLFQGTFPD
 301 GFLWAVGSAA YQTEGGWQGH GKGASIWDTF THHPLAPPGD SRNASLPLGA
 351 PSPLQPATGD VASDSYNNVF RDTEALRELG VTHYRFSISW ARVLNPGSAG
 401 VPNREGLRYY RRLRLRLREL GVQPVVTLVH WDLPLRLQDA YGGWANRALA
 451 DHFRDYAELC FRHFGGQVKY WITIDNPYVV AWHGYATGRL APGIRGSPRL
 501 GYLVAHNLLL AHAKVWHLYN TSFRPTQGGQ VSIALSSHWI NPRRMTDHSI
 551 KECQKSLDFV LGWFAKPVFI DGDYPESMKN NLSSILPDFT ESEKKFIKGT
 601 ADFFALCFGP TLSFQLLDPH MKFRQLESPN LRQLLSWIDL EFNHPQIFIV
 651 ENGWFVSGTT KRDDAKYMY LKKFIMETLK AIKLDGVDVI GYTAWSLMDG
 701 FEWHRGYSIR RGLFYVDVFLS QDKMLLPKSS ALFYQKLIK NGFPPLPENQ
 751 PLEGTFCDF AFGVVDNYIQ VDTLSQFTD LNVYLWDVHH SKRLIKVDGV
 801 VTKKRKSYCV DAAIQPQIA LLQEMHVTHF RFLDWALIL PLGNQSQVNH
 851 TILQYYRCMA SELVRVNITP VVALWQPMAP NQGLPRLLAR QGAWENPYTA

901 LAFAEYARLC FQELGHHVKL WITMNEPYTR NMTYSAGHNL LKAHALAWHV
 951 YNEKFRHAQN GKISIALQAD WIEPACPFSSQ KDKEVAERVL EFDIGWLAEP
 1001 IFGSGDYPVW MRDWNLRNN FLLPYFTEDE KKLIQGTDFD LALSHYTTIL
 1051 VDSEKEDPIK YNDYLEVQEM TDITWLNSPS QVAVVPWGLR KVLNWLKFKY
 1101 GDLPMYIISN GIDDGLHAED DQLRVYYMQN YINEALKAHI LDGINLCGYF
 1151 AYSFNDRTAP RFGLYRYAAD QFEPKASMKH YRKIIDSNGF PGPETLERFC
 1201 PEEFTVCTEC SFFHTRKSL*

FGF23(R179Q)-KL-D1氨基酸序列(SEQ ID NO: 26)

1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARN
 51 YHLQIHKNHG VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQT
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IQGTFFPDGFL WAVGSAAYQT EGGWQQHKGK ASIWDTFTHH PLAPPGDSRN
 301 ASLPLGAPSP LQPATGDVAS DSYNNVFRDT EALRELGVT
 351 LPNGSAGVPN REGLRYRRL LERLRELGVT PVVTLYHWDL PQRLQDAYGG
 401 WANRALADHF RDYAEALCFR FGGQVKYWIT IDNPYVVAWH GYATGRLAPG
 451 IRGSPRLGYL VAHNLLLAHA KVVHLYNTSF RPTQGGQVSI ALSSHWINPR
 501 RMTDHSIKEC QKSLDFVLGW FAKPVFIDGD YPESMKNNLS SILPDFTESE
 551 KKFIKGTADF FALCFGPTLS FQLLDPHMKF RQLESPNLRQ LLSWIDLEFN
 601 HPQIFIVENG WFSVGTTRD DAKYMYLKK FIMETLKAIK LDGVDVIGYT
 651 AWSLMDGFEW HRGYSIRRLG FYVDFLSQDK MLLPKSSALF YQKLIKNGF
 652 *

FGF23(R179Q)-KL-D2氨基酸序列(SEQ ID NO: 27)

1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARN
 51 YHLQIHKNHG VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQT
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IGTFPCDFAW GVVDNYIQVD TTLSQFTDLN VYLWDVHHSK RLIKVDGVVT
 301 KKRKSYCVDF AAIQPQIAL QEMHVTHFRF SLDWALILPL GNQSQVNHTI
 351 LQYYRCMASE LVRVNITPVV ALWQPMAPNQ GLPRLARQG AWENPYTALA
 401 FAEYARLCFQ ELGHHVKLWI TMNEPYTRNM TYSAGHNLK AHALAWHVYN
 451 EKFRHAQNGK ISIALQADWI EPACPFSSQD KEVAERVLEF DIGWLAEPF
 501 GSGDYPWVMR DWLNQRNNFL LPYFTEDEK LIQGTDFDLA LSHYTTILVD
 551 SEKEDPIKYN DYLEVQEMTD ITWLNSPSQV AVVPWGLRKV LNWKFKYGD
 601 LPMYIISNGI DDGLHAEDDQ LRVYYMQNYI NEALKAHIL GINLCGYFAY
 651 SFNDRTAPRF GLYRYAADQF EPKASMKHYR KIIDSNGF*

FGF23(R179Q)-(KL-D1)₂氨基酸序列(SEQ ID NO: 28)

1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARN
 51 YHLQIHKNHG VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQT
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IQGTFFPDGFL WAVGSAAYQT EGGWQQHKGK ASIWDTFTHH PLAPPGDSRN
 301 ASLPLGAPSP LQPATGDVAS DSYNNVFRDT EALRELGVT
 351 LPNGSAGVPN REGLRYRRL LERLRELGVT PVVTLYHWDL PQRLQDAYGG
 401 WANRALADHF RDYAEALCFR FGGQVKYWIT IDNPYVVAWH GYATGRLAPG
 451 IRGSPRLGYL VAHNLLLAHA KVVHLYNTSF RPTQGGQVSI ALSSHWINPR
 501 RMTDHSIKEC QKSLDFVLGW FAKPVFIDGD YPESMKNNLS SILPDFTESE
 551 KKFIKGTADF FALCFGPTLS FQLLDPHMKF RQLESPNLRQ LLSWIDLEFN
 601 HPQIFIVENG WFSVGTTRD DAKYMYLKK FIMETLKAIK LDGVDVIGYT
 651 AWSLMDGFEW HRGYSIRRLG FYVDFLSQDK MLLPKSSALF YQKLIKNGF
 701 QGTFFPDGFLW AVGSAAYQTE GGWQQHKGGA SIWDTFTHHP LAPPGDSRNA

751 SLPLGAPSPL QPATGDVASE SYNNVFRDTE ALRELGVTHY RFSISWARVL
 801 PNGSAGVPMR EGLRYRRLR ERLRELGVQP VVTLYHWDLP QRLQDAYGGW
 851 ANRALADHFR DYAEFCFRHF GGQVKYWTI DNPYVVAWHG YATGR LAPGI
 901 RGSPLRGYLV AHNLLLAHAK VWHLYNTSFR PTQGGQVISA LSSHWINPRR
 951 MTDHSIKECQ KSLDFVLGWF AKPVFIDGDY PESMKNNLSS ILPDFTESEK
 1001 KFIKGTADFF ALCFGPTLSF QLLDPHMKFR QLESPNLRQL LSWIDLEFNH
 1051 PQIFIVENGW FVSGTTKRDD AKYMYLKKF IMETLKAIKL DGVDVIGYTA
 1101 WSLMDGFEWH RGYSIRRGFL YVDFLSQDKM LLPKSSALFY QKLEKNGF*

FGF23(R179Q)-(KL-D2)₂胺基酸序列(SEQ ID NO: 29)

1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARN5
 51 YHLQIHKNHG VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
 101 NIFGSHYFDP ENCRFQHQTL ENGVDVYHSP QYHFLVSLGR AKRAFLPGMN
 151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
 201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
 251 IGTFPDCFADW GVVDNYIQVD TTLSQFTDLN VYLWDVHHSK RLIKVDGVVT
 301 KKRKSYCVDF AAIQPQIALI QEMHVTFRF SLDWALILPL GNQSQVNHTI
 351 LQYYRCMASE LVRVNITPVV ALWQPMAPNQ GLPRLARQG AWENPYTALA
 401 FAEYARLCFQ ELGHVVKLWI TMNEPYTRNM TYSAGHNLLK AHALAWHVYN
 451 EKFRHAQNGK ISIALQADWI EPACPFSSQD KEVAERVLEF DIGWLAEPF
 501 GSGDYPWVMR DWLNQRNNFL LPYFTEDEKK LIQGTDFDLA LSHYTTILVD
 551 SEKEDPIKYN DYLEVQEMTD ITWLNSPSQV AVVPWGLRKV LNWLFKFKYGD
 601 LPMYIISNGI DDGLHAEDDQ LRVYMQNYI NEALKAHILD GINLCGYFAY
 651 SFNDRTAPRF GLYRYAADQF EPKASMKHYR KIIDSNGFGT FPCDFAWGVV
 701 DNYIQVDITL SQFTDLNVYL WDVHHSKRLI KVDGVVTKKR KSYCVDFAAI
 751 VQPIALLQEM HVTHFRFLD WALILPLGNQ SQVNHTILQY YRCMASELVR
 801 VNITPVVALW QPMAPNQGLP RLLARQGAWE NPYTALAFAY YARLCFQELG
 851 HHVKLWITMN EPYTRNMTYS AGHNLLKAHA LAWHVYNEKF RHAQNGKISI
 901 ALQADWIEPA CPFSQDKKEV AERVLEFDIG WLAEPFSGS DYPWVMRDWL
 951 NQRNFFLLPY FTEDEKKLIQ GTFDFLALSH YTTILVDSEK EDPIKYNDYL
 1001 EVQEMTDITW LNSPSQVAVV PWGLRKVLNW LKFKYGDLP YIISNGIDDG
 1051 LHAEDDQLRV YMQNYINEA LKAHILDGIN LCGYFAYSFN DRTAPRFGLY
 1101 RYAADQFEPK ASMKHYRKII DSNFG*

FGF19核酸序列(NM_005117)(SEQ ID NO: 30)

蛋白質編碼區(464-1114)

1 gctccagcc aagaacctcg gggccgctgc gcggtgggga ggagttccc gaaacccggc
 61 cgctaagcga ggcctcctcc tcccgcagat ccgaacggcc tgggcgggggt caccgccggt
 121 gggacaagaa gccgcgcgct gcctgcccgg gcccggggag ggggctgggg ctggggccgg
 181 aggcgggggtg tgagtggtgt tgtgcggggg gcggaggctt gatgcaatcc cgataagaaa
 241 tgctcgggtg tcttgggcac ctaccgctgg gggccgtaag gcgctactat ataaggctgc
 301 cggcccgagg ccgcccgcgc gtcagagcag gacgctgctg tccaggatct agggccacga
 361 ccatcccaac ccggcactca cagccccgca gcgcaccccg gtcgcccggc agcctcccgc
 421 acccccatcg ccggagctgc gccgagagcc ccaggagggt gccatgcgga gcgggtgtgt
 481 ggtggtccac gatatggatc tggccggcct ctggctgggc gtggccgggc gcccctcgc
 541 cttctcggac gcggggcccc acgtgcacta cggctggggc gaccccatcc gcctgcggca
 601 cctgtacacc tccggccccc acgggctctc cagctgcttc ctgcgcatcc gtgcgcagcg
 661 cgtcgtggac tgcgcgcggg gccagagcgc gcacagtttg ctggagatca aggcagtcgc
 721 tctgcggacc gtggccatca agggcgtgca cagcgtgcgg tacctctgca tgggcgcgga
 781 cggcaagatg caggggctgc ttcagtactc ggaggaagac tgtgctttcg aggaggagat
 841 ccgcccagat ggctacaatg tgtaccgatc cgagaagcac cgcctcccgg tctccctgag
 901 cagtgccaaa cagcggcagc tgtacaagaa cagaggcttt cttccactct ctcatttctt
 961 gcccatgctg cccatggctc cagaggagcc tgaggacctc agggggccact tgggaatctga
 1021 catgttctct tcgcccctgg agaccgcagc catggaccga tttgggcttg tcaccggact
 1081 ggaggccgtg aggagtccca gctttgagaa gtaactgaga ccatgcccgg gcctcttcac
 1141 tgctgccagg ggctgtggta cctgcagcgt gggggacgtg cttctacaag aacagtcttg
 1201 agtccacgtt ctgttttagt ttaggaagaa acatctagaa gttgtacata ttcagagttt
 1261 tccattggca gtgcagttt ctagccaata gacttgtctg atcataacat tgtaagcctg

1321 tagcttgccc agctgctgcc tgggccccca ttctgctccc tcgagggtgc tggacaagct
 1381 gctgcaactgt ctcagttctg cttgaatacc tccatcgatg gggaactcac ttcttttggg
 1441 aaaattctta tgtcaagctg aaattctcta attttttctc atcacttccc caggagcagc
 1501 cagaagacag gcagtagttt taatttcagg aacagggtgat ccactctgta aaacagcagg
 1561 taaattttcac tcaaccccat gtgggaattg atctatatct ctacttccag ggaccatttg
 1621 cccttcccaa atccctccag gccagaactg actggagcag gcatggccca ccaggcttca
 1681 ggagtagggg aagcctggag cccactcca gccctgggac aacttgáaa ttccccctga
 1741 ggccagttct gtcatggatg ctgtcctgag aataacttgc tgtcccggg tgacctgctt
 1801 ccatctccca gccaccagc cctctgccc cctcacatgc ctccccatgg attggggcct
 1861 cccaggcccc ccaccttatg tcaacctgca cttcttggtc aaaaatcagg aaaagaaaag
 1921 atttgaagac cccaagtctt gtcaataact tgctgtgtgg aagcagcggg ggaagaccta
 1981 gaaccctttc cccagcactt ggttttccaa catgatattt atgagtaatt tattttgata
 2041 tgtacatctc ttattttctt acattattta tgcccccaaa ttatatttat gtatgtaagt
 2101 gaggtttggt ttgtatatta aaatggagtt tgtttgtaaa aaaaaaaaaa aaaaaaa

FGF19胺基酸序列(NP_005108)(SEQ ID NO: 31)

1 MRSGCVVHVH WILAGLWLAV AGRPLAFSDA GPHVHYGWD PIRLRHLYTS GPHGLSSCFL
 61 RIRADGVVDC ARGQSAHSL EIKAVALT RV AIKGVHVSRY LCMGADGKMQ GLLQYSEEDC
 121 AFEEIRPDG YNVYRSEKHR LPVSLSSAQ RQLYKNRGFL PLSHFLPMLP MVPEEPEDLR
 181 GHLESDMFSS PLETDSDPF GLVTGLEAVR SPSFEK

FGF21核酸序列(NM_019113)(SEQ ID NO: 32)

蛋白質編碼區151-780

1 CTGTCAGCTG AGGATCCAGC CGAAAGAGGA GCCAGGCACT CAGGCCACCT GAGTCTACTC
 61 ACCTGGACAA CTGGAATCTG GCACCAATTC TAAACCACTC AGCTTCTCCG AGCTCACACC
 121 CCGGAGATCA CCTGAGGACC CGAGCCATTG ATGGACTCGG ACAGAGACCG GTTCGAGCAC
 181 TCAGGACTGT GGGTTTCTGT GCTGGCTGGT CTTCTGCTGG GAGCCTGCCA GGCACACCCC
 241 ATCCCTGACT CCAGTCTCTT CTGCAATTC GGGGGCCAAG TCCGGCAGCG GTACCTCTAC
 301 ACAGATGATG CCCAGCAGAC AGAAGCCAC CTGGAGATCA GGGAGGATGG GACGGTGGGG
 361 GGCGCTGCTG ACCAGAGCCC CGAAAGTCTC CTGCAGCTGA AAGCCTTGAA GCCGGGAGTT
 421 ATTCAAATCT TGGGAGTCAA GACATCCAGG TTCTGTGCC AGCGGCCAGA TGGGGCCCTG
 481 TATGGATCGC TCCACTTTGA CCTGAGGCC TGCAGCTTCC GGGAGCTGCT TCTTGAGGAC
 541 GGATACAATG TTTACCAAGT CGAAGCCAC GGCTTCCCGC TGCACCTGCC AGGGAACAAG
 601 TCCCCACACC GGGACCCTGC ACCCGGAGGA CCAGCTCGCT TCCTGCCACT ACCAGGCCCTG
 661 CCCCCGCAC TCCCGGAGCC ACCCGGAATC CTGGCCCCC AGCCCCCAG TGTGGGCTCC
 721 TCGGACCCTC TGAGCATGGT GGGACCTTCC CAGGGCCGAA GCCCAGCTA CGCTTCTGA
 781 AGCCAGAGGC TGTCTACTAT GACATCTCCT CTTTATTAT TAGGTTATT ATCTTATTAT
 841 TTTTATTAT TTTCTTACTT GAGATAATA AGAGTTCCAG AGGAGAAAA AAAAAAAAAA
 901 AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA

FGF21胺基酸序列(NP_061986)(SEQ ID NO: 33)

1 MDSDETFEH SGLWVSVLG LLLGACQAH IPDSSPLLQF GGQVRQRYLY TDDAQQTEAH
 61 LEIREDGTVG GAADQSPESL LQLKALKPGV IQILGVKTSR FLCQRPDGL YGSLHFDPEA
 121 CSFRELLLED GYNVYQSEAH GLPLHLPNGK SPHRDPAPRG PARFLPLPGL PPALPEPPGI
 181 LAPQPPDVGS SDPLSMVGPS QGRSPSYAS

FGF23核酸序列(NM_020638)(SEQ ID NO: 34)

蛋白質編碼區147-902

1 cggcaaaaag gaggggaatcc agtctaggat cctcacacca gctacttgca agggagaagg
 61 aaaaggccag taaggcctgg gccaggagag tcccagacagg agtgctcagg ttcaatctca
 121 gcaccagcca ctcagagcag ggcacgatgt tgggggccc cctcaggctc tgggtctgtg
 181 ccttgtgcag cgtctgcagc atgagcgtcc tcagagccta tcccaatgcc tccccactgc
 241 tcggctccag ctgggggtggc ctgatccacc tgtacacagc cacagccagg aacagctacc
 301 acctgcagat ccacaagaat ggccatgtgg atggcgcacc ccatcagacc atctacagtg
 361 ccctgatgat cagatcagag gatgctggct ttgtggtgat tacagggtgt atgagcagaa

421 gatacctctg catggatttc agaggcaaca tttttggatc acactatttc gacccggaga
481 actgcagggt ccaacaccag acgctggaaa acgggtacga cgtctaccac tctcctcagt
541 atcacttcct ggtcagtcct ggccgggcca agagagcctt cctgccaggc atgaaccac
601 ccccgacttc ccagttcctg tcccggagga acgagatccc cctaattcac ttcaacaccc
661 ccataccacg gcggcacacc cggagcgccg aggacgactc ggagcgggac cccctgaacg
721 tgctgaagcc cggggcccgg atgaccccg cccggcctc ctgttcacag gagtcccga
781 gcgccgagga caacagccc atggcagtg acccattagg ggtggtcagg ggcggtcgag
841 tgaacacgca cgctggggga acgggcccgg aaggctgccg ccccttcgcc aagttcatct
901 agggctcgtg gaagggcacc ctctttaacc catccctcag caaacgcagc tcttcccaag
961 gaccaggtcc cttgacgttc cgaggatggg aaagggtgaca ggggcatgta tggaaatttg
1021 tgcttctctg ggggtcccttc cacaggaggt cctgtgagaa ccaacctttg agggcccaagt
1081 catgggggtt caccgccttc ctcaactccat atagaacacc tttcccaata ggaaacccca
1141 acaggtaaac tagaaatttc cccttcattg aggtagagag aaggggtctc tcccaacata
1201 tttctcttcc ttgtgcctct cctctttatc acttttaagc ataaaaaaaa aaaaaaaaaa
1261 aaaaaaaaaa aaaagcagtg ggttctctgag ctcaagactt tgaagggtgta gggaagagga
1321 aatcggagat cccagaagct tctccactgc cctatgcatt tatgttagat gccccgatcc
1381 cactggcatt tgagtgtgca aaccttgaca ttaacagctg aatggggcaa gttgatgaaa
1441 acactacttt caagccttcg ttcttccttg agcatctctg gggaagagct gtcaaaagac
1501 tgggtgtagg ctggtgaaaa cttgacagct agacttgatg cttgctgaaa tgaggcagga
1561 atcataatag aaaactcagc ctcccctacg ggtgagcacc tctgtctcgc ctgtctccct
1621 ctgtgcagcc acagccagag ggcccagaat ggccccactc tgttcccaag cagttcatga
1681 tacagcctca ccttttggcc ccactctctg tttttgaaaa tttggtctaa ggaataaata
1741 gcttttacac tggctcacga aaatctgccc tgctagaatt tgcttttcaa aatggaaata
1801 aattccaaact ctccaaagag gcatttaatt aaggctctac ttccaggttg agtaggaatc
1861 cattctgaac aaactacaaa aatgtgactg ggaagggggc tttgagagac tgggactgct
1921 ctggggttagg ttttctgttg actgaaaaat cgtgtccttt tctctaaatg aagtggcatc
1981 aaggactcag ggggaaagaa atcaggggac atgttataga agttatgaaa agacaaccac
2041 atgggtcaggc tcttgtctgt ggtctctagg gctctgcagc agcagtggtc cttcgattag
2101 ttaaaactct cctaggctga cacatctggg tctcaatccc cttggaaatt cttggtgcat
2161 taaatgaagc cttaccccat tactgcggtt ctctctgtaa gggggtcca ttttctccc
2221 tctctttaa taccaccta aaggacagta tattaacaag caaagtcgat tcaacaacag
2281 ctcttcccca gtcacttttt tttttctcac tgccatcaca tactaacctt atactttgat
2341 ctattctttt tggttatgag agaaatggtt ggcaactgtt tttacctgat ggttttaagc
2401 tgaacttgaa ggactgggtc ctattctgaa acagtaaaac tatgtataat agtatatagc
2461 catgcatggc aaatatttta atatttctgt tttcatttcc tgttggaat attatcctgc
2521 ataatagcta ttggaggctc ctcaagtcaa gatcccaaaa ggattttggt ggaaaactag
2581 ttgtaatctc acaaaactca cactaccatc aggggttttc tttatggcaa agccaaaata
2641 gctcctacaa tttcttatat cctcgtcat gtggcagtat ttatttattt atttggaagt
2701 ttgcctatcc ttctatatat atagatatat ataaaaatgt aaccctttt tcctttctc
2761 tgtttaaaat aaaaaataaa tttatctcag ctctgttag cttatcctct ttgtagtact
2821 acttaaaagc atgtcggaat ataagaataa aaaggattat gggaggggaa cattagggaa
2881 atccagagaa ggcaaaattg aaaaaaagat tttagaattt taaaattttc aaagatttct
2941 tccattcata aggagactca atgattttta ttgatctaga cagaattatt taagttttat
3001 caatattgga tttctggt

FGF23氨基酸序列(NP_065689)(SEQ ID NO: 35)

1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNs YHLQIHKNGH
61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQT
121 ENGVDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTRS
181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
241 PEGCRPFAKF I

FGF23(R179Q)氨基酸序列(SEQ ID NO: 36)

1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNs YHLQIHKNGH
61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQT
121 ENGVDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTRS
181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
241 PEGCRPFAKF I

人類β-Klotho域1(b-KL-D1)胺基酸序列(SEQ ID NO: 37)

```

77          ydt fpknffwgig tgalqvegs w kkdgkgsiw dhfihthlkn
121 vsstngssds yiflekdlsa ldfigvsfyq fsiswprlfp dgi tvanak glqyystlld
181 alvlrniepi vtlyhwdlpl alqekyggwk ndtiidifnd yatycfmgf drvkywiti h
241 npylvawhgy gtgmhapsek gnlaavytv g hnlikahskv whnynthfrp hqkgwlsitl
301 gshwiepnrs entmdifkcg qsmvsvlgwf anpihgddy pegmrkklfs vlpifseaek
361 hemrgtadff afsfgpnnfk plntmakmgq nvslnlreal nwikleynnp riliaengwf
421 tdsrvktedt taiymknfl sqvlqairld eirvfgytaw slldgfewqd aytirrgl fy
481 vdfnskqker kpkssahyyk qiirengf

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人類β-Klotho域2(b-KL-D2)胺基酸序列(SEQ ID NO: 38)

```

571          trpaqctdfv nikkqlemla
rmkvthyrf a
601 ldwasvlptg nlsavnrqal ryyrcvvseg lklgisamvt lyyphahlg
lpepllhada g
661 wlnpstaeaf qayaglcfe lgdlvklwit inepnrlsdi ynrs gndtyg
aahnllvaha
721 lawrlydrqf rpsqrgavsl slhadwaepa npyadshwra aerflqfeia
wfaeplfktg
781 dypaamreyi askhrrglss salprlteae rrllkgtvdf calnhfttrf
vmheqlagsr
841 ydsdrdiqfl qditrlsspt rlavipwgv r kllrwrrny gdm diyitas
giddqaledd
901 rlrkyylgky lqevlkayli dkvrkgyya fkl aeekskp rfgfftsdfk
akssiqfynk
961 vissrgf

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β-Klotho細胞外域(無信號肽)胺基酸序列(SEQ ID NO: 39)

```

52          gfsgdgrai
61 wsknpnftpv nesqlflydt fpknffwgig tgalqvegs w kkdgkgsiw dhfihthlkn
121 vsstngssds yiflekdlsa ldfigvsfyq fsiswprlfp dgi tvanak glqyystlld
181 alvlrniepi vtlyhwdlpl alqekyggwk ndtiidifnd yatycfmgf drvkywiti h
241 npylvawhgy gtgmhapsek gnlaavytv g hnlikahskv whnynthfrp hqkgwlsitl
301 gshwiepnrs entmdifkcg qsmvsvlgwf anpihgddy pegmrkklfs vlpifseaek
361 hemrgtadff afsfgpnnfk plntmakmgq nvslnlreal nwikleynnp riliaengwf
421 tdsrvktedt taiymknfl sqvlqairld eirvfgytaw slldgfewqd aytirrgl fy
481 vdfnskqker kpkssahyyk qiirengfsl kestpdvqgg fpcdfswgt esvlkpesva
541 sspqfsdphl yvwnatgnrl lhrvegvrk trpaqctdfv nikkqlemla rmkvthyrf a
601 ldwasvlptg nlsavnrqal ryyrcvvseg lklgisamvt lyyphahlg lpepllhada g
661 wlnpstaeaf qayaglcfe lgdlvklwit inepnrlsdi ynrs gndtyg aahnllvaha
721 lawrlydrqf rpsqrgavsl slhadwaepa npyadshwra aerflqfeia wfaeplfktg
781 dypaamreyi askhrrglss salprlteae rrllkgtvdf calnhfttrf vmheqlagsr
841 ydsdrdiqfl qditrlsspt rlavipwgv r kllrwrrny gdm diyitas giddqaledd
901 rlrkyylgky lqevlkayli dkvrkgyya fkl aeekskp rfgfftsdfk akssiqfynk
961 vissrgfpfe nsssrscqtq entectvcf lvqkkpl

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無信號肽之sKlotho-FGF23胺基酸序列(無信號肽)(SEQ ID NO: 40)

```

          EPGDGAQ TWARFSRPPA
51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYYRRLRLERL RELGVQPVVT LYHWDLPQRL

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201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
351 DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGIFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTSLQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLOEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIDS
951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLIY TATARNHYHL QIHKNHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTP
1151 PRRHTRSAED DSERDPLNVL KPRARMTAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*

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無信號肽sKlotho-FGF23(R179Q)(無信號肽)胺基酸序列(SEQ ID NO:

41)

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EPGDGAQ TWARFSRPPA
51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYRRLLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
351 DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGIFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTSLQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLOEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIDS
951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLIY TATARNHYHL QIHKNHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTP
1151 PRRHTQSAED DSERDPLNVL KPRARMTAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*

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無信號肽之FGF23(SEQ ID NO: 42)

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YPNASP LLGSSWGGLI HLYTATARN YHLQIHKNH
61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTL
121 ENGVDYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRHTRS
181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
241 PEGCRPFAKFI

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無信號肽之FGF23(R179Q)(SEQ ID NO: 43)

YPNASP LLGSSWGGLI HLYTATARNs YHLQIHKNHG
 61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQT
 121 ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS
 181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
 241 PEGCRPFAKF I

具有Klotho信號肽之sKlotho(SEQ ID NO: 44)

1 MPASAPRRRP RPPPPSLSL LVLGLGGR LRAEPGDGAQ TWARFSRPPA
 51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHKGASIW DTFTTHPLAP
 101 PGDSRNASLP LGAPSLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRRLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTSEKKFI KGTAFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFWEHGRY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTSLQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKRKS YCVDFAAIQP QIALQLQEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YALAFAYEA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SL

具有IgG信號肽之sKlotho(SEQ ID NO: 45)

1 MSVLTVLAL LLLWLTGLGG RRLRAEPGDG AQTWARFSRP PAPEAAGLFQ
 51 GTFPDGLFWA VGSAAYQTEG GWQHGKGAS IWDTFTTHPL APPGDSRNAS
 101 LPLGAPSPLQ PATGDVADS YNNVFRDTEA LRELGVTHYR FSISWARVLP
 151 NGSAGVPNRE GLRYRRLLE RLRELGVQPV VTLYHWDLPQ RLQDAYGGWA
 201 NRALADHFRD YAELECFRHFQ GQVKYWITID NPVVAWHGY ATGRLAPGIR
 251 GSPRLGYLVA HNLLAHAKV WHLYNTSFRP TQGGQVSIAL SSHWINPRRM
 301 TDHSIKECQK SLDFVLGWFA KPVFIDGDYP ESMKNNLSSI LPDFTESEKK
 351 FIKGTADFFA LCFGPTLSFQ LLDPHMKFRQ LESPNLRQLL SWIDLEFNHP
 401 QIFIVENGWF VSGTTKRDDA KYMYLKKFI METLKAIKLD GVDVIGYTAW
 451 SLMDGFWEHR GYSIRRGLFY VDFLSQDKML LPKSSALFYQ KLIKNGFP
 501 LPENQPLEGT FPCDFAWGVV DNYIQVDTTL SQFTDLNVYL WDVHHSKRLI
 551 KVDGVVTKKR KSYCVDFAAI QPQIALQEM HVTHFRFSLD WALILPLGNQ
 601 SQVNHTILQY YRCMASELVR VNITPVVALW QPMAPNQGLP RLLARQGAWE
 651 NPYTALAFAYE YARLCFQELG HHVKLWITMN EPYTRNMTYS AGHNLLKAHA
 701 LAWHVYNEKF RHAQNGKISI ALQADWIEPA CPFSQKDKEV AERVLEFDIG
 751 WLAEPFGSG DYPWVMDWL NQRNNFLLPY FTEDEKKLIQ GTFDFLALSH
 801 YTTILVDSEK EDPIKYNDYL EVQEMTDITW LNSPSQVAVV PWGLRKVLNW
 851 LKPKYGDLPY YIISNGIDDG LHAEDDQLRV YMQNYINEA LKAHILDGIN
 901 LCGYFAYSFN DRTAPRFGLY RYAADQFEPK ASMKHYRKII DSNFGFPET
 951 LERFCPEEFT VTECSFFHT RKSL*

sKlotho-FGF23-FcLALA v1(SEQ ID NO: 46)

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1  ATGCCCCGCA GCGCCCCGCC GCGCCGCCCG CGGCCGCCGC CGCCGTGCTG
   GTCGCTGCTG
61  CTGGTGCCTG TGGGCCTGGG CGGCCGCCGC CTGCGTGCGG AGCCGGGCGA
   CGGCGCGCAG
121 ACCTGGGCCC GTTCTCTCGG GCCTCCTGCC CCCGAGGCCG CGGGCCTCTT
   CCAGGGCACC
181 TTCCCCGACG GCTTCCTCTG GGCCGTGGGC AGCGCCGCCT ACCAGACCGA
   GGGCGGCTGG
241 CAGCAGCACG GCAAGGGTGC GTCCATCTGG GATACGTTCA CCCACCACCC
   CCTGGCACCC
301 CCGGGAGACT CCCGGAACGC CAGTCTGCCG TTGGGCGCCC CGTCGCCGCT
   GCAGCCCGCC
361 ACCGGGGACG TAGCCAGCGA CAGCTACAAC AACGTCTTCC GCGACACGGA
   GGCCTGCGC
421 GAGCTCGGGG TCACTACTA CCGCTTCTCC ATCTCGTGGG CGCGAGTGCT
   CCCCAATGGC
481 AGCGCGGGCG TCCCCAACCG CGAGGGGCTG CGCTACTACC GGCGCCTGCT
   GGAGCGGCTG
541 CGGGAGCTGG GCGTGCAGCC CGTGGTCACC CTGTACCACT GGGACCTGCC
   CCAGCGCCTG
601 CAGGACGCCT ACGGCGGCTG GGCCAACCGC GCCCTGGCCG ACCACTTCAG
   GGATTACGCG
661 GAGCTCTGCT TCCGCCACTT CGGCGGTCAG GTCAAGTACT GGATCACCAT
   CGACAACCCC
721 TACGTGGTGG CCTGGCACGG CTACGCCACC GGGCGCCTGG CCCCCGGCAT
   CCGGGGCGAG
781 CCGCGGCTCG GGTACCTGGT GGCGCACAAAC CTCCTCCTGG CTCATGCCAA
   AGTCTGGCAT
841 CTCTACAATA CTTCTTTCCG TCCCACTCAG GGAGGTCAGG TGTCCATTGC
   CCTAAGCTCT
901 CACTGGATCA ATCCTCGAAG AATGACCGAC CACAGCATCA AAGAATGTCA
   AAAATCTCTG
961 GACTTTGTAC TAGGT'TGGT' TGCCAAACCC GTATTTAT'TG ATGGTGACTA
   TCCCGAGAGC
1021 ATGAAGAATA ACCTTTCATC TATTCTGCCT GATTTTACTG AATCTGAGAA
   AAAGTTCATC
1081 AAAGGAAC TGACTTTTTT TGCTCTTTGC TTTGGACCCA CCTTGAGTTT
   TCAACTTTTG
1141 GACCCTCACA TGAAGTTCCG CCAATTGGAA TCTCCCAACC TGAGGCAACT
   GCTTTCCTGG
1201 ATTGACCTTG AATTTAACCA TCCTCAAATA TTTATTGTGG AAAATGGCTG
   GTTTGTCTCA
1261 GGGACCACCA AGAGAGATGA TGCCAAATAT ATGTATTACC TCAAAAAGTT
   CATCATGGAA
1321 ACCTTAAAAG CCATCAAGCT GGATGGGGTG GATGTCATCG GGTATACCGC
   ATGGTCCCTC
1381 ATGGATGGTT TCGAGTGGCA CAGAGGTTAC AGCATCAGGC GTGGACTCTT
   CTATGTTGAC
1441 TTTCTAAGCC AGGACAAGAT GTTGTTGCCA AAGTCTTCAG CCTTGTTCTA
   CCAAAAGCTG
1501 ATAGAGAAAA ATGGCTTCCC TCCTTTACCT GAAAATCAGC CCCTAGAAGG
   GACATTTCCC
1561 TGTGACTTTG CTTGGGGAGT TGTGACAAC TACATTCAAG TAGATACCAC
   TCTGTCTCAG
1621 TTTACCGACC TGAATGTTTA CCTGTGGGAT GTCCACCACA GTAAAAGGCT
   TATTAAAGTG

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1681 GATGGGGTTG TGACCAAGAA GAGGAAATCC TACTGTGTTG ACTTTGCTGC
 CATCCAGCCC
 1741 CAGATCGCTT TACTCCAGGA AATGCACGTT ACACATTTTC GCTTCTCCCT
 GGACTGGGCC
 1801 CTGATTCTCC CTCTGGGTAA CCAGTCCCAG GTGAACCACA CCATCCTGCA
 GTACTATCGC
 1861 TGCATGGCCA GCGAGCTTGT CCGTGTCAAC ATCACCCCAG TGGTGGCCCT
 GTGGCAGCCT
 1921 ATGGCCCCGA ACCAAGGACT GCCGCGCCTC CTGGCCAGGC AGGGCGCCTG
 GGAGAACCCC
 1981 TACACTGCCC TGGCCTTTGC AGAGTATGCC CGACTGTGCT TTCAAGAGCT
 CGGCCATCAC
 2041 GTCAAGCTTT GGATAACGAT GAATGAGCCG TATACAAGGA ATATGACATA
 CAGTGCTGGC
 2101 CACAACCTTC TGAAGGCCCA TGCCCTGGCT TGGCATGTGT ACAATGAAAA
 GTTTAGGCAT
 2161 GCTCAGAATG GGAAAATATC CATAGCCTTG CAGGCTGATT GGATAGAACC
 TGCCTGCCCT
 2221 TTCTCCCAA AGGACAAAGA GGTGGCCGAG AGAGTTTTGG AATTTGACAT
 TGGCTGGCTG
 2281 GCTGAGCCCA TTTTCGGCTC TGGAGATTAT CCATGGGTGA TGAGGGACTG
 GCTGAACCAA
 2341 AGAAACAATT TTCTTCTTCC TTATTTCACT GAAGATGAAA AAAAGCTAAT
 CCAGGGTACC
 2401 TTTGACTTTT TGGCTTTAAG CCATTATACC ACCATCCTTG TAGACTCAGA
 AAAAGAAGAT
 2461 CCAATAAAAT ACAATGATTA CCTAGAAGTG CAAGAAATGA CCGACATCAC
 GTGGCTCAAC
 2521 TCCCCCAGTC AGGTGGCGGT AGTGCCCTGG GGGTTGCGCA AAGTGCTGAA
 CTGGCTGAAG
 2581 TTCAAGTACG GAGACCTCCC CATGTACATA ATATCCAACG GAATCGATGA
 CGGGCTGCAT
 2641 GCTGAGGACG ACCAGCTGAG GGTGTATTAT ATGCAGAATT ACATAAACGA
 AGCTCTCAAA
 2701 GCCACATAC TGGATGGTAT CAATCTTTGC GGATACTTTG CTTATTTCGT
 TAACGACCGC
 2761 ACAGCTCCGA GGTTTGGCCT CTATCGTTAT GCTGCAGATC AGTTTGAGCC
 CAAGGCATCC
 2821 ATGAAACATT ACAGGAAAAT TATTGACAGC AATGGTTTCC CGGGCCCAGA
 AACTCTGGAA
 2881 AGATTTTGTC CAGAAGAATT CACCGTGTGT ACTGAGTGCA GTTTTTTTCA
 CACCCGAAAG
 2941 TCTTTAGGAT CCGGAGGTGG AGGTTCAAGG GGTGGAGGTT CAGGAGGTGG
 AGGTTCACTT
 3001 AAGTATCCCA ATGCCCTCCC ACTGCTCGGC TCCAGCTGGG GTGGCCTGAT
 CCACCTGTAC
 3061 ACAGCCACAG CCAGGAACAG CTACCACCTG CAGATCCACA AGAATGGCCA
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 3181 GTGATTACAG GTGTGATGAG CAGAAGATAC CTCTGCATGG ATTTTCAGAG
 CAACATTTTT
 3241 GGATCACACT ATTTTCGACCC GGAGAACTGC AGGTTCCAAC ACCAGACGCT
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 3301 TACGACGTCT ACCACTCTCC TCAGTATCAC TTCCTGGTCA GTCTGGGCCC
 GGCGAAGAGA
 3361 GCCTTCCTGC CAGGCATGAA CCCACCCCG TACTCCAGT TCCTGTCCCC
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 3421 ATCCCCCTAA TTCACTTCAA CACCCCATTA CCACGGCGGC ACACCCAGAG
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 3481 GACTCGGAGC GGGACCCCCCT GAACGTGCTG AAGCCCCGGG CCCGGATGAC
 CCCGGCCCCG

3541 GCCTCCTGTT CACAGGAGCT CCCGAGCGCC GAGGACAACA GCCCGATGGC
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 3601 TTAGGGGTGG TCAGGGGCGG TCGAGTGAAC ACGCACGCTG GGGGAACGGG
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 3661 TGCCGCCCCT TCGCCAAGTT CATCGGAGGT GGAGGTTCAA AAACCCACAC
 GTGTCCTCCT
 3721 TGTCTTGCCC CAGAAGCAGC AGGTGGTCCA TCAGTTTTTC TTTTCCCTCC
 CAAACCCAAG
 3781 GATACGCTGA TGATCTCTCG CACGCCTGAG GTGACATGCG TCGTAGTAGA
 CGTGAGCCAC
 3841 GAAGATCCCG AGGTGAAGTT CAATTGGTAT GTGGACGGAG TAGAAGTGCA
 TAACGCGAAA
 3901 ACTAAGCCGC GCGAGGAACA ATATAACAGT ACTTACAGGG TGGTATCCGT
 GCTCACAGTC
 3961 CTGCACCAGG ACTGGCTGAA CGGTAAGGAA TACAAGTGCA AAGTAAGCAA
 CAAGGCACTT
 4021 CCCGCGCCTA TTGAGAAAAC AATCTCCAAG GCGAAGGGAC AACCAAGAGA
 ACCTCAGGTT
 4081 TACACTCTCC CGCCTTCCAG GGAAGAGATG ACCAAAAATC AAGTTTCCCT
 GACTTGCCCTC
 4141 GTCAAAGGAT TCTACCCTTC CGACATTGCT GTTGAATGGG AAAGCAATGG
 ACAACCAGAG
 4201 AACAACTACA AGACAACACC CCCGGTGCTG GATAGTGACG GATCTTTCTT
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 4261 AAGCTGACCG TGGATAAGTC CAGGTGGCAG CAGGGAAACG TGTTTTCTCTG
 CTCTGTCATG
 4321 CATGAAGCGC TGCATAATCA CTATACCCAG AAGTCTCTGA GCTTGAGCCC
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sKlotho-FGF23-FcLALA v1(SEQ ID NO: 47)

1 MPASAPRRRP RPPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
 51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
 101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
 151 ISWARVLPNG SAGVPNREGL RYYRLLERL RELGVQPVVT LYHWDLPQRL
 201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
 251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
 301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
 351 DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
 401 IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
 451 DVIGYTAWSL MDGFEWHRGY SIRRGFLYVD FLSQDKMLLP KSSALFYQKL
 501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTLSQ FTDLNVYLWD
 551 VHHSKRLIKV DGVVTKRKRS YCVDFAAIQP QIALLOEMHV THFRFSLDWA
 601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
 651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
 701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
 751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
 801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
 851 GLRKVLNWLK FKYGDLPYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
 901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
 951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
 1001 KYPNASPLLG SSWGGLIHLY TATARNHYHL QIHKNHVDG APHQTIYSAL
 1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
 1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPFP YSQFLSRNE IPLIHFNTPPI
 1151 PRRHTQSAED DSERDPLNVL KPRARMTAP ASCSQELPSA EDNSPMASDP
 1201 LGVVRGGRVN THAGGTGPEG CRPFAKFIGG GSKTHTCPP CPAPEAAGGP
 1251 SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK
 1301 TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK
 1351 AKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE
 1401 NNYKTTTPVL DSDGSFFLYS KLTVDKSRWQ QGNVFCSSVM HEALHNHYTQ

1451 KSLSLSPGK*

sKlotho-FGF23-FcLALA v2(SEQ ID NO: 48)

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1  ATGCCCCGCCA GCGCCCCGCC GCGCCGCCCG CGGCCGCCGC CGCCGTCGCT
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61  CTGGTGCTGC TGGGCCTGGG CGGCCGCCGC CTGCGTGCGG AGCCGGGCGA
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121 ACCTGGGCCC GTTTCCTCGG GCCTCCTGCC CCCGAGGCCG CGGGCCTCTT
   CCAGGGCACC
181 TTCCCCGACG GCTTCCTCTG GGCCGTGGGC AGCGCCGCCT ACCAGACCGA
   GGGCGGCTGG
241 CAGCAGCACG GCAAGGGTGC GTCCATCTGG GATACGTTCA CCCACCACCC
   CCTGGCACCC
301 CCGGGAGACT CCCGGAACGC CAGTCTGCCG TTGGGCGCCC CGTCGCCGCT
   GCAGCCCCGC
361 ACCGGGGACG TAGCCAGCGA CAGCTACAAC AACGTCTTCC GCGACACGGA
   GGCGCTGCGC
421 GAGCTCGGGG TCACTACTA CCGCTTCTCC ATCTCGTGGG CGCGAGTGCT
   CCCCAATGGC
481 AGCGCGGGCG TCCCCAACCG CGAGGGGCTG CGCTACTACC GGCGCCTGCT
   GGAGCGGCTG
541 CGGGAGCTGG GCGTGCAGCC CGTGGTCACC CTGTACCACT GGGACCTGCC
   CCAGCGCCTG
601 CAGGACGCCT ACGGCGGCTG GGCCAACCGC GCCCTGGCCG ACCACTTCAG
   GGATTACGCG
661 GAGCTCTGCT TCCGCCACTT CGGCGGTCAG GTCAGTACT GGATCACCAT
   CGACAACCCC
721 TACGTGGTGG CCTGGCACGG CTACGCCACC GGGCGCCTGG CCCCCGGCAT
   CCGGGGCAGC
781 CCGCGGCTCG GGTACCTGGT GGCGCACAA C'TCCTCCTGG CTCATGCCAA
   AGTCTGGCAT
841 CTCTACAATA CTTCTTTCCG TCCCCTCAG GGAGGTCAGG TGTCCATTGC
   CCTAAGCTCT
901 CACTGGATCA ATCCTCGAAG AATGACCGAC CACAGCATCA AAGAATGTCA
   AAAATCTCTG
961 GACTTTGTAC TAGGTTGGTT TGCCAAACCC GTATTTATTG ATGGTGACTA
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1021 ATGAAGAATA ACC'TTTCATC TATTCTGCCCT GATTTTACTG AATCTGAGAA
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1081 AAAGGAACTG CTGACTTTTT TGCTCTTTGC TTTGGACCCA CCTTGAGTTT
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1141 GACCCTCACA TGAAGTTCGG CCAATGGAA TCTCCCAACC TGAGGCAACT
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1201 ATTGACCTTG AATTTAACCA TCCTCAAATA TTTATTGTGG AAAATGGCTG
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   CATCATGGAA
1321 ACC'TTAAAG CCATCAAGCT GGATGGGGTG GATGTCATCG GGTATACCGC
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1381 ATGGATGGTT TCGAGTGGCA CAGAGGTTAC AGCATCAGGC GTGGACTCTT
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1441 TTTCTAAGCC AGGACAAGAT GTTGTGTTGCA AAGTCTTCAG CCTTGT'TCTA
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1501 ATAGAGAAAA ATGGCTTCCC TCCTTTACCT GAAAATCAGC CCCTAGAAGG
   GACATTTCCC
1561 TGTGACTTTG CTTGGGGAGT TGTGACAAC TACATTCAAG TAGATACCAC
   TCTGTCTCAG
1621 TTTACCAGAC TGAATGTTTA CCTGTGGGAT GTCCACCACA GTAAAAGGCT
   TATTAAAGTG

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1681 GATGGGGTTG TGACCAAGAA GAGGAAATCC TACTGTGTTG ACTTTGCTGC
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 1741 CAGATCGCTT TACTCCAGGA AATGCACGTT ACACATTTTC GCTTCTCCCT
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 1801 CTGATTCTCC CTC TGGGTAA CCAGTCCCAG GTGAACCACA CCATCCTGCA
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 1861 TGCATGGCCA GCGAGCTTGT CCGTGTCAAC ATCACCCCAG TGGTGGCCCT
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 1921 ATGGCCCCGA ACCAAGGACT GCCGCGCCTC CTGGCCAGGC AGGGCGCCTG
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 1981 TACACTGCCC TGGCCTTTGC AGAGTATGCC CGACTGTGCT TTCAAGAGCT
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 2041 GTCAAGCTTT GGATAACGAT GAATGAGCCG TATACAAGGA ATATGACATA
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 2161 GCTCAGAATG GGAAAATATC CATAGCCTTG CAGGCTGATT GGATAGAACC
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 2221 TTCTCCCAAA AGGACAAAGA GGTGGCCGAG AGAGTTTTGG AATTTGACAT
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 2281 GCTGAGCCCA TTTTCGGCTC TGGAGATTAT CCATGGGTGA TGAGGGACTG
 GCTGAACCAA
 2341 AGAAACAATT TTC TTCTTCC TTATTTCACT GAAGATGAAA AAAAGCTAAT
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 2401 TTTGACTTTT TGGCTTTAAG CCATTATACC ACCATCCTTG TAGACTCAGA
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 2521 TCCCCCAGTC AGGTGGCGGT AGTGCCCTGG GGGTTGCGCA AAGTGCTGAA
 CTGGCTGAAG
 2581 TTCAAGTACG GAGACCTCCC CATGTACATA ATATCCAACG GAATCGATGA
 CGGGCTGCAT
 2641 GCTGAGGACG ACCAGCTGAG GGTGTATTAT ATGCAGAATT ACATAAACGA
 AGCTCTCAAA
 2701 GCCCACATAC TGGATGGTAT CAATCTTTGC GGATACTTTG CTTATTCTGT
 TAACGACCGC
 2761 ACAGCTCCGA GGTTTGGCCT CTATCGTTAT GCTGCAGATC AGTTTGAGCC
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 2881 AGATTTTGT CAGAAGAATT CACCGTGTGT ACTGAGTGCA GTTTTTTTCA
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 3061 ACAGCCACAG CCAGGAACAG CTACCACCTG CAGATCCACA AGAATGGCCA
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 3181 GTGATTACAG GTGTGATGAG CAGAAGATAC CTC TGCATGG ATTTTCAGAGG
 CAACATTTTT
 3241 GGATCACACT ATTTTCGACCC GGAGAACTGC AGGTTCCAAC ACCAGACGCT
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 3361 GCCTTCCTGC CAGGCATGAA CCCACCCCG TACTCCCAGT TCCTGTCCCG
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 3421 ATCCCCCTAA TTCATTCAA CACCCCATTA CCACGGCGGC ACACCCAGAG
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 3481 GACTCGGAGC GGGACCCCT GAACGTGCTG AAGCCCCGGG CCCGGATGAC
 CCCGGCCCCG

3541 GCCTCCTGTT CACAGGAGCT CCCGAGCGCC GAGGACAACA GCCCGATGGC
CAGTGACCCA
3601 TTAGGGGTGG TCAGGGGCGG TCGAGTGAAC ACGCACGCTG GGGGAACGGG
CCCGGAAGGC
3661 TGCCGCCCTT TCGCCAAGTT CATCGGAGGT GGAGGTTTCTAG CCCAGAAGC
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3721 CCATCAGTTT TTCTTTTCCC TCCCAAACCC AAGGATACGC TGATGATCTC
TCGCACGCCCT
3781 GAGGTGACAT GCGTCGTAGT AGACGTGAGC CACGAAGATC CCGAGGTGAA
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3841 TATGTGGACG GAGTAGAAGT GCATAACGCG AAACTAAGC CGCGCGAGGA
ACAATATAAC
3901 AGTACTTACA GGGTGGTATC CGTGCTCACA GTCCTGCACC AGGACTGGCT
GAACGGTAAG
3961 GAATACAAGT GCAAAGTAAG CAACAAGGCA CTTCCCGCGC CTATTGAGAA
ACAATCTCC
4021 AAGGCGAAGG GACAACCAAG AGAACCTCAG GTTTACACTC TCCCGCCTTC
CAGGGAAGAG
4081 ATGACCAAAA ATCAAGTTTC CCTGACTTGC CTCGTCAAAG GATTCTACCC
TTCCGACATT
4141 GCTGTTGAAT GGGAAAGCAA TGGACAACCA GAGAACAACCT ACAAGACAAC
ACCCCCGGTG
4201 CTGGATAGTG ACGGATCTTT CTTTCTCTAC TCAAAGCTGA CCGTGGATAA
GTCCAGGTGG
4261 CAGCAGGGAA ACGTGTTTTT CTGCTCTGTC ATGCATGAAG CGCTGCATAA
TCACTATACC
4321 CAGAAGTCTC TGAGCTTGAG CCCAGGCAAG TAA

sKlotho-FGF23-FcLALA v2(SEQ ID NO: 49)

1 MPASAPRRRP RPPPPSLSL LVLLGLGRR LRAEPGDAQ TWARFSRPPA
51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPLOPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYRRLRLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
351 DFTESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFWEHRGY SIRRGFLFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTSLQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALAQEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTALAFAYEA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIDS
951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHL TATARNSYHL QIHKNHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTP
1151 PRRHTQSAED DSERDPLNVL KPRARMTAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFIGG GGSAPAAAGG PSVFLFPPKP
1251 KDTLMIS RTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
1301 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ
1351 VYTLPPSREE MTKNQVSLT LKVGFPYPSI AVEWESNGQP ENNYKTTPPV
1401 LDSGDSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
1451 *

FGF23-FcLALA v1(SEQ ID NO: 50)

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1 ATGTTGGGGG CCCGCCTCAG GCTCTGGGTC TGTGCCTTGT GCAGCGTCTG
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61 GTCCTCAGAG CCTATCCCAA TGCCTCCCCA CTGCTCGGCT CCAGCTGGGG
  TGGCCTGATC
121 CACCTGTACA CAGCCACAGC CAGGAACAGC TACCACCTGC AGATCCACAA
  GAATGGCCAT
181 GTGGATGGCG CACCCCATCA GACCATCTAC AGTGCCCTGA TGATCAGATC
  AGAGGATGCT
241 GGCTTTGTGG TGATTACAGG TGTGATGAGC AGAAGATACC TCTGCATGGA
  TTTCAGAGGC
301 AACATTTTTG GATCACACTA TTTCGACCCG GAGAACTGCA GGTTCACAAC
  CCAGACGCTG
361 GAAAACGGGT ACGACGTCTA CCACTCTCCT CAGTATCACT TCCTGGTCAG
  TCTGGGCCGG
421 GCGAAGAGAG CCTTCCTGCC AGGCATGAAC CCACCCCCGT ACTCCCAGTT
  CCTGTCCCGG
481 AGGAACGAGA TCCCCCTAAT TCACTTCAAC ACCCCCATAC CACGGCGGCA
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541 GCCGAGGACG ACTCGGAGCG GGACCCCCTG AACGTGCTGA AGCCCCGGGC
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601 CCGGCCCCCG CCTCCTGTTC ACAGGAGCTC CCGAGCGCCG AGGACAACAG
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661 AGTGACCCAT TAGGGGTGGT CAGGGGCGGT CGAGTGAACA CGCACGCTGG
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721 CCGGAAGGCT GCCGCCCTT CGCCAAGTTC ATCGGAGGTG GAGGTTCAAA
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781 TGTCTCTCTT GTCCTGCCCC AGAAGCAGCA GGTGGTCCAT CAGTTTTTCT
  TTTCCCTCCC
841 AAACCAAGG ATACGCTGAT GATCTCTCGC ACGCTGAGG TGACATGCGT
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901 GTGAGCCACG AAGATCCCGA GGTGAAGTTC AATTGGTATG TGGACGGAGT
  AGAAGTGCAT
961 AACGCGAAAA CTAAGCCGCG CGAGGAACAA TATAACAGTA CTTACAGGGT
  GGTATCCGTG
1021 CTCACAGTCC TGCACCAGGA CTGGCTGAAC GGTAAGGAAT ACAAGTGCAA
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1081 AAGGCACTTC CCGCGCCTAT TGAGAAAACA ATCTCCAAGG CGAAGGGACA
  ACCAAGAGAA
1141 CCTCAGGTTT ACACTCTCCC GCCTTCCAGG GAAGAGATGA CCAAAAATCA
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1201 ACTTGCCTCG TCAAAGGATT CTACCCCTCC GACATTGCTG TTGAATGGGA
  AAGCAATGGA
1261 CAACCAGAGA ACAACTACAA GACAACACCC CCGGTGCTGG ATAGTGACGG
  ATCTTTCTTT
1321 CTCTACTCAA AGCTGACCGT GGATAAGTCC AGGTGGCAGC AGGGAAACGT
  GTTTTCCTGC
1381 TCTGTCATGC ATGAAGCGCT GCATAATCAC TATACCCAGA AGTCTCTGAG
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1441 GGCAAGTAA

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FGF23(R179Q)-FcLALAv1(SEQ ID NO: 51)

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1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNs
51 YHLQIHKNHG VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IGGGGSKTHT CPPCPAPEAA GGPSVFLFPP KPKDTLMISR TPEVTCVVVD
301 VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN
351 GKEYKCKVSN KALPAPIEKT ISKAKQPRE PQVYTLPPSR EEMTKNQVSL
401 TCLVKGFYPS DIAVEWESNG QPENNYKTP PVLDSGDSFF LYSKLTVDKS
451 RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK*

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FGF23-FcLALA v2(SEQ ID NO: 52)

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   TGGCCTGATC
121 CACCTGTACA CAGCCACAGC CAGGAACAGC TACCACCTGC AGATCCACAA
   GAATGGCCAT
181 GTGGATGGCG CACCCCATCA GACCATCTAC AGTGCCCTGA TGATCAGATC
   AGAGGATGCT
241 GGC TTTGTGG TGATTACAGG TGTGATGAGC AGAAGATACC TCTGCATGGA
   TTTCAGAGGC
301 AACATTTTTG GATCACACTA TTTCGACCCG GAGAACTGCA GGTTCACAAC
   CCAGACGCTG
361 GAAAACGGGT ACGACGTCTA CCACTCTCCT CAGTATCACT TCCTGGTCAG
   TCTGGGCCCG
421 GCGAAGAGAG CCTTCCTGCC AGGCATGAAC CCACCCCGT ACTCCCAGTT
   CCTGTCCCGG
481 AGGAACGAGA TCCCCCTAAT TCACTTCAAC ACCCCCATAC CACGGCGGCA
   CACCAGAGC
541 GCCGAGGACG ACTCGGAGCG GGACCCCTG AACGTGCTGA AGCCCCGGGC
   CCGGATGACC
601 CCGGCCCCCG CCTCCTGTTT ACAGGAGCTC CCGAGCGCCG AGGACAACAG
   CCCGATGGCC
661 AGTGACCCAT TAGGGGTGGT CAGGGGCGGT CGAGTGAACA CGCACGCTGG
   GGGAACGGGC
721 CCGGAAGGCT GCCGCCCTT CGCCAAGTTC ATCGGAGGTG GAGGTTTACG
   CCCAGAAGCA
781 GCAGGTGGTC CATCAGTTTT TCTTTTCCCT CCCAAACCCA AGGATACGCT
   GATGATCTCT
841 CGCACGCCTG AGGTGACATG CGTCGTAGTA GACGTGAGCC ACGAAGATCC
   CGAGGTGAAG
901 TTCAATTGGT ATGTGGACGG AGTAGAAGTG CATAACGCGA AACTAAGCC
   GCGCGAGGAA
961 CAATATAACA GTACTTACAG GGTGGTATCC GTGCTCACAG TCCTGCACCA
   GGAATGGCTG
1021 AACGTAAGG AATACAAGTG CAAAGTAAGC AACAAGGCAC TTCCCGCGCC
   TATTGAGAAA
1081 ACAATCTCCA AGGCGAAGGG ACAACCAAGA GAACCTCAGG TTTACTCTCT
   CCCGCCTTCC
1141 AGGGAAGAGA TGACCAAAAA TCAAGTTTCC CTGACTTGCC TCGTCAAAGG
   ATTCTACCTT
1201 TCCGACATTG CTGTTGAATG GGAAAGCAAT GGACAACCAG AGAACAATA
   CAAGACAACA
1261 CCCCCGGTGC TGGATAGTGA CGGATCTTTC TTTCTCTACT CAAAGCTGAC
   CGTGGATAAG
1321 TCCAGGTGGC AGCAGGGAAA CGTGTTTTCC TGCTCTGTCA TGCATGAAGC
   GCTGCATAAT
1381 CACTATACCC AGAAGTCTCT GAGCTTGAGC CCAGGCAAGT AA

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FGF23(R179Q)-FcLALA v2(SEQ ID NO: 53)

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1  MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARN
51  YHLQIHKNGH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IGGGSAPEA AGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK
301 FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS
351 NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP
401 SDIAVEWESN GPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS
451 CSVMHEALHN HYTQKSLSL PGK*

```

sKlotho-FGF23(R1156Q, C1183S)之胺基酸序列(SEQ ID NO: 54)

sKlotho : aa [胺基酸] 1-982 ; 連接子1 : aa 983-1001 ; FGF23 : aa 1002-1228

```

1 MPASAPRRRP RPPPPSLSL LVLGLGGR LRAEPGDAQ TWARFSRPPA
51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYRRLRLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNLSSILP
351 DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTLSQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALQEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTAFAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWMRDNLN RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIDS
951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTP
1151 PRRHTQSAED DSERDPLNVL KPRARMTAP ASQSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*

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sKlotho-FGF23(R1156Q, C1221S)之胺基酸序列(SEQ ID NO: 55)

sKlotho : 1-982 ; 連接子1 : 983-1001 ; FGF23 : 1002-1228 ;

```

1 MPASAPRRRP RPPPPSLSL LVLGLGGR LRAEPGDAQ TWARFSRPPA
51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYRRLRLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNLSSILP
351 DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTLSQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALQEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTAFAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWMRDNLN RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIDS
951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLLG SSWGGLIHLY TATARNSYHL QIHKNHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTP
1151 PRRHTQSAED DSERDPLNVL KPRARMTAP ASQSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG SRPFAKFI*

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sKlotho-FGF23(R1156Q, Q1133A)之胺基酸序列(SEQ ID NO: 56)

sKlotho : 1-982 ; 連接子 : 983-1001 ; FGF23 : 1002-1228

```

1 MPASAPRRP RPPPPSLSL LVLGLGRR LRAEPDGAQ TWARFSRPPA
51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYRRLRLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNLSSILP
351 DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRLQLLSW
401 IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFF CDFAWGVVDN YIQVDTTSLQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWVMDWLNQ RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLL GSSWGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPFP YSFLSRRNE IPLIHFNTP
1151 PRRHTQSAED DSERDPLNVL KPRARMTAP ASQSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*

```

sKlotho-FGF23(R1156Q, C1183S, C1221S)之胺基酸序列 (SEQ ID NO: 57)

sKlotho : 1-982 ; 連接子 : 983-1001 ; FGF23 : 1002-1228

```

1 MPASAPRRP RPPPPSLSL LVLGLGRR LRAEPDGAQ TWARFSRPPA
51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYRRLRLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNLSSILP
351 DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRLQLLSW
401 IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFF CDFAWGVVDN YIQVDTTSLQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWVMDWLNQ RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLL GSSWGLIHLY TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPFP YSFLSRRNE IPLIHFNTP
1151 PRRHTQSAED DSERDPLNVL KPRARMTAP ASQSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG SRPFAKFI*

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sKlotho-FGF23(R1156Q, C1183S, C1221S, Q1133A)之胺基酸序列 (SEQ ID NO: 58)

sKlotho : 1-982 ; 連接子 : 983-1001 ; FGF23 : 1002-1228

```

1 MPASAPRRP RPPPSLSLL LVLLGLGRR LRAEPGDGAQ TWARFSRPPA
51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYYRLLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNLSSILP
351 DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRLQLSW
401 IDLEFNHPQI FIVENGWFSV GTTKRDDAKY MYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTSLQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPFSGSDY PWVMDLWLNQ RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYGDLPYI ISNGIDDGLH AEDDQLRVYV MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
951 NGFPGPETLE RFCPEEFTVC TECSFFHTRK SLGSGGGSG GGGSGGGSL
1001 KYPNASPLLG SSWGGLIHL TATARNSYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSAFLSRRNE IPLIHFNTP
1151 PRRHTQSAED DSERDPLNVL KPRARMTAP ASQSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG SRPFAKFI*

```

FGF23(R179Q; C206S)-FcLALAv1之胺基酸序列(SEQ ID NO: 59)

FGF23 : 1-251 ; 連接子 : 252-256 ; FcLALA : 257-482

```

1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARN
51 YHLQIHKNHG VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IGGGGSKTHT CPPCPAPEAA GGPSVFLFPP KPKDTLMISR TPEVTCVVVD
301 VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN
351 GKEYKCKVSN KALPAPIEKT ISKAKQPRE PQVYTLPPSR EEMTKNQVSL
401 TCLVKGFYPS DIAVEWESNG QPENNYKTP PVLDSDGSFF LYSKLTVDKS
451 RWQQGNVFC SVMHEALHNH YTKSLSLSP GK*

```

FGF23(R179Q, C244S)-FcLALAv1之胺基酸序列(SEQ ID NO: 60)

FGF23 : 1-251 ; 連接子 : 252-256 ; FcLALA : 257-482

```

1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARN
51 YHLQIHKNHG VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGSRPFAKF
251 IGGGGSKTHT CPPCPAPEAA GGPSVFLFPP KPKDTLMISR TPEVTCVVVD
301 VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN
351 GKEYKCKVSN KALPAPIEKT ISKAKQPRE PQVYTLPPSR EEMTKNQVSL
401 TCLVKGFYPS DIAVEWESNG QPENNYKTP PVLDSDGSFF LYSKLTVDKS
451 RWQQGNVFC SVMHEALHNH YTKSLSLSP GK*

```

FGF23(R179Q, Q156A)-FcLALAv1之胺基酸序列(SEQ ID NO: 61)

FGF23 : 1-251 ; Linker : 252-256 ; FcLALA : 257-482

```

1  MLGARLRLWV  CALCSVCSMS  VLRAYPNASP  LLGSSWGGLI  HLYTATARNs
51 YHLQIHKNHG  VDGAPHQTIY  SALMIRSEDA  GFVVITGVMS  RRYLCMDFRG
101 NIFGSHYFDP  ENCRFQHQTl  ENGyDVYHSP  QYHFLVSLGR  AKRAFLPGMN
151 PPPYSAFLSR  RNEIPLIHFN  TPIPRRHTQS  AEDDSERDPL  NVLKPRARMT
201 PAPASSSQEL  PSAEDNSPMA  SDPLGVVRGG  RVNTHAGGTG  PEGCRPFAKF
251 IGGGGSKTHT  CPPCPAPEAA  GGPSVFLFPP  KPKDTLMISR  TPEVTCVVVD
301 VSHEDPEVKF  NWYVDGVEVH  NAKTKPREEQ  YNSTYRVVSV  LTVLHQDWLN
351 GKEYKCKVSN  KALPAPIEKT  ISKAKGQPRE  PQVYTLPPSR  EEMTKNQVSL
401 TCLVKGFYPS  DIAVEWESNG  QPENNYKTTP  PVLDSGGSFF  LYSKLTVDKS
451 RWQQGNVFSC  SVMHEALHNH  YTQKSLSLSP  GK*

```

FGF23(R179Q, C206S, C244S)-FcLALAv1之胺基酸序列(SEQ ID NO: 62)

FGF23 : 1-251 ; 連接子 : 252-256 ; FcLALA : 257-482

```

1  MLGARLRLWV  CALCSVCSMS  VLRAYPNASP  LLGSSWGGLI  HLYTATARNs
51 YHLQIHKNHG  VDGAPHQTIY  SALMIRSEDA  GFVVITGVMS  RRYLCMDFRG
101 NIFGSHYFDP  ENCRFQHQTl  ENGyDVYHSP  QYHFLVSLGR  AKRAFLPGMN
151 PPPYSAFLSR  RNEIPLIHFN  TPIPRRHTQS  AEDDSERDPL  NVLKPRARMT
201 PAPASSSQEL  PSAEDNSPMA  SDPLGVVRGG  RVNTHAGGTG  PEGSRPFAKF
251 IGGGGSKTHT  CPPCPAPEAA  GGPSVFLFPP  KPKDTLMISR  TPEVTCVVVD
301 VSHEDPEVKF  NWYVDGVEVH  NAKTKPREEQ  YNSTYRVVSV  LTVLHQDWLN
351 GKEYKCKVSN  KALPAPIEKT  ISKAKGQPRE  PQVYTLPPSR  EEMTKNQVSL
401 TCLVKGFYPS  DIAVEWESNG  QPENNYKTTP  PVLDSGGSFF  LYSKLTVDKS
451 RWQQGNVFSC  SVMHEALHNH  YTQKSLSLSP  GK*

```

FGF23(R179Q, C206S, C244S, Q156A)-FcLALAv1之胺基酸序列(SEQ ID NO: 63)

FGF23 : 1-251 ; 連接子 : 252-256 ; FcLALA : 257-482

```

1  MLGARLRLWV  CALCSVCSMS  VLRAYPNASP  LLGSSWGGLI  HLYTATARNs
51 YHLQIHKNHG  VDGAPHQTIY  SALMIRSEDA  GFVVITGVMS  RRYLCMDFRG
101 NIFGSHYFDP  ENCRFQHQTl  ENGyDVYHSP  QYHFLVSLGR  AKRAFLPGMN
151 PPPYSAFLSR  RNEIPLIHFN  TPIPRRHTQS  AEDDSERDPL  NVLKPRARMT
201 PAPASSSQEL  PSAEDNSPMA  SDPLGVVRGG  RVNTHAGGTG  PEGSRPFAKF
251 IGGGGSKTHT  CPPCPAPEAA  GGPSVFLFPP  KPKDTLMISR  TPEVTCVVVD
301 VSHEDPEVKF  NWYVDGVEVH  NAKTKPREEQ  YNSTYRVVSV  LTVLHQDWLN
351 GKEYKCKVSN  KALPAPIEKT  ISKAKGQPRE  PQVYTLPPSR  EEMTKNQVSL
401 TCLVKGFYPS  DIAVEWESNG  QPENNYKTTP  PVLDSGGSFF  LYSKLTVDKS
451 RWQQGNVFSC  SVMHEALHNH  YTQKSLSLSP  GK*

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FGF23(R179Q, C206S)-FcLALAv2之胺基酸序列(SEQ ID NO: 64)

FGF23 : 1-251 ; 連接子 : 252-256 ; FcLALA : 257-473

```

1  MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNs
51 YHLQIHKNHG VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTl ENGyDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPiPRRHtQS AEDDSERDPL NVLKPRARMT
201 PAPASSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IGGGGSAPeA AGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK
301 FNWYVDGVEV HNAKTKPREe QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS
351 NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP
401 SDIAVEWESN GQPENNYKTT PPVLDSGDSF FLYSKLTVDK SRWQQGNVFS
451 CSVMHEALHN HYtQKSLSLS PGK*

```

FGF23(R179Q, C244S)-FcLALAv2之胺基酸序列(SEQ ID NO: 65)

FGF23 : 1-251 ; 連接子 : 252-256 ; FcLALA : 257-473

```

1  MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNs
51 YHLQIHKNHG VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTl ENGyDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPiPRRHtQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGSRPFAKF
251 IGGGGSAPeA AGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK
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FGF23(R179Q, Q156A)-FcLALAv2之胺基酸序列(SEQ ID NO: 66)

FGF23 : 1-251 ; 連接子 : 252-256 ; FcLALA : 257-473

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FGF23(R179Q, C206S, C244S)-FcLALAv2之胺基酸序列(SEQ ID NO: 67)

FGF23 : 1-251 ; 連接子 : 252-256 ; FcLALA : 257-473

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1  MLGARLRLWV  CALCSVCSMS  VLRAYPNASP  LLGSSWGGLI  HLYTATARNs
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151 PPPYSQFLSR  RNEIPLIHFN  TPIPRRHTQS  AEDDSERDPL  NVLKPRARMT
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FGF23(R179Q, C206S, C244S, Q156A)-FcLALAv2之胺基酸序列(SEQ

ID NO: 68)

FGF23 : 1-251 ; 連接子 : 52-256 ; FcLALA : 257-473

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251 IGGGSAPEA  AGGPSVFLFP  PKPKDTLMIS  RTPEVTCVVV  DVSHEDPEVK
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【符號說明】

(無)

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<140> 100103508

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<150> 12/696,693

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ttttgagaac agtagttcta gatgcagtca gaccaagaa aatacagagt gcacigtctg 3060
cttattcctt gtgcagaaga aaccactgat attcctgggt tgttgcttct tctccacct 3120
ggttctactc ttatcaattg ccatttttca aaggcagaag agaagaaagt tttggaaagc 3180
aaaaaacitc caacacatac caltaagaa aggcaagaga gttgttagct aaactgatct 3240
gtctgcatga tagacagttt aaaaaticat cccagttcc 3279

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

Ala Val Thr Gly Phe Ser Gly Asp Gly Arg Ala Ile Trp Ser Lys Asn
 50 55 60

Pro Asn Phe Thr Pro Val Asn Glu Ser Gln Leu Phe Leu Tyr Asp Thr
 65 70 75 80

Phe Pro Lys Asn Phe Phe Trp Gly Ile Gly Thr Gly Ala Leu Gln Val
 85 90 95

Glu Gly Ser Trp Lys Lys Asp Gly Lys Gly Pro Ser Ile Trp Asp His
 100 105 110

Phe Ile His Thr His Leu Lys Asn Val Ser Ser Thr Asn Gly Ser Ser
115 120 125

Asp Ser Tyr Ile Phe Leu Glu Lys Asp Leu Ser Ala Leu Asp Phe Ile
130 135 140

Gly Val Ser Phe Tyr Gln Phe Ser Ile Ser Trp Pro Arg Leu Phe Pro
145 150 155 160

Asp Gly Ile Val Thr Val Ala Asn Ala Lys Gly Leu Gln Tyr Tyr Ser
165 170 175

Thr Leu Leu Asp Ala Leu Val Leu Arg Asn Ile Glu Pro Ile Val Thr
180 185 190

Leu Tyr His Trp Asp Leu Pro Leu Ala Leu Gln Glu Lys Tyr Gly Gly
195 200 205

Trp Lys Asn Asp Thr Ile Ile Asp Ile Phe Asn Asp Tyr Ala Thr Tyr
210 215 220

Cys Phe Gln Met Phe Gly Asp Arg Val Lys Tyr Trp Ile Thr Ile His
225 230 235 240

Asn Pro Tyr Leu Val Ala Trp His Gly Tyr Gly Thr Gly Met His Ala
245 250 255

Pro Gly Glu Lys Gly Asn Leu Ala Ala Val Tyr Thr Val Gly His Asn
260 265 270

Leu Ile Lys Ala His Ser Lys Val Trp His Asn Tyr Asn Thr His Phe
275 280 285

Arg Pro His Gln Lys Gly Trp Leu Ser Ile Thr Leu Gly Ser His Trp
290 295 300

Ile Glu Pro Asn Arg Ser Glu Asn Thr Met Asp Ile Phe Lys Cys Gln
305 310 315 320

Gln Ser Met Val Ser Val Leu Gly Trp Phe Ala Asn Pro Ile His Gly
325 330 335

Asp Gly Asp Tyr Pro Glu Gly Met Arg Lys Lys Leu Phe Ser Val Leu
340 345 350

Pro Ile Phe Ser Glu Ala Glu Lys His Glu Met Arg Gly Thr Ala Asp
355 360 365

Phe Phe Ala Phe Ser Phe Gly Pro Asn Asn Phe Lys Pro Leu Asn Thr
370 375 380

Met Ala Lys Met Gly Gln Asn Val Ser Leu Asn Leu Arg Glu Ala Leu
385 390 395 400

Asn Trp Ile Lys Leu Glu Tyr Asn Asn Pro Arg Ile Leu Ile Ala Glu

	405		410		415
Asn Gly Trp Phe Thr Asp Ser Arg Val Lys Thr Glu Asp Thr Thr Ala	420		425		430
Ile Tyr Met Met Lys Asn Phe Leu Ser Gln Val Leu Gln Ala Ile Arg	435		440		445
Leu Asp Glu Ile Arg Val Phe Gly Tyr Thr Ala Trp Ser Leu Leu Asp	450		455		460
Gly Phe Glu Trp Gln Asp Ala Tyr Thr Ile Arg Arg Gly Leu Phe Tyr	465		470		475
Val Asp Phe Asn Ser Lys Gln Lys Glu Arg Lys Pro Lys Ser Ser Ala	485		490		495
His Tyr Tyr Lys Gln Ile Ile Arg Glu Asn Gly Phe Ser Leu Lys Glu	500		505		510
Ser Thr Pro Asp Val Gln Gly Gln Phe Pro Cys Asp Phe Ser Trp Gly	515		520		525
Val Thr Glu Ser Val Leu Lys Pro Glu Ser Val Ala Ser Ser Pro Gln	530		535		540
Phe Ser Asp Pro His Leu Tyr Val Trp Asn Ala Thr Gly Asn Arg Leu	545		550		555
Leu His Arg Val Glu Gly Val Arg Leu Lys Thr Arg Pro Ala Gln Cys	565		570		575
Thr Asp Phe Val Asn Ile Lys Lys Gln Leu Glu Met Leu Ala Arg Met	580		585		590
Lys Val Thr His Tyr Arg Phe Ala Leu Asp Trp Ala Ser Val Leu Pro	595		600		605
Thr Gly Asn Leu Ser Ala Val Asn Arg Gln Ala Leu Arg Tyr Tyr Arg	610		615		620
Cys Val Val Ser Glu Gly Leu Lys Leu Gly Ile Ser Ala Met Val Thr	625		630		635
Leu Tyr Tyr Pro Thr His Ala His Leu Gly Leu Pro Glu Pro Leu Leu	645		650		655
His Ala Asp Gly Trp Leu Asn Pro Ser Thr Ala Glu Ala Phe Gln Ala	660		665		670
Tyr Ala Gly Leu Cys Phe Gln Glu Leu Gly Asp Leu Val Lys Leu Trp	675		680		685
Ile Thr Ile Asn Glu Pro Asn Arg Leu Ser Asp Ile Tyr Asn Arg Ser	690		695		700

Gly Asn Asp Thr Tyr Gly Ala Ala His Asn Leu Leu Val Ala His Ala
 705 710 715 720
 Leu Ala Trp Arg Leu Tyr Asp Arg Gln Phe Arg Pro Ser Gln Arg Gly
 725 730 735
 Ala Val Ser Leu Ser Leu His Ala Asp Trp Ala Glu Pro Ala Asn Pro
 740 745 750
 Tyr Ala Asp Ser His Trp Arg Ala Ala Glu Arg Phe Leu Gln Phe Glu
 755 760 765
 Ile Ala Trp Phe Ala Glu Pro Leu Phe Lys Thr Gly Asp Tyr Pro Ala
 770 775 780
 Ala Met Arg Glu Tyr Ile Ala Ser Lys His Arg Arg Gly Leu Ser Ser
 785 790 795 800
 Ser Ala Leu Pro Arg Leu Thr Glu Ala Glu Arg Arg Leu Leu Lys Gly
 805 810 815
 Thr Val Asp Phe Cys Ala Leu Asn His Phe Thr Thr Arg Phe Val Met
 820 825 830
 His Glu Gln Leu Ala Gly Ser Arg Tyr Asp Ser Asp Arg Asp Ile Gln
 835 840 845
 Phe Leu Gln Asp Ile Thr Arg Leu Ser Ser Pro Thr Arg Leu Ala Val
 850 855 860
 Ile Pro Trp Gly Val Arg Lys Leu Leu Arg Trp Val Arg Arg Asn Tyr
 865 870 875 880
 Gly Asp Met Asp Ile Tyr Ile Thr Ala Ser Gly Ile Asp Asp Gln Ala
 885 890 895
 Leu Glu Asp Asp Arg Leu Arg Lys Tyr Tyr Leu Gly Lys Tyr Leu Gln
 900 905 910
 Glu Val Leu Lys Ala Tyr Leu Ile Asp Lys Val Arg Ile Lys Gly Tyr
 915 920 925
 Tyr Ala Phe Lys Leu Ala Glu Glu Lys Ser Lys Pro Arg Phe Gly Phe
 930 935 940
 Phe Thr Ser Asp Phe Lys Ala Lys Ser Ser Ile Gln Phe Tyr Asn Lys
 945 950 955 960
 Val Ile Ser Ser Arg Gly Phe Pro Phe Glu Asn Ser Ser Ser Arg Cys
 965 970 975
 Ser Gln Thr Gln Glu Asn Thr Glu Cys Thr Val Cys Leu Phe Leu Val
 980 985 990
 Gln Lys Lys Pro Leu Ile Phe Leu Gly Cys Cys Phe Phe Ser Thr Leu
 995 1000 1005

Val Leu Leu Ser Ile Ala Ile Phe Gln Arg Gln Lys Arg Arg
 1010 1015 1020
 Lys Phe Trp Lys Ala Lys Asn Leu Gln His Ile Pro Leu Lys Lys
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 Gly Lys Arg Val Val Ser
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 <213> 智人
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 Tyr Gln Thr Glu Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile
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 Trp Asp Thr Phe Thr His His Pro Leu Ala Pro Pro Gly Asp Ser Arg
 35 40 45
 Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr
 50 55 60
 Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu
 65 70 75 80
 Ala Leu Arg Glu Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp
 85 90 95
 Ala Arg Val Leu Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly
 100 105 110
 Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val
 115 120 125
 Gln Pro Val Val Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln
 130 135 140
 Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg
 145 150 155 160
 Asp Tyr Ala Glu Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr
 165 170 175
 Trp Ile Thr Ile Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala
 180 185 190
 Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr
 195 200 205
 Leu Val Ala His Asn Leu Leu Leu Ala His Ala Lys Val Trp His Leu
 210 215 220

Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala
 225 230 235 240
 Leu Ser Ser His Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile
 245 250 255
 Lys Glu Cys Gln Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys
 260 265 270
 Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu
 275 280 285
 Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys
 290 295 300
 Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser Phe
 305 310 315 320
 Gln Leu Leu Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn
 325 330 335
 Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln
 340 345 350
 Ile Phe Ile Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg
 355 360 365
 Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu Thr
 370 375 380
 Leu Lys Ala Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr Thr Ala
 385 390 395 400
 Trp Ser Leu Met Asp Gly Phe Glu Trp His Arg Gly Tyr Ser Ile Arg
 405 410 415
 Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser Gln Asp Lys Met Leu Leu
 420 425 430
 Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn Gly
 435 440 445

Phe

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Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr Ile
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Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu
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Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly Val Val
 35 40 45
 Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro
 50 55 60
 Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg Phe Ser
 65 70 75 80
 Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val Asn
 85 90 95
 His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val Arg
 100 105 110
 Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro Asn
 115 120 125
 Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro
 130 135 140
 Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln Glu
 145 150 155 160
 Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr Thr
 165 170 175
 Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His Ala
 180 185 190
 Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn Gly
 195 200 205
 Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys Pro
 210 215 220
 Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe Asp
 225 230 235 240
 Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro Trp
 245 250 255
 Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro Tyr
 260 265 270
 Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe Leu
 275 280 285
 Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu Asp
 290 295 300
 Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp Ile
 305 310 315 320
 Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly Leu
 325 330 335

Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro Met
340 345 350

Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala Glu Asp Asp
355 360 365

Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu Lys
370 375 380

Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr Ser
385 390 395 400

Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala Ala
405 410 415

Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile Ile
420 425 430

Asp Ser Asn Gly Phe
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<212> PRT
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Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro
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Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
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Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45

Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60

Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80

Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95

Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110

His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125

Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140

Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160

Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175

Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190

His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205

Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220

Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240

Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255

Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270

Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285

Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320

Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335

Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350

Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365

Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380

Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400

Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415

Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430

Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445

Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr

450	455	460
Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln 465 470 475 480		
Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp 485 490 495		
Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn 500 505 510		
Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp 515 520 525		
Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala 530 535 540		
Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe 545 550 555 560		
Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser 565 570 575		
Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu 580 585 590		
Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met 595 600 605		
Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp 610 615 620		
Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys 625 630 635 640		
Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu 645 650 655		
Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys 660 665 670		
Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala 675 680 685		
Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro 690 695 700		
Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu 705 710 715 720		
Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp 725 730 735		
Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu 740 745 750		

Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765

Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780

Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800

Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815

Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830

Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845

Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860

Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865 870 875 880

Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895

Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910

Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925

Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
930 935 940

Thr Arg Lys Ser Leu
945

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<213> 智人

<400> 8

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Ser
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Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
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Ala

<210> 9
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<212> PRT
<213> 智人

<400> 9

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Thr Arg Cys Arg Arg Leu Arg Ala
20 25

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<212> DNA
<213> 智人

<400> 10
ggaggaggagg gticaggagg tggagggtica ggaggaggagg gtica 45

<210> 11
<211> 15
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<213> 智人

<400> 11

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 12
<211> 5
<212> PRT
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<400> 12

Gly Gly Gly Gly Ser
1 5

<210> 13
<211> 1
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<400> 13

Gly
1

<210> 14
<211> 2
<212> PRT
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<400> 14

Gly Gly
1

<210> 15
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<400> 15

Gly Ser
1

<210> 16
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<400> 16

Gly Gly Ser
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<210> 17
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<400> 17

Ala
 1

<210> 18
 <211> 2
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 <213> 智人

<400> 18

Ala Ala
 1

<210> 19
 <211> 1228
 <212> PRT
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<400> 19

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Ser
 1 5 10 15

Leu Ser Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
 20 25 30

Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
 35 40 45

Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
 50 55 60

Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
 65 70 75 80

Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
 85 90 95

Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
 100 105 110

Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
 115 120 125

Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
 130 135 140

Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
 145 150 155 160
 Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
 165 170 175
 Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
 180 185 190
 His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
 195 200 205
 Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
 210 215 220
 Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
 225 230 235 240
 Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
 245 250 255
 Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
 260 265 270
 Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
 275 280 285
 Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
 290 295 300
 Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
 305 310 315 320
 Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
 325 330 335
 Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
 340 345 350
 Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
 355 360 365
 Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
 370 375 380
 Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
 385 390 395 400
 Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
 405 410 415
 Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
 420 425 430
 Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
 435 440 445

Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
 450 455 460
 Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
 465 470 475 480
 Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
 485 490 495
 Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
 500 505 510
 Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
 515 520 525
 Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
 530 535 540
 Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
 545 550 555 560
 Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
 565 570 575
 Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
 580 585 590
 Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
 595 600 605
 Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
 610 615 620
 Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
 625 630 635 640
 Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
 645 650 655
 Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
 660 665 670
 Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
 675 680 685
 Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
 690 695 700
 Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
 705 710 715 720
 Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
 725 730 735
 Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val

740	745	750
Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly 755 760 765		
Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe 770 775 780		
Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr 785 790 795 800		
Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser 805 810 815		
Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu 820 825 830		
Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val 835 840 845		
Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly 850 855 860		
Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His 865 870 875 880		
Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn 885 890 895		
Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr 900 905 910		
Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr 915 920 925		
Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr 930 935 940		
Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu 945 950 955 960		
Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe 965 970 975		
His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly 980 985 990		
Gly Ser Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn Ala Ser Pro Leu 995 1000 1005		
Leu Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr 1010 1015 1020		
Ala Arg Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val 1025 1030 1035		

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

Ser Glu Asp Ala Gly Phe Val Val Ile Thr Gly Val Met Ser Arg
1055 1060 1065

Arg Tyr Leu Cys Met Asp Phe Arg Gly Asn Ile Phe Gly Ser His
1070 1075 1080

Tyr Phe Asp Pro Glu Asn Cys Arg Phe Gln His Gln Thr Leu Glu
1085 1090 1095

Asn Gly Tyr Asp Val Tyr His Ser Pro Gln Tyr His Phe Leu Val
1100 1105 1110

Ser Leu Gly Arg Ala Lys Arg Ala Phe Leu Pro Gly Met Asn Pro
1115 1120 1125

Pro Pro Tyr Ser Gln Phe Leu Ser Arg Arg Asn Glu Ile Pro Leu
1130 1135 1140

Ile His Phe Asn Thr Pro Ile Pro Arg Arg His Thr Gln Ser Ala
1145 1150 1155

Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val Leu Lys Pro Arg
1160 1165 1170

Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln Glu Leu Pro
1175 1180 1185

Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu Gly Val
1190 1195 1200

Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly Pro
1205 1210 1215

Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
1220 1225

<210> 20
<211> 1220
<212> PRT
<213> 智人

<400> 20

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Leu Gly Gly Arg Arg Leu Arg Ala Glu Pro Gly Asp Gly Ala Gln
20 25 30

Thr Trp Ala Arg Phe Ser Arg Pro Pro Ala Pro Glu Ala Ala Gly Leu
35 40 45

Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala
50 55 60

Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser
65 70 75 80

Ile Trp Asp Thr Phe Thr His His Pro Leu Ala Pro Pro Gly Asp Ser
85 90 95

Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala
100 105 110

Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr
115 120 125

Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser
130 135 140

Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu
145 150 155 160

Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly
165 170 175

Val Gln Pro Val Val Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu
180 185 190

Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe
195 200 205

Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys
210 215 220

Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr
225 230 235 240

Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly
245 250 255

Tyr Leu Val Ala His Asn Leu Leu Leu Ala His Ala Lys Val Trp His
260 265 270

Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile
275 280 285

Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser
290 295 300

Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala
305 310 315 320

Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn
325 330 335

Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile
340 345 350

Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser
355 360 365

Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro
 370 375 380
 Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro
 385 390 395 400
 Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys
 405 410 415
 Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu
 420 425 430
 Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr Thr
 435 440 445
 Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His Arg Gly Tyr Ser Ile
 450 455 460
 Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser Gln Asp Lys Met Leu
 465 470 475 480
 Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn
 485 490 495
 Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro
 500 505 510
 Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr
 515 520 525
 Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His
 530 535 540
 His Ser Lys Arg Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg
 545 550 555 560
 Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu
 565 570 575
 Leu Gln Glu Met His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala
 580 585 590
 Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu
 595 600 605
 Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr
 610 615 620
 Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro
 625 630 635 640
 Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu
 645 650 655
 Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His
 660 665 670

Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr
675 680 685

Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His
690 695 700

Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile
705 710 715 720

Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys
725 730 735

Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu
740 745 750

Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp
755 760 765

Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp
770 775 780

Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His
785 790 795 800

Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr
805 810 815

Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn
820 825 830

Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu
835 840 845

Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser
850 855 860

Asn Gly Ile Asp Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val
865 870 875 880

Tyr Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu
885 890 895

Asp Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg
900 905 910

Thr Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu
915 920 925

Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly
930 935 940

Phe Pro Gly Pro Glu Thr Leu Glu Arg Phe Cys Pro Glu Glu Phe Thr
945 950 955 960

Val Cys Thr Glu Cys Ser Phe Phe His Thr Arg Lys Ser Leu Gly Ser

965	970	975
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu		
980	985	990
Lys Tyr Pro Asn Ala Ser Pro Leu Leu Gly Ser Ser Trp Gly Gly Leu		
995	1000	1005
Ile His Leu Tyr Thr Ala Thr Ala Arg Asn Ser Tyr His Leu Gln		
1010	1015	1020
Ile His Lys Asn Gly His Val Asp Gly Ala Pro His Gln Thr Ile		
1025	1030	1035
Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala Gly Phe Val Val		
1040	1045	1050
Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met Asp Phe Arg		
1055	1060	1065
Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn Cys Arg		
1070	1075	1080
Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His Ser		
1085	1090	1095
Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala		
1100	1105	1110
Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser		
1115	1120	1125
Arg Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro		
1130	1135	1140
Arg Arg His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro		
1145	1150	1155
Leu Asn Val Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala		
1160	1165	1170
Ser Cys Ser Gln Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met		
1175	1180	1185
Ala Ser Asp Pro Leu Gly Val Val Arg Gly Gly Arg Val Asn Thr		
1190	1195	1200
His Ala Gly Gly Thr Gly Pro Glu Gly Cys Arg Pro Phe Ala Lys		
1205	1210	1215
Phe Ile		
1220		

<210> 21
 <211> 762
 <212> PRT
 <213> 智人

<400> 21

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Ser
1 5 10 15

Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
20 25 30

Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
35 40 45

Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60

Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80

Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95

Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110

Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125

Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140

Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160

Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
355 360 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
370 375 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385 390 395 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
405 410 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445

Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510

Gln Pro Leu Glu Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
515 520 525

Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn Ala Ser Pro Leu Leu Gly
530 535 540

Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg Asn
545 550 555 560

Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala Pro
565 570 575

His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala Gly
580 585 590

Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met Asp
595 600 605

Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn Cys
610 615 620

Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His Ser
625 630 635 640

Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala Phe
645 650 655

Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg Arg
660 665 670

Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg His
675 680 685

Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val Leu
690 695 700

Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln Glu
705 710 715 720

Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu Gly
725 730 735

Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly Pro
740 745 750

Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
755 760

<210> 22
<211> 752
<212> PRT
<213> 智人

<400> 22

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Ser
1 5 10 15

Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Pro
20 25 30

Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala
35 40 45

Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln
50 55 60

Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg
65 70 75 80

Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys
85 90 95

Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met
100 105 110

His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro
115 120 125

Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg
130 135 140

Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala
145 150 155 160

Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala
165 170 175

Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu
180 185 190

Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp
195 200 205

Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly
210 215 220

His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu
225 230 235 240

Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala
245 250 255

Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val
260 265 270

Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile
275 280 285

Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln
290 295 300

Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu
305 310 315 320

Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile
325 330 335

Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu
340 345 350

Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln
355 360 365

Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys
370 375 380

Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp
385 390 395 400

Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln
405 410 415

Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn
420 425 430

Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg
435 440 445

Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser
450 455 460

Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro
465 470 475 480

Glu Thr Leu Glu Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu
485 490 495

Cys Ser Phe Phe His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly
500 505 510

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn
515 520 525

Ala Ser Pro Leu Leu Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr
530 535 540

Thr Ala Thr Ala Arg Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly
545 550 555 560

His Val Asp Gly Ala Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile
565 570 575

Arg Ser Glu Asp Ala Gly Phe Val Val Ile Thr Gly Val Met Ser Arg
580 585 590

Arg Tyr Leu Cys Met Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr
595 600 605

Phe Asp Pro Glu Asn Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly
610 615 620

Tyr Asp Val Tyr His Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly
625 630 635 640

Arg Ala Lys Arg Ala Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser
645 650 655

Gln Phe Leu Ser Arg Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr
660 665 670

Pro Ile Pro Arg Arg His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg
675 680 685

Asp Pro Leu Asn Val Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro

690	695	700
Ala Ser Cys Ser Gln Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met		
705	710	715 720
Ala Ser Asp Pro Leu Gly Val Val Arg Gly Gly Arg Val Asn Thr His		
	725	730 735
Ala Gly Gly Thr Gly Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile		
	740	745 750
<210> 23		
<211> 1215		
<212> PRT		
<213> 智人		
<400> 23		
Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Pro Ser		
1	5	10 15
Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg		
	20	25 30
Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro		
	35	40 45
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly		
	50	55 60
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp		
65	70	75 80
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His		
	85	90 95
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly		
	100	105 110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser		
	115	120 125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val		
	130	135 140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly		
145	150	155 160
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu		
	165	170 175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr		
	180	185 190
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala		
	195	200 205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe		

210	215	220
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro 225 230 235 240		
Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly 245 250 255		
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu 260 265 270		
Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro 275 280 285		
Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn 290 295 300		
Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu 305 310 315 320		
Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp 325 330 335		
Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe 340 345 350		
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala 355 360 365		
Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met 370 375 380		
Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp 385 390 395 400		
Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly 405 410 415		
Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr 420 425 430		
Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp 435 440 445		
Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe 450 455 460		
Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp 465 470 475 480		
Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe 485 490 495		
Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn 500 505 510		

Gln Pro Leu Glu Gly Ser Gly Thr Phe Pro Asp Gly Phe Leu Trp Ala
515 520 525

Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His Gly
530 535 540

Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala Pro
545 550 555 560

Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser Pro
565 570 575

Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn Val
580 585 590

Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr Arg
595 600 605

Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly Val
610 615 620

Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg Leu
625 630 635 640

Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp Leu
645 650 655

Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala Leu
660 665 670

Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe Gly
675 680 685

Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val Ala
690 695 700

Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly Ser
705 710 715 720

Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His Ala
725 730 735

Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly Gly
740 745 750

Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg Met
755 760 765

Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val Leu
770 775 780

Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu Ser
785 790 795 800

Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser Glu
805 810 815

Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe Gly
 820 825 830
 Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg Gln
 835 840 845
 Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu Glu
 850 855 860
 Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val Ser
 865 870 875 880
 Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys Lys
 885 890 895
 Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp Val
 900 905 910
 Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His Arg
 915 920 925
 Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser Gln
 930 935 940
 Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys Leu
 945 950 955 960
 Ile Glu Lys Asn Gly Phe Pro Glu Phe Gly Ser Gly Gly Gly Ser
 965 970 975
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn Ala
 980 985 990
 Ser Pro Leu Leu Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr
 995 1000 1005
 Ala Thr Ala Arg Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly
 1010 1015 1020
 His Val Asp Gly Ala Pro His Gln Thr Ile Tyr Ser Ala Leu Met
 1025 1030 1035
 Ile Arg Ser Glu Asp Ala Gly Phe Val Val Ile Thr Gly Val Met
 1040 1045 1050
 Ser Arg Arg Tyr Leu Cys Met Asp Phe Arg Gly Asn Ile Phe Gly
 1055 1060 1065
 Ser His Tyr Phe Asp Pro Glu Asn Cys Arg Phe Gln His Gln Thr
 1070 1075 1080
 Leu Glu Asn Gly Tyr Asp Val Tyr His Ser Pro Gln Tyr His Phe
 1085 1090 1095
 Leu Val Ser Leu Gly Arg Ala Lys Arg Ala Phe Leu Pro Gly Met
 1100 1105 1110

Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg Arg Asn Glu Ile
1115 1120 1125

Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg His Thr Gin
1130 1135 1140

Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val Leu Lys
1145 1150 1155

Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln Glu
1160 1165 1170

Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
1175 1180 1185

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr
1190 1195 1200

Gly Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
1205 1210 1215

<210> 24
<211> 1189
<212> PRT
<213> 智人

<400> 24

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Ser
1 5 10 15

Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Pro
20 25 30

Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala
35 40 45

Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln
50 55 60

Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg
65 70 75 80

Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys
85 90 95

Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met
100 105 110

His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro
115 120 125

Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg
130 135 140

Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala
145 150 155 160

Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala
165 170 175

Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu
180 185 190

Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp
195 200 205

Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly
210 215 220

His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu
225 230 235 240

Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala
245 250 255

Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val
260 265 270

Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile
275 280 285

Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln
290 295 300

Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu
305 310 315 320

Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile
325 330 335

Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu
340 345 350

Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln
355 360 365

Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys
370 375 380

Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp
385 390 395 400

Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln
405 410 415

Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn
420 425 430

Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg
435 440 445

Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser

450	455	460
Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro 465 470 475 480		
Glu Thr Leu Glu Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu 485 490 495		
Cys Ser Phe Phe His Thr Arg Lys Ser Leu Gly Thr Phe Pro Cys Asp 500 505 510		
Phe Ala Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu 515 520 525		
Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His His Ser 530 535 540		
Lys Arg Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg Lys Ser 545 550 555 560		
Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln 565 570 575		
Glu Met His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile 580 585 590		
Leu Pro Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu Gln Tyr 595 600 605		
Tyr Arg Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr Pro Val 610 615 620		
Val Ala Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro Arg Leu 625 630 635 640		
Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe 645 650 655		
Ala Glu Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His Val Lys 660 665 670		
Leu Trp Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser 675 680 685		
Ala Gly His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His Val Tyr 690 695 700		
Asn Glu Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu 705 710 715 720		
Gln Ala Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys 725 730 735		
Glu Val Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu 740 745 750		

Pro Ile Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp Trp Leu
755 760 765

Asn Gln Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys
770 775 780

Lys Leu Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His Tyr Thr
785 790 795 800

Thr Ile Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp
805 810 815

Tyr Leu Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn Ser Pro
820 825 830

Ser Gln Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu Asn Trp
835 840 845

Leu Lys Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly
850 855 860

Ile Asp Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr
865 870 875 880

Met Gln Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu Asp Gly
885 890 895

Ile Asn Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala
900 905 910

Pro Arg Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys
915 920 925

Ala Ser Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly Phe Gly
930 935 940

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
945 950 955 960

Leu Lys Tyr Pro Asn Ala Ser Pro Leu Leu Gly Ser Ser Trp Gly Gly
965 970 975

Leu Ile His Leu Tyr Thr Ala Thr Ala Arg Asn Ser Tyr His Leu Gln
980 985 990

Ile His Lys Asn Gly His Val Asp Gly Ala Pro His Gln Thr Ile Tyr
995 1000 1005

Ser Ala Leu Met Ile Arg Ser Glu Asp Ala Gly Phe Val Val Ile
1010 1015 1020

Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met Asp Phe Arg Gly
1025 1030 1035

Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn Cys Arg Phe
1040 1045 1050

Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His Ser Pro
1055 1060 1065

Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala Phe
1070 1075 1080

Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
1085 1090 1095

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg
1100 1105 1110

Arg His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu
1115 1120 1125

Asn Val Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser
1130 1135 1140

Cys Ser Gln Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala
1145 1150 1155

Ser Asp Pro Leu Gly Val Val Arg Gly Gly Arg Val Asn Thr His
1160 1165 1170

Ala Gly Gly Thr Gly Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe
1175 1180 1185

Ile

<210> 25
<211> 1219
<212> PRT
<213> 智人

<400> 25

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
1 5 10 15

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
 115 120 125
 Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
 130 135 140
 Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
 145 150 155 160
 Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
 165 170 175
 His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
 180 185 190
 Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
 195 200 205
 Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
 210 215 220
 Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
 225 230 235 240
 Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Ser Gly Gly Gly
 245 250 255
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Leu Lys Glu Pro
 260 265 270
 Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro Ala Pro
 275 280 285
 Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp
 290 295 300
 Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His
 305 310 315 320
 Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro Leu Ala
 325 330 335
 Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser
 340 345 350
 Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn
 355 360 365
 Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr
 370 375 380
 Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly
 385 390 395 400
 Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg
 405 410 415

Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His Trp Asp
 420 425 430
 Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala
 435 440 445
 Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe
 450 455 460
 Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val
 465 470 475 480
 Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly
 485 490 495
 Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu Ala His
 500 505 510
 Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly
 515 520 525
 Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg
 530 535 540
 Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val
 545 550 555 560
 Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu
 565 570 575
 Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser
 580 585 590
 Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe
 595 600 605
 Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg
 610 615 620
 Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu
 625 630 635 640
 Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val
 645 650 655
 Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys
 660 665 670
 Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp
 675 680 685
 Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His
 690 695 700
 Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser

705		710		715		720
Gln Asp Lys Met	Leu 725	Leu Pro Lys Ser	Ser 730	Ala Leu Phe Tyr	Gln 735	Lys
Leu Ile Glu Lys	Asn 740	Gly Phe Pro	Pro 745	Leu Pro Glu Asn	Gln 750	Pro Leu
Glu Gly Thr	Phe 755	Pro Cys Asp	Phe 760	Ala Trp Gly Val	Val 765	Asp Asn Tyr
Ile Gln Val	Asp 770	Thr Thr	Leu 775	Ser Gln Phe Thr	Asp 780	Leu Asn Val Tyr
Leu Trp Asp Val	His 785	His Ser Lys Arg	Leu 790	Ile Lys Val Asp	Gly 800	Val
Val Thr Lys Lys	Arg 805	Lys Ser Tyr Cys	Val 810	Asp Phe Ala Ala	Ile 815	Gln
Pro Gln Ile	Ala 820	Leu Leu Gln Glu	Met 825	His Val Thr His	Phe 830	Arg Phe
Ser Leu Asp	Trp 835	Ala Leu Ile	Leu 840	Pro Leu Gly Asn	Gln 845	Ser Gln Val
Asn His Thr	Ile 850	Leu Gln Tyr	Tyr 855	Arg Cys Met	Ala 860	Ser Glu Leu Val
Arg Val Asn Ile	Thr 865	Pro Val Val	Ala 870	Leu Trp Gln	Pro 875	Met Ala Pro
Asn Gln Gly Leu	Pro 885	Arg Leu Leu Ala	Arg 890	Gln Gly Ala Trp	Glu 895	Asn
Pro Tyr Thr	Ala 900	Leu Ala Phe Ala	Glu 905	Tyr Ala Arg Leu	Cys 910	Phe Gln
Glu Leu Gly	His 915	His Val Lys	Leu 920	Trp Ile Thr Met	Asn 925	Glu Pro Tyr
Thr Arg Asn Met	Thr 930	Tyr Ser	Ala 935	Gly His Asn	Leu 940	Leu Lys Ala His
Ala Leu Ala Trp	His 945	Val Tyr Asn	Glu 950	Lys Phe Arg His	Ala 955	Gln Asn
Gly Lys Ile Ser	Ile 965	Ala Leu Gln Ala	Asp 970	Trp Ile Glu Pro	Ala 975	Cys
Pro Phe Ser	Gln 980	Lys Asp Lys Glu	Val 985	Ala Glu Arg Val	Leu 990	Glu Phe
Asp Ile Gly Trp	Leu 995	Ala Glu Pro	Ile 1000	Phe Gly Ser Gly	Asp 1005	Tyr Pro

Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu
1010 1015 1020

Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
1025 1030 1035

Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
1040 1045 1050

Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln
1055 1060 1065

Glu Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala
1070 1075 1080

Val Val Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe
1085 1090 1095

Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp
1100 1105 1110

Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met
1115 1120 1125

Gln Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu Asp Gly
1130 1135 1140

Ile Asn Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr
1145 1150 1155

Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu
1160 1165 1170

Pro Lys Ala Ser Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn
1175 1180 1185

Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg Phe Cys Pro Glu Glu
1190 1195 1200

Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His Thr Arg Lys Ser
1205 1210 1215

Leu

<210> 26
<211> 700
<212> PRT
<213> 智人

<400> 26

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
1 5 10 15

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala-Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
115 120 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
130 135 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145 150 155 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
165 170 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
180 185 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
195 200 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
210 215 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225 230 235 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gln Gly Thr Phe Pro
245 250 255

Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly
260 265 270

Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr
275 280 285

His His Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro
290 295 300

Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser
305 310 315 320

Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu
325 330 335

Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro
340 345 350

Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg
355 360 365

Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr
370 375 380

Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly
385 390 395 400

Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu
405 410 415

Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp
420 425 430

Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala
435 440 445

Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn
450 455 460

Leu Leu Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe
465 470 475 480

Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp
485 490 495

Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys
500 505 510

Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp
515 520 525

Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro
530 535 540

Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe
545 550 555 560

Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro
565 570 575

His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu
580 585 590

Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu
595 600 605

Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr
610 615 620

Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys
625 630 635 640

Leu Asp Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp
645 650 655

Gly Phe Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr
660 665 670

Val Asp Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala
675 680 685

Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe
690 695 700

<210> 27

<211> 688

<212> PRT

<213> 智人

<400> 27

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
1 5 10 15

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
115 120 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
130 135 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145 150 155 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
165 170 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
180 185 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
195 200 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
 210 215 220
 Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
 225 230 235 240
 Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Thr Phe Pro Cys
 245 250 255
 Asp Phe Ala Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr
 260 265 270
 Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His His
 275 280 285
 Ser Lys Arg Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg Lys
 290 295 300
 Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu Leu
 305 310 315 320
 Gln Glu Met His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala Leu
 325 330 335
 Ile Leu Pro Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu Gln
 340 345 350
 Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr Pro
 355 360 365
 Val Val Ala Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro Arg
 370 375 380
 Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu Ala
 385 390 395 400
 Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His Val
 405 410 415
 Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr Tyr
 420 425 430
 Ser Ala Gly His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His Val
 435 440 445
 Tyr Asn Glu Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile Ala
 450 455 460
 Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys Pro Phe Ser Gln Lys Asp
 465 470 475 480
 Lys Glu Val Ala Glu Arg Val Leu Glu Phe Asp Ile Gly Trp Leu Ala
 485 490 495
 Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro Trp Val Met Arg Asp Trp

500	505	510
Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro Tyr Phe Thr Glu Asp Glu		
515	520	525
Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe Leu Ala Leu Ser His Tyr		
530	535	540
Thr Thr Ile Leu Val Asp Ser Glu Lys Glu Asp Pro Ile Lys Tyr Asn		
545	550	555
Asp Tyr Leu Glu Val Gln Glu Met Thr Asp Ile Thr Trp Leu Asn Ser		
565	570	575
Pro Ser Gln Val Ala Val Val Pro Trp Gly Leu Arg Lys Val Leu Asn		
580	585	590
Trp Leu Lys Phe Lys Tyr Gly Asp Leu Pro Met Tyr Ile Ile Ser Asn		
595	600	605
Gly Ile Asp Asp Gly Leu His Ala Glu Asp Asp Gln Leu Arg Val Tyr		
610	615	620
Tyr Met Gln Asn Tyr Ile Asn Glu Ala Leu Lys Ala His Ile Leu Asp		
625	630	635
Gly Ile Asn Leu Cys Gly Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr		
645	650	655
Ala Pro Arg Phe Gly Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu Pro		
660	665	670
Lys Ala Ser Met Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly Phe		
675	680	685
<210> 28		
<211> 1149		
<212> PRT		
<213> 智人		
<400> 28		
Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val		
1	5	10
Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu		
20	25	30
Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg		
35	40	45
Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala		
50	55	60
Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala		
65	70	75
Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met		
		80

	85		90		95
Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn	100		105		110
Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His	115		120		125
Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala	130		135		140
Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg	145		150		155
Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg	165		170		175
His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val	180		185		190
Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln	195		200		205
Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu	210		215		220
Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly	225		230		235
Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gln Gly Thr Phe Pro	245		250		255
Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly	260		265		270
Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr	275		280		285
His His Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro	290		295		300
Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser	305		310		315
Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu	325		330		335
Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro	340		345		350
Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg	355		360		365
Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr	370		375		380

Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly
385 390 395 400

Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu
405 410 415

Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp
420 425 430

Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala
435 440 445

Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn
450 455 460

Leu Leu Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe
465 470 475 480

Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp
485 490 495

Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys
500 505 510

Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp
515 520 525

Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro
530 535 540

Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe
545 550 555 560

Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro
565 570 575

His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu
580 585 590

Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu
595 600 605

Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr
610 615 620

Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys
625 630 635 640

Leu Asp Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp
645 650 655

Gly Phe Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr
660 665 670

Val Asp Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala
675 680 685

Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Gln Gly Thr Phe
 690 695 700
 Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu
 705 710 715 720
 Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe
 725 730 735
 Thr His His Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu
 740 745 750
 Pro Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala
 755 760 765
 Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu
 770 775 780
 Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu
 785 790 795 800
 Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr
 805 810 815
 Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val
 820 825 830
 Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly
 835 840 845
 Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu
 850 855 860
 Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile
 865 870 875 880
 Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu
 885 890 895
 Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His
 900 905 910
 Asn Leu Leu Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser
 915 920 925
 Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His
 930 935 940
 Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln
 945 950 955 960
 Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile
 965 970 975
 Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu
 980 985 990

Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp
995 1000 1005

Phe Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu
1010 1015 1020

Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg
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Gln Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro Gln Ile
1040 1045 1050

Phe Ile Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys Arg
1055 1060 1065

Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu
1070 1075 1080

Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr
1085 1090 1095

Thr Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His Arg Gly Tyr
1100 1105 1110

Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser Gln Asp
1115 1120 1125

Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys Leu
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Ile Glu Lys Asn Gly Phe
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<210> 29
<211> 1125
<212> PRT
<213> 智人

<400> 29

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
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Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
 100 105 110
 Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
 115 120 125
 Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
 130 135 140
 Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
 145 150 155 160
 Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
 165 170 175
 His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
 180 185 190
 Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
 195 200 205
 Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
 210 215 220
 Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
 225 230 235 240
 Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Thr Phe Pro Cys
 245 250 255
 Asp Phe Ala Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr Thr
 260 265 270
 Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His His
 275 280 285
 Ser Lys Arg Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg Lys
 290 295 300
 Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu Leu
 305 310 315 320
 Gln Glu Met His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala Leu
 325 330 335
 Ile Leu Pro Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu Gln
 340 345 350
 Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr Pro
 355 360 365
 Val Val Ala Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro Arg
 370 375 380
 Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu Ala

385		390		395		400
Phe	Ala	Glu	Tyr	Ala	Arg	Leu
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				Phe	Gln	Glu
				410		
				Leu	Gly	His
						415
						Val
Lys	Leu	Trp	Ile	Thr	Met	Asn
		420				425
						430
						Met
						Thr
						Tyr
Ser	Ala	Gly	His	Asn	Leu	Leu
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						445
						Trp
						His
						Val
Tyr	Asn	Glu	Lys	Phe	Arg	His
		450				455
						460
						Lys
						Ile
						Ser
						Ile
						Ala
Leu	Gln	Ala	Asp	Trp	Ile	Glu
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						475
						480
						Pro
						Phe
						Ser
						Gln
						Lys
						Asp
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						490
						495
						Leu
						Ala
Glu	Pro	Ile	Phe	Gly	Ser	Gly
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						505
						510
						Arg
						Asp
						Trp
Leu	Asn	Gln	Arg	Asn	Asn	Phe
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						525
						Thr
						Glu
						Asp
						Glu
Lys	Lys	Leu	Ile	Gln	Gly	Thr
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						540
						Ala
						Leu
						Ser
						His
						Tyr
Thr	Thr	Ile	Leu	Val	Asp	Ser
				550		
						555
						560
						Pro
						Ile
						Lys
						Tyr
						Asn
Asp	Tyr	Leu	Glu	Val	Gln	Glu
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						570
						575
						Leu
						Asn
						Ser
Pro	Ser	Gln	Val	Ala	Val	Val
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						585
						590
						Val
						Leu
						Asn
Trp	Leu	Lys	Phe	Lys	Tyr	Gly
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						610
						615
						620
						Gln
						Leu
						Arg
						Val
						Tyr
Gly	Ile	Asp	Asp	Gly	Leu	His
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						995
						1000

Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr Ile
690 695 700

Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu
705 710 715 720

Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp Gly Val Val
725 730 735

Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro
740 745 750

Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe Arg Phe Ser
755 760 765

Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val Asn
770 775 780

His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val Arg
785 790 795 800

Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro Asn
805 810 815

Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro
820 825 830

Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln Glu
835 840 845

Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr Thr
850 855 860

Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His Ala
865 870 875 880

Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn Gly
885 890 895

Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro Ala Cys Pro
900 905 910

Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu Glu Phe Asp
915 920 925

Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp Tyr Pro Trp
930 935 940

Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu Leu Pro Tyr
945 950 955 960

Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe Asp Phe Leu
965 970 975

Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu Lys Glu Asp
980 985 990

Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met Thr Asp Ile
995 1000 1005

Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro Trp Gly
1010 1015 1020

Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp Leu
1025 1030 1035

Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
1040 1045 1050

Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
1055 1060 1065

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly
1070 1075 1080

Tyr Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly
1085 1090 1095

Leu Tyr Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met
1100 1105 1110

Lys His Tyr Arg Lys Ile Ile Asp Ser Asn Gly Phe
1115 1120 1125

<210> 30
<211> 2157
<212> DNA
<213> 智人

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gggacaagaa gccgcgcctt gccctgcccg gcccgggag ggggctgggg ctggggccgg 180
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cagtgccaaa cagcggcagc tglacaagaa cagaggcttt ctccactct ctcatttct 960

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<210> 31
 <211> 216
 <212> PRT
 <213> 智人

<400> 31

Met Arg Ser Gly Cys Val Val Val His Val Trp Ile Leu Ala Gly Leu
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Trp Leu Ala Val Ala Gly Arg Pro Leu Ala Phe Ser Asp Ala Gly Pro
20 25 30

His Val His Tyr Gly Trp Gly Asp Pro Ile Arg Leu Arg His Leu Tyr
35 40 45

Thr Ser Gly Pro His Gly Leu Ser Ser Cys Phe Leu Arg Ile Arg Ala
50 55 60

Asp Gly Val Val Asp Cys Ala Arg Gly Gln Ser Ala His Ser Leu Leu
65 70 75 80

Glu Ile Lys Ala Val Ala Leu Arg Thr Val Ala Ile Lys Gly Val His
85 90 95

Ser Val Arg Tyr Leu Cys Met Gly Ala Asp Gly Lys Met Gln Gly Leu
100 105 110

Leu Gln Tyr Ser Glu Glu Asp Cys Ala Phe Glu Glu Glu Ile Arg Pro
 115 120 125
 Asp Gly Tyr Asn Val Tyr Arg Ser Glu Lys His Arg Leu Pro Val Ser
 130 135 140
 Leu Ser Ser Ala Lys Gln Arg Gln Leu Tyr Lys Asn Arg Gly Phe Leu
 145 150 155 160
 Pro Leu Ser His Phe Leu Pro Met Leu Pro Met Val Pro Glu Glu Pro
 165 170 175
 Glu Asp Leu Arg Gly His Leu Glu Ser Asp Met Phe Ser Ser Pro Leu
 180 185 190
 Glu Thr Asp Ser Met Asp Pro Phe Gly Leu Val Thr Gly Leu Glu Ala
 195 200 205
 Val Arg Ser Pro Ser Phe Glu Lys
 210 215

<210> 32
 <211> 940
 <212> PRT
 <213> 智人

<400> 32

Cys Thr Gly Thr Cys Ala Gly Cys Thr Gly Ala Gly Gly Ala Thr Cys
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 20 25 30
 Cys Ala Gly Gly Cys Ala Cys Thr Cys Ala Gly Gly Cys Cys Ala Cys
 35 40 45
 Cys Thr Gly Ala Gly Thr Cys Thr Ala Cys Thr Cys Ala Cys Cys Thr
 50 55 60
 Gly Gly Ala Cys Ala Ala Cys Thr Gly Gly Ala Ala Thr Cys Thr Gly
 65 70 75 80
 Gly Cys Ala Cys Cys Ala Ala Thr Thr Cys Thr Ala Ala Ala Cys Cys
 85 90 95
 Ala Cys Thr Cys Ala Gly Cys Thr Thr Cys Thr Cys Cys Gly Ala Gly
 100 105 110
 Cys Thr Cys Ala Cys Ala Cys Cys Cys Cys Gly Gly Ala Gly Ala Thr
 115 120 125
 Cys Ala Cys Cys Thr Gly Ala Gly Gly Ala Cys Cys Cys Gly Ala Gly
 130 135 140
 Cys Cys Ala Thr Thr Gly Ala Thr Gly Gly Ala Cys Thr Cys Gly Gly
 145 150 155 160

Ala Cys Gly Ala Gly Ala Cys Cys Gly Gly Gly Thr Thr Cys Gly Ala
 165 170 175
 Gly Cys Ala Cys Thr Cys Ala Gly Gly Ala Cys Thr Gly Thr Gly Gly
 180 185 190
 Gly Thr Thr Thr Cys Thr Gly Thr Gly Cys Thr Gly Gly Cys Thr Gly
 195 200 205
 Gly Thr Cys Thr Thr Cys Thr Gly Cys Thr Gly Gly Gly Ala Gly Cys
 210 215 220
 Cys Thr Gly Cys Cys Ala Gly Gly Cys Ala Cys Ala Cys Cys Cys Cys
 225 230 235 240
 Ala Thr Cys Cys Cys Thr Gly Ala Cys Thr Cys Cys Ala Gly Thr Cys
 245 250 255
 Cys Thr Cys Thr Cys Cys Thr Gly Cys Ala Ala Thr Thr Cys Gly Gly
 260 265 270
 Gly Gly Gly Cys Cys Ala Ala Gly Thr Cys Cys Gly Gly Cys Ala Gly
 275 280 285
 Cys Gly Gly Thr Ala Cys Cys Thr Cys Thr Ala Cys Ala Cys Ala Gly
 290 295 300
 Ala Thr Gly Ala Thr Gly Cys Cys Cys Ala Gly Cys Ala Gly Ala Cys
 305 310 315 320
 Ala Gly Ala Ala Gly Cys Cys Cys Ala Cys Cys Thr Gly Gly Ala Gly
 325 330 335
 Ala Thr Cys Ala Gly Gly Gly Ala Gly Gly Ala Thr Gly Gly Gly Ala
 340 345 350
 Cys Gly Gly Thr Gly Gly Gly Gly Gly Gly Cys Gly Cys Thr Gly Cys
 355 360 365
 Thr Gly Ala Cys Cys Ala Gly Ala Gly Cys Cys Cys Cys Gly Ala Ala
 370 375 380
 Ala Gly Thr Cys Thr Cys Cys Thr Gly Cys Ala Gly Cys Thr Gly Ala
 385 390 395 400
 Ala Ala Gly Cys Cys Thr Thr Gly Ala Ala Gly Cys Cys Gly Gly Gly
 405 410 415
 Ala Gly Thr Thr Ala Thr Thr Cys Ala Ala Ala Thr Cys Thr Thr Gly
 420 425 430
 Gly Gly Ala Gly Thr Cys Ala Ala Gly Ala Cys Ala Thr Cys Cys Ala
 435 440 445
 Gly Gly Thr Thr Cys Cys Thr Gly Thr Gly Cys Cys Ala Gly Cys Gly
 450 455 460

Gly Cys Cys Ala Gly Ala Thr Gly Gly Gly Gly Cys Cys Cys Thr Gly
465 470 475 480

Thr Ala Thr Gly Gly Ala Thr Cys Gly Cys Thr Cys Cys Ala Cys Thr
485 490 495

Thr Thr Gly Ala Cys Cys Cys Thr Gly Ala Gly Gly Cys Cys Thr Gly
500 505 510

Cys Ala Gly Cys Thr Thr Cys Cys Gly Gly Gly Ala Gly Cys Thr Gly
515 520 525

Cys Thr Thr Cys Thr Thr Gly Ala Gly Gly Ala Cys Gly Gly Ala Thr
530 535 540

Ala Cys Ala Ala Thr Gly Thr Thr Thr Ala Cys Cys Ala Gly Thr Cys
545 550 555 560

Cys Gly Ala Ala Gly Cys Cys Cys Ala Cys Gly Gly Cys Cys Thr Cys
565 570 575

Cys Cys Gly Cys Thr Gly Cys Ala Cys Cys Thr Gly Cys Cys Ala Gly
580 585 590

Gly Gly Ala Ala Cys Ala Ala Gly Thr Cys Cys Cys Cys Ala Cys Ala
595 600 605

Cys Cys Gly Gly Gly Ala Cys Cys Cys Thr Gly Cys Ala Cys Cys Cys
610 615 620

Cys Gly Ala Gly Gly Ala Cys Cys Ala Gly Cys Thr Cys Gly Cys Thr
625 630 635 640

Thr Cys Cys Thr Gly Cys Cys Ala Cys Thr Ala Cys Cys Ala Gly Gly
645 650 655

Cys Cys Thr Gly Cys Cys Cys Cys Cys Cys Gly Cys Ala Cys Thr Cys
660 665 670

Cys Cys Gly Gly Ala Gly Cys Cys Ala Cys Cys Cys Gly Gly Ala Ala
675 680 685

Thr Cys Cys Thr Gly Gly Cys Cys Cys Cys Cys Ala Gly Cys Cys
690 695 700

Cys Cys Cys Cys Gly Ala Thr Gly Thr Gly Gly Gly Cys Thr Cys Cys
705 710 715 720

Thr Cys Gly Gly Ala Cys Cys Cys Thr Cys Thr Gly Ala Gly Cys Ala
725 730 735

Thr Gly Gly Thr Gly Gly Gly Ala Cys Cys Thr Thr Cys Cys Cys Ala
740 745 750

Gly Gly Gly Cys Cys Gly Ala Ala Gly Cys Cys Cys Cys Ala Gly Cys

755	760	765
Thr Ala Cys Gly Cys Thr	Thr Cys Cys Thr Gly	Ala Ala Gly Cys Cys
770	775	780
Ala Gly Ala Gly Gly Cys	Thr Gly Thr Thr Thr	Ala Cys Thr Ala Thr
785	790	795
Gly Ala Cys Ala Thr	Cys Thr Cys Cys Thr	Cys Thr Thr Thr Ala Thr
805	810	815
Thr Thr Ala Thr	Thr Ala Gly Gly Thr	Thr Ala Thr Thr Thr
820	825	830
Cys Thr Thr Ala Thr	Thr Thr Thr Thr Thr	Thr Thr Thr Thr Ala
835	840	845
Thr Thr Thr Thr Thr Cys	Thr Thr Ala Cys Thr	Thr Gly Ala Gly Ala
850	855	860
Thr Ala Ala Thr Ala	Ala Ala Gly Ala Gly	Thr Thr Cys Cys Ala Gly
865	870	875
Ala Gly Gly Ala Gly	Ala Ala Ala Ala Ala	Ala Ala Ala Ala Ala
885	890	895
Ala Ala Ala Ala Ala	Ala Ala Ala Ala Ala	Ala Ala Ala Ala Ala
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<210> 33
 <211> 209
 <212> PRT
 <213> 智人
 <400> 33

Met Asp Ser Asp Glu Thr Gly Phe Glu His Ser Gly Leu Trp Val Ser
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Val Leu Ala Gly Leu Leu Leu Gly Ala Cys Gln Ala His Pro Ile Pro
20 25 30
Asp Ser Ser Pro Leu Leu Gln Phe Gly Gly Gln Val Arg Gln Arg Tyr
35 40 45
Leu Tyr Thr Asp Asp Ala Gln Gln Thr Glu Ala His Leu Glu Ile Arg
50 55 60
Glu Asp Gly Thr Val Gly Gly Ala Ala Asp Gln Ser Pro Glu Ser Leu
65 70 75 80
Leu Gln Leu Lys Ala Leu Lys Pro Gly Val Ile Gln Ile Leu Gly Val

	85		90		95
Lys Thr Ser Arg Phe Leu Cys Gln Arg Pro Asp Gly Ala Leu Tyr Gly	100	105	110		
Ser Leu His Phe Asp Pro Glu Ala Cys Ser Phe Arg Glu Leu Leu Leu	115	120	125		
Glu Asp Gly Tyr Asn Val Tyr Gln Ser Glu Ala His Gly Leu Pro Leu	130	135	140		
His Leu Pro Gly Asn Lys Ser Pro His Arg Asp Pro Ala Pro Arg Gly	145	150	155	160	
Pro Ala Arg Phe Leu Pro Leu Pro Gly Leu Pro Pro Ala Leu Pro Glu	165	170	175		
Pro Pro Gly Ile Leu Ala Pro Gln Pro Pro Asp Val Gly Ser Ser Asp	180	185	190		
Pro Leu Ser Met Val Gly Pro Ser Gln Gly Arg Ser Pro Ser Tyr Ala	195	200	205		

Ser

<210> 34
 <211> 3018
 <212> DNA
 <213> 智人

<400> 34
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 gcaccagcca ctacagagcag ggcacgatgt tgggggcccg cctcaggctc tgggtctgtg 180
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 agggctcgtg gaagggcacc ctctttaacc catccctcag caaacgcagc tcttcccaag 960
 gaccaggctc ctgacgttc cgaggatggg aaaggtaga ggggcaltga tggaaattgc 1020

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acactacttt caagccttcg ttcttccitt agcatctctg gggaagagct gtcaaaagac 1500
tgglggtagg cgggtgaaaa cttagacagct agactttagt ctgtctgaaa tgaggcagga 1560
atcataatag aaactcagc ctccctacag ggtgagcacc ttctgtctcg ctgtctccct 1620
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aatccaact ctccaaagag gcattlaatt aaggctctac ttccaggttg agtaggaatc 1860
cattctgaac aaactacaaa aalgtgactg ggaagggggc tttagagagc tgggactgct 1920
ctgggttagg ttttctgtg actgaaaaat cgtgtccttt tctctaaatg aagtggcatc 1980
aaggactcag ggggaagaa atcaggggac atgttataga agttatgaaa agacaaccac 2040
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tgittaaaat aaaaataaaa ttatctcag ctctgttag ctatctctt ttgtagtact 2820
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atccagagaa ggcaaaattg aaaaaagat tttagaattt laaaaatttc aaagatttct 2940
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caatatigga ttcttgtt 3018

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 <212> PRT
 <213> 智人
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Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
1 5 10 15

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
115 120 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
130 135 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145 150 155 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
165 170 175

His Thr Arg Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
180 185 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
195 200 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
210 215 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225 230 235 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
245 250

<210> 36
<211> 251
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<213> 智人

<400> 36

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
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Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
115 120 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
130 135 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145 150 155 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
165 170 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
180 185 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
195 200 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
210 215 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225 230 235 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
245 250

<210> 37
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<212> PRT
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<400> 37

Tyr Asp Thr Phe Pro Lys Asn Phe Phe Trp Gly Ile Gly Thr Gly Ala
1 5 10 15

Leu Gln Val Glu Gly Ser Trp Lys Lys Asp Gly Lys Gly Pro Ser Ile
20 25 30

Trp Asp His Phe Ile His Thr His Leu Lys Asn Val Ser Ser Thr Asn
35 40 45

Gly Ser Ser Asp Ser Tyr Ile Phe Leu Glu Lys Asp Leu Ser Ala Leu
50 55 60

Asp Phe Ile Gly Val Ser Phe Tyr Gln Phe Ser Ile Ser Trp Pro Arg
65 70 75 80

Leu Phe Pro Asp Gly Ile Val Thr Val Ala Asn Ala Lys Gly Leu Gln
85 90 95

Tyr Tyr Ser Thr Leu Leu Asp Ala Leu Val Leu Arg Asn Ile Glu Pro
100 105 110

Ile Val Thr Leu Tyr His Trp Asp Leu Pro Leu Ala Leu Gln Glu Lys
115 120 125

Tyr Gly Gly Trp Lys Asn Asp Thr Ile Ile Asp Ile Phe Asn Asp Tyr
130 135 140

Ala Thr Tyr Cys Phe Gln Met Phe Gly Asp Arg Val Lys Tyr Trp Ile
145 150 155 160

Thr Ile His Asn Pro Tyr Leu Val Ala Trp His Gly Tyr Gly Thr Gly
165 170 175

Met His Ala Pro Gly Glu Lys Gly Asn Leu Ala Ala Val Tyr Thr Val
180 185 190

Gly His Asn Leu Ile Lys Ala His Ser Lys Val Trp His Asn Tyr Asn
195 200 205

Thr His Phe Arg Pro His Gln Lys Gly Trp Leu Ser Ile Thr Leu Gly
210 215 220

Ser His Trp Ile Glu Pro Asn Arg Ser Glu Asn Thr Met Asp Ile Phe
225 230 235 240

Lys Cys Gln Gln Ser Met Val Ser Val Leu Gly Trp Phe Ala Asn Pro
245 250 255

Ile His Gly Asp Gly Asp Tyr Pro Glu Gly Met Arg Lys Lys Leu Phe
260 265 270

Ser Val Leu Pro Ile Phe Ser Glu Ala Glu Lys His Glu Met Arg Gly
275 280 285

Thr Ala Asp Phe Phe Ala Phe Ser Phe Gly Pro Asn Asn Phe Lys Pro
290 295 300

Leu Asn Thr Met Ala Lys Met Gly Gln Asn Val Ser Leu Asn Leu Arg
305 310 315 320

Glu Ala Leu Asn Trp Ile Lys Leu Glu Tyr Asn Asn Pro Arg Ile Leu
325 330 335

Ile Ala Glu Asn Gly Trp Phe Thr Asp Ser Arg Val Lys Thr Glu Asp
 340 345 350
 Thr Thr Ala Ile Tyr Met Met Lys Asn Phe Leu Ser Gln Val Leu Gln
 355 360 365
 Ala Ile Arg Leu Asp Glu Ile Arg Val Phe Gly Tyr Thr Ala Trp Ser
 370 375 380
 Leu Leu Asp Gly Phe Glu Trp Gln Asp Ala Tyr Thr Ile Arg Arg Gly
 385 390 395 400
 Leu Phe Tyr Val Asp Phe Asn Ser Lys Gln Lys Glu Arg Lys Pro Lys
 405 410 415
 Ser Ser Ala His Tyr Tyr Lys Gln Ile Ile Arg Glu Asn Gly Phe
 420 425 430
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 <213> 智人
 <400> 38
 Thr Arg Pro Ala Gln Cys Thr Asp Phe Val Asn Ile Lys Lys Gln Leu
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 Glu Met Leu Ala Arg Met Lys Val Thr His Tyr Arg Phe Ala Leu Asp
 20 25 30
 Trp Ala Ser Val Leu Pro Thr Gly Asn Leu Ser Ala Val Asn Arg Gln
 35 40 45
 Ala Leu Arg Tyr Tyr Arg Cys Val Val Ser Glu Gly Leu Lys Leu Gly
 50 55 60
 Ile Ser Ala Met Val Thr Leu Tyr Tyr Pro Thr His Ala His Leu Gly
 65 70 75 80
 Leu Pro Glu Pro Leu Leu His Ala Asp Gly Trp Leu Asn Pro Ser Thr
 85 90 95
 Ala Glu Ala Phe Gln Ala Tyr Ala Gly Leu Cys Phe Gln Glu Leu Gly
 100 105 110
 Asp Leu Val Lys Leu Trp Ile Thr Ile Asn Glu Pro Asn Arg Leu Ser
 115 120 125
 Asp Ile Tyr Asn Arg Ser Gly Asn Asp Thr Tyr Gly Ala Ala His Asn
 130 135 140
 Leu Leu Val Ala His Ala Leu Ala Trp Arg Leu Tyr Asp Arg Gln Phe
 145 150 155 160
 Arg Pro Ser Gln Arg Gly Ala Val Ser Leu Ser Leu His Ala Asp Trp
 165 170 175

Ala Glu Pro Ala Asn Pro Tyr Ala Asp Ser His Trp Arg Ala Ala Glu
180 185 190

Arg Phe Leu Gln Phe Glu Ile Ala Trp Phe Ala Glu Pro Leu Phe Lys
195 200 205

Thr Gly Asp Tyr Pro Ala Ala Met Arg Glu Tyr Ile Ala Ser Lys His
210 215 220

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

Arg Arg Leu Leu Lys Gly Thr Val Asp Phe Cys Ala Leu Asn His Phe
245 250 255

Thr Thr Arg Phe Val Met His Glu Gln Leu Ala Gly Ser Arg Tyr Asp
260 265 270

Ser Asp Arg Asp Ile Gln Phe Leu Gln Asp Ile Thr Arg Leu Ser Ser
275 280 285

Pro Thr Arg Leu Ala Val Ile Pro Trp Gly Val Arg Lys Leu Leu Arg
290 295 300

Trp Val Arg Arg Asn Tyr Gly Asp Met Asp Ile Tyr Ile Thr Ala Ser
305 310 315 320

Gly Ile Asp Asp Gln Ala Leu Glu Asp Asp Arg Leu Arg Lys Tyr Tyr
325 330 335

Leu Gly Lys Tyr Leu Gln Glu Val Leu Lys Ala Tyr Leu Ile Asp Lys
340 345 350

Val Arg Ile Lys Gly Tyr Tyr Ala Phe Lys Leu Ala Glu Glu Lys Ser
355 360 365

Lys Pro Arg Phe Gly Phe Phe Thr Ser Asp Phe Lys Ala Lys Ser Ser
370 375 380

Ile Gln Phe Tyr Asn Lys Val Ile Ser Ser Arg Gly Phe
385 390 395

<210> 39
<211> 946
<212> PRT
<213> 智人

<400> 39

Gly Phe Ser Gly Asp Gly Arg Ala Ile Trp Ser Lys Asn Pro Asn Phe
1 5 10 15

Thr Pro Val Asn Glu Ser Gln Leu Phe Leu Tyr Asp Thr Phe Pro Lys
20 25 30

Asn Phe Phe Trp Gly Ile Gly Thr Gly Ala Leu Gln Val Glu Gly Ser
35 40 45

Trp Lys Lys Asp Gly Lys Gly Pro Ser Ile Trp Asp His Phe Ile His
50 55 60

Thr His Leu Lys Asn Val Ser Ser Thr Asn Gly Ser Ser Asp Ser Tyr
65 70 75 80

Ile Phe Leu Glu Lys Asp Leu Ser Ala Leu Asp Phe Ile Gly Val Ser
85 90 95

Phe Tyr Gln Phe Ser Ile Ser Trp Pro Arg Leu Phe Pro Asp Gly Ile
100 105 110

Val Thr Val Ala Asn Ala Lys Gly Leu Gln Tyr Tyr Ser Thr Leu Leu
115 120 125

Asp Ala Leu Val Leu Arg Asn Ile Glu Pro Ile Val Thr Leu Tyr His
130 135 140

Trp Asp Leu Pro Leu Ala Leu Gln Glu Lys Tyr Gly Gly Trp Lys Asn
145 150 155 160

Asp Thr Ile Ile Asp Ile Phe Asn Asp Tyr Ala Thr Tyr Cys Phe Gln
165 170 175

Met Phe Gly Asp Arg Val Lys Tyr Trp Ile Thr Ile His Asn Pro Tyr
180 185 190

Leu Val Ala Trp His Gly Tyr Gly Thr Gly Met His Ala Pro Gly Glu
195 200 205

Lys Gly Asn Leu Ala Ala Val Tyr Thr Val Gly His Asn Leu Ile Lys
210 215 220

Ala His Ser Lys Val Trp His Asn Tyr Asn Thr His Phe Arg Pro His
225 230 235 240

Gln Lys Gly Trp Leu Ser Ile Thr Leu Gly Ser His Trp Ile Glu Pro
245 250 255

Asn Arg Ser Glu Asn Thr Met Asp Ile Phe Lys Cys Gln Gln Ser Met
260 265 270

Val Ser Val Leu Gly Trp Phe Ala Asn Pro Ile His Gly Asp Gly Asp
275 280 285

Tyr Pro Glu Gly Met Arg Lys Lys Leu Phe Ser Val Leu Pro Ile Phe
290 295 300

Ser Glu Ala Glu Lys His Glu Met Arg Gly Thr Ala Asp Phe Phe Ala
305 310 315 320

Phe Ser Phe Gly Pro Asn Asn Phe Lys Pro Leu Asn Thr Met Ala Lys
325 330 335

Met Gly Gln Asn Val Ser Leu Asn Leu Arg Glu Ala Leu Asn Trp Ile

340	345	350
Lys Leu Glu Tyr Asn Asn Pro Arg Ile Leu Ile Ala Glu Asn Gly Trp 355 360 365		
Phe Thr Asp Ser Arg Val Lys Thr Glu Asp Thr Thr Ala Ile Tyr Met 370 375 380		
Met Lys Asn Phe Leu Ser Gln Val Leu Gln Ala Ile Arg Leu Asp Glu 385 390 395 400		
Ile Arg Val Phe Gly Tyr Thr Ala Trp Ser Leu Leu Asp Gly Phe Glu 405 410 415		
Trp Gln Asp Ala Tyr Thr Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe 420 425 430		
Asn Ser Lys Gln Lys Glu Arg Lys Pro Lys Ser Ser Ala His Tyr Tyr 435 440 445		
Lys Gln Ile Ile Arg Glu Asn Gly Phe Ser Leu Lys Glu Ser Thr Pro 450 455 460		
Asp Val Gln Gly Gln Phe Pro Cys Asp Phe Ser Trp Gly Val Thr Glu 465 470 475 480		
Ser Val Leu Lys Pro Glu Ser Val Ala Ser Ser Pro Gln Phe Ser Asp 485 490 495		
Pro His Leu Tyr Val Trp Asn Ala Thr Gly Asn Arg Leu Leu His Arg 500 505 510		
Val Glu Gly Val Arg Leu Lys Thr Arg Pro Ala Gln Cys Thr Asp Phe 515 520 525		
Val Asn Ile Lys Lys Gln Leu Glu Met Leu Ala Arg Met Lys Val Thr 530 535 540		
His Tyr Arg Phe Ala Leu Asp Trp Ala Ser Val Leu Pro Thr Gly Asn 545 550 555 560		
Leu Ser Ala Val Asn Arg Gln Ala Leu Arg Tyr Tyr Arg Cys Val Val 565 570 575		
Ser Glu Gly Leu Lys Leu Gly Ile Ser Ala Met Val Thr Leu Tyr Tyr 580 585 590		
Pro Thr His Ala His Leu Gly Leu Pro Glu Pro Leu Leu His Ala Asp 595 600 605		
Gly Trp Leu Asn Pro Ser Thr Ala Glu Ala Phe Gln Ala Tyr Ala Gly 610 615 620		
Leu Cys Phe Gln Glu Leu Gly Asp Leu Val Lys Leu Trp Ile Thr Ile 625 630 635 640		

Asn Glu Pro Asn Arg Leu Ser Asp Ile Tyr Asn Arg Ser Gly Asn Asp
 645 650 655
 Thr Tyr Gly Ala Ala His Asn Leu Leu Val Ala His Ala Leu Ala Trp
 660 665 670
 Arg Leu Tyr Asp Arg Gln Phe Arg Pro Ser Gln Arg Gly Ala Val Ser
 675 680 685
 Leu Ser Leu His Ala Asp Trp Ala Glu Pro Ala Asn Pro Tyr Ala Asp
 690 695 700
 Ser His Trp Arg Ala Ala Glu Arg Phe Leu Gln Phe Glu Ile Ala Trp
 705 710 715 720
 Phe Ala Glu Pro Leu Phe Lys Thr Gly Asp Tyr Pro Ala Ala Met Arg
 725 730 735
 Glu Tyr Ile Ala Ser Lys His Arg Arg Gly Leu Ser Ser Ser Ala Leu
 740 745 750
 Pro Arg Leu Thr Glu Ala Glu Arg Arg Leu Leu Lys Gly Thr Val Asp
 755 760 765
 Phe Cys Ala Leu Asn His Phe Thr Thr Arg Phe Val Met His Glu Gln
 770 775 780
 Leu Ala Gly Ser Arg Tyr Asp Ser Asp Arg Asp Ile Gln Phe Leu Gln
 785 790 795 800
 Asp Ile Thr Arg Leu Ser Ser Pro Thr Arg Leu Ala Val Ile Pro Trp
 805 810 815
 Gly Val Arg Lys Leu Leu Arg Trp Val Arg Arg Asn Tyr Gly Asp Met
 820 825 830
 Asp Ile Tyr Ile Thr Ala Ser Gly Ile Asp Asp Gln Ala Leu Glu Asp
 835 840 845
 Asp Arg Leu Arg Lys Tyr Tyr Leu Gly Lys Tyr Leu Gln Glu Val Leu
 850 855 860
 Lys Ala Tyr Leu Ile Asp Lys Val Arg Ile Lys Gly Tyr Tyr Ala Phe
 865 870 875 880
 Lys Leu Ala Glu Glu Lys Ser Lys Pro Arg Phe Gly Phe Phe Thr Ser
 885 890 895
 Asp Phe Lys Ala Lys Ser Ser Ile Gln Phe Tyr Asn Lys Val Ile Ser
 900 905 910
 Ser Arg Gly Phe Pro Phe Glu Asn Ser Ser Ser Arg Cys Ser Gln Thr
 915 920 925
 Gln Glu Asn Thr Glu Cys Thr Val Cys Leu Phe Leu Val Gln Lys Lys
 930 935 940

Pro Leu
945

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<213> 智人

<400> 40

Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro Pro
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Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
20 25 30

Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45

Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60

Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80

Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95

Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110

His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125

Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140

Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160

Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175

Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190

His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205

Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
210 215 220

Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
225 230 235 240

Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
245 250 255

Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
260 265 270

Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
275 280 285

Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
290 295 300

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
305 310 315 320

Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
325 330 335

Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
340 345 350

Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
355 360 365

Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
370 375 380

Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
385 390 395 400

Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
405 410 415

Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
420 425 430

Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
435 440 445

Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
450 455 460

Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
465 470 475 480

Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
485 490 495

Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
500 505 510

Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
515 520 525

Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
530 535 540

Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545 550 555 560

Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575

Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590

Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
595 600 605

Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
610 615 620

Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640

Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655

Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670

Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685

Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700

Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705 710 715 720

Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735

Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750

Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765

Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780

Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800

Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815

Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830

Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845

Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu

850	855	860
Ala Leu Lys Ala His 865	Ile Leu Asp Gly Ile 870	Asn Leu Cys Gly Tyr Phe 880
Ala Tyr Ser Phe 885	Asn Asp Arg Thr Ala 890	Pro Arg Phe Gly Leu Tyr Arg 895
Tyr Ala Ala 900	Asp Gln Phe Glu Pro Lys 905	Ala Ser Met Lys His Tyr Arg 910
Lys Ile 915	Ile Asp Ser Asn Gly Phe 920	Pro Gly Pro Glu Thr Leu Glu Arg 925
Phe Cys 930	Pro Glu Glu Phe Thr Val 935	Cys Thr Glu Cys Ser Phe Phe His 940
Thr Arg Lys Ser Leu 945	Gly Ser Gly Gly Gly 950	Gly Ser Gly Gly Gly Gly 955
Ser Gly Gly Gly 965	Gly Ser Leu Lys Tyr 970	Pro Asn Ala Ser Pro Leu Leu 975
Gly Ser Ser 980	Trp Gly Gly Leu Ile His 985	Leu Tyr Thr Ala Thr Ala Arg 990
Asn Ser Tyr His Leu Gln 995	Ile His Lys Asn Gly His Val 1000	Asp Gly Ala 1005
Pro His 1010	Gln Thr Ile Tyr Ser 1015	Ala Leu Met Ile Arg Ser Glu Asp 1020
Ala Gly 1025	Phe Val Val Ile Thr 1030	Gly Val Met Ser Arg Arg Tyr Leu 1035
Cys Met 1040	Asp Phe Arg Gly Asn 1045	Ile Phe Gly Ser His Tyr Phe Asp 1050
Pro Glu 1055	Asn Cys Arg Phe Gln 1060	His Gln Thr Leu Glu Asn Gly Tyr 1065
Asp Val 1070	Tyr His Ser Pro Gln 1075	Tyr His Phe Leu Val Ser Leu Gly 1080
Arg Ala 1085	Lys Arg Ala Phe Leu 1090	Pro Gly Met Asn Pro Pro Pro Tyr 1095
Ser Gln 1100	Phe Leu Ser Arg Arg 1105	Asn Glu Ile Pro Leu Ile His Phe 1110
Asn Thr 1115	Pro Ile Pro Arg Arg 1120	His Thr Arg Ser Ala Glu Asp Asp 1125
Ser Glu 1130	Arg Asp Pro Leu Asn 1135	Val Leu Lys Pro Arg Ala Arg Met 1140

Thr Pro Ala Pro Ala Ser Cys Ser Gln Glu Leu Pro Ser Ala Glu
1145 1150 1155

Asp Asn Ser Pro Met Ala Ser Asp Pro Leu Gly Val Val Arg Gly
1160 1165 1170

Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly Pro Glu Gly Cys
1175 1180 1185

Arg Pro Phe Ala Lys Phe Ile
1190 1195

<210> 41
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<212> PRT
<213> 智人
<400> 41

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

Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly Phe
20 25 30

Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp Gln
35 40 45

Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His Pro
50 55 60

Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly Ala
65 70 75 80

Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser Tyr
85 90 95

Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val Thr
100 105 110

His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly Ser
115 120 125

Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu Leu
130 135 140

Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr His
145 150 155 160

Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala Asn
165 170 175

Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe Arg
180 185 190

His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro Tyr
195 200 205

Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly Ile
 210 215 220

Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu Leu
 225 230 235 240

Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro Thr
 245 250 255

Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn Pro
 260 265 270

Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu Asp
 275 280 285

Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp Tyr
 290 295 300

Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe Thr
 305 310 315 320

Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala Leu
 325 330 335

Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met Lys
 340 345 350

Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp Ile
 355 360 365

Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly Trp
 370 375 380

Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr Tyr
 385 390 395 400

Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp Gly
 405 410 415

Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe Glu
 420 425 430

Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp Phe
 435 440 445

Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe Tyr
 450 455 460

Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn Gln
 465 470 475 480

Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val Asp
 485 490 495

Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu Asn
 500 505 510

Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val Asp
515 520 525

Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala Ala
530 535 540

Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His Phe
545 550 555 560

Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln Ser
565 570 575

Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser Glu
580 585 590

Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro Met
595 600 605

Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala Trp
610 615 620

Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu Cys
625 630 635 640

Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn Glu
645 650 655

Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu Lys
660 665 670

Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His Ala
675 680 685

Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu Pro
690 695 700

Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val Leu
705 710 715 720

Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly Asp
725 730 735

Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe Leu
740 745 750

Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr Phe
755 760 765

Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser Glu
770 775 780

Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu Met
785 790 795 800

Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val Pro
805 810 815

Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly Asp
820 825 830

Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His Ala
835 840 845

Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn Glu
850 855 860

Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr Phe
865 870 875 880

Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr Arg
885 890 895

Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr Arg
900 905 910

Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu Arg
915 920 925

Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe His
930 935 940

Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
945 950 955 960

Ser Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn Ala Ser Pro Leu Leu
965 970 975

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
980 985 990

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Al
995 1000 1005

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp
1010 1015 1020

Ala Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu
1025 1030 1035

Cys Met Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp
1040 1045 1050

Pro Glu Asn Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr
1055 1060 1065

Asp Val Tyr His Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly
1070 1075 1080

Arg Ala Lys Arg Ala Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr
1085 1090 1095

Ser Gln Phe Leu Ser Arg Arg Asn Glu Ile Pro Leu Ile His Phe

1100	1105	1110
Asn Thr Pro Ile Pro Arg Arg His Thr Gln Ser Ala Glu Asp Asp		
1115	1120	1125
Ser Glu Arg Asp Pro Leu Asn Val Leu Lys Pro Arg Ala Arg Met		
1130	1135	1140
Thr Pro Ala Pro Ala Ser Cys Ser Gln Glu Leu Pro Ser Ala Glu		
1145	1150	1155
Asp Asn Ser Pro Met Ala Ser Asp Pro Leu Gly Val Val Arg Gly		
1160	1165	1170
Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly Pro Glu Gly Cys		
1175	1180	1185
Arg Pro Phe Ala Lys Phe Ile		
1190	1195	
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Tyr Pro Asn Ala Ser Pro Leu Leu Gly Ser Ser Trp Gly Gly Leu Ile		
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His Leu Tyr Thr Ala Thr Ala Arg Asn Ser Tyr His Leu Gln Ile His		
20	25	30
Lys Asn Gly His Val Asp Gly Ala Pro His Gln Thr Ile Tyr Ser Ala		
35	40	45
Leu Met Ile Arg Ser Glu Asp Ala Gly Phe Val Val Ile Thr Gly Val		
50	55	60
Met Ser Arg Arg Tyr Leu Cys Met Asp Phe Arg Gly Asn Ile Phe Gly		
65	70	75 80
Ser His Tyr Phe Asp Pro Glu Asn Cys Arg Phe Gln His Gln Thr Leu		
85	90	95
Glu Asn Gly Tyr Asp Val Tyr His Ser Pro Gln Tyr His Phe Leu Val		
100	105	110
Ser Leu Gly Arg Ala Lys Arg Ala Phe Leu Pro Gly Met Asn Pro Pro		
115	120	125
Pro Tyr Ser Gln Phe Leu Ser Arg Arg Asn Glu Ile Pro Leu Ile His		
130	135	140
Phe Asn Thr Pro Ile Pro Arg Arg His Thr Arg Ser Ala Glu Asp Asp		
145	150	155 160
Ser Glu Arg Asp Pro Leu Asn Val Leu Lys Pro Arg Ala Arg Met Thr		

	165		170		175
Pro	Ala	Pro	Ala	Ser	Cys
	180				
		Ser	Gln	Glu	Leu
			185		
		Pro	Ser	Ala	Glu
				190	Asp
		Asn			
Ser	Pro	Met	Ala	Ser	Asp
	195				
		Pro	Leu	Gly	Val
		200			
		Val	Arg	Gly	Gly
			205		Arg
		Val			
Asn	Thr	His	Ala	Gly	Gly
	210				
		Thr	Gly	Pro	Glu
		215			
		Gly	Cys	Arg	Pro
			220		Phe
					Ala
Lys	Phe	Ile			
225					
<210>	43				
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<212>	PRT				
<213>	智人				
<400>	43				
Tyr	Pro	Asn	Ala	Ser	Pro
1		5			
		Leu	Leu	Gly	Ser
			10		
		Ser	Ser	Trp	Gly
					Gly
					Leu
					15
His	Leu	Tyr	Thr	Ala	Thr
	20				
		Arg	Asn	Ser	Tyr
		25			
		His	Leu	Gln	Ile
			30		His
Lys	Asn	Gly	His	Val	Asp
	35				
		Gly	Ala	Pro	His
		40			
		Gln	Thr	Ile	Tyr
		45			Ser
					Ala
Leu	Met	Ile	Arg	Ser	Glu
	50				
		Asp	Ala	Gly	Phe
		55			
		Val	Val	Ile	Thr
		60			Gly
					Val
Met	Ser	Arg	Arg	Tyr	Leu
	65				
		Cys	Met	Asp	Phe
		70			
		Arg	Gly	Asn	Ile
		75			
					Phe
					80
Ser	His	Tyr	Phe	Asp	Pro
		Pro	Glu	Asn	Cys
		Arg	Phe	Gln	His
		90			
		Gln	Thr	Leu	
				95	
Glu	Asn	Gly	Tyr	Asp	Val
		Tyr	His	Ser	Pro
		100			
					Gln
					Tyr
					His
					Phe
					Leu
					Val
Ser	Leu	Gly	Arg	Ala	Lys
	115				
		Arg	Ala	Phe	Leu
		120			
		Pro	Gly	Met	Asn
					Pro
					Pro
Pro	Tyr	Ser	Gln	Phe	Leu
	130				
		Ser	Arg	Arg	Asn
		135			
		Glu	Ile	Pro	Leu
					Ile
					His
Phe	Asn	Thr	Pro	Ile	Pro
	145				
		Arg	Arg	His	Thr
		150			
		Gln	Ser	Ala	Glu
		155			
					Asp
					Asp
Ser	Glu	Arg	Asp	Pro	Leu
		Asn	Val	Leu	Lys
		165			
		Pro	Arg	Ala	Arg
					Met
					Thr
					175
Pro	Ala	Pro	Ala	Ser	Cys
	180				
		Ser	Gln	Glu	Leu
		Pro	Ser	Ala	Glu
					Asp
					Asn
Ser	Pro	Met	Ala	Ser	Asp
		Pro	Leu	Gly	Val
		Val	Arg	Gly	Gly
					Arg
					Val

195	200	205
Asn Thr His Ala Gly Gly Thr Gly Pro Glu Gly Cys Arg Pro Phe Ala 210 215 220		
Lys Phe Ile 225		
<210> 44 <211> 982 <212> PRT <213> 智人 <400> 44		
Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Ser 1 5 10 15		
Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg 20 25 30		
Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro 35 40 45		
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly 50 55 60		
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp 65 70 75 80		
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His 85 90 95		
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly 100 105 110		
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser 115 120 125		
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val 130 135 140		
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly 145 150 155 160		
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu 165 170 175		
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr 180 185 190		
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala 195 200 205		
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe 210 215 220		
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro		

225		230		235		240
Tyr Val Val Ala	Trp His Gly Tyr Ala	Thr Gly Arg Leu Ala	Pro Gly			
	245		250		255	
Ile Arg Gly Ser	Pro Arg Leu Gly Tyr	Leu Val Ala His	Asn Leu Leu			
	260		265		270	
Leu Ala His Ala	Lys Val Trp His	Leu Tyr Asn Thr	Ser Phe Arg Pro			
	275		280		285	
Thr Gln Gly Gly	Gln Val Ser Ile Ala Leu Ser	Ser His Trp Ile Asn				
	290		295		300	
Pro Arg Arg Met	Thr Asp His Ser Ile Lys	Glu Cys Gln Lys Ser	Leu			
305		310		315		320
Asp Phe Val Leu	Gly Trp Phe Ala Lys	Pro Val Phe Ile Asp	Gly Asp			
	325		330		335	
Tyr Pro Glu Ser	Met Lys Asn Asn Leu Ser	Ser Ile Leu Pro Asp	Phe			
	340		345		350	
Thr Glu Ser Glu	Lys Lys Phe Ile Lys Gly Thr	Ala Asp Phe Phe Ala				
	355		360		365	
Leu Cys Phe Gly	Pro Thr Leu Ser Phe Gln Leu	Leu Asp Pro His Met				
	370		375		380	
Lys Phe Arg Gln	Leu Glu Ser Pro Asn Leu Arg	Gln Leu Leu Ser Trp				
385		390		395		400
Ile Asp Leu Glu	Phe Asn His Pro Gln Ile Phe	Ile Val Glu Asn Gly				
	405		410		415	
Trp Phe Val Ser	Gly Thr Thr Lys Arg Asp Asp	Ala Lys Tyr Met Tyr				
	420		425		430	
Tyr Leu Lys Lys	Phe Ile Met Glu Thr Leu Lys	Ala Ile Lys Leu Asp				
	435		440		445	
Gly Val Asp Val	Ile Gly Tyr Thr Ala Trp Ser	Leu Met Asp Gly Phe				
	450		455		460	
Glu Trp His Arg	Gly Tyr Ser Ile Arg Arg Gly	Leu Phe Tyr Val Asp				
465		470		475		480
Phe Leu Ser Gln	Asp Lys Met Leu Leu Pro	Lys Ser Ser Ala Leu Phe				
	485		490		495	
Tyr Gln Lys Leu	Ile Glu Lys Asn Gly Phe Pro	Pro Leu Pro Glu Asn				
	500		505		510	
Gln Pro Leu Glu	Gly Thr Phe Pro Cys Asp Phe	Ala Trp Gly Val Val				
	515		520		525	

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545 550 555 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575

Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
580 585 590

Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
595 600 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
610 615 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625 630 635 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
645 650 655

Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
660 665 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
675 680 685

Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
690 695 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705 710 715 720

Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
725 730 735

Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
740 745 750

Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
755 760 765

Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
770 775 780

Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
785 790 795 800

Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
805 810 815

Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
820 825 830

Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
835 840 845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
850 855 860

Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865 870 875 880

Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
885 890 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
900 905 910

Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
915 920 925

Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
930 935 940

Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945 950 955 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
965 970 975

His Thr Arg Lys Ser Leu
980

<210> 45
<211> 974
<212> PRT
<213> 智人

<400> 45

Met Ser Val Leu Thr Gln Val Leu Ala Leu Leu Leu Trp Leu Thr
1 5 10 15

Gly Leu Gly Gly Arg Arg Leu Arg Ala Glu Pro Gly Asp Gly Ala Gln
20 25 30

Thr Trp Ala Arg Phe Ser Arg Pro Pro Ala Pro Glu Ala Ala Gly Leu
35 40 45

Phe Gln Gly Thr Phe Pro Asp Gly Phe Leu Trp Ala Val Gly Ser Ala
50 55 60

Ala Tyr Gln Thr Glu Gly Gly Trp Gln Gln His Gly Lys Gly Ala Ser
65 70 75 80

Ile Trp Asp Thr Phe Thr His His Pro Leu Ala Pro Pro Gly Asp Ser
85 90 95

Arg Asn Ala Ser Leu Pro Leu Gly Ala Pro Ser Pro Leu Gln Pro Ala
100 105 110

Thr Gly Asp Val Ala Ser Asp Ser Tyr Asn Asn Val Phe Arg Asp Thr
115 120 125

Glu Ala Leu Arg Glu Leu Gly Val Thr His Tyr Arg Phe Ser Ile Ser
130 135 140

Trp Ala Arg Val Leu Pro Asn Gly Ser Ala Gly Val Pro Asn Arg Glu
145 150 155 160

Gly Leu Arg Tyr Tyr Arg Arg Leu Leu Glu Arg Leu Arg Glu Leu Gly
165 170 175

Val Gln Pro Val Val Thr Leu Tyr His Trp Asp Leu Pro Gln Arg Leu
180 185 190

Gln Asp Ala Tyr Gly Gly Trp Ala Asn Arg Ala Leu Ala Asp His Phe
195 200 205

Arg Asp Tyr Ala Glu Leu Cys Phe Arg His Phe Gly Gly Gln Val Lys
210 215 220

Tyr Trp Ile Thr Ile Asp Asn Pro Tyr Val Val Ala Trp His Gly Tyr
225 230 235 240

Ala Thr Gly Arg Leu Ala Pro Gly Ile Arg Gly Ser Pro Arg Leu Gly
245 250 255

Tyr Leu Val Ala His Asn Leu Leu Leu Ala His Ala Lys Val Trp His
260 265 270

Leu Tyr Asn Thr Ser Phe Arg Pro Thr Gln Gly Gly Gln Val Ser Ile
275 280 285

Ala Leu Ser Ser His Trp Ile Asn Pro Arg Arg Met Thr Asp His Ser
290 295 300

Ile Lys Glu Cys Gln Lys Ser Leu Asp Phe Val Leu Gly Trp Phe Ala
305 310 315 320

Lys Pro Val Phe Ile Asp Gly Asp Tyr Pro Glu Ser Met Lys Asn Asn
325 330 335

Leu Ser Ser Ile Leu Pro Asp Phe Thr Glu Ser Glu Lys Lys Phe Ile
340 345 350

Lys Gly Thr Ala Asp Phe Phe Ala Leu Cys Phe Gly Pro Thr Leu Ser
355 360 365

Phe Gln Leu Leu Asp Pro His Met Lys Phe Arg Gln Leu Glu Ser Pro
370 375 380

Asn Leu Arg Gln Leu Leu Ser Trp Ile Asp Leu Glu Phe Asn His Pro
385 390 395 400

Gln Ile Phe Ile Val Glu Asn Gly Trp Phe Val Ser Gly Thr Thr Lys
405 410 415

Arg Asp Asp Ala Lys Tyr Met Tyr Tyr Leu Lys Lys Phe Ile Met Glu
420 425 430

Thr Leu Lys Ala Ile Lys Leu Asp Gly Val Asp Val Ile Gly Tyr Thr
435 440 445

Ala Trp Ser Leu Met Asp Gly Phe Glu Trp His Arg Gly Tyr Ser Ile
450 455 460

Arg Arg Gly Leu Phe Tyr Val Asp Phe Leu Ser Gln Asp Lys Met Leu
465 470 475 480

Leu Pro Lys Ser Ser Ala Leu Phe Tyr Gln Lys Leu Ile Glu Lys Asn
485 490 495

Gly Phe Pro Pro Leu Pro Glu Asn Gln Pro Leu Glu Gly Thr Phe Pro
500 505 510

Cys Asp Phe Ala Trp Gly Val Val Asp Asn Tyr Ile Gln Val Asp Thr
515 520 525

Thr Leu Ser Gln Phe Thr Asp Leu Asn Val Tyr Leu Trp Asp Val His
530 535 540

His Ser Lys Arg Leu Ile Lys Val Asp Gly Val Val Thr Lys Lys Arg
545 550 555 560

Lys Ser Tyr Cys Val Asp Phe Ala Ala Ile Gln Pro Gln Ile Ala Leu
565 570 575

Leu Gln Glu Met His Val Thr His Phe Arg Phe Ser Leu Asp Trp Ala
580 585 590

Leu Ile Leu Pro Leu Gly Asn Gln Ser Gln Val Asn His Thr Ile Leu
595 600 605

Gln Tyr Tyr Arg Cys Met Ala Ser Glu Leu Val Arg Val Asn Ile Thr
610 615 620

Pro Val Val Ala Leu Trp Gln Pro Met Ala Pro Asn Gln Gly Leu Pro
625 630 635 640

Arg Leu Leu Ala Arg Gln Gly Ala Trp Glu Asn Pro Tyr Thr Ala Leu
645 650 655

Ala Phe Ala Glu Tyr Ala Arg Leu Cys Phe Gln Glu Leu Gly His His
660 665 670

Val Lys Leu Trp Ile Thr Met Asn Glu Pro Tyr Thr Arg Asn Met Thr
675 680 685

Tyr Ser Ala Gly His Asn Leu Leu Lys Ala His Ala Leu Ala Trp His
690 695 700

Val Tyr Asn Glu Lys Phe Arg His Ala Gln Asn Gly Lys Ile Ser Ile

705	710	715	720
Ala Leu Gln Ala	Asp Trp Ile Glu Pro	Ala Cys Pro Phe Ser	Gln Lys
	725	730	735
Asp Lys Glu Val	Ala Glu Arg Val	Leu Glu Phe Asp Ile	Gly Trp Leu
	740	745	750
Ala Glu Pro Ile	Phe Gly Ser Gly Asp Tyr Pro	Trp Val Met Arg Asp	
	755	760	765
Trp Leu Asn Gln Arg	Asn Asn Phe Leu Leu Pro	Tyr Phe Thr Glu Asp	
	770	775	780
Glu Lys Lys Leu Ile	Gln Gly Thr Phe Asp	Phe Leu Ala Leu Ser	His
	785	790	800
Tyr Thr Thr Ile	Leu Val Asp Ser Glu	Lys Glu Asp Pro Ile	Lys Tyr
	805	810	815
Asn Asp Tyr Leu	Glu Val Gln Glu Met Thr	Asp Ile Thr Trp	Leu Asn
	820	825	830
Ser Pro Ser Gln	Val Ala Val Val Pro	Trp Gly Leu Arg	Lys Val Leu
	835	840	845
Asn Trp Leu Lys Phe	Lys Tyr Gly Asp Leu Pro	Met Tyr Ile Ile Ser	
	850	855	860
Asn Gly Ile Asp	Asp Gly Leu His Ala Glu	Asp Asp Gln Leu Arg	Val
	865	870	875
Tyr Tyr Met Gln	Asn Tyr Ile Asn Glu	Ala Leu Lys Ala His	Ile Leu
	885	890	895
Asp Gly Ile Asn	Leu Cys Gly Tyr Phe	Ala Tyr Ser Phe	Asn Asp Arg
	900	905	910
Thr Ala Pro Arg	Phe Gly Leu Tyr Arg Tyr	Ala Ala Asp	Gln Phe Glu
	915	920	925
Pro Lys Ala Ser	Met Lys His Tyr Arg Lys	Ile Ile Asp Ser	Asn Gly
	930	935	940
Phe Pro Gly Pro	Glu Thr Leu Glu Arg Phe	Cys Pro Glu Glu	Phe Thr
	945	950	955
Val Cys Thr Glu	Cys Ser Phe Phe His Thr	Arg Lys Ser Leu	
	965	970	

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 <211> 4380
 <212> DNA
 <213> 智人

<400> 46
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acctggggccc gtttctcgcg gcctcctgcc cccgaggccg cgggcctctt ccagggcacc	180
ttccccgacg gcctcctctg ggccgtgggc agcggccgt accagaccga gggcggctgg	240
cagcagcagc gcaagggtgc gtccatctgg gatacgttca ccaccaccc cctggcacc	300
ccgggagact cccggaacgc cagctcgcg ttgggcggcc cgtcggcgt gcagcccgc	360
accggggacg tagccagcga cagctacaac aacgtctcc gcgacacgga ggcgtgcgc	420
gagctcgggg tcactacta ccgtctctcc atctcgtgg cgcgagtct ccccaatggc	480
agcgcgggcg tcccaaccg cgaggggctg cgtactacc ggcgcctgt ggagcggctg	540
cgggagctgg gcgtgcagcc cgtggtcacc ctgtaccact gggacctgcc ccagcgcctg	600
caggacgcct acggggctg ggccaaccgc gccctggccg accacttcag ggattacgcg	660
gagctcgtct tccgccactt cggcggtcag gtcaagtacl ggatcaccat cgacaacccc	720
tacgtggtag cctggcacgg ctacgccacc ggcgcctgg ccccgccat ccggggcagc	780
ccgcggctcg gglacctgg ggcgacacac ctctcctgg ctcatgcaa agtctggcat	840
ctctacaata ctctcttccg tcccatcag ggaggicagg tglccattgc cctaagctct	900
cactggatca atcctcgaag aatgaccgac cacagcatca aagaatgtca aaaatctctg	960
gacttltgac taggtltggt tgcgaaccc gttttatgt atggtgacta tcccagagc	1020
atgaagaata accttctac taltctgcct gattttactg aatctgagaa aaagtctac	1080
aaaggaaact ctgactttt tgccttttg ttggaccga ccttgagttt tcaactttg	1140
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accttaaaag ccatcaagct ggaatgggtg gatgtatcg ggtataccgc atggtccctc	1380
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atagagaaaa atggcttccc tcttttacct gaaaatcagc cctagaagg gacatttccc	1560
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gatggggtg tgaccaagaa gaggaaatcc tactgtgtg actttgctgc catccagccc	1740
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Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
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Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro	625	630	635
Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala	645	650	655
Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu	660	665	670
Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn	675	680	685
Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu	690	695	700
Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His	705	710	715
Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu	725	730	735
Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val	740	745	750
Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly	755	760	765
Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe	770	775	780
Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr	785	790	795
Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser	805	810	815
Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu	820	825	830
Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val	835	840	845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
850 855 860

Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
865 870 875 880

Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
885 890 895

Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
900 905 910

Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
915 920 925

Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
930 935 940

Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945 950 955 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
965 970 975

His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
980 985 990

Gly Ser Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn Ala Ser Pro Leu
995 1000 1005

Leu Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr
1010 1015 1020

Ala Arg Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val
1025 1030 1035

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

Ser Glu Asp Ala Gly Phe Val Val Ile Thr Gly Val Met Ser Arg
1055 1060 1065

Arg Tyr Leu Cys Met Asp Phe Arg Gly Asn Ile Phe Gly Ser His
1070 1075 1080

Tyr Phe Asp Pro Glu Asn Cys Arg Phe Gln His Gln Thr Leu Glu
1085 1090 1095

Asn Gly Tyr Asp Val Tyr His Ser Pro Gln Tyr His Phe Leu Val
1100 1105 1110

Ser Leu Gly Arg Ala Lys Arg Ala Phe Leu Pro Gly Met Asn Pro
1115 1120 1125

Pro Pro Tyr Ser Gln Phe Leu Ser Arg Arg Asn Glu Ile Pro Leu
1130 1135 1140

Ile His Phe Asn Thr Pro Ile Pro Arg Arg His Thr Gln Ser Ala
1145 1150 1155

Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val Leu Lys Pro Arg
1160 1165 1170

Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln Glu Leu Pro
1175 1180 1185

Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu Gly Val
1190 1195 1200

Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly Pro
1205 1210 1215

Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
1220 1225 1230

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
1235 1240 1245

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
1250 1255 1260

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
1265 1270 1275

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
1280 1285 1290

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
1295 1300 1305

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
1310 1315 1320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
1325 1330 1335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
1340 1345 1350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
1355 1360 1365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
1370 1375 1380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
1385 1390 1395

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
1400 1405 1410

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
1415 1420 1425

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
1430 1435 1440

Leu Ser Leu Ser Pro Gly Lys
1445 1450

<210> 50
<211> 1449
<212> DNA
<213> 智人

<400> 50
atgttggggg cccgcctcag gctctgggtc tgtgccttgt gcagcgtctg cagcatgagc 60
gtcctcagag cctatcccaa tgcctcccca ctgctcggct ccagctgggg tggcctgac 120
cacctglaca cagccacagc caggaacagc taccacctgc agatccaca gaatggccat 180
gtggatggcg caccocatca gaccatctac agtgccctga tgatcagatc agaggatgct 240
ggctttgttg tgattacagg tgtgatgagc agaagatacc tctgcatgga tttcagaggc 300
aacatttttg gatcacacta tttcgacctg gagaactgca ggltccaaca ccagacgtcg 360
gaaaacgggt acgacgtcta ccactctcct cagtatcact tcttgggtcag tctgggcccg 420
gcgaagagag ccttccctgcc aggcataaac ccacccccgt acitccagti cctgtcccgg 480
aggaacgaga tccccctaat tcacttcaac acccccatat cacggcgga caccagagc 540
gccgaggagc acitcgagcg ggacccccg aacgtgctga agccccgggc ccgatgacc 600
ccggccccgg cctcctgttc acaggagctc ccgagcgccg aggacaacag cccgatggcc 660
agtgacccat taggggttgt cagggcggtt cgagtgaaca cgcacgttgg gggaacgggc 720
ccggaaggct gccgccctt cgccaagttc atcggagggtg gagggtcaaa aaccacacg 780
tgtcctctt gtctgcccc agaagcagca ggtgggtccat cagtttttct tttccctccc 840
aaacccaagg atacgtgat gatctctcgc acgcctgagg tgacatgcgt cgtagtagac 900
gtgagccacg aagatcccg ggtgaagttc aattggtaig tggacggagt agaagtgcac 960
aacgcgaaaa ctaagccgcg cgaggaacaa tataacagta cttacagggt ggtatccgtg 1020
ctcacagtcc tgcaccagga ctggctgaac ggttaaggaa acaagtgcaa agtaagcaac 1080
aaggcacttc ccgcgcctat tgagaaaaca atctccaagg cgaagggaca accaagagaa 1140
cctcagggtt acactctccc gccttccagg gaagagatga ccaaaaatca aglttccctg 1200
acttgcctcg tcaaaggatt ctaccccttc gacattgctg ttgaatggga aagcaalga 1260
caaccagaga acaactacaa gacaacaccc ccggtgctgg atagtacgg atcttcttt 1320
ctctactcaa agctgaccgt ggataagtc aggtggcagc agggaaacgt gttttcctgc 1380
tctgtcatgc atgaagcgt gcataatcac tataccaga agtctctgag cttagagcca 1440
ggcaagtaa 1449

<210> 51
<211> 482
<212> PRT
<213> 智人

<400> 51

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val

1	5	10	15
Cys Ser Met	Ser Val Leu Arg Ala Tyr	Pro Asn Ala Ser	Pro Leu Leu
	20	25	30
Gly Ser Ser	Trp Gly Gly Leu Ile His Leu Tyr Thr	Ala Thr Ala Arg	
	35	40	45
Asn Ser Tyr	His Leu Gln Ile His Lys Asn Gly His	Val Asp Gly Ala	
	50	55	60
Pro His Gln Thr	Ile Tyr Ser Ala Leu Met	Ile Arg Ser Glu Asp Ala	
	65	70	75
Gly Phe Val Val	Ile Thr Gly Val Met	Ser Arg Arg Tyr Leu Cys Met	
	85	90	95
Asp Phe Arg Gly	Asn Ile Phe Gly Ser His Tyr Phe Asp	Pro Glu Asn	
	100	105	110
Cys Arg Phe Gln	His Gln Thr Leu Glu Asn Gly Tyr	Asp Val Tyr His	
	115	120	125
Ser Pro Gln Tyr	His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala		
	130	135	140
Phe Leu Pro Gly Met	Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg		
	145	150	155
Arg Asn Glu Ile	Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg		
	165	170	175
His Thr Gln Ser	Ala Glu Asp Asp Ser Glu Arg Asp Pro	Leu Asn Val	
	180	185	190
Leu Lys Pro Arg	Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln		
	195	200	205
Glu Leu Pro Ser	Ala Glu Asp Asn Ser Pro Met	Ala Ser Asp Pro Leu	
	210	215	220
Gly Val Val Arg	Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly		
	225	230	235
Pro Glu Gly Cys	Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser		
	245	250	255
Lys Thr His Thr	Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly		
	260	265	270
Pro Ser Val Phe	Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile		
	275	280	285
Ser Arg Thr Pro	Glu Val Thr Cys Val Val Val Asp Val Ser His Glu		
	290	295	300

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 305 310 315 320
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
 325 330 335
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 340 345 350
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 355 360 365
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 370 375 380
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
 385 390 395 400
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 405 410 415
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 420 425 430
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 435 440 445
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 450 455 460
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 465 470 475 480

Gly Lys

<210> 52
 <211> 1422
 <212> DNA
 <213> 智人

<400> 52
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 gtccctcagag cctatcccaa tgcctcccca clgctcggct ccagctgggg tggcctgac 120
 caccigtaca cagccacagc caggaacagc taccacctgc agatccacaa gaatggccat 180
 gtggatggcg caccocatca gaccatctac agtgccttga tcatcagatc agaggatgct 240
 ggctttgtgg tgattacagg tigtatgagc agaagatacc tctgcatgga tticagaggc 300
 aacatttttg gatcacacta tticgacctg gagaactgca ggttccaaca ccagacgctg 360
 gaaaacgggt acgacgtcia ccactctcct cagtatcact tcctggtcag tctgggccgg 420
 gcgaagagag ccttctcggc aggcattgaac ccacccccgt actccagtt cctgtcccg 480
 aggaacgaga tcccciaat tcacttcaac acccccatat cagggcggca caccagagc 540
 gccgaggacg actcggagcg ggacccccctg aacgtgctga agccccgggc ccgcatgacc 600
 ccggccccgg cctcctgttc acaggagctc ccgagcgccg aggacaacag cccgatggcc 660

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agtgaacccat taggggaggc caggggaggc cgagtgaaac cgcacgcagg gggaacgggc 720
ccggaaggct gccgccccct cgccaagttc atcggagggt gaggttcagc cccagaagca 780
gcaggagggt catcagtttt tcttttccct cccaaaccca aggatacgt gatgatctct 840
cgcacgcctg aggtgacatg cgtcgtatga gacgtgagcc acgaagatcc cgaggtaag 900
ttcaattggt atgtggacgg agtagaagtg cataacgcga aaactaagcc gcgcgaggaa 960
caatataaca gtacttacag ggaggtaacc gtgtcacag tctgcacca ggactggctg 1020
aacggtaagg aatacaagtg caaagtaagc aacaaggcac tccccgcgc tattgagaaa 1080
acaatctcca aggcgaaggg acaaccaaga gaacctcagg ttacacict cccgccttcc 1140
agggaagaga tgacaaaaa tcaagtttcc ctgacttgcc tctgcaaagg attctacct 1200
tccgacattg ctgttgaatg ggaagcaat ggacaaccag agaacaacta caagacaaca 1260
cccccggtgc tggatagiga cggatcttcc ttctctact caaagctgac cgtggataag 1320
tccagggtgc agcagggaaa cgtgttttcc tctctgttca tgcataagc gctgcataat 1380
cactataccc agaagttctt gagcttgagc ccaggcaagt aa 1422

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<210> 53
 <211> 473
 <212> PRT
 <213> 智人
 <400> 53

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
1 5 10 15

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
115 120 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
130 135 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145 150 155 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
165 170 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
180 185 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
195 200 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
210 215 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225 230 235 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
245 250 255

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
275 280 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290 295 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305 310 315 320

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
325 330 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355 360 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
370 375 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 54
<211> 1228
<212> PRT
<213> 智人

<400> 54

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Ser
1 5 10 15

Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
20 25 30

Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
35 40 45

Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60

Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80

Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95

Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110

Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125

Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140

Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160

Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
355 360 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
370 375 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385 390 395 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
405 410 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445

Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545 550 555 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
 565 570 575
 Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
 580 585 590
 Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
 595 600 605
 Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
 610 615 620
 Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
 625 630 635 640
 Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
 645 650 655
 Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
 660 665 670
 Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
 675 680 685
 Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
 690 695 700
 Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
 705 710 715 720
 Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
 725 730 735
 Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
 740 745 750
 Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
 755 760 765
 Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
 770 775 780
 Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
 785 790 795 800
 Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
 805 810 815
 Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
 820 825 830
 Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
 835 840 845
 Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly

850	855	860
Asp Leu Pro Met Tyr	Ile Ile Ser Asn Gly	Ile Asp Asp Gly Leu His
865	870	875 880
Ala Glu Asp Asp	Gln Leu Arg Val Tyr	Tyr Met Gln Asn Tyr Ile Asn
	885	890 895
Glu Ala Leu Lys	Ala His Ile Leu Asp	Gly Ile Asn Leu Cys Gly Tyr
	900	905 910
Phe Ala Tyr Ser Phe	Asn Asp Arg Thr Ala Pro Arg	Phe Gly Leu Tyr
	915	920 925
Arg Tyr Ala Ala Asp	Gln Phe Glu Pro Lys Ala	Ser Met Lys His Tyr
	930	935 940
Arg Lys Ile Ile Asp	Ser Asn Gly Phe Pro	Gly Pro Glu Thr Leu Glu
	945	950 955 960
Arg Phe Cys Pro Glu	Glu Phe Thr Val Cys Thr	Glu Cys Ser Phe Phe
	965	970 975
His Thr Arg Lys Ser	Leu Gly Ser Gly Gly Gly Gly	Ser Gly Gly Gly
	980	985 990
Gly Ser Gly Gly Gly	Gly Ser Leu Lys Tyr Pro Asn Ala	Ser Pro Leu
	995	1000 1005
Leu Gly Ser Ser Trp	Gly Gly Leu Ile His Leu Tyr	Thr Ala Thr
	1010	1015 1020
Ala Arg Asn Ser Tyr	His Leu Gln Ile His Lys Asn	Gly His Val
	1025	1030 1035
Asp Gly Ala Pro His	Gln Thr Ile Tyr Ser Ala	Leu Met Ile Arg
	1040	1045 1050
Ser Glu Asp Ala Gly	Phe Val Val Ile Thr Gly	Val Met Ser Arg
	1055	1060 1065
Arg Tyr Leu Cys Met	Asp Phe Arg Gly Asn Ile	Phe Gly Ser His
	1070	1075 1080
Tyr Phe Asp Pro Glu	Asn Cys Arg Phe Gln His	Gln Thr Leu Glu
	1085	1090 1095
Asn Gly Tyr Asp Val	Tyr His Ser Pro Gln Tyr	His Phe Leu Val
	1100	1105 1110
Ser Leu Gly Arg Ala	Lys Arg Ala Phe Leu Pro	Gly Met Asn Pro
	1115	1120 1125
Pro Pro Tyr Ser Gln	Phe Leu Ser Arg Arg Asn	Glu Ile Pro Leu
	1130	1135 1140

Ile His Phe Asn Thr Pro Ile Pro Arg Arg His Thr Gln Ser Ala
1145 1150 1155

Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val Leu Lys Pro Arg
1160 1165 1170

Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln Glu Leu Pro
1175 1180 1185

Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu Gly Val
1190 1195 1200

Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly Pro
1205 1210 1215

Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
1220 1225

<210> 55
<211> 1228
<212> PRT
<213> 智人

<400> 55

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Ser
1 5 10 15

Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
20 25 30

Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
35 40 45

Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60

Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80

Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95

Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110

Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125

Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140

Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160

Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
 180 185 190
 His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
 195 200 205
 Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
 210 215 220
 Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
 225 230 235 240
 Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
 245 250 255
 Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
 260 265 270
 Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
 275 280 285
 Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
 290 295 300
 Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
 305 310 315 320
 Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
 325 330 335
 Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
 340 345 350
 Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
 355 360 365
 Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
 370 375 380
 Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
 385 390 395 400
 Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
 405 410 415
 Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
 420 425 430
 Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
 435 440 445
 Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
 450 455 460
 Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
 465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545 550 555 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575

Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
580 585 590

Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
595 600 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
610 615 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625 630 635 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
645 650 655

Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
660 665 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
675 680 685

Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
690 695 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
705 710 715 720

Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
725 730 735

Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
740 745 750

Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
755 760 765

Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
770 775 780

Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
 785 790 795 800
 Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
 805 810 815
 Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
 820 825 830
 Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
 835 840 845
 Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
 850 855 860
 Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
 865 870 875 880
 Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
 885 890 895
 Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
 900 905 910
 Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
 915 920 925
 Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
 930 935 940
 Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
 945 950 955 960
 Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
 965 970 975
 His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 980 985 990
 Gly Ser Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn Ala Ser Pro Leu
 995 1000 1005
 Leu Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr
 1010 1015 1020
 Ala Arg Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val
 1025 1030 1035
 Asp Gly Ala Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg
 1040 1045 1050
 Ser Glu Asp Ala Gly Phe Val Val Ile Thr Gly Val Met Ser Arg
 1055 1060 1065
 Arg Tyr Leu Cys Met Asp Phe Arg Gly Asn Ile Phe Gly Ser His

1070	1075	1080
Tyr Phe Asp Pro Glu Asn Cys 1085	Arg Phe Gln His Gln 1090	Thr Leu Glu 1095
Asn Gly Tyr Asp Val Tyr His 1100	Ser Pro Gln Tyr His 1105	Phe Leu Val 1110
Ser Leu Gly Arg Ala Lys Arg 1115	Ala Phe Leu Pro Gly 1120	Met Asn Pro 1125
Pro Pro Tyr Ser Gln Phe Leu 1130	Ser Arg Arg Asn Glu 1135	Ile Pro Leu 1140
Ile His Phe Asn Thr Pro Ile 1145	Pro Arg Arg His Thr 1150	Gln Ser Ala 1155
Glu Asp Asp Ser Glu Arg Asp 1160	Pro Leu Asn Val Leu 1165	Lys Pro Arg 1170
Ala Arg Met Thr Pro Ala Pro 1175	Ala Ser Cys Ser Gln 1180	Glu Leu Pro 1185
Ser Ala Glu Asp Asn Ser Pro 1190	Met Ala Ser Asp Pro 1195	Leu Gly Val 1200
Val Arg Gly Gly Arg Val Asn 1205	Thr His Ala Gly Gly 1210	Thr Gly Pro 1215
Glu Gly Ser Arg Pro Phe Ala 1220	Lys Phe Ile 1225	
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<211> 1228		
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<213> 智人		
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Leu Ser Leu Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg 20 25 30		
Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro 35 40 45		
Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly 50 55 60		
Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp 65 70 75 80		
Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His 85 90 95		
Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly		

100	105	110
Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser		
115	120	125
Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val		
130	135	140
Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly		
145	150	155
Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu		
165	170	175
Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr		
180	185	190
His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala		
195	200	205
Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe		
210	215	220
Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro		
225	230	235
Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly		
245	250	255
Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu		
260	265	270
Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro		
275	280	285
Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn		
290	295	300
Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu		
305	310	315
Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp		
325	330	335
Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe		
340	345	350
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala		
355	360	365
Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met		
370	375	380
Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp		
385	390	395
		400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
405 410 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445

Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val
545 550 555 560

Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala
565 570 575

Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His
580 585 590

Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln
595 600 605

Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser
610 615 620

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
625 630 635 640

Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
645 650 655

Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
660 665 670

Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
675 680 685

Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
690 695 700

Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
 705 710 715 720
 Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
 725 730 735
 Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
 740 745 750
 Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
 755 760 765
 Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
 770 775 780
 Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
 785 790 795 800
 Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
 805 810 815
 Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
 820 825 830
 Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
 835 840 845
 Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
 850 855 860
 Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
 865 870 875 880
 Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
 885 890 895
 Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
 900 905 910
 Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
 915 920 925
 Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
 930 935 940
 Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
 945 950 955 960
 Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
 965 970 975
 His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 980 985 990
 Gly Ser Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn Ala Ser Pro Leu
 995 1000 1005

Leu Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr
1010 1015 1020

Ala Arg Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val
1025 1030 1035

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

Ser Glu Asp Ala Gly Phe Val Val Ile Thr Gly Val Met Ser Arg
1055 1060 1065

Arg Tyr Leu Cys Met Asp Phe Arg Gly Asn Ile Phe Gly Ser His
1070 1075 1080

Tyr Phe Asp Pro Glu Asn Cys Arg Phe Gln His Gln Thr Leu Glu
1085 1090 1095

Asn Gly Tyr Asp Val Tyr His Ser Pro Gln Tyr His Phe Leu Val
1100 1105 1110

Ser Leu Gly Arg Ala Lys Arg Ala Phe Leu Pro Gly Met Asn Pro
1115 1120 1125

Pro Pro Tyr Ser Ala Phe Leu Ser Arg Arg Asn Glu Ile Pro Leu
1130 1135 1140

Ile His Phe Asn Thr Pro Ile Pro Arg Arg His Thr Gln Ser Ala
1145 1150 1155

Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val Leu Lys Pro Arg
1160 1165 1170

Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln Glu Leu Pro
1175 1180 1185

Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu Gly Val
1190 1195 1200

Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly Pro
1205 1210 1215

Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
1220 1225

<210> 57
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<400> 57

Met Pro Ala Ser Ala Pro Pro Arg Arg Pro Arg Pro Pro Pro Ser
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Leu Ser Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
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Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
35 40 45

Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60

Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80

Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95

Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110

Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125

Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140

Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160

Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp

325	330	335
Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe 340 345 350		
Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala 355 360 365		
Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met 370 375 380		
Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp 385 390 395 400		
Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly 405 410 415		
Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr 420 425 430		
Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp 435 440 445		
Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe 450 455 460		
Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp 465 470 475 480		
Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe 485 490 495		
Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn 500 505 510		
Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val 515 520 525		
Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu 530 535 540		
Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val 545 550 555 560		
Asp Gly Val Val Thr Lys Lys Arg Lys Ser Tyr Cys Val Asp Phe Ala 565 570 575		
Ala Ile Gln Pro Gln Ile Ala Leu Leu Gln Glu Met His Val Thr His 580 585 590		
Phe Arg Phe Ser Leu Asp Trp Ala Leu Ile Leu Pro Leu Gly Asn Gln 595 600 605		
Ser Gln Val Asn His Thr Ile Leu Gln Tyr Tyr Arg Cys Met Ala Ser 610 615 620		

Glu Leu Val Arg Val Asn Ile Thr Pro Val Val Ala Leu Trp Gln Pro
 625 630 635 640
 Met Ala Pro Asn Gln Gly Leu Pro Arg Leu Leu Ala Arg Gln Gly Ala
 645 650 655
 Trp Glu Asn Pro Tyr Thr Ala Leu Ala Phe Ala Glu Tyr Ala Arg Leu
 660 665 670
 Cys Phe Gln Glu Leu Gly His His Val Lys Leu Trp Ile Thr Met Asn
 675 680 685
 Glu Pro Tyr Thr Arg Asn Met Thr Tyr Ser Ala Gly His Asn Leu Leu
 690 695 700
 Lys Ala His Ala Leu Ala Trp His Val Tyr Asn Glu Lys Phe Arg His
 705 710 715 720
 Ala Gln Asn Gly Lys Ile Ser Ile Ala Leu Gln Ala Asp Trp Ile Glu
 725 730 735
 Pro Ala Cys Pro Phe Ser Gln Lys Asp Lys Glu Val Ala Glu Arg Val
 740 745 750
 Leu Glu Phe Asp Ile Gly Trp Leu Ala Glu Pro Ile Phe Gly Ser Gly
 755 760 765
 Asp Tyr Pro Trp Val Met Arg Asp Trp Leu Asn Gln Arg Asn Asn Phe
 770 775 780
 Leu Leu Pro Tyr Phe Thr Glu Asp Glu Lys Lys Leu Ile Gln Gly Thr
 785 790 795 800
 Phe Asp Phe Leu Ala Leu Ser His Tyr Thr Thr Ile Leu Val Asp Ser
 805 810 815
 Glu Lys Glu Asp Pro Ile Lys Tyr Asn Asp Tyr Leu Glu Val Gln Glu
 820 825 830
 Met Thr Asp Ile Thr Trp Leu Asn Ser Pro Ser Gln Val Ala Val Val
 835 840 845
 Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
 850 855 860
 Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
 865 870 875 880
 Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
 885 890 895
 Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
 900 905 910
 Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
 915 920 925

Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
930 935 940

Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
945 950 955 960

Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
965 970 975

His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
980 985 990

Gly Ser Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn Ala Ser Pro Leu
995 1000 1005

Leu Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr
1010 1015 1020

Ala Arg Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val
1025 1030 1035

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

Ser Glu Asp Ala Gly Phe Val Val Ile Thr Gly Val Met Ser Arg
1055 1060 1065

Arg Tyr Leu Cys Met Asp Phe Arg Gly Asn Ile Phe Gly Ser His
1070 1075 1080

Tyr Phe Asp Pro Glu Asn Cys Arg Phe Gln His Gln Thr Leu Glu
1085 1090 1095

Asn Gly Tyr Asp Val Tyr His Ser Pro Gln Tyr His Phe Leu Val
1100 1105 1110

Ser Leu Gly Arg Ala Lys Arg Ala Phe Leu Pro Gly Met Asn Pro
1115 1120 1125

Pro Pro Tyr Ser Gln Phe Leu Ser Arg Arg Asn Glu Ile Pro Leu
1130 1135 1140

Ile His Phe Asn Thr Pro Ile Pro Arg Arg His Thr Gln Ser Ala
1145 1150 1155

Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val Leu Lys Pro Arg
1160 1165 1170

Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln Glu Leu Pro
1175 1180 1185

Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu Gly Val
1190 1195 1200

Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly Pro
1205 1210 1215

Glu Gly Ser Arg Pro Phe Ala Lys Phe Ile
1220 1225

<210> 58
<211> 1228
<212> PRT
<213> 智人
<400> 58

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Leu Ser Leu Leu Val Leu Leu Gly Leu Gly Gly Arg Arg Leu Arg
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Ala Glu Pro Gly Asp Gly Ala Gln Thr Trp Ala Arg Phe Ser Arg Pro
35 40 45

Pro Ala Pro Glu Ala Ala Gly Leu Phe Gln Gly Thr Phe Pro Asp Gly
50 55 60

Phe Leu Trp Ala Val Gly Ser Ala Ala Tyr Gln Thr Glu Gly Gly Trp
65 70 75 80

Gln Gln His Gly Lys Gly Ala Ser Ile Trp Asp Thr Phe Thr His His
85 90 95

Pro Leu Ala Pro Pro Gly Asp Ser Arg Asn Ala Ser Leu Pro Leu Gly
100 105 110

Ala Pro Ser Pro Leu Gln Pro Ala Thr Gly Asp Val Ala Ser Asp Ser
115 120 125

Tyr Asn Asn Val Phe Arg Asp Thr Glu Ala Leu Arg Glu Leu Gly Val
130 135 140

Thr His Tyr Arg Phe Ser Ile Ser Trp Ala Arg Val Leu Pro Asn Gly
145 150 155 160

Ser Ala Gly Val Pro Asn Arg Glu Gly Leu Arg Tyr Tyr Arg Arg Leu
165 170 175

Leu Glu Arg Leu Arg Glu Leu Gly Val Gln Pro Val Val Thr Leu Tyr
180 185 190

His Trp Asp Leu Pro Gln Arg Leu Gln Asp Ala Tyr Gly Gly Trp Ala
195 200 205

Asn Arg Ala Leu Ala Asp His Phe Arg Asp Tyr Ala Glu Leu Cys Phe
210 215 220

Arg His Phe Gly Gly Gln Val Lys Tyr Trp Ile Thr Ile Asp Asn Pro
225 230 235 240

Tyr Val Val Ala Trp His Gly Tyr Ala Thr Gly Arg Leu Ala Pro Gly
245 250 255

Ile Arg Gly Ser Pro Arg Leu Gly Tyr Leu Val Ala His Asn Leu Leu
260 265 270

Leu Ala His Ala Lys Val Trp His Leu Tyr Asn Thr Ser Phe Arg Pro
275 280 285

Thr Gln Gly Gly Gln Val Ser Ile Ala Leu Ser Ser His Trp Ile Asn
290 295 300

Pro Arg Arg Met Thr Asp His Ser Ile Lys Glu Cys Gln Lys Ser Leu
305 310 315 320

Asp Phe Val Leu Gly Trp Phe Ala Lys Pro Val Phe Ile Asp Gly Asp
325 330 335

Tyr Pro Glu Ser Met Lys Asn Asn Leu Ser Ser Ile Leu Pro Asp Phe
340 345 350

Thr Glu Ser Glu Lys Lys Phe Ile Lys Gly Thr Ala Asp Phe Phe Ala
355 360 365

Leu Cys Phe Gly Pro Thr Leu Ser Phe Gln Leu Leu Asp Pro His Met
370 375 380

Lys Phe Arg Gln Leu Glu Ser Pro Asn Leu Arg Gln Leu Leu Ser Trp
385 390 395 400

Ile Asp Leu Glu Phe Asn His Pro Gln Ile Phe Ile Val Glu Asn Gly
405 410 415

Trp Phe Val Ser Gly Thr Thr Lys Arg Asp Asp Ala Lys Tyr Met Tyr
420 425 430

Tyr Leu Lys Lys Phe Ile Met Glu Thr Leu Lys Ala Ile Lys Leu Asp
435 440 445

Gly Val Asp Val Ile Gly Tyr Thr Ala Trp Ser Leu Met Asp Gly Phe
450 455 460

Glu Trp His Arg Gly Tyr Ser Ile Arg Arg Gly Leu Phe Tyr Val Asp
465 470 475 480

Phe Leu Ser Gln Asp Lys Met Leu Leu Pro Lys Ser Ser Ala Leu Phe
485 490 495

Tyr Gln Lys Leu Ile Glu Lys Asn Gly Phe Pro Pro Leu Pro Glu Asn
500 505 510

Gln Pro Leu Glu Gly Thr Phe Pro Cys Asp Phe Ala Trp Gly Val Val
515 520 525

Asp Asn Tyr Ile Gln Val Asp Thr Thr Leu Ser Gln Phe Thr Asp Leu
530 535 540

Asn Val Tyr Leu Trp Asp Val His His Ser Lys Arg Leu Ile Lys Val

545		550		555		560
Asp Gly Val Val	Thr 565	Lys Lys Arg Lys	Ser 570	Tyr Cys Val	Asp Phe Ala	575
Ala Ile Gln Pro	Gln 580	Ile Ala Leu	Leu 585	Gln Glu Met His	Val Thr His	590
Phe Arg Phe Ser	Leu 595	Asp Trp Ala	Leu 600	Ile Leu Pro	Leu Gly Asn Gln	605
Ser Gln Val Asn	His 610	Thr Ile Leu	Gln 615	Tyr Tyr Arg	Cys Met Ala Ser	620
Glu Leu Val Arg	Val 625	Asn Ile Thr	Pro 630	Val Val Ala	Leu Trp Gln Pro	635 640
Met Ala Pro Asn	Gln 645	Gly Leu Pro	Arg 650	Leu Leu Ala	Arg Gln Gly Ala	655
Trp Glu Asn Pro	Tyr 660	Thr Ala Leu	Ala 665	Phe Ala Glu	Tyr Ala Arg Leu	670
Cys Phe Gln Glu	Leu 675	Gly His His	Val 680	Lys Leu Trp	Ile Thr Met Asn	685
Glu Pro Tyr Thr	Arg 690	Asn Met Thr	Tyr 695	Ser Ala Gly	His Asn Leu Leu	700
Lys Ala His Ala	Leu 705	Ala Trp His	Val 710	Tyr Asn Glu	Lys Phe Arg His	715 720
Ala Gln Asn Gly	Lys 725	Ile Ser Ile	Ala 730	Leu Gln Ala	Asp Trp Ile Glu	735
Pro Ala Cys Pro	Phe 740	Ser Gln Lys	Asp 745	Lys Glu Val	Ala Glu Arg Val	750
Leu Glu Phe Asp	Ile 755	Gly Trp Leu	Ala 760	Glu Pro Ile	Phe Gly Ser Gly	765
Asp Tyr Pro Trp	Val 770	Met Arg Asp	Trp 775	Leu Asn Gln	Arg Asn Asn Phe	780
Leu Leu Pro Tyr	Phe 785	Thr Glu Asp	Glu 790	Lys Lys Leu	Ile Gln Gly Thr	795 800
Phe Asp Phe Leu	Ala 805	Leu Ser His	Tyr 810	Thr Thr Ile	Leu Val Asp Ser	815
Glu Lys Glu Asp	Pro 820	Ile Lys Tyr	Asn 825	Asp Tyr Leu	Glu Val Gln Glu	830
Met Thr Asp Ile	Thr 835	Trp Leu Asn	Ser 840	Pro Ser Gln	Val Ala Val Val	845

Pro Trp Gly Leu Arg Lys Val Leu Asn Trp Leu Lys Phe Lys Tyr Gly
 850 855 860
 Asp Leu Pro Met Tyr Ile Ile Ser Asn Gly Ile Asp Asp Gly Leu His
 865 870 875 880
 Ala Glu Asp Asp Gln Leu Arg Val Tyr Tyr Met Gln Asn Tyr Ile Asn
 885 890 895
 Glu Ala Leu Lys Ala His Ile Leu Asp Gly Ile Asn Leu Cys Gly Tyr
 900 905 910
 Phe Ala Tyr Ser Phe Asn Asp Arg Thr Ala Pro Arg Phe Gly Leu Tyr
 915 920 925
 Arg Tyr Ala Ala Asp Gln Phe Glu Pro Lys Ala Ser Met Lys His Tyr
 930 935 940
 Arg Lys Ile Ile Asp Ser Asn Gly Phe Pro Gly Pro Glu Thr Leu Glu
 945 950 955 960
 Arg Phe Cys Pro Glu Glu Phe Thr Val Cys Thr Glu Cys Ser Phe Phe
 965 970 975
 His Thr Arg Lys Ser Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 980 985 990
 Gly Ser Gly Gly Gly Gly Ser Leu Lys Tyr Pro Asn Ala Ser Pro Leu
 995 1000 1005
 Leu Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr
 1010 1015 1020
 Ala Arg Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val
 1025 1030 1035
 Asp Gly Ala Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg
 1040 1045 1050
 Ser Glu Asp Ala Gly Phe Val Val Ile Thr Gly Val Met Ser Arg
 1055 1060 1065
 Arg Tyr Leu Cys Met Asp Phe Arg Gly Asn Ile Phe Gly Ser His
 1070 1075 1080
 Tyr Phe Asp Pro Glu Asn Cys Arg Phe Gln His Gln Thr Leu Glu
 1085 1090 1095
 Asn Gly Tyr Asp Val Tyr His Ser Pro Gln Tyr His Phe Leu Val
 1100 1105 1110
 Ser Leu Gly Arg Ala Lys Arg Ala Phe Leu Pro Gly Met Asn Pro
 1115 1120 1125
 Pro Pro Tyr Ser Ala Phe Leu Ser Arg Arg Asn Glu Ile Pro Leu
 1130 1135 1140

Ile His Phe Asn Thr Pro Ile Pro Arg Arg His Thr Gln Ser Ala
1145 1150 1155

Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val Leu Lys Pro Arg
1160 1165 1170

Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln Glu Leu Pro
1175 1180 1185

Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu Gly Val
1190 1195 1200

Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly Pro
1205 1210 1215

Glu Gly Ser Arg Pro Phe Ala Lys Phe Ile
1220 1225

<210> 59
<211> 482
<212> PRT
<213> 智人
<400> 59

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
1 5 10 15

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
115 120 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
130 135 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145 150 155 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
165 170 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
180 185 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln
195 200 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
210 215 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225 230 235 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
245 250 255

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
260 265 270

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
275 280 285

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
290 295 300

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
305 310 315 320

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
325 330 335

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
340 345 350

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
355 360 365

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
370 375 380

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
385 390 395 400

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
405 410 415

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
420 425 430

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
435 440 445

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
450 455 460

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
465 470 475 480

Gly Lys

<210> 60
<211> 482
<212> PRT
<213> 智人

<400> 60

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
1 5 10 15

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
115 120 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
130 135 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145 150 155 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
165 170 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
180 185 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
195 200 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
210 215 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225 230 235 240

Pro Glu Gly Ser Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
245 250 255

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
260 265 270

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
275 280 285

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
290 295 300

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
305 310 315 320

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
325 330 335

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
340 345 350

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
355 360 365

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
370 375 380

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
385 390 395 400

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
405 410 415

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
420 425 430

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
435 440 445

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
450 455 460

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
465 470 475 480

Gly Lys

<210> 61
<211> 482
<212> PRT
<213> 智人

<400> 61

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
1 5 10 15

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
115 120 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
130 135 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Ala Phe Leu Ser Arg
145 150 155 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
165 170 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
180 185 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
195 200 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
210 215 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225 230 235 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
245 250 255

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
260 265 270

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
275 280 285

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
290 295 300

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
305 310 315 320

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg

325 330 335
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 340 345 350
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 355 360 365
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 370 375 380
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
 385 390 395 400
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 405 410 415
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 420 425 430
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 435 440 445
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 450 455 460
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 465 470 475 480
 Gly Lys

 <210> 62
 <211> 482
 <212> PRT
 <213> 智人
 <400> 62
 Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
 1 5 10 15
 Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
 20 25 30
 Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
 35 40 45
 Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
 50 55 60
 Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
 65 70 75 80
 Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
 85 90 95
 Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn

100	105	110
Cys Arg Phe Gln His Gln Thr	Leu Glu Asn Gly Tyr Asp Val Tyr His	
115	120	125
Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala		
130	135	140
Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg		
145	150	155
Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg		
165	170	175
His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val		
180	185	190
Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln		
195	200	205
Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu		
210	215	220
Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly		
225	230	235
Pro Glu Gly Ser Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser		
245	250	255
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly		
260	265	270
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile		
275	280	285
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu		
290	295	300
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His		
305	310	315
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg		
325	330	335
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys		
340	345	350
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu		
355	360	365
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr		
370	375	380
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu		
385	390	395
		400

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
405 410 415

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
420 425 430

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
435 440 445

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
450 455 460

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
465 470 475 480

Gly Lys

<210> 63
<211> 482
<212> PRT
<213> 智人

<400> 63

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
1 5 10 15

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
115 120 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
130 135 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Ala Phe Leu Ser Arg
145 150 155 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
165 170 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
 180 185 190
 Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln
 195 200 205
 Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
 210 215 220
 Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
 225 230 235 240
 Pro Glu Gly Ser Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
 245 250 255
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
 260 265 270
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 275 280 285
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 290 295 300
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 305 310 315 320
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
 325 330 335
 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 340 345 350
 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 355 360 365
 Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 370 375 380
 Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
 385 390 395 400
 Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 405 410 415
 Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 420 425 430
 Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 435 440 445
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 450 455 460
 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 465 470 475 480

Gly Lys

<210> 64
 <211> 473
 <212> PRT
 <213> 智人

<400> 64

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
 1 5 10 15

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
 20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
 35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
 50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
 65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
 85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
 100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
 115 120 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
 130 135 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
 145 150 155 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
 165 170 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
 180 185 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln
 195 200 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
 210 215 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
 225 230 235 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
 245 250 255

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
275 280 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290 295 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305 310 315 320

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
325 330 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355 360 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
370 375 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 65
<211> 473
<212> PRT
<213> 智人
<400> 65

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
1 5 10 15

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
115 120 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
130 135 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145 150 155 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
165 170 175

His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
180 185 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
195 200 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
210 215 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225 230 235 240

Pro Glu Gly Ser Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
245 250 255

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
275 280 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290 295 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305 310 315 320

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
325 330 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
 355 360 365
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
 370 375 380
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 385 390 395 400
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 405 410 415
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
 420 425 430
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
 435 440 445
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 450 455 460
 Lys Ser Leu Ser Leu Ser Pro Gly Lys
 465 470
 <210> 66
 <211> 473
 <212> PRT
 <213> 智人
 <400> 66
 Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
 1 5 10 15
 Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
 20 25 30
 Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
 35 40 45
 Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
 50 55 60
 Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
 65 70 75 80
 Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
 85 90 95
 Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
 100 105 110
 Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
 115 120 125
 Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
 130 135 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Ala Phe Leu Ser Arg
 145 150 155 160
 Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
 165 170 175
 His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
 180 185 190
 Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
 195 200 205
 Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
 210 215 220
 Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
 225 230 235 240
 Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser
 245 250 255
 Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 260 265 270
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 275 280 285
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 290 295 300
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 305 310 315 320
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
 325 330 335
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
 340 345 350
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
 355 360 365
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
 370 375 380
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 385 390 395 400
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 405 410 415
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
 420 425 430
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val

435 440 445
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 450 455 460

 Lys Ser Leu Ser Leu Ser Pro Gly Lys
 465 470

 <210> 67
 <211> 473
 <212> PRT
 <213> 智人

 <400> 67

 Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
 1 5 10 15

 Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
 20 25 30

 Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
 35 40 45

 Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
 50 55 60

 Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
 65 70 75 80

 Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
 85 90 95

 Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
 100 105 110

 Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
 115 120 125

 Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
 130 135 140

 Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
 145 150 155 160

 Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
 165 170 175

 His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
 180 185 190

 Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln
 195 200 205

 Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
 210 215 220

 Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly

225	230	235	240
Pro Glu Gly Ser Arg	Pro Phe Ala Lys	Phe Ile Gly Gly Gly Gly Ser	
	245	250	255
Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys			
	260	265	270
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val			
	275	280	285
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr			
	290	295	300
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu			
	305	310	315
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His			
	325	330	335
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys			
	340	345	350
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln			
	355	360	365
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met			
	370	375	380
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro			
	385	390	395
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn			
	405	410	415
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu			
	420	425	430
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val			
	435	440	445
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln			
	450	455	460
Lys Ser Leu Ser Leu Ser Pro Gly Lys			
	465	470	
<210> 68			
<211> 473			
<212> PRT			
<213> 智人			
<400> 68			
Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val			
1	5	10	15
Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu			

	20		25		30				
Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg	35		40		45				
Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala	50		55		60				
Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala	65		70		75			80	
Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met		85		90				95	
Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn		100		105				110	
Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His		115		120				125	
Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala		130		135				140	
Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Ala Phe Leu Ser Arg		145		150			155		160
Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg		165		170				175	
His Thr Gln Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val		180		185				190	
Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Ser Ser Gln		195		200				205	
Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu		210		215				220	
Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly		225		230			235		240
Pro Glu Gly Ser Arg Pro Phe Ala Lys Phe Ile Gly Gly Gly Gly Ser		245		250				255	
Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys		260		265				270	
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val		275		280				285	
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr		290		295				300	
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu		305		310			315		320

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
325 330 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355 360 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
370 375 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 69
<211> 251
<212> PRT
<213> 智人

<400> 69

Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
1 5 10 15

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
20 25 30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65 70 75 80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
85 90 95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
100 105 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
 115 120 125
 Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
 130 135 140
 Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
 145 150 155 160
 Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
 165 170 175
 His Thr Arg Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
 180 185 190
 Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
 195 200 205
 Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
 210 215 220
 Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
 225 230 235 240
 Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
 245 250
 <210> 70
 <211> 251
 <212> PRT
 <213> 恒河猴
 <400> 70
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 1 5 10 15
 Cys Ser Met Ser Val Ile Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
 20 25 30
 Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
 35 40 45
 Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
 50 55 60
 Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
 65 70 75 80
 Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
 85 90 95
 Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asn Pro Glu Asn
 100 105 110
 Cys Arg Phe Arg His Trp Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
 115 120 125

Ser Pro Gln His His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
130 135 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145 150 155 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Arg Pro Arg Arg
165 170 175

His Thr Arg Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
180 185 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
195 200 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Val Ala Ser Asp Pro Leu
210 215 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225 230 235 240

Pro Glu Ala Cys Arg Pro Phe Pro Lys Phe Ile
245 250

<210> 71
<211> 245
<212> PRT
<213> 溫帶牛
<400> 71

Met Leu Gly Ala Arg Leu Gly Leu Trp Val Cys Thr Leu Ser Cys Val
1 5 10 15

Val Gln Ala Tyr Pro Asn Ser Ser Pro Leu Leu Gly Ser Ser Trp Gly
20 25 30

Gly Leu Thr His Leu Tyr Thr Ala Thr Ala Arg Asn Ser Tyr His Leu
35 40 45

Gln Ile His Gly Asp Gly His Val Asp Gly Ser Pro Gln Gln Thr Val
50 55 60

Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala Gly Phe Val Val Ile
65 70 75 80

Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met Asp Phe Thr Gly Asn
85 90 95

Ile Phe Gly Ser His His Phe Ser Pro Glu Ser Cys Arg Phe Arg Gln
100 105 110

Arg Thr Leu Glu Asn Gly Tyr Asp Val Tyr His Ser Pro Gln His Arg
115 120 125

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

Asn Pro Pro Pro Tyr Ala Gln Phe Leu Ser Arg Arg Asn Glu Ile Pro
145 150 155 160

Leu Pro His Phe Ala Ala Thr Ala Arg Pro Arg Arg His Thr Arg Ser
165 170 175

Ala His Asp Ser Gly Asp Pro Leu Ser Val Leu Lys Pro Arg Ala Arg
180 185 190

Ala Thr Pro Val Pro Ala Ala Cys Ser Gln Glu Leu Pro Ser Ala Glu
195 200 205

Asp Ser Gly Pro Ala Ala Ser Asp Pro Leu Gly Val Leu Arg Gly His
210 215 220

Arg Leu Asp Val Arg Ala Gly Ser Ala Gly Ala Glu Arg Cys Arg Pro
225 230 235 240

Phe Pro Gly Phe Ala
245

<210> 72
<211> 251
<212> PRT
<213> 小家鼠

<400> 72

Met Leu Gly Thr Cys Leu Arg Leu Leu Val Gly Val Leu Cys Thr Val
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Cys Ser Leu Gly Thr Ala Arg Ala Tyr Pro Asp Thr Ser Pro Leu Leu
20 25 30

Gly Ser Asn Trp Gly Ser Leu Thr His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Thr Ser Tyr His Leu Gln Ile His Arg Asp Gly His Val Asp Gly Thr
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Thr Ser Glu Asp Ala
65 70 75 80

Gly Ser Val Val Ile Thr Gly Ala Met Thr Arg Arg Phe Leu Cys Met
85 90 95

Asp Leu His Gly Asn Ile Phe Gly Ser Leu His Phe Ser Pro Glu Asn
100 105 110

Cys Lys Phe Arg Gln Trp Thr Leu Glu Asn Gly Tyr Asp Val Tyr Leu
115 120 125

Ser Gln Lys His His Tyr Leu Val Ser Leu Gly Arg Ala Lys Arg Ile
130 135 140

Phe Gln Pro Gly Thr Asn Pro Pro Pro Phe Ser Gln Phe Leu Ala Arg
145 150 155 160

Arg Asn Glu Val Pro Leu Leu His Phe Tyr Thr Val Arg Pro Arg Arg
165 170 175

His Thr Arg Ser Ala Glu Asp Pro Pro Glu Arg Asp Pro Leu Asn Val
180 185 190

Leu Lys Pro Arg Pro Arg Ala Thr Pro Val Pro Val Ser Cys Ser Arg
195 200 205

Glu Leu Pro Ser Ala Glu Glu Gly Gly Pro Ala Ala Ser Asp Pro Leu
210 215 220

Gly Val Leu Arg Arg Gly Arg Gly Asp Ala Arg Gly Gly Ala Gly Gly
225 230 235 240

Ala Asp Arg Cys Arg Pro Phe Pro Arg Phe Val
245 250

<210> 73
<211> 251
<212> PRT
<213> 褐家鼠
<400> 73

Met Leu Gly Ala Cys Leu Arg Leu Leu Val Gly Ala Leu Cys Thr Val
1 5 10 15

Cys Ser Leu Gly Thr Ala Arg Ala Tyr Ser Asp Thr Ser Pro Leu Leu
20 25 30

Gly Ser Asn Trp Gly Ser Leu Thr His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Arg Asp Gly His Val Asp Gly Thr
50 55 60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Thr Ser Glu Asp Ala
65 70 75 80

Gly Ser Val Val Ile Ile Gly Ala Met Thr Arg Arg Phe Leu Cys Met
85 90 95

Asp Leu Arg Gly Asn Ile Phe Gly Ser Tyr His Phe Ser Pro Glu Asn
100 105 110

Cys Arg Phe Arg Gln Trp Thr Leu Glu Asn Gly Tyr Asp Val Tyr Leu
115 120 125

Ser Pro Lys His His Tyr Leu Val Ser Leu Gly Arg Ser Lys Arg Ile
130 135 140

Phe Gln Pro Gly Thr Asn Pro Pro Pro Phe Ser Gln Phe Leu Ala Arg
145 150 155 160

Arg Asn Glu Val Pro Leu Leu His Phe Tyr Thr Ala Arg Pro Arg Arg
165 170 175

His Thr Arg Ser Ala Glu Asp Pro Pro Glu Arg Asp Pro Leu Asn Val
 180 185 190

Leu Lys Pro Arg Pro Arg Ala Thr Pro Ile Pro Val Ser Cys Ser Arg
 195 200 205

Glu Leu Pro Ser Ala Glu Glu Gly Gly Pro Ala Ala Ser Asp Pro Leu
 210 215 220

Gly Val Leu Arg Arg Gly Arg Gly Asp Ala Arg Arg Gly Ala Gly Gly
 225 230 235 240

Thr Asp Arg Cys Arg Pro Phe Pro Arg Phe Val
 245 250

申請專利範圍

1. 一種組合物，其包含纖維母細胞生長因子23(FGF23)變異多肽或其功能活性衍生物或片段，其中該FGF23變異多肽或其功能活性衍生物或片段具有

在胺基酸位置179及視情況在胺基酸位置206及/或244之一或更多者之突變，其位置編碼係參照如SEQ ID NO: 35所示之FGF23序列，且

其中該變異多肽或其功能活性衍生物或片段保有至少一種FGF23活性。

2. 如請求項1之組合物，其中該至少一種FGF23活性係選自於：活化Egr-1、與 α -Klotho合作結合至FGF受體、改變細胞增殖、改變肌管(myotube)直徑，以及使信號傳導路徑蛋白質磷酸化。
3. 如請求項1之組合物，其中該一或多個胺基酸位置係位置206及244。
4. 如請求項1之組合物，其中該突變進一步包含在胺基酸位置156之額外突變，其位置編碼係參照如SEQ ID NO: 35所示之FGF23序列。
5. 如請求項1之組合物，其中該多肽、衍生物或片段之序列包含SEQ ID NO: 64之胺基酸1至251之序列。
6. 如請求項1之組合物，其中該多肽、衍生物或片段之序列包含SEQ ID NO: 65之胺基酸1至251之序列。
7. 如請求項1之組合物，其中該多肽、衍生物或片段之序列包含SEQ ID NO: 67之胺基酸1至251之序列。
8. 如請求項1之組合物，其進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。

9. 如請求項1之組合物，其係經聚乙二醇化。
10. 一種組合物，其包含融合多肽，該融合多肽自N-端至C-端包含：
 - (a) 包含可溶性 α Klotho (sKlotho)或其變異體或片段之多肽；
 - (b) 包含纖維母細胞生長因子23(FGF23)變異體或其功能活性衍生物或片段之多肽，其包含在胺基酸位置179及視情況在胺基酸位置206及/或244之一或多者之突變，其位置編碼係參照如SEQ ID NO: 35所示之FGF23序列；及視情況
 - (c) 連接子；其中該融合多肽在HEK293T細胞中Egr-1螢光素酶報導子檢定中具有活性，及/或在C2C12肌母細胞中能夠誘導或增強肌管生長。
11. 一種包含FGF23變異多肽之組合物，其中該FGF23變異多肽可衍生自具有至少一種FGF23活性之親本多肽，其中該FGF23變異多肽具有在位置179、206及244之胺基酸突變，且其中該FGF23變異多肽保有Egr-1活化之活性。
12. 如請求項11之組合物，其中該多肽或片段之序列包含SEQ ID NO: 67之胺基酸1至251之序列。
13. 如請求項11之組合物，其中該突變進一步包含在胺基酸位置156之額外突變。
14. 如請求項11之組合物，其中該多肽或片段之序列包含SEQ ID NO: 68之胺基酸1至251之序列。
15. 如請求項11之組合物，其進一步包含具有降低對Fc- γ 受體之親和力及/或增加之血清半衰期的經修飾之Fc片段。
16. 如請求項11之組合物，其係經聚乙二醇化。
17. 一種編碼FGF23變異多肽或其功能活性衍生物或片段之核酸，其

中該FGF23變異多肽可衍生自具有至少一種FGF23活性之親本多肽，且其中該FGF23變異多肽具有在位置179及視情況在位置206及/或244之胺基酸突變，其位置編碼係參照如SEQ ID NO: 35所示之FGF23序列，且其中該FGF23變異多肽或其功能活性衍生物或片段保有至少一種FGF23活性。

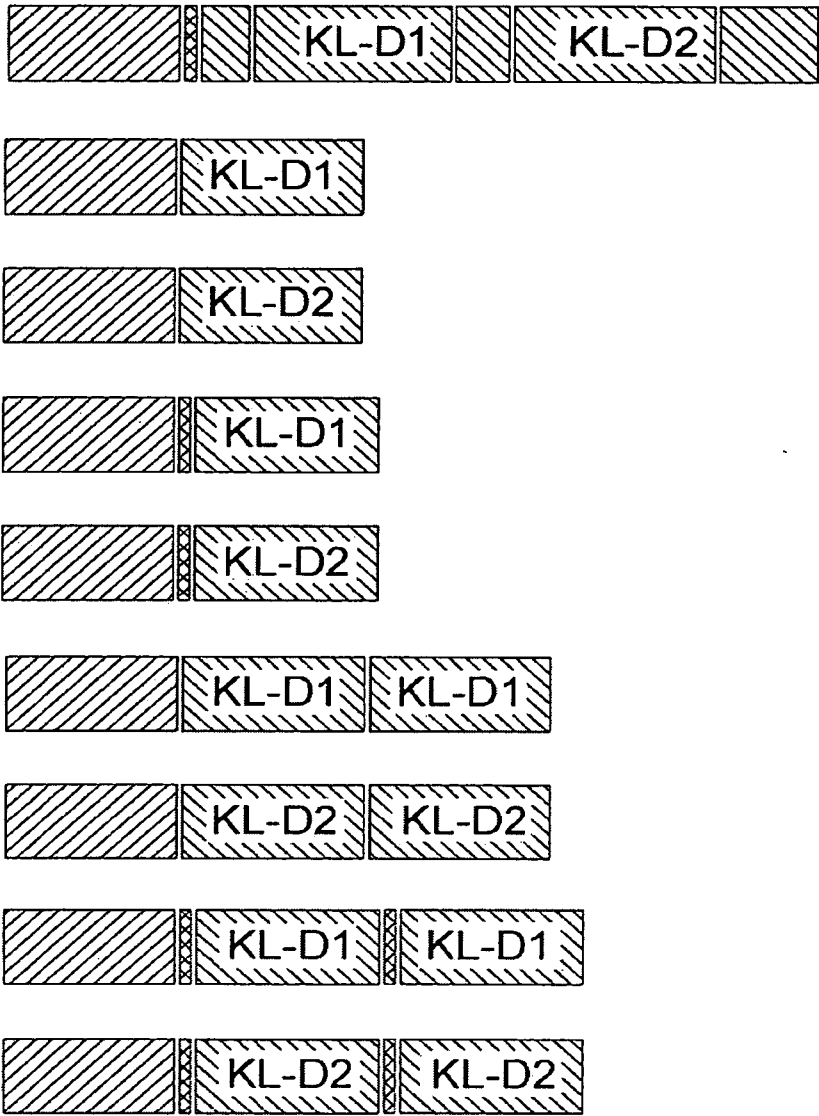
18. 如請求項17之核酸，其中該FGF23變異多肽或其功能活性衍生物或片段進一步包含在位置156之額外突變。
19. 如請求項17之核酸，其中該FGF23變異多肽或其功能活性衍生物或片段進一步包含在位置156之額外突變。

圖式



 :Klotho (細胞外域) 或Klotho活性片段;
 : FGF23(R179Q)、FGF23、FGF19、FGF21 ;  :連接子 ;  :IgG信號肽。

圖 1



 : Klotho (細胞外域) 或Klotho活性片段
 : FGF23(R179Q)、FGF23、FGF19、FGF21 ;  : 連接子 ;  : IgG信號肽

圖 1 (續)

人類Klotho核酸序列 (NM_004795) (SEQ ID NO: 1)

蛋白質編碼區: 9-3047

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1  cgcgcgagcat  gcccgcagc  gcccgcgcgc  gccgcccgcg  gccgcccgcg  ccgtcgctgt
61  cgctgctgct  ggtgctgctg  ggcttgggcg  gccgcccgcct  gcgtgctggag  ccgggcgagc
121  gcgcgcagac  ctgggcccgt  ttctcgcggc  ctcttgcctc  cgaggccgcg  ggccctcttc
181  agggcacctt  ccccgacggc  ttctcttggg  ccgtgggcag  cgccgcctac  cagaccgagg
241  gcggctggca  gcagcacggc  aagggtgcgt  ccactctggga  tacgttcacc  caccaccccc
301  tggcaccccc  gggagactcc  cggaacgcca  gtctgccglt  gggcgccccg  tcgcccgtgc
361  agcccgcac  cggggacgta  gccagcgaca  gctacaacaa  cgtcttccgc  gacacggagg
421  cgctgcgcga  gctcggggtc  actcaactacc  gcttctccat  ctcttgggcg  cgagtgtctc
481  ccaatggcag  cgcggggcgc  cccaaccgcg  aggggtgcg  ctactaccgg  cgcttgcctg
541  gcggctgcg  ggagctgggc  gtgcagcccg  tggtcaccc  gtaccactgg  gacctgccc
601  agcgctgca  ggacgcctac  ggcggctggg  ccaaccgcgc  cctggccgac  cacttcaggg
661  attacgcgga  gctctgcttc  cgcaacttcg  gcggtcaggt  caagtactgg  atcaccatcg
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781  ggggcagccc  gcgctcggg  tacctggtgg  cgcacaacct  cctctggtct  catgcaaaag
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2461  aagaagatcc  aataaaatcc  aalgattacc  tagaagtgc  agaaatgacc  gacalcacgt
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2941  cccgaaaagtc  ttactggct  ttcatagctt  ttctattttt  tgcttctatt  atttctctct
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圖 2

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3061 tctattcatt ctttttga aaattatgca gacacatcag ctgttaacca tttgcacctc
3121 taagtgttgt gaaactgtaa atttcataca tttgacttct agaaaacatt tttgtggctt
3181 atgacagagg ttttgaaatg ggcataaggat atcgtaaaat attgaataat gcgaatagt
3241 cctgaatttg ttctcttttt ggggtattaa aaaactgaca ggcactataa tttctgtaac
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3781 tgcggaaaaa caaacatgaa tctgtgtgata ttgggctctt cagggaagcat aaagcaattg
3841 tgaaatacag tataccgacg tggctctagg tggaggaaag gaggaaaaag tgccttattat
3901 gtgcaacatt atgattaatc tgattataca ccatttttga gcagatcttg gaatgaatga
3961 catgaccttt ccctagagaa taaggatgaa ataactcact attctatgaa cagtgcact
4021 actttctatt ctttagctgt actgtaattt ctttgagttg atagttttac aaattcttaa
4081 taggttcaaa agcaatctgg tctgaataac actggatttg tttctgtgat ctctgaggtc
4141 tattttatgt ttttgctgct acttctgtgg aagtagcttt gaactagttt tactttgaac
4201 tttcacgctg aaacatgcta gtgatatcta gaaagggcta attaggtctc atcttttaac
4261 gccccttaaa taagtcttgc tgattttcag acagggaagt ctctctatta cactggagct
4321 gttttataga taagtcaata ttgtatcagg caagataaac caatgtcata acaggcattg
4381 ccaacctcac tgacacaggg tcatagtgtg taataatata ctgtactata taatatatca
4441 tcttttagagg tatgattttt tcatgaaaga taagcttttg gtaatatcca ttttaaagtg
4501 gacttattaa aattggatgc tagagaatca agtttatttt atgtatata ttttctgatt
4561 ataagagtaa tatatgttca ttgtaaaaaa ttttaaaaca cagaaactat atgcaaagaa
4621 aaaataaaaa ttatctataa tctcagaacc cagaaatagc cactattaac atttctacg
4681 tatttttatt tacatagatc atattgtata tagttagtat ctttattaat ttttattatg
4741 aaacttttct ttgtcattat tagtcttcaa aagcatgatt ttaaatagtt gttgagttat
4801 ccaccacagg aatgtatcac aacttaaccg ttcccgtttg ttagactagt ttcttattaa
4861 tgttgatgaa tgttgtttaa aaataatttt gttgctacat ttactttaat ttccttgact
4921 gtaaagagaa gtaattttgc tcttgataa agtattatat taataataaa tctgcctgca
4981 actttttgcc ttctttcata atc

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Klotho胺基酸序列 (NP_004786) (SEQ ID NO: 2)

```

1 MPASAPRRP RPPPSLSLL LVLLGLGRR LRAEPDGAQ TWARFSRPPA PEAAGLFQGT
61 FPDGFLWAVG SAAYQTEGGW QHGKKGASIW DTFTHHPLAP PGDSRNASLP LGAPSPLQPA
121 TGDVASDSYN NVFRDTEALR ELGVTHYRFS ISWARVLPNG SAGVPNREGL RYYRLLERL
181 RELGVQPVVT LYHWDLPQRL QDAYGCWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP
241 YVVAWHGYAT GRLAPGIRGS PRLGYLVANH LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP DFESEKKFI
361 KGTADEFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW IDLEFNHPQI FIVENGWFS
421 GTTKRDDAKY MYYLKKFIME TLKAIKLDGV DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD
481 FLSQDKMLLP KSSALFYQKL IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTSLQ
541 FTDLNVYLWD VHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLOEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL LARQGAWENP
661 YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG HNLLKAHALA WHVYNEKFRH
721 AQNGKISIAL QADWIEPACP FSQKDKEVAE RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ
781 RNNFLLPYFT EDEKLIQGT FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN
841 SPSQVAVVPW GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSENR TAPRFGLYRY AADQFEPKAS MKHYRKIDS NGFPGPETLE
961 RFCPEEFTVC TECSFFHTRK SLLAFIAFLF FASIISLSLI FYYSKKGRS YK

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圖 2 (續)

β-Klotho核酸序列 (NM_175737) (SEQ ID NO: 3)
蛋白質編碼區: 9-3232

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1  atcctcagtc tcccagttca agctaatacat tgacagagct ttacaatcac aagctttttac
61 tgaagctttg ataagacagt ccagcagttg gtggcaaatg aagccaggct gtgcggcagg
121 atctccaggg aatgaatgga ttttcttcag cactgatgaa ataaccacac gctataggaa
181 tacaatgtcc aacgggggat tgcaaagatc tgtcatcctg tcagcactta ttctgctacg
241 agctgttact ggattctctg gagatggaag agctatatgg tctaaaaatc ctaattttac
301 tccggtaaat gaaaglcagc tgtttctcta tgacactttc ctaaaaaact ttttctgggg
361 tattgggact ggagcattgc aagtgggaag gagttggaag aaggatggaa aaggaccttc
421 tatatgggat catttcatcc acacacacct taaaaatgtc agcagcacga atggttccag
481 tgacagttat attttctctg aaaaagactt atcagccctg gattttatag gagtttcttt
541 ttatcaattt tcaatttcct ggccaaggct tttccccgat ggaatagtaa cagttgccaa
601 cgcaaaaagg ctgcagtact acagtactct tctggagcgt ctagtgtcta gaaacattga
661 acctatagtt actttatacc actgggattt gcctttggca ctacaagaaa aatatggggg
721 gtggaaaaat gataccataa tagatatctt caatgactat gccacatact gtttccagat
781 gtttggggac cgtgtcaaat attggattac aattcacaac ccatatctag tggcttggca
841 tgggtatggg acaggtatgc atgccccctg agagaaggga aatttagcag ctgtctacac
901 tgtgggacac aacttgatca aggtcactc gaaagtgttg cataactaca acacacattt
961 ccgcccacat cagaagggtt ggttatcgat cacgttggga tctcattgga tcgagccaaa
1021 ccggtcggaa aacacgatgg atatatcaaa atgtcaacaa tccatggttt ctgtgcttgg
1081 atggtttgcc aacctatccc atggggatgg cgactatcca gaggggatga gaaagaagtt
1141 gttctccggt ctacccattt tctctgaagc agagaagcat gagatgagag gcacagctga
1201 tttctttgcc ttttcttttg gacccaacaa cttcaagccc ctaaaacaca tggtaataaa
1261 gggacaaaat gtttcaacta atttaagaga agcgtgaac tggattaaac tggaaataaa
1321 caaccctcga atcttgattg ctgagaatgg ctggttcaca gacagtctgt tgaacacaga
1381 agacaccacg gccatctaca tgatgaagaa tttctcagc caggtgtctc aagcaataag
1441 gttagatgaa atacgagtggt ttggttatac tgccctggtc ctccctggatg gctttgaatg
1501 gcaggatgct tacaccatcc gccgaggatt attttatgtg gattttaaca gtaaacagaa
1561 agagcggaaa cctaagtcct cagcacacta ctacaaacag atcatacgag aaaaatggtt
1621 ttcttttaaa gagtccacgc cagatgtgca gggccagttt ccctgtgact tctcctgggg
1681 tgcactgaa tctgttctta agccccagtc tgtggcttcg tccccacagt tcagcgatcc
1741 tcatctgtac gtgtggaacg ccactggcaa cagactgttg caccgagtgg aaggggtgag
1801 gctgaaaaca cgaccgctc aatgcacaga ttttgtaaac atcaaaaaac aacttgagat
1861 gttggcaaga atgaaagtca ccactaccg gtttgctctg gattgggcct cggctcttcc
1921 cactggcaac ctgtccgcgg tgaaccgaca ggccttgagg tactacaggt gcgtggtcag
1981 tgaggggctg aagcttgcca tctccgcgat ggtcaccctg tattatccga cccacgcca
2041 cctaggcctc cccgagcctc tgttgcatgc cgacgggtgg ctgaacccat cgacggccga
2101 ggccttccag gcctacgctg ggctgtgctt ccaggagctg ggggacctgg tgaagctctg
2161 gatcaccatc aacgagccta accggctaag tgacatctac aaccgctctg gcaacgacac
2221 ctacggggcg gcgcacaacc tgctggtggc ccacgcctg gcctggcgcc tctacgaccg
2281 gcagttcagg ccctcacagc gcggggccgt gtcgctgtcg ctgcacgcgg actgggcgga
2341 acccgccaac ccctatgctg actcgcactg gagggcgggc gagcgcttcc tgcagttcga
2401 gatcgctggt ttcgcccagc cgctcttcaa gaccggggac taccggcgcg ccattgagga
2461 atacattgcc tccaagcacc gacggggggt ttccagctcg gccctgccgc gcctcaccga
2521 ggccgaaagg aggcctgctc agggcacggt cgacttctgc gcgctcaacc acttcaccac
2581 taggttcgtg atgcacgagc agctggccgg cagccgctac gactcggaac gggacatcca
2641 gtttctgcag gacatcaccc gcctgagctc cccacgcgcg ctggctgtga ttccctgggg
2701 ggtgcgcaag ctgctgcggt gggctccgga gaactacggc gacatggaca ttacatcac
2761 cgccagtggc atcgacgacc aggcctcggg ggatgaccgg ctccggaagt actacctagg
2821 gaagtacctt caggaggtgc tgaaagcata cctgattgat aaagtcagaa tcaaaggcta
2881 ttatgcatct aaactggctg aagagaaatc taaaccagaa tttggattct tcacatctga
2941 ttttaaaagt aaatcctcaa tacaatttta caacaaagt atcagcagca ggggcttccc
3001 ttttgagaac agtagttcta gatgcagtca gacccaagaa aatacagagt gcactgtctg
3061 cttattcctt gtgcagaaga aaccactgat attcctgggt tgttgcttct tctccacct
3121 ggttctactc ttatcaattg ccatttttca aaggcagaag agaagaaagt tttggaaagc

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圖 2 (續)

3181 aaaaaactta caacacatac cattaaagaa aggcaagaga gttgtagct aaactgatct
3241 gtctgcatga tagacagttt aaaaattcat cccagttcc

β-Klotho 胺基酸序列 (NP_783864) (SEQ ID NO: 4)

1 mkpgcaagsp gnewiffstd eittryntm sngglqrsvi lsalillrav tgfsgdgrai
61 wsknpnftpv nesqlflydt fpknffwgig tgalqvegsw kkdgkgsiw dhfihthlkn
121 vsstngssds yiflekdlsa ldfigvsfyq fsiswprlfp dgivtvanak glqyystlld
181 alvlrniepi vtlyhwdlpl alqekyggwk ndtiidifnd yatycfqmfg drvkywiti
241 npylvawhgy gtgmhapsek gnlaavytv gnhlikahskv whnynthfrp hqkgwlsitl
301 gshwiepnrs entmdifkcc qsmvsvlgwf anpihgcdgy pegmrkklfs vlpifseae
361 hemrgtadff afsfgpnnfk plntmakmgq nvslnlreal nwikleyennp riliaengwf
421 tdsrvktedt taiymknfl sqvlqairld eirvfgytaw slldgfewqd aytirglfy
481 vdfnskqker kpkssahyyk qiirengfsl kestdpvqgg fpcdfswgvt esvlkpesva
541 sspqfscphl yvwnatgnrl lhrvegvrk trpaqctdfv nikkqlemle rmkvthyrfa
601 ldwasvlptg nlsavnrqal ryyrcvsvseg lklgisamvt lypthahlg lpepllhadd
661 wlnpstaeaf qayaglcfe lgdlvklwit inepnrlsdi ynrsngndtyg aahnlhvaha
721 lawlydrqf rpsqrgavsl slhadwaepa npyadshwra aerflqfeia wfaeplfktg
781 dypaamreyi askhrrglss salprlteae rrlkgtvdf calnhfttrf vmheqlagsr
841 ydsdrdiqfl qditrlsspt rlvapwgvv kllrwvrrny gdmidiyitas giddqaledd
901 rlrkyylgky lqevlkayli dkvrkgyya fklaeekskp rfgfftsdfk akssiqfynk
961 vissrgfpfe nsssrscstq entectvcif lvqkkplifl gccffstlvi llsiaifqrq
1021 krrkfwkakn lqhiplkkkg rvvs

人類Klotho域1 (KL-D1) 胺基酸序列 (SEQ ID NO: 5)

58 qgt
61 fpdgflwavg saayqteggw qhgkgasiw dtfthhplap pgdsrnaslp lgapsplqpa
121 tgdvasdsyn nvfrdtealr elgvthyrfis iswarvlpng sagvpnregl ryyrrillerl
181 relgvqpvt lyhwdlpqrl qdayggwanr aladhfrdya elcfrhfagg vkywitidnp
241 yvawhgyat qrlapgirgs prlgylvahn lllahakvwh lyntsfrptg ggqvsialss
301 hwinprmt dhsikecqs sl dfvlgwafakp vfidgdypes mknslsilp dftesekkfi
361 kgtacffalc fgptlsfql dphmkfrole spnlrqllsw idlefnpqi fivengwfv
421 gttkrddaky myylkkfime tlkaiklogv dvigytawsl mdgfewhrgy sirrglfyvd
481 flsqckmlp kssalfyqkl iekngf

人類Klotho域2 (KL-D2) 胺基酸序列 (SEQ ID NO: 6)

517 gtfp cdfawgvvdn yiqvdttsq
541 ftdlnvylwd vhhskrlikv dgvttkrks ycvdfaaiqp qiallqemhv thfrfsldwa
601 lilplgnqsq vnhtilqyyr cmaselvrn itpvvalwq mapnqglprl larqgawenp
661 ytalafaeya rlcfcqlghh vkwitmnep ytrnmtysag hnllkahala whvynekrfh
721 aqngkisial qadwiepacp fsqkdkevae rvlef digwl aepifgsgdy pwvmrdwlnq
781 rnnfllpyft edekkliggt fdflalshyt tilvdseked pikyndylev qemtditwln
841 spsqvavpw glrkvlwlv fkygdipmyi isngiddglh aeddqlrvyy mqnyinealk
901 ahildginlc gyfaysfndr taprfglyry aadqfepkas mkhyrkiiis ngf

Klotho細胞外域 (無信號肽) 胺基酸序列 (SEQ ID NO: 7)

28 epgdgaq twarfsrppa peaaglfqgt
61 fpdgflwavg saayqteggw qhgkgasiw dtfthhplap pgdsrnaslp lgapsplqpa
121 tgdvasdsyn nvfrdtealr elgvthyrfis iswarvlpng sagvpnregl ryyrrillerl
181 relgvqpvt lyhwdlpqrl qdayggwanr aladhfrdya elcfrhfagg vkywitidnp

圖 2 (續)

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241 yvvawhgyat grlapgirgs prlgylvahn lllahakvwh lyntsfrptq gggvsialss
301 hwinprrrtd hsiyecqksl dfvlgwafakp vfidgdypes mknnlssilp dftesekekfi
361 kgtadffalc fgptlsfql1 dphmkfrqle spnlrqllsw idlefhnpi fivengwfv
421 gttkrddaky myylkkfime tlkaikldgv dvigytawsl mdfewhrgy sirrglfyvd
481 flsqdkmlp kssalfyqkl iekngfpplp enqplegtfp cdfawgvvdn yiqvdttsq
541 ftdlnvylwd vhhskrlikv dgvttkrks ycvdfaaiqp qiallqemhv thfrfslwa
601 lilplngsq vnhtlqyyr cmaselvrn itpvvalwqp mapnqglprl larogawenp
661 ytalafaeya rlcqelghh vklwitmneq ytrnmtysag hnllkahala whvynekfrh
721 aqngkisial qadwiepacp fsqkdkevae rvlef digwl aepifgsgdy pwvmdwlnq
781 rnnfllpyft edekkligt fdfllalshyt tilvdseked pikyndylev qemtditwln
841 spsqvavpw glrkvlwllk fkygdipmyi isngiddglh aeddqlrvyy mnyinealk
901 ahildginlc gyfaysfndr taprfglyry aadqfepkas mkhyrkiids ngfpgpetle
961 rfcpeeftvc tecsffhtrk sl

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Klotho信號肽胺基酸序列 (SEQ ID NO: 8)

```

1 mpasapprp rpppslsll lvllglgrr lra

```

IgG信號肽胺基酸序列 (SEQ ID NO: 9)

```

1 msvltqvlal lllwltgtrc rrlra

```

(Gly₄ Ser)₃多肽連接子核酸序列 (SEQ ID NO: 10)

```

1 ggaggtggag gttcaggagg tggaggttca ggaggtggag gttca

```

(Gly₄ Ser)₃多肽連接子胺基酸序列 (SEQ ID NO: 11)

```

1 GGGSGGGGS GGGGS

```

(Gly₄ Ser)多肽連接子胺基酸序列 (SEQ ID NO: 12)

```

1 GGGGS

```

(Gly)多肽連接子胺基酸序列 (SEQ ID NO: 13)

```

1 G

```

(Gly Gly)多肽連接子胺基酸序列 (SEQ ID NO: 14)

```

1 GG

```

(Gly Ser)多肽連接子胺基酸序列 (SEQ ID NO: 15)

```

1 GS

```

(Gly₂ Ser)多肽連接子胺基酸序列 (SEQ ID NO: 16)

```

1 GGS

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圖 2 (續)

(Ala)多肽連接子胺基酸序列 (SEQ ID NO: 17)

1 A

(Ala Ala)多肽連接子胺基酸序列 (SEQ ID NO: 18)

1 AA

Klotho信號肽-Klotho細胞外域-FGF23 (R179Q)胺基酸序列 (SEQ ID NO: 19)

```

1 MPASAPRRRP RPPPPSLSL LVLGLGGR LRAEPGDGAQ TWARFSRPPA
51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYRRLLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFLGWFAKP VFIDGDYPES MKNNLSSILP
351 DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWFSV GTTKRDDAKY MYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGIFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTSLQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTAFAAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWVMDWLNQ RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
951 NGFPGPETLE RFCPEEFTVC TECSEFFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLL GSSWGGLIHL YATARNSYHL QIHKNHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPFP YSQFLSRNE IPLIHENTPI
1151 PRRHTQSAED DSERDPLNVL KPRARMTAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGCTGPEG CRFFAKFI*

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IgG信號肽-Klotho細胞外域-FGF23 (R179Q)胺基酸序列 (SEQ ID NO: 20)

```

1 MSVLTQVLAL LLLWLTGLCG RRLRAEPGDG AQTWARFSRP PAPEAAGLFQ
51 GTFPDGFLEW VGSAAAYQTEG GWQQHGKGAS IWDTFTHHPL APPGDSRNAS
101 LPLGAPSPLQ PATGDVASDS YNNVFRDTEA LRELGVTHYR FSIWARVLP
151 NGSAGVPNRE GLRYRRLLE RLRELGVQPV VTLYHWDLPQ RLQDAYGGWA
201 NRALADHFRD YAELECFRHFQ GQVKYWITID NPYVVAWHGY ATGRLAPGIR
251 GSPRLCYLVA HNLLAHAKV WHLYNTSFRP TQGGQVSIAL SSHWINPRRM
301 TDHSIKECQK SLDFVLGWFA KPVFIDGDYP ESMKNNLSSI LPDFTESEKK
351 FIKGTADFFA LCFGPTLSFQ LLDPHMKFRQ LESPNLRQLL SWIDLEFNHP
401 QIFIVENGWF VSGTTKRDDA KYMYLKKFI METLKAIKLD GVDVIGYTAW
451 SLMDGFEWHR GYSIRRGIFY VDFLSQDKML LPKSSALFYQ KLIKNGFPP
501 LPENQPLEGT FPCDFAWGVV DNYIQVDTTL SQFTDLNVYL WDVHHSKRLI
551 KVDGVVTKKR KSYCVDFAAI QPQIALLQEM HVTHFRFSLD WALILPLGNQ

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圖 2 (續)

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601 SQVNHTILQY YRCMASELVR VNITPVVALW QPMAPNQGLP RLLARQGAWE
651 NPYTALAE YARLCFQELG HHVKLWITMN EPYTRNMTYS AGHNLLKAHA
701 LAWHVYNEKF RHAQNGKISI ALQADWIEPA CPFSQKDKEV AERVLEFDIG
751 WLAEPFIFGSG DYPWVMRDWL NQRNNFLLPY FTEDEKKLIQ GTFDFLALSH
801 YTTILVDSEK EDPIKYNDYL EVQEMTDITW LNSPSQVAVV PWGLRKVLNW
851 LKFKYGDLP YIISNGIDDG LHAEDDQLRV YYMQNYINEA LKAHILDGIN
901 LCGYFAYSFN DRTAPRFGly RYAADQFEPK ASMKHYRKII DSNGFPGPET
951 LERFCPEEFT VCTECSEFFHT RKSLSGSGGGG SGGGSGGGGG SLKYPNASPL
1001 LGSSWGGLIH LYTATARN SY HLQIHKNHGV DGAPHQTIYS ALMIRSEDAG
1051 FVVITGVMSR RYLCMDFRGN IFGSHYFDPE NCRFQHQTL NGYDVYHSPQ
1101 YHFLVSLGRA KRAFLPGMNP PPYSQFLSRR NEIPLIHFT PIPRRHTQSA
1151 EDDSERDPLN VLKPRARMTF APASCSQELP SAEDNSPMAS DPLGVVRGGR
1201 VNTHAGGTGP EGCPRFAKFI *

```

KL-D1-FGF23 (R179Q)氨基酸序列 (SEQ ID NO: 21)

```

1 MPASAPRRP RPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA
51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QHKGKASIW DTFTTHPLAP
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVFNREGL RYRRLLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNLSSILP
351 DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWFS GTTKRDDAKY MYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGIFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGSGG GSGGGGSGG GGSLSKYPNAS PLLGSSWGGL
551 IHLTYATARN SYHLQIHKNH HVDGAPHQTI YSALMIRSED AGFVVITGVM
601 SRRYLCMDFR GNIFGSHYFD PENCRFQHQT LENGVDVYHS PQYHFLVSLG
651 RAKRAFLPGM NPPYSQFLS RRNEIPLIHF NTPIPRRHTQ SAEDDSERDP
701 LNVLKPRARM TPAPASCSQE LPSAEDNSPM ASDPLGVVRG GRVNTHAGGT
751 GPEGCRFAK FI*

```

KL-D2-FGF23 (R179Q)氨基酸序列 (SEQ ID NO: 22)

```

1 MPASAPRRP RPPPSLSLL LVLLGLGGRR LPLPENQPLE GTFPCDFAWG
51 VVDNYIQVDT TLSQFTDLNV YLWDVHHSKR LIKVDGVVTK KRKSYCVDFFA
101 AIQPQIALLO EMHVTHFRFS LDWALILPLG NQSQVNHTIL QYYRCMASEL
151 VRVNITPVVA LWQPMAPNQG LPRLLARQGA WENPYTALAE AEYARLCFQE
201 LGHHVKLWIT MNEPYTRNMT YSAGHNLLKA HALAWHVYNE KFRHAQNCKI
251 SIALQADWIE PACPFQKDK EVAERVLEFD IGWLAEPFIFG SGDYPWVMRD
301 WLNQRNNFLL PYTTEDEKKL IQGTDFLAL SHYTTILVDS EKEDPIKYND
351 YLEVQEMTDI TWLNSPSQVA VVPWGLRKVL NWLKFYKGDY PMYIISNGID
401 DGLHAEDDQL RVYYMQNYIN EALKAHILDG INLCGYFAYS FNDRTAPRFG
451 LYRYAADQFE PKASMKHYRK IIDSNGFPGP ETLERFCPEE FTVCTECSEFF
501 HTRKSLGSGG GSGGGGSGG GGSLSKYPNAS PLLGSSWGGL IHLTYATARN
551 SYHLQIHKNH HVDGAPHQTI YSALMIRSED AGFVVITGVM SRRYLCMDFR
601 GNIFGSHYFD PENCRFQHQT LENGVDVYHS PQYHFLVSLG RAKRAFLPGM
651 NPPYSQFLS RRNEIPLIHF NTPIPRRHTQ SAEDDSERDP LNVLKPRARM
701 TPAPASCSQE LPSAEDNSPM ASDPLGVVRG GRVNTHAGGT GPEGCRFAK
751 FI*

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(KL-D1)2-FGF23 (R179Q)氨基酸序列 (SEQ ID NO: 23)

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1 MPASAPRRP RPPPSLSLL LVLLGLGGRR LRAEPGDGAQ TWARFSRPPA

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圖 2 (續)

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51  PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTTHPLAP
101 PGDSRNASLP LGAPSPLOPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYRRLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
351 DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGSGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW
551 DTFTTHPLAP PGDSRNASLP LGAPSPLOPA TGDVASDSYN NVFRDTEALR
601 ELGVTHYRFS ISWARVLPNG SAGVPNREGL RYRRLERL RELGVQPVVT
651 LYHWDLPQRL QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP
701 YVVAWHGYAT GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ
751 GGQVSIALSS HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES
801 MKNNLSSILP DFTSEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE
851 SPNLRQLLSW IDLEFNHPQI FIVENGWVFS GTTKRDDAKY MYYLKKFIME
901 TLKAIKLDGV DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP
951 KSSALFYQKL IEKNGFPPEFG SGGGSGGGG SGGGSLKYP NASPLLGSSW
1001 GGLIHYLTAT ARNSYHLQIH KNGHVDGAPH QTIYSALMIR SEDAGFVVIT
1051 GVMSRRYLCM DFRGNIFGSH YFDPENCRFQ HQTLENGYDV YHSPQYHFLV
1101 SLGRAKRAFL PGMNPPYSQ FLSRRNEIPL IHFNTPIPRR HTQSAEDDSE
1151 RDPLNLVKPR ARMTAPAPASC SQELPSAEDN SPMASDPLGV VRGGRVNTHA
1201 GGTGPEGCRP FAKFI*

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(KL-D2)₂-FGF23 (R179Q)氨基酸序列 (SEQ ID NO: 24)

```

1  MPASAPPRRP RPPPSLSLL LVLLGLGGRR LPLPENQPLE GTFPCDFAWG
51  VVDNYIQVDT TLSQFTDLNV YLWDVHHSKR LIKVDGVVTK KRKSYCVDFDFA
101 AIQPQIALLO EMHVTHFRFS LDWALILPLG NQSQVNHTIL QYYRCMASEL
151 VVRNITPVVA LWQPMAPNQG LPRLLARQGA WENPYTALAF AEYARLCFQE
201 LGHHVKLWIT MNEPYTRNMT YSAGHNLKA HALAHVYNE KFRHAQNGKI
251 SIALQADWIE PACPFSQKDK EVAERVLEFD IGWLAEPFIC SGDYPWVMRD
301 WLNQRNFFLL PYFTEDEKKL IQGTFDFLAL SHYTTILVDS EKEDEPIKYN
351 YLEVQEMTDI TWLNSPSQVA VVPWGLRKVL NWLKFYKGD LPMYIISNGID
401 DGLHAEDDQL RYVYMQNYIN EALKAHILDG INLCGYFAYS FNDRTAPRFG
451 LYRYAADQFE PKASMKHYRK IIDSNGFFGP ETLERFCPEE FTVCTECSSF
501 HTRKSLGTFP CDFAWGVVDN YIQVDTTSLQ FTDNLVYLWD VHHSKRLIKV
551 DGVVTKKRKS YCVDFAAIQP QIALLOEMHV THFRFSLDWA LILPLGNQSQ
601 VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL LARQGAWENP
651 YALAFAYEA RLCFQELGHH VKLWITMNEP YTRNMTYSAG HNLLKAHALA
701 WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE RVLEFDIGWL
751 AEPIFGSGDY PWVMDWLNQ RNNFLLPYFT EDEKKLIQGT FDFLALSHYT
801 TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW GLRKVLNWLK
851 FKYCDLPMYI ISNCIDDGLH AEDDQLRVYY MQNYINEALK AHILDGINLC
901 GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIDS NGFGSGGGGS
951 GGGSGGGGS LKYPNASPLL GSSWGGLIHL YTATARNYSY LQIHKNHVD
1001 GAPHQTIYSA LMIRSEDAGF VVITGVMSRR YLCMDFRGNI FGSHYFDPEN
1051 CRFQHQTLN GYDVYHSPQY HFLVSLGRAK RAFLPGMNPP PYSQFLSRRN
1101 EIPLIHFNTP IPRRHTQSAE DSDERDPLNV LKPRARMTPA PASCSEQLPS
1151 AEDNSPMASD PLGVVRGGRV NTHAGGTGPE GCRPFKFI*

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FGF23 (R179Q)-Klotho细胞外域氨基酸序列 (SEQ ID NO: 25)

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1  MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARN

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圖 2 (續)

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51 YHLQIHKNKGH VDCAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IGSGGGSGG GSGGGGSLK EPGDGAQTWA RFSRPPAPEA AGLFQGTFFD
301 GFLWAVGSAA YQTEGGWQQH GKASIWDTF THHPLAPPGD SRNASLPLGA
351 PSPLQPATGD VASDSYNNVF RDTEALRELG VTHYRFSISW ARVLNPGSAG
401 VPNREGLRYY RLLERLREL GVQPVVTLYH WDLPQRLQDA YGGWANRALA
451 DHFRDYAELC FRHFGGQVKY WITIDNPYVV AWHGYATCRL APGIRGSPRL
501 GYLVAHNLLL AHAKVWHLYN TSFRPTQGGQ VSIALSSHWI NPPRMTDHSI
551 KECQKSLDFV LGWFAKPVFI DGDYPESMKN NLSSILPDFT ESEKKFIKGT
601 ADFFALCFGP TFSFQLLDPH MKFRQLESPN LRQLLSWIDL EFNHPQIFIV
651 ENGWFVSGTT KRDDAKYMY LKKFIMETLK AIKLDGVDDVI GYTAWSLMDG
701 FEWHRGYSIR RGLFYVDFLS QDKMLLPKSS ALFYQKLIK NGFPPLPENQ
751 PLEGTFFCDF AWGVVDNYIQ VDTTLSQFTD LNVYLWDVHH SKRLIKVDGV
801 VTKKRKSYCV DFAAIQPIA LLQEMHVTHF RSLDWALIL PLGNQSQVNH
851 TILQYYRCMA SELVRVNITP VVALWQPMAP NQGLPRLLAR QGAWENPYTA
901 LAFAYEARLC FQELGHHVKL WITMNEPYTR NMTYSAGHNL LKAHALAWHV
951 YNEKFRHAQN GKISIALQAD WIEPACFFSQ KDKVAERVL EFDIGWLAEP
1001 IFGSGDYPWV MRDWLNQRNN FLLPYFTEDE KKLIQCTFDF LALSHYTTIL
1051 VDSEKEDPIK YNDYLEVQEM TDITWLNPS QVAVVPWGLR KVLNWLKFKY
1101 GDLPMYIISN GIDGGLHAE DQLRVYMQN YINEALKAHI LDGINLCGYF
1151 AYSNDRTAP RFGLYRYAAD QFEPKASKH YRKIIDSNF PGPETLERFC
1201 PEEFTVCTEC SFFHTRKSL*

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FGF23 (R179Q)-KL-D1胺基酸序列 (SEQ ID NO: 26)

```

1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARN
51 YHLQIHKNKGH VDCAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IQGTFFPDGFL WAVGSAAYQT EGGWQQHGKG ASIWDTFTH PLAPPGDSRN
301 ASLPLGAPSP LQPATGDVAS DSYNNVFRDT EALRELGVTH YRFSISWARV
351 LPNGSAGVPN REGRLYYRRL LERLRELGVQ PVVTLYHWDL PQRLQDAYGG
401 WANRALADHF RDYAELCFRH FGGQVKYWIT IDNPYVVAWH GYATGRLAPG
451 IRGSPRLGYL VAHNLLLAHA KVWHLYNTSF RPTQCCQVSI ALSSHWINPR
501 RMTDHSIKEC QKSLDFVLGW FAKPVFIDGD YPESMKNNLS SILPDFTSE
551 KKFIKGTADF FALCFGPTLS FQLLDPHMKF RQLESPNLRQ LLSWIDLEFN
601 HPQIFIVENG WFSVGTTRKD DAKYMYLKK FIMETLKAIK LDGVDVICYT
651 AWSLMDGFEW HRGYSIRRL FYVDFLSQDK MLLPKSSALF YQKLIKENG
652 *

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FGF23 (R179Q)-KL-D2胺基酸序列 (SEQ ID NO: 27)

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1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARN
51 YHLQIHKNKGH VDCAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IGTFFPCDFAW GVVDNYIQVD TTLSQFTDLN VYLWDVHHK RLIKVDGVVT
301 KKRKSYCVDF AAIQPIALL QEMHVTHFRF SLDWALILPL GNQSQVNHTI
351 LQYYRCMASE LVRVNITPVV ALWQPMAPNQ GLPRLLARQG AWENPYTALA
401 FAEYARLCFQ ELGHHVKLWI TMNEPYTRNM TYSAGHNLK AHALAWHVYN
451 EKFRHAQNGK ISIALQADWI EPACFFSQKD KEVAERVLEF DIGWLAEPF

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圖 2 (續)

501 GSGDYPWVMR DWLNQRNNFL LPYFTEDEKK LIQGTDFDLA LSHYTTILVD
551 SEKEDPIKYN DYLEVQEMTD ITWLNSPSQV AVVPWGLRKY LNWLKFKYGD
601 LPMYIISNGI DDGLHAEDDQ LRVYMQNYI NEALKAHILD GINLCGYFAY
651 SFNDRTAPRF GLYRYAADQF EPKASKHYR KIIDSNGF*

FGF23 (R179Q)-(KL-D1)₂ 胺基酸序列 (SEQ ID NO: 28)

1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARN
51 YHLQIHKNH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IQGTFFPDGFL WAVGSAAYQT EGGWQQHGKG ASIWDTFTHH PLAPPEDSRN
301 ASPLGAPSP LQPATGDVAS DSYNNVFRDT EALRELGVTH YRFSISWARV
351 LPNGSAGVPN REGLRYRRL LERLRELGVQ PVVTLYHWDL PQRLQDAYGG
401 WANRALADHF RDYAECLFRH FGGQVKYWT IDNPYVVAWH GYATGRLAPG
451 IRGSPRLGYL VAHNLLLAHA KVWHLYNTSF RPTQGGQVSI ALSSHWINPR
501 RMTDHSIKEC QKSLDFVLGW FAKPVFIDGD YPESMKNNLS SILPDFTESE
551 KFKIKGTADF FALCFGPTLS FQLLDPHMKF QLESPLNRQ LLSWIDLEFN
601 HPQIFIVENG WFSVGTTRKD DAKYMYLKK FIMETLKAIK LDGVDVIGYT
651 AWSLMDGFEW HRGYSIRRLG FYVDFLSQDK MLLPKSSALF YQKLIKNGF
701 QGTFFPDGFLW AVGSAAYQTE GGWQQHGKGA SIWDTFTHHP LAPPEDSRNA
751 SLPLGAPSP QPATGDVASD SYNNVFRDTE ALRELGVTHY RFSISWARVL
801 PNGSAGVPRN EGLRYRRL ERLRELGVQ PVVTLYHWDLP QRLQDAYGGW
851 ANRALADHFR DYAECLFRHF GGGQVKYWTI DNPYVVAWHG YATGRLAPGI
901 RGSPLRGYLV AHNLLLAHAK VWHLYNTSFR PTQGGQVSI LSSHWINPR
951 MTDHSIKEC KSLDFVLGW FAKPVFIDGD YPESMKNNLS ILPDFTESEK
1001 KFKIKGTADFF ALCFGPTLSF QLLDPMKFR QLESPLNRQL LSWIDLEFNH
1051 PQIFIVENGW FVSGTTRKDD AKYMYLKKF IMETLKAIKL DGVDVIGYTA
1101 WSLMDGFEWH RGYSIRRLGF YVDFLSQDKM LLPKSSALFY QKLIKNGF*

FGF23 (R179Q)-(KL-D1)₂ 胺基酸序列 (SEQ ID NO: 29)

1 MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARN
51 YHLQIHKNH VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG
101 NIFGSHYFDP ENCRFQHQTL ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN
151 PPPYSQFLSR RNEIPLIHFN TPIPRRHTQS AEDDSERDPL NVLKPRARMT
201 PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG PEGCRPFAKF
251 IGTFPCDFAW GVVDNYIQVD TTLSQFTDLN VYLWDVHHSK RLIKVDGVVT
301 KKRKSYCVDF AAIQPQIAL QEMHVTHFRF SLDWALILPL GNQSQVNHTI
351 LQYRCMASE LVRVNIPTVV ALWQPMAPNQ GLPRLARQG AWENPYTALA
401 FAEYARLCFQ ELGHHVKLWI TMNEPYTRNM TYSAGHNLK AHALAWHVYN
451 EKFRHAQNGK ISIALQADWI EPACPFQSKD KEVAERVLEF DIGWLAEPF
501 GSGDYPWVMR DWLNQRNNFL LPYFTEDEKK LIQGTDFDLA LSHYTTILVD
551 SEKEDPIKYN DYLEVQEMTD ITWLNSPSQV AVVPWGLRKY LNWLKFKYGD
601 LPMYIISNGI DDGLHAEDDQ LRVYMQNYI NEALKAHILD GINLCGYFAY
651 SFNDRTAPRF GLYRYAADQF EPKASKHYR KIIDSNGFGT FPCDFAWGVV
701 DNYIQVDTTL SQFTDLNVYL WDVHHSKRLI KVDGVVTKKR KSYCVDFAAI
751 QPQIALQEM HVTHFRFSLD WALILPLGNQ SQVNHTILQY YRCMASELVR
801 VNITPVVALW QPMAPNQGLP RLLARQGAWE NPYTALAFAE YARLCFQELG
851 HHVKLWITMN EPYTRNMTYS AGHNLKAHA LAWHVYNEKF RHAQNGKISI
901 ALQADWIEPA CPFSQKDKEV AERVLEFDIG WLAEPFQSG DYPWVMRDWL
951 NQRNNFLLPY FTEDEKKLIQ GTFDLALSH YTTILVDSEK EDPIKYNLYL
1001 EVQEMTDITW LNSPSQVAVV PWGLRKVLNW LKFKYGDLP YIISNGIDDG
1051 LHAEDDQLRV YMQNYINEA LKAHILDGIN LCGYFAYSFN DRTAPRFGLY
1101 RYAADQFEPK ASMKHYRKII DSNFG*

圖 2 (續)

FGF19核酸序列 (NM_005117) (SEQ ID NO: 30)

蛋白質編碼區 (464-1114)

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1  gctcccagcc aagaacctcg gggccgctgc gcggtgggga ggagttcccc gaaacccggc
61  cgctaagcga ggcctcctcc tcccgcagat ccgaacggcc tgggcggggg caccgccgct
121  gggacaagaa gccgcgcgct gcctgcccgg gcccggggag ggggctgggg ctggggccgg
181  aggcgggggtg tgagtgggtg tgtgcggggg gcggaggctt gatgcaatcc cgataagaaa
241  tgctcgggtg tcttgggcac ctaccctggg gggccgtaag gcgctactat ataaggctgc
301  cggcccggag ccgcccgcgc gtcagagcag gagcgctgcg tccaggatct agggccacga
361  ccatcccaac ccggcactca cagccccgca gcgcalcccg glcgccgccc agcctcccgc
421  acccccatcg ccggagctgc gccgagagcc ccaggagggt gccatgcgga gcgggtgtgt
481  ggtggtccac gtatggatcc tggccggcct ctggctggcc gtggccgggc gcccccctgc
541  cttctcggac gcggggcccc acgtgcacta cggtgggggc gaccccatcc gcctgcggca
601  cctgtacacc tccggcccc acgggctctc cagctgcttc ctgcgcatcc gtgcgcagcg
661  cgtcgtggac tgcgcgcggg gccagagcgc gcacagtttg ctggagatca aggcagtcgc
721  tctgcggacc gtggccatca agggcgtgca cagcgtgcgg tacctctgca lggcgccga
781  cggcaagatg caggggctgc ttcagtactc ggaggaagac tgtgctttcg aggaggagat
841  ccgcccagat ggctacaatg lglaccgatc cgagaagcac cgctcccgg tctccctgag
901  cagtgcacaa cagcggcagc tgtacaagaa cagaggcttt cttccactct ctcatttctt
961  gccatgctg cccatggtcc cagaggagcc tgaggacctc aggggccact tggaatctga
1021 catgttctct tcgcccctgg agaccgacag catggaccga tttgggcttg tcaccggact
1081 ggaggccgtg aggagtccca gctttgagaa gtaactgaga ccatgccggg gcctcttcac
1141 tgctgccagg ggctgtggtg cctgcagcgt gggggacgtg cttctacaag aacagtcctg
1201 agtccacgtt ctgtttagct ttaggaagaa acatctagaa gttgtacata ttcagagttt
1261 tccattggca gtgccagttt ctagccaata gacttgtctg atcataacat tgtaagcctg
1321 tagcttgccc agctgctgcc tgggccccca tctgctccc tcgaggttgc tggacaagct
1381 gctgcaactg ctcaagttct cttgaatacc tccatcgatg gggaaactcac ttcctttgga
1441 aaaattctta tglcaagctg aaattctcta atttttctc alcacttccc caggagcagc
1501 cagaagacag gcagtagttt taatttcagg aacagggtgat ccactctgta aaacagcagg
1561 taaatttcac tcaaccccat gtgggaattg atctatatct ctacttccag ggaccatttg
1621 cccttcccaa atccctccag gccagaactg actggagcag gcatggccca ccaggcttca
1681 ggagtggggg aagcctggag cccactcca gccctgggac aacttgagaa tccccctga
1741 ggccagttct gtcattggat ctgtcctgag aataacttgc tgtcccgtg tcactgctt
1801 ccatctccca gccaccagc cctctgccc cctcacatgc clcccalgg attggggcct
1861 cccaggcccc ccaccttatg tcaacctgca cttcttggtc aaaaatcagg aaaagaaaag
1921 atttgaagac cccaagtctt gtcaataact tgctgtgtgg aagcagcggg ggaagacctt
1981 gaaccctttc cccagcactt ggttttccaa catgatattt atgagtaatt tattttgata
2041 tgtacatctc ttattttctt acattattta tgccccaaa ttataattat gtatgtaagt
2101 gaggttttgt ttgtatatta aaatggagtt tgtttgtaaa aaaaaaaaaa aaaaaaa

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FGF19胺基酸序列 (NP_005108) (SEQ ID NO: 31)

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1  MRSGCVVHV WILAGLWLAV AGRPLAFSDA GPHVHYGWD PIRLRHLYTS GPHGLSSCFL
61  RIRADGVVDC ARGQSAHSLI EIKAVLRV AIKGVHSVRY LCMGADGKMQ GLLQYSEEDC
121  AFEEIIRPDG YNVYRSEKHR LPVSLSSAKQ RQLYKNRGFL PLSHFLPMLP MVPEEPEDLR
181  GHLESDMFSS PLETDSMDPF GLVTGLEAVR SPSFEK

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FGF21核酸序列 (NM_019113) (SEQ ID NO: 32)

蛋白質編碼區151-780

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1  CTGTCACTG AGGATCCAGC CGAAAGAGGA GCCAGGCACT CAGGCCACCT GAGTCTACTC
61  ACCTGACAAA CTGGAATCTG GCACCAATTC TAAACCACTC AGCTTCTCCG AGCTCACACC
121  CCGGAGATCA CCTGAGGACC CGAGCCATTG ATGGACTCCG ACGAGACCGG GTTCGAGCAC

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圖 2 (續)

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181 TCAGGACTGT GGGTTTCTGT GCTGGCTGGT CTTCTGCTGS GAGCCTGCCA GGCACACCCC
241 ATCCCTGACT CCAGTCCTCT CCTGCAATTC GGGGGCCAAG TCCGGCAGCG GTACCTCTAC
301 ACAGATGATG CCCAGCAGAC AGAAGCCCAC CTGGAGATCA GGGAGGATGG GACGGTGGGG
361 GGCGCTGCTG ACCAGAGCCC CGAAAGTCTC CTGCAGCTGA AAGCCTTGAA GCCGGGAGTT
421 ATTCAAATCT TGGGAGTCAA GACATCCAGG TTCCTGTGCC AGCGGCCAGA TGGGGCCCTG
481 TATGGATCGC TCCACTTTGA CCCTGAGGCC TGCAGCTTCC GGGAGCTGCT TCTTGAGGAC
541 GGATACAATG TTTACCACTC CGAAGCCCAC GGCCTCCCGC TGCACCTGCC AGGGAACAAG
601 TCCCCACACC GGGACCCTGC ACCCCGAGGA CCAGCTCGCT TCCTGCCACT ACCAGGCCTG
661 CCCCCCGCAC TCCCGGAGCC ACCCGGAATC CTGGCCCCCC AGCCCCCGA TGTGGGCTCC
721 TCGGACCTC TGAGCATGGT GGGACCTTCC CAGGGCCGAA GCCCCAGCTA CGCTTCCTGA
781 AGCCAGAGGC TGTTTACTAT GACATCTCCT CTTTATTTAT TAGGTTATTT ATCTTATTTA
841 TTTTTTTATT TTTCTTACTT GAGATAATAA AGAGTTCCAG AGGAGAAAAA AAAAAAAAAA
901 AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA
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FGF21胺基酸序列 (NP_061986) (SEQ ID NO: 33)

```
1 MDSDETFGEH SGLWVSVLAG LLLGACQAH IPDSSPLLQF GGQVRQRYLY TDDAQQTEAH
61 LEIREDGTVG GAADQSPESL LQIKALKPGV IQILGVKTSR FLCQRPDGL YGSLHFDPEA
121 CSFRELLED GYNVYQSEAH GLPLHLPGNK SPHRDPAPRG PARFLPLPGL PPALPEPPGI
181 LAPQPPDVGS SDPLSMVGPS QGRSPSYAS
```

FGF23核酸序列 (NM_020638) (SEQ ID NO: 34)

蛋白質編碼區147-902

```
1 cggcaaaaag gagggaatcc agtctaggat cctcacacca gctacttgca agggagaag
61 aaaaggccag taaggcctgg gccaggagag tcccgcacag agtgtcagg ttcaatctca
121 gcaccagcca ctgagagcag ggcacgatgt tgggggccc cctcaggctc tgggtctgtg
181 ccttgctcag cgtctgcagc atgagcgtcc tcagagccta tcccaatgcc tccccactgc
241 tcggctccag ctgggggtggc ctgatccacc tgtacacagc cacagccagg aacagctacc
301 acctgcagat ccacaagaat ggccatgtgg atggcgaccc ccacagacc atctacagt
361 ccctgatgat cagatcagag gatgctggct ttgtggtgat tacagggtg atgagcagaa
421 gatacctctg catggatttc agaggcaaca tttttggatc aactatttc gacccggaga
481 actgacaggt ccaacaccag acgctggaaa acgggtacga cgtctaccac tctcctcagt
541 atcacttcct ggtcagtctg ggcggggcga agagagcctt cctgccaggc atgaaccac
601 ccccgctact ccagttcctg tcccggagga acgagatccc cctaattcac ttcaacaccc
661 ccataccacg gcggcacacc cggagcggcg aggacgactc ggagcgggag cccctgaacg
721 tgctgaagcc ccggggcccg atgaccccgg ccccgccctc ctgttcacag gagctcccga
781 gcgcccagga caacagcccg atggccagtg acccattagg ggtggtcagg ggcggtcag
841 tgaacacgca cgtctgggga acgggcccgg aaggctgccg ccccttcgcc aagttcatct
901 agggctcgtg gaagggcacc ctctttaacc catccctcag caaacgcagc tcttcccaag
961 gaccagggtc ctgacgttc cgaggatgg aaaggtgaca ggggcatgta tggatttgc
1021 tgcttctctg gggctccctc cacaggaggt cctgtgagaa ccaacccttg aggcccaagt
1081 catggggttt caccgccttc ctactccat atagaacacc tttcccaata ggaaacccca
1141 acaggtaaac tagaaatttc cccttcctga aggtagagag aagggtctc tcccaacata
1201 tttctcttcc ttgtgcctct cctctttatg acttttaagc ataaaaaaa aaaaaaaaaa
1261 aaaaaaaaaa aaaagcagtg ggttcctgag ctcaagactt tgaagggtga gggaagagga
1321 aatcggagat cccagaagct tctccactgc cctatgcatt tatgttagat gccccgatcc
1381 cactggcatt tgagtgtgca aaccttgaca ttaacagctg aatggggcaa gttgatgaaa
1441 aactactttt caagccttcg ttcttccttg agcatctctg gggaagagct gtcaaaagac
1501 tgggtgtagg ctggtgaaaa cttgacagct agacttgatg cttgctgaaa tgaggcagga
1561 atcataatag aaaactcagc ctccctacag ggtgagcacc ttctgtctcg ctgtctccct
1621 ctgtgcagcc acagccagag ggcccagaat ggcccactc tgttcccaag cagttcatga
1681 tacagcctca ccttttggcc ccatctctgg tttttgaaaa tttgggtctaa ggaataaata
1741 gcttttacac tggctcacga aaatctgcc tgctagaatt tgcttttcaa aatggaataa
1801 aattccaact ctctaagag gcatttaatt aaggctctac ttccaggttg agtaggaatc
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圖 2 (續)

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1861 cattctgaac aaactacaaa aatgtgactg ggaagggggc tttgagagac tgggactgct
1921 ctgggttagg ttttctgtgg actgaaaaat cgtgtccttt tctctaaatg aagtggcatc
1981 aaggactcag ggggaaagaa atcaggggac atgttataga agttatgaaa agacaaccac
2041 atggtcaggc tcttgtctgt ggtctctagg gctctgcagc agcagtggct cttcgattag
2101 ttaaaactct cctaggctga cacatctggg tctcaatccc cttggaaaatt cttgggtgcat
2161 taaatgaagc cttaccccat tactgcggtt cttcctgtaa gggggctcca ttttctctcc
2221 tctctttaaa tgaccaccta aaggacagta tattaacaag caaagtcgat tcaacaacag
2281 cttcttccca gtcacttttt ttttctcac tgccatcaca tactaacctt atactttgat
2341 ctattctttt tggttatgag agaaatggtt ggcaactggt ttacctgat ggttttaagc
2401 tgaacttgaa ggactggttc ctattctgaa acagtaaaac tatgtataat agtatatagc
2461 catgcatggc aaatatatta atatttctgt tttcatttcc tgttgaaaat attatcctgc
2521 ataatagcta ttggaggctc ctcaagttaa gatcccaaaa ggatttttgg ggaaaactag
2581 ttgtaatctc acaaaactcaa cactaccatc aggggttttc tttatggcaa agccaaaata
2641 gctcctacaa tttcttatat ccctcgtcat gtggcagtat ttatttattt atttgggaag
2701 ttgacctatcc ttctatatat atagatatatt ataaaaatgt aaccctttt tcctttcttc
2761 tgtttaaaat aaaaaataaaa tttatctcag cttctgttag cttatcctct ttgtagtact
2821 acttaaaaagc atgtcgggaat ataaagaataa aaaggattat gggaggggaa cattagggaa
2881 atccagagaa ggcaaaaattg aaaaaaagat tttagaattt taaaattttc aaagatttct
2941 tccattcata aggagactca atgattttta ttgatctaga cagaattatt taagttttat
3001 caatattgga tttctggt

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FGF23胺基酸序列 (NP_065689) (SEQ ID NO: 35)

```

1  MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNs YHLQIHKNGH
61  VDGAHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTl
121 ENGVDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTRS
181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
241 PEGCRPFAKF I

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FGF23 (R179Q)胺基酸序列 (SEQ ID NO: 36)

```

1  MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI HLYTATARNs YHLQIHKNGH
61  VDGAHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTl
121 ENGVDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHQS
181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
241 PEGCRPFAKF I

```

人類β-Klotho域1 (b-KL-D1) 胺基酸序列 (SEQ ID NO: 37)

```

77          ydt fpknffwig tgalqvegs kkgkgsiw dhfihthlkn
121 vsstngssds yiflekdlsa ldfigvsfyq fsiswprlfp dgi tvanag glqyystlld
181 alvlrniepi vtlyhwdlpl alqekyggwk ndtiidifnd yatycfmgf drvkywiti
241 npylvawhgy gtgmhagek gnlaavytv ghnlikahskv whnynthfrp hqkgwlsitl
301 gshwiepnrs entmdifkcy qsmvsvlgwf anpihgdydy pegmrklfs vlpifseaek
361 hemrgtadff afsfgpnnfk plntmakmgq nvslnlreal nwikleynnp rilieangwf
421 tdsrvktedt taiymknfl sqvlqairld eirvfgytaw slldgfewqd aytirrglly
481 vdfnsqker kpkssahyyk qiirengf

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人類β-Klotho域2 (b-KL-D2) 胺基酸序列 (SEQ ID NO: 38)

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571          trpaqctdfv nikkqlemla rmkvthyrf
601 ldwasvlptg nlsavnrqal ryyrcvseg lklgisamvt lyyphahlg lpepllhag
661 wlnpstaeaf qayaglcfe lgdlvklwit inepnrlsdi ynrsndtyg aahnllvaha
721 lawrlydrqf rpsqrgavsl slhadwaepa npyadshwra aerflqfeia wfaeplfktg

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圖 2 (續)

781 dypaamreyi askhrrglss salprlteae rrlkgtvdf calnhfttrf vmheqlagsr
841 ydsdrdiqfl qditrlsspt rlavipwgv rllrwvrrny gdm diyitas giddqaledd
901 rlrkyylgky lqevlkayli dkvrkgyya fklaeekskp rfgfftsdfk akssiqfynk
961 vissrgf

β-Klotho細胞外域（無信號肽）胺基酸序列（SEQ ID NO: 39）

52 gfsqdgrai
61 wsknpnftpv nesqlflydt fpknffwgig tgalqvegs kkdgkgsiw dhfihthlkn
121 vsstngssds yiflekdlas ldfigvsfyq fsiswprlfp dgivtvanak glqyystlld
181 alvlrniepi vtlyhwdlpl alqekyggwk ndtiidifnd yatycfmgf drvkywiti
241 npylvawhgy gtgmhapgek gnlaavytv ghnlikahskv whnynthfrp hqkgwlsitl
301 gshwiepnrs entmdifkcy qsmvsvlgwf anpihgddgy pegmrkkkfs vlpifseae
361 hemrgtadff afsfgpnnfk plntmakmgq nvslnlreal nwikleyennp rilieangwf
421 tdsrvktedt taiymmknfl sqvlqairld eirvfgytaw slldgfewed aytirrglgy
481 vdfnskqker kpkssahyyk qiirengfsl kestpdvqgg fpcdfswgvt esvlkpesva
541 sspqfscphl yvwnatgnrl lhrvegvrkl trpaqctdfv nikkqllemla rmkvthyrfa
601 ldwasvlptg nlsavnrqal ryyrcvvseg lklgisamvt lyyphthahlg lpepllhadd
661 wlnpstaeaf qayaglcfe lgdlvklwit inepnrlsdi ynrsngndtyg aahnlhvaha
721 lawrlydrqf rpsqrgavsl slhadwaepa npyadshwra aerflqfeia wfaeplfktg
781 dypaamreyi askhrrglss salprlteae rrlkgtvdf calnhfttrf vmheqlagsr
841 ydsdrdiqfl qditrlsspt rlavipwgv rllrwvrrny gdm diyitas giddqaledd
901 rlrkyylgky lqevlkayli dkvrkgyya fklaeekskp rfgfftsdfk akssiqfynk
961 vissrgfpfe nsssrcsqtg entectvcfl lvqkkpl

無信號肽之sKlotho-FGF23胺基酸序列（無信號肽）（SEQ ID NO: 40）

51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW EPGDGAQ TWARFSRPPA
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYYRRLLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHCYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
351 DFTSEKKFI KGTADFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWVVS GTTKRDDAKY MYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGFLYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTSLQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTAFAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQCT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYGDLPYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIDS
951 NGFPGPETLE RFCPEEFTVC TECSEFHTRK SLGSGGGGSG GGGSGGGGSL
1001 KYPNASPLL GSSWGCLHLY TATARNSYHL QIHKNCHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNI GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTP
1151 PRRHTRSAED DSERDPLNVL KPRAEMTPAP ASCSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*

圖 2 (續)

無信號肽之sKlotho-FGF23(R179Q) (無信號肽)
胺基酸序列 (SEQ ID NO: 41)

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                    EPGDGAQ TWARFSRPPA
51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYYRRLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNNLSSILP
351 DFTSEKKFI KGTADEFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWFVS GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
451 DVIGYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTLSQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLQEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YTALAFAEYA RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWVMDWLNQ RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYGDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
951 NGFPGPETLE RFCPEETVC TECSEFFHTRK SLGSGGGGSG GGS GGGGSL
1001 KYPNASPLL GSSWGLIHL TATARN SYHL QIHKNGHVDG APHQTIYSAL
1051 MIRSEDAGFV VITGVMSRRY LCMDFRGNIF GSHYFDPENC RFQHQTLENG
1101 YDVYHSPQYH FLVSLGRAKR AFLPGMNPPP YSQFLSRRNE IPLIHFNTP I
1151 PRRHTQSAED DSERDPLNVL KPRARMTAP ASQSQELPSA EDNSPMASDP
1201 LGVVRGGRVN THAGGTGPEG CRPFAKFI*

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無信號肽之FGF23 (SEQ ID NO:42)

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                    YPNASP LLGSSWGGLI HLYTATARN YHLQIHKNGH
61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTL
121 ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTRS
181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
241 PEGCRPFAKF I

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無信號肽之FGF23(R179Q) (SEQ ID NO:43)

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                    YPNASP LLGSSWGGLI HLYTATARN YHLQIHKNGH
61 VDGAPHQTIY SALMIRSEDA GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTL
121 ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR RNEIPLIHFN TPIPRRHTRS
181 AEDDSERDPL NVLKPRARMT PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG
241 PEGCRPFAKF I

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圖 2 (續)

具有Klotho信號肽之sKlotho (SEQ ID NO:44)

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1 MPASAPRRP RPPPSLSLL LVLLGLGGR LRAEPGDGAQ TWARFSRPPA
51 PEAAGLFQGT FPDGFLWAVG SAAYQTEGGW QQHGKGASIW DTFTHHPLAP
101 PGDSRNASLP LGAPSPLQPA TGDVASDSYN NVFRDTEALR ELGVTHYRFS
151 ISWARVLPNG SAGVPNREGL RYRRLLERL RELGVQPVVT LYHWDLPQRL
201 QDAYGGWANR ALADHFRDYA ELCFRHFGGQ VKYWITIDNP YVVAWHGYAT
251 GRLAPGIRGS PRLGYLVAHN LLLAHAKVWH LYNTSFRPTQ GGQVSIALSS
301 HWINPRRMTD HSIKECQKSL DFVLGWFAKP VFIDGDYPES MKNLSSILP
351 DTFESEKKFI KGTADFFALC FGPTLSFQLL DPHMKFRQLE SPNLRQLLSW
401 IDLEFNHPQI FIVENGWFSV GTTKRDDAKY MYYLKKFIME TLKAIKLDGV
451 DVIQYTAWSL MDGFEWHRGY SIRRGLFYVD FLSQDKMLLP KSSALFYQKL
501 IEKNGFPPLP ENQPLEGTFP CDFAWGVVDN YIQVDTTSLQ FTDLNVYLWD
551 VHHSKRLIKV DGVVTKKRKS YCVDFAAIQP QIALLOEMHV THFRFSLDWA
601 LILPLGNQSQ VNHTILQYYR CMASELVRVN ITPVVALWQP MAPNQGLPRL
651 LARQGAWENP YALAFAYEY RLCFQELGHH VKLWITMNEP YTRNMTYSAG
701 HNLLKAHALA WHVYNEKFRH AQNGKISIAL QADWIEPACP FSQKDKEVAE
751 RVLEFDIGWL AEPIFGSGDY PWVMRDWLNQ RNNFLLPYFT EDEKKLIQGT
801 FDFLALSHYT TILVDSEKED PIKYNDYLEV QEMTDITWLN SPSQVAVVPW
851 GLRKVLNWLK FKYCDLPMYI ISNGIDDGLH AEDDQLRVYY MQNYINEALK
901 AHILDGINLC GYFAYSFNDR TAPRFGLYRY AADQFEPKAS MKHYRKIIDS
951 NGFPGPETLE RFCPEEFTVC TECSFHTRK SL

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具有IgG信號肽之sKlotho (SEQ ID NO:45)

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1 MSVLQVLAL LLLWLTGLGG RRLRAEPGDG AQTWARFSRP PAPEAAGLFQ
51 GTFPDGFLWA VGSAAAYQTEG GWQQHGKGAS IWDTFTHHPL APPGDSRNAS
101 LPLCAPSPLQ PATGDVASDS YNNVFRDTEA LRELGVTHYR FSISWARVLP
151 NGSAGVPNRE GLRYRRLLLE RLRELGVQPV VTLYHWDLPQ RLQDAYGGWA
201 NRALADHFRD YAEFCFRHFG QVKYWITID NPYVVAWHGY ATGRLAPGIR
251 GSPRLGYLVA HNLLLAHAKV WHLYNTSERP TQGGQVSIAL SSHWINPRRM
301 TDHSIKECQK SLDFVLGWFA KPVFIDGDYP ESMKNLSSI LPDFTSEKK
351 FIKGTADFFA LCFGPTLSFQ LLDPHMKFRQ LESPNLRQLL SWIDLEFNHP
401 QIFIVENGWF VSGTTKRDDA KYMYLKKFI METLKAIKLD GVDVIQYTAW
451 SLMDGFEWHR GYSIRRGLFY VDFLSQDKML LPKSSALFYQ KLIKNGFPP
501 LPENQPLEGT FPCDFAWGVV DNYIQVDTTL SQFTDLNVYL WDVHHSKRLI
551 KVDGVVTKKR KSYCVDFAAI QPQIALLOEM HVTHFRFSLD WALILPLGNQ
601 SQVNHTILQY YRCASELVR VNITPVVALW QPMAPNQGLP RLLARQGAWE
651 NPYTALAFAYE YARLCFQELG HHVKLWITMN EPTYTRNMTYS AGHNLLKAHA
701 LAWHVYNEKF RHAQNGKISI ALQADWIEPA CPFSQKDKEV AERVLEFDIG
751 WLAEPFSGSG DYPWVMRDWL NQRNNFLLPY FTEDEKKLIQ GTFDFLALSH
801 YTTILVDSEK EDPIKYNDYL EVQEMTDITW LNSPSQVAVV PWGLRKVLNW
851 LKFKYGDLPY YIISNGIDDG LHAEDDQLRV YYMQNYINEA LKAHILDGIN
901 LCGYFAYSFN DRTAPRFGLY RYAADQFEPK ASMKHYRKII DSNGFPGPET
951 LERFCPEEFT VCTECSEFT RKSL*

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圖 2 (續)