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(56)參考文獻：

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(54)名稱

GDF15 融合蛋白及其用途

(57)摘要

所描述者係含有半衰期延長蛋白、連接子、及 GDF15 蛋白的融合蛋白。亦描述者係編碼融合蛋白之核酸、其重組細胞、包含融合蛋白之組成物、以及使用融合蛋白以治療或預防代謝疾病、病症或病況之方法。

Fusion proteins containing a half-life extension protein, a linker, and a GDF15 protein are described. Also described are nucleic acids encoding the fusion proteins, recombinant cells thereof, compositions comprising the fusion proteins, and methods of using the fusion proteins for treating or preventing metabolic diseases, disorders or conditions.

指定代表圖：

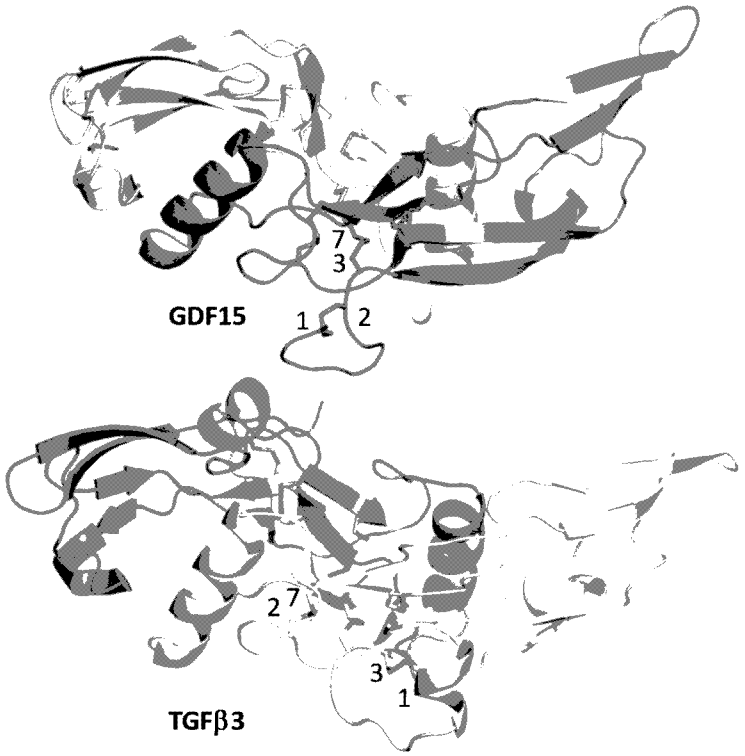

7
3
GDF15
1
2
2
7
3
1
TGFβ3

圖 1A

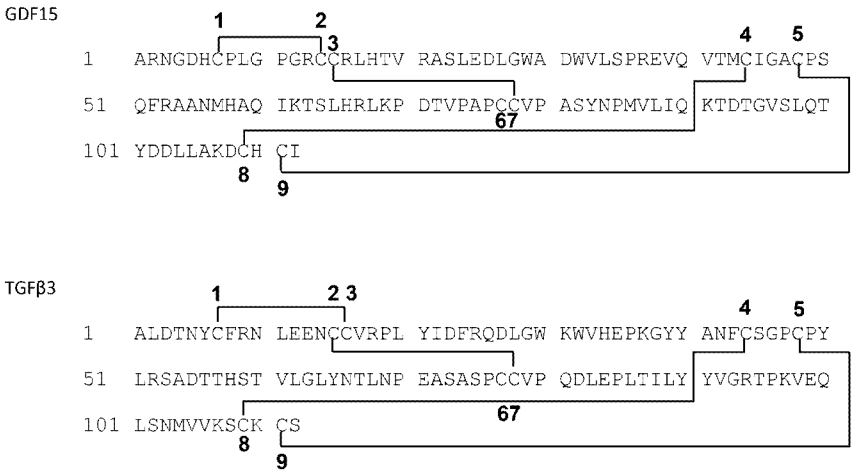

GDF15
1
2
3
4
5
1 ARNGDHCPLG PGRCCRLHTV RASLEDLGWA DWVLSPREVQ VTMCIGACPS
51 QFRAANMHAQ IKTSLHRLKP DTVPAPCCVP ASYNPMVLIQ KTDTGVSLQT
67
101 YDDLLAKDCH CI
8
9
TGFβ3
1
2 3
4
5
1 ALDTNYCFRN LEENCCVRPL YIDFRQDLGW KWVHEPKGYY ANFCSGPCPY
51 LRSADTTHST VLGLYNTLNP EASASPCCVP QDLEPLTILY YVGRTPKVEQ
67
101 LSNMVVKSCK CS
8
9

圖1B

公告本

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【發明摘要】

【中文發明名稱】GDF15融合蛋白及其用途

【英文發明名稱】GDF15 FUSION PROTEINS AND USES THEREOF

【中文】

所描述者係含有半衰期延長蛋白、連接子、及GDF15蛋白的融合蛋白。亦描述者係編碼融合蛋白之核酸、其重組細胞、包含融合蛋白之組成物、以及使用融合蛋白以治療或預防代謝疾病、病症或病況之方法。

【英文】

Fusion proteins containing a half-life extension protein, a linker, and a GDF15 protein are described. Also described are nucleic acids encoding the fusion proteins, recombinant cells thereof, compositions comprising the fusion proteins, and methods of using the fusion proteins for treating or preventing metabolic diseases, disorders or conditions.

【指定代表圖】圖1

【代表圖之符號簡單說明】無

【特徵化學式】無

【發明說明書】

【中文發明名稱】GDF15融合蛋白及其用途

【英文發明名稱】GDF15 FUSION PROTEINS AND USES THEREOF

【技術領域】

【0001】 本發明係關於GDF15融合蛋白。具體而言，本發明係關於一種融合蛋白，其包含半衰期延長蛋白、連接子及GDF15蛋白；編碼該等融合蛋白之核酸及表現載體；其重組細胞；及醫藥組成物，其包含該等融合蛋白。亦提供者係產生融合蛋白及使用該等融合蛋白以治療代謝病症之方法。

【先前技術】

【0002】 GDF15（屬於TGFβ家族的成員）是在血漿中循環且為25 kDa同二聚體(homodimer)的分泌蛋白。大多數個體內的血漿GDF15水平是在介於150與1150 pg/ml之間的範圍內（Tsai等人，*J Cachexia Sarcopenia Muscle*. 2012, 3: 239-243）。在受到損傷、心血管疾病、及某些類型的癌症之情況下，血漿GDF15水平會增加。此調升現象被認為係細胞保護機制。高血漿GDF15水平係相關於由於癌症以及腎臟和心臟衰竭中的厭食及惡病質所致之體重流失。在臨床試驗中，在肥胖的非糖尿病性對象中，GDF15水平是胰島素抗性的獨立預測因子（Kempf等人，*Eur.J.Endo*. 2012, 167: 671-678）。在雙胞胎中的研究顯示，成對雙胞胎內的GDF15水平之差異與該對雙胞胎內的BMI差異具有相關性，此意味著GDF15可作為能量恆定的長期調節劑（Tsai等人，*PLoS One*. 2015,10(7):e0133362）。

【0003】 雖然GDF15已作為數種心血管及其他疾病狀態的生物標記而經大量研究，亦已描述GDF15於心肌肥厚症及缺血性損傷的保護性角色（Collinson, *Curr. Opin.Cardiol*. 2014, 29: 366-371；Kempf等人，*Nat. Med*. 2011, 17: 581-589；Xu等人，*Circ Res*. 2006, 98:342-50）。在第1型與第2型糖尿病的小鼠模型中，GDF15已顯示可在預防腎小管及組織間隙傷害的保護上扮演重要角色（Mazagova等人，*Am. J. Physiol. Renal Physiol*. 2013; 305: F1249-F1264）。已提出GDF15對年齡相關性感覺與運動神經元損失具有保護效應，且其改善周邊神經傷害之後的恢復情形（Strelau等人，*J. Neurosci*. 2009, 29: 13640-13648；Mensching等人，*Cell Tissue Res*. 2012, 350: 225-238）。事實上，GDF15基因轉殖小鼠顯示出具有較其同窩對照組長的壽命，其可指示此分子作用為長期存活因子（Wang等人，*Aging*. 2014, 6: 690-700）。

【0004】 已有許多報導證實，小鼠模型經過GDF15蛋白的治療，葡萄糖耐受性與胰島素敏感性有所改善。在過度表現GDF15的基因轉殖小鼠中，有二個獨立品系的小鼠體重與脂肪量降低，和葡萄糖耐受性改善（Johnen等人，*Nat. Med*. 2007, 13:1333-1340；Macia等人，*PLoS One*. 2012, 7:e34868；Chrysovergis等人，*Int. J. Obesity*. 2014, 38: 1555-1564）。在GDF15基因轉殖小鼠中，已報導過全身能量消耗與氧化代謝的增加情形（Chrysovergis等人，2014, *Id.*）。這些情形伴隨著褐色脂肪組織的產熱基因表現增加，以及白色脂肪組織的脂解基因表現增加。缺乏GDF15基因的小鼠之體重及脂肪質量會增加（Tsai等人，*PLoS One*. 2013, 8(2):e55174）。GDF15的Fc融合在肥胖石蟹獼猴模型中，經過為期六週的每週投予後，已顯示可減輕體重並改善葡萄糖耐受性以及胰島素敏感性(WO 2013/113008)。

【0005】 GDF15對體重的效果被認為係透過減少攝食量及增加能量消耗而媒介。GDF15可經由體重依賴性與體重獨立性機制改善血糖控制。

【0006】 綜觀此等現象，意味著GDF15水平增加可有利於代謝疾病治療。在所屬技術領域中，需要基於GDF15之組成物，該組成物可用於治療或預防代謝疾病、病症、或病況。

【發明內容】

【0007】 本發明提供GDF15之融合蛋白以滿足此需要，該等融合蛋白證實可增加溶解度/穩定性，並展現指示其等可用於治療或預防代謝疾病、病症、或病況之特徵。此類特徵包括例如經過投予根據本發明實施例之融合蛋白的對象減輕體重、增加葡萄糖耐受性、且改善胰島素敏感性。

【0008】 在一個通常態樣中，本發明係關於一種融合蛋白，該融合蛋白包含：(a)半衰期延長蛋白、(b)連接子、及(c)GDF15蛋白，其中該融合蛋白係以(a)-(b)-(c)之順序自N端至C端配置。

【0009】 在本發明之一實施例中，該GDF15蛋白係人類GDF15蛋白或其功能性變體。在具體實施例中，該GDF15蛋白包含成熟GDF15蛋白或其功能性變體。在更多具體實施例中，該GDF15蛋白包含與SEQ ID NO: 6至11具有至少90%序列同一性的胺基酸序列。在其他具體實施例中，該GDF15蛋白包含SEQ ID NO: 11之胺基酸序列，諸如選自由SEQ ID NO: 6至11所組成之群組的胺基酸序列。

【0010】 在本發明之一實施例中，該半衰期延長蛋白係人類血清白蛋白(HSA)或其功能性變體。在具體實施例中，該半衰期延長蛋白包含與SEQ ID NO:

1具有至少90%同一性的胺基酸序列。在其他具體實施例中，該半衰期延長蛋白包含選自由SEQ ID NO: 1至3所組成之群組的胺基酸序列。

【0011】 在本發明之一實施例中，該連接子係柔性連接子(flexible linker)。在具體實施例中，該柔性連接子含有序列(GGGGS)n，其中n係2至20，較佳的是4至10。在本發明之另一實施例中，該融合蛋白之連接子係結構化連接子(structured linker)。在具體實施例中，該結構化連接子含有序列(AP)n或(EAAAK)n，其中n係2至20，較佳的是4至10。

【0012】 在本發明之實施例中，該融合蛋白包含與SEQ ID NO: 5、25至30、36至37、40、48、55至60、或64至75具有至少90%序列同一性的胺基酸序列。在本發明之具體實施例中，該融合蛋白包含選自由SEQ ID NO: 5、25至30、40、55至60、及70所組成之群組的胺基酸序列。在本發明之更多具體實施例中，該融合蛋白包含SEQ ID NO: 60之胺基酸序列。

【0013】 在另一通常態樣中，本發明係關於一種單離核酸分子，該核酸分子編碼本發明之融合蛋白。

【0014】 在另一通常態樣中，本發明係關於一種表現載體，該表現載體包含編碼本發明之融合蛋白的核酸分子。

【0015】 在另一通常態樣中，本發明係關於一種重組宿主細胞，該重組宿主細胞包含編碼本發明之融合蛋白的核酸分子。

【0016】 在另一通常態樣中，本發明係關於一種獲得本發明之融合蛋白之方法。該方法包含：(1)在產生該融合蛋白的條件下培養宿主細胞，該宿主細胞包含編碼該融合蛋白的核酸分子；及(2)回收由該宿主細胞產生的該融合蛋白。

【0017】在另一通常態樣中，本發明係關於一種醫藥組成物，該醫藥組成物包含本發明之融合蛋白及醫藥上可接受之載劑。

【0018】在另一通常態樣中，本發明係關於一種醫藥組成物，該醫藥組成物包含編碼本發明之融合蛋白的核酸分子及醫藥上可接受之載劑。

【0019】在另一通常態樣中，本發明係關於一種套組，該套組包含本發明之醫藥組成物。

【0020】在另一通常態樣中，本發明係關於一種治療或預防代謝疾病、病症、或病況之方法，該方法包含向有需要之對象投予治療或預防有效量的本發明之醫藥組成物。在一具體實施例中，醫藥組成物係經皮下或靜脈內投予至該對象。

【0021】根據本發明之實施例，一種治療有需要之對象的代謝病症之方法，該代謝病症係選自由第2型糖尿病、升高葡萄糖水平、升高胰島素水平、肥胖、異常血脂症、糖尿病性腎病變、心肌缺血性損傷、充血性心臟衰竭、或類風濕性關節炎所組成之群組，該方法包含向該對象投予治療有效量的醫藥組成物，該醫藥組成物包含：融合蛋白，其包含選自由SEQ ID NO: 5、25至30、40、55至60、及70所組成之群組的胺基酸序列；及醫藥上可接受之載劑。在一具體實施例中，該方法包含向該對象投予治療有效量之包含含SEQ ID NO: 60胺基酸序列之融合蛋白及醫藥上可接受之載劑的醫藥組成物。

【0022】本發明之其他態樣、特徵、及優點，自下文揭露（包括實施方式與其較佳實施例，以及附加之申請專利範圍）觀之，係顯而易見者。

【圖式簡單說明】

【0023】 前述發明內容以及下文實施方式在結合附圖閱讀時可更有利理解。應理解的是，本發明並不受限於圖式中所示確切實施例。

【0024】 在圖式中：

【0025】 圖1A及1B顯示GDF15之晶體結構，其中第一與第二半胱胺酸殘基(C1-C2)的雙硫鍵配對在該蛋白之N端處形成環圈。

【0026】 圖2顯示皮下投予根據本發明之實施例之融合蛋白，例如融合蛋白FP1（SEQ ID NO: 60）及6xHis-FP1（SEQ ID NO: 26，具有附接於N端的6xHis標籤）對於C57BL/6小鼠攝食量的效果，即呈現在投予後24小時的累積攝食量。直條內的數值係相較於媒劑(PBS)組的減少幅度+SEM（以%表示）；N=8隻動物/組，適用於所有組別，但以FP1 16 nmol/kg組的N=9為例外。*-p<0.05，與媒劑相較；p值是利用單因子ANOVA及杜凱(Tukey)檢定進行多重比較而計算。

【0027】 圖3顯示皮下投予FP1及6xHis-FP1（SEQ ID NO: 26，具有附接於N端的6xHis標籤）對於SD大鼠(Sprague-Dawley rat)攝食量的效果，即呈現在投予後48小時的累積攝食量。直條內的數值係相較於媒劑(PBS)組的減少幅度+SEM（以%表示）；N=8隻動物/組。*-p<0.05，與媒劑相較；p值是利用單因子ANOVA及杜凱(Tukey)檢定進行多重比較而計算。

【0028】 圖4顯示FP1治療期間膳食誘發肥胖(DIO)小鼠的體重變化。箭頭指示初始給藥（第0天）後皮下投予的時間（天數）；N=8隻動物/組。*-p<0.05，FP1 1 nmol/kg組相較於媒劑時；# - p<0.05，FP1 10 nmol/kg組相較於媒劑時；p值是利用二因子RM ANOVA及杜凱檢定進行多重比較而計算。

【0029】 圖5A及5B顯示DIO小鼠經過為期14天的每3天(q3d) FP1給藥之後進行口服葡萄糖耐受性試驗(OGTT)期間的血糖水平，水平以曲線下面積表示。

N=8隻動物/組。*-p<0.05，FP1 1 nmol/kg組相較於媒劑時；p值是利用單因子ANOVA及杜凱檢定進行多重比較而計算。

【0030】 圖6顯示DIO小鼠在FP1治療期間的餐後血糖水平。N=8隻動物/組。*-p<0.05，與媒劑相較；p值是利用二因子RM ANOVA及杜凱檢定進行多重比較而計算。

【0031】 圖7顯示DIO小鼠在經過FP1治療14天後的4小時空腹的胰島素抗性之平衡模型評估(homeostatic model assessment of insulin resistance, HOMA-IR)。N=8隻動物/組。*-p<0.05，與媒劑相較；p值是利用單因子ANOVA及杜凱檢定進行多重比較而計算。

【0032】 圖8顯示*ob/ob*小鼠在經過每3天(qd3) FP1治療期間的體重變化。箭頭指示初始給藥（第0天）後皮下投予的時間（天數）；N=9隻動物/組。*-p<0.05，FP1 10 nmol/kg組相較於媒劑時；# - p<0.05，FP1 1 nmol/kg組相較於媒劑時；p值是利用二因子RM ANOVA及杜凱檢定進行多重比較而計算。

【0033】 圖9顯示*ob/ob*小鼠在FP1治療期間的血糖水平。箭頭指示初始給藥（第0天）後皮下投予的時間（天數）；N=9隻動物/組。*-p<0.05，FP1 10 nmol/kg組相較於媒劑時；# - p<0.05，FP1 1 nmol/kg組相較於媒劑時；p值是利用二因子RM ANOVA及杜凱檢定進行多重比較而計算。

【0034】 圖10顯示C57BI/6小鼠經過2 mg/kg靜脈內(IV)與皮下(SC)投予之後，其FP1的血清藥物濃度-時間曲線平均值（±標準差(SD)）。

【0035】 圖11顯示SD大鼠經過2 mg/kg IV與SC投予之後，其FP1的血清藥物濃度-時間曲線平均值(±SD)。

【0036】 圖12顯示石蟹獼猴經過1 mg/kg IV與SC投予之後，其依免疫檢定所測定的FP1之血清藥物濃度-時間曲線平均值(±SD)。

【0037】 圖13顯示石蟹獼猴經過單次IV投予之後，其依免疫親和性(IA)捕捉LCMS分析所測定之隨時間的呈完整二聚體的血清FP1濃度(ng/mL)。

【0038】 圖14顯示石蟹獼猴經過單次SC投予之後，其依免疫親和性捕捉LCMS分析所測定之隨時間的呈完整二聚體的血清FP1濃度(ng/mL)。

【0039】 圖15顯示在獲自二名人類對象(Sub)的血漿中離體培養0、4、24、及48小時之後，依免疫檢定測定的FP1濃度，以開始濃度的%表示。

【0040】 圖16顯示在獲自二名人類對象(Sub)的血漿中離體培養0、4、24、及48小時之後，依完整質量免疫親和性捕捉LCMS分析測定的呈完整二聚體之平均FP1濃度，以時間0的%表示。

【0041】 圖17顯示對瘦小C57BL6N雄性小鼠投予GDF15的各種N端缺失變體前後的短時間攝食量。（SEQ ID NO: 92、111、及112，相較於沒有缺失之野生型融合（SEQ ID NO: 26，具有附接於N端的6xHis標籤））。N=8隻動物/組；*-p<0.05，與媒劑相較；p值是利用二因子RM ANOVA及杜凱檢定進行多重比較而計算。

【0042】 圖18顯示FP2的單次給藥對C57BL/6小鼠攝食量的效果；確切而言，其顯示投予後24小時的累積攝食量。直條內的數值係相較於PBS組的減少幅度（平均值+SEM），以%表示；N=8隻動物/組，適用於所有組別，但以6xHis-FP1組的N=6為例外。**-p<0.01，***-p<0.001，****-p<0.0001；p值是利用二因子ANOVA及鄧奈特(Dunnett)檢定進行多重比較而計算。

【0043】 圖19顯示SD大鼠在FP2的單次劑量投予後24小時所測得的累積攝食量。直條內的數值係相較於PBS組的減少幅度（平均值+SEM），以%表示；N=8隻動物/組。**-p<0.01，p值是利用二因子ANOVA及杜凱檢定進行多重比較而計算。

【0044】 圖20顯示以FP2 q3d治療DIO小鼠的期間，其體重的變化百分比。箭頭指示FP2的皮下注射時間；N=6隻動物/組；*- p,0.05，與媒劑相較，利用二因子ANOVA及杜凱檢定進行多重比較；

【0045】 圖21A及21B顯示DIO小鼠經過為期14天的FP2 q3d給藥後進行OGTT試驗期間的血糖濃度水平之曲線下面積(AUC)。*- p<0.05，利用單因子ANOVA及杜凱多重比較檢定，採用n=8隻動物/組。

【0046】 圖22A顯示DIO小鼠經過為期8天的FP2 q3d給藥後進行OGTT期間的血漿胰島素水平。*- p<0.05，媒劑與FP2 (0.3 nmol/kg)；FP2 (10 nmol/kg)；及羅格列酮(Rosiglitazone)。# - p<0.05，與羅格列酮 (10 mg/kg)相較，利用二因子RM ANOVA及杜凱多重比較檢定。

【0047】 圖22B顯示DIO小鼠經過為期8天的FP2 q3d給藥後進行OGTT期間的血漿胰島素水平之AUC。*-p<0.05，與媒劑相較；# - p<0.05，與羅格列酮相較。

【0048】 圖23顯示DIO小鼠經過為期8天的FP2 q3d給藥後的餐後血糖水平。*- p<0.05，與媒劑相較，利用二因子RM ANOVA及杜凱多重比較檢定，n=8隻動物/組。

【0049】 圖24顯示DIO小鼠經過為期14天的FP2 q3d治療且接著在第14天空腹5小時後的空腹HOMA-IR。*- p<0.05，與媒劑相較，利用單因子ANOVA及杜凱多重比較檢定，n=8隻動物/組。

【0050】 圖25顯示C57Bl/6小鼠經過2 mg/kg靜脈內(IV)與2 mg/kg皮下(SC)投予後的血清FP2濃度。數值代表平均值±SD（n=每個時間點5個樣本）。

【0051】 圖26顯示SD大鼠經過2 mg/kg靜脈內(IV)與2 mg/kg皮下(SC)投予後的血清FP2濃度。N=每個時間點5個樣本。

【0052】 圖27顯示由免疫檢定分析之在石蟹獼猴中的血漿FP2濃度。數值代表平均值±SD，其中n=3，例外的是，第22天(528 hr) IV採n=2。IV –靜脈內，SC –皮下。

【0053】 圖28顯示由LCMS分析之在石蟹獼猴中呈完整二聚體的血漿FP2濃度。數值代表平均值±SEM，其中n=3，例外的是，168小時皮下(SC)採n=2，120小時與432小時SC採n=1，且168小時與432小時IV（靜脈內）採n=1。

【0054】 圖29顯示由免疫檢定測得的人類血漿中FP2在48小時內的離體穩定性（標準化回復百分比）。

【0055】 圖30顯示由完整LC/MS測得的人類血漿中FP2在48小時內的離體穩定性（標準化回復百分比）。

【0056】 圖31顯示在表現重組人類GFRAL受體的SK-N-AS細胞中利用pAKT分析法所得FP2與HSA-GDF15:GDF15異二聚體(heterodimer)之濃度反應曲線(N=3)。

【0057】 圖32顯示石蟹獼猴經過FP1的單次給藥前後的每日攝食量。*- p<0.05，針對10 mg/kg的FP1，相較於媒劑。

【0058】 圖33顯示石蟹獼猴經過FP1的單次給藥前後的體重變化百分比。*- p<0.05，針對10 mg/kg FP1，與媒劑相較；# - p<0.05，針對3 mg/kg，與媒劑相較，利用二因子RM ANOVA及杜凱多重比較檢定，n=8隻動物/組。

【0059】 圖34顯示石蟹獼猴經過FP2的單次給藥前後的每日攝食量。*- p<0.05，與媒劑相較，利用二因子RM ANOVA及杜凱多重比較檢定，n=8隻動物/組。

【0060】 圖35顯示石蟹獼猴經過FP2的單次給藥前後的體重變化百分比。*- p<0.05，針對10 nmol/kg的FP2，與媒劑相較；# - p<0.05，針對3 nmol/kg的FP2，與媒劑相較；& - p<0.05，針對1 nmol/kg的FP2，與媒劑相較，利用二因子RM ANOVA及杜凱多重比較檢定，n=8隻動物/組。

【實施方式】

【0061】 各篇公開案、論文、及專利已於先前技術及整份說明書引用或描述；此等參考文獻之各者全文係以引用方式併入本文中。在本說明書中所包括之對於文件、行動、材料、裝置、物品、或其類似物的論述，目的在於提供關於本發明的脈絡。此等論述並非承認，任一或所有此等情事形成了關於任何所揭示或請求之發明的先前技術部分。

【0062】 除非另有定義，否則本文中所使用之所有技術及科學用語，均與本發明有關技術領域中具有通常知識者所通常了解之意義相同。在其他方面，在本文中所使用的某些用語具有如本說明書所定之意義。在本文中所引用的所有專利、已公開專利申請案及公開案係以引用方式併入，猶如全文說明於本文

中。必須注意的是，本文及附加之申請專利範圍中所使用之單數形式「一(a/an)」及「該(the)」皆包括複數指稱，除非上下文另有明確說明。

【0063】 本發明係關於一種融合蛋白，該融合蛋白包含：(a)半衰期延長蛋白、(b)連接子、及(c)GDF15蛋白，其中該融合蛋白係以(a)-(b)-(c)之順序自N端至C端配置。

【0064】 已發現的是，當根據本發明之實施例的融合蛋白包含半衰期延長蛋白、連接子、及GDF15蛋白時，其導致GDF15蛋白延長半衰期，且本發明之融合蛋白顯示有代謝效果，該等效果證實了彼等作為用於治療或預防代謝疾病、病症、或病況之治療劑時的適用性。此類效果包括（但不限於）經投予融合蛋白之動物減輕體重、增加葡萄糖耐受性、及改善胰島素敏感性。

【0065】 如本文中所使用，用語「融合蛋白(fusion protein)」係指一種具有二或更多個共價連接在一起之部分的蛋白質，其中該等部分之各者係衍生自不同蛋白。

【0066】 根據本發明之實施例的融合蛋白可包括任何GDF15蛋白。如本文中所使用，用語「GDF15蛋白(GDF15 protein)」係指任何天然發生的野生型生長分化因子15蛋白或其功能性變體。GDF15蛋白可來自任何哺乳動物，諸如人類或另一種合適的哺乳動物（諸如小鼠、兔、大鼠、豬、狗、或靈長類動物）。在具體實施例中，該GDF15蛋白係人類GDF15蛋白或其功能性變體。在較佳實施例中，該GDF15蛋白係成熟GDF15蛋白或其功能性變體。

【0067】 如本文中所使用，用語「成熟GDF15蛋白(mature GDF15 protein)」係指GDF15的前原蛋白之部分，該部分是在RXXR弗林(furin)類似裂解位置發生細胞內裂解後自全長蛋白釋放。成熟GDF15蛋白經分泌成為由雙硫鍵連接之同

二聚體(homodimer)。在本發明之一個實施例中，一種成熟GDF15蛋白，簡稱GDF15(197-308)（SEQ ID NO: 6），其含有全長人類GDF15蛋白之胺基酸197至308。

【0068】 如本文中所使用，「功能性變體(functional variant)」係指一種親本蛋白(parent protein)的變體，該變體與該親本蛋白具有實質或顯著的序列同一性，且保留該親本蛋白之至少一種生物活性。親本蛋白之功能性變體可在考量到本揭露內容下利用所屬技術領域中已知手段製備。功能性變體可包括親本蛋白之胺基酸序列經一或多個修改者。該等修改可例如藉由改善多肽的熱穩定性、變更受質特異性、改變 pH 最佳化、以及其類似者，來改變多肽的物理化學特性。該等修改亦可變更親本蛋白的生物活性，只要彼等不會破壞或消除親本蛋白的所有生物活性。

【0069】 根據本發明之實施例，親本蛋白之功能性變體包含親本蛋白經取代（較佳的是保守型胺基酸取代）者，該取代不會顯著影響親本蛋白之生物活性。保守型取代包括（但不限於）下列胺基酸之群組內的胺基酸取代：鹼性胺基酸（精胺酸、離胺酸、及組胺酸）、酸性胺基酸（麩胺酸及天冬胺酸）、極性胺基酸（麩醯胺酸及天冬醯胺酸）、疏水性胺基酸（白胺酸、異白胺酸、及纈胺酸）、芳族胺基酸（苯丙胺酸、色胺酸、及酪胺酸）、及小胺基酸（甘胺酸、丙胺酸、絲胺酸、蘇胺酸、及甲硫胺酸）。非標準或不自然胺基酸（諸如4-羥脯胺酸、6-N-甲基離胺酸、2-胺異丁酸、異纈胺酸、及 α-甲基絲胺酸）亦可用來取代親本蛋白中的標準胺基酸殘基。

【0070】 根據本發明之其他實施例，親本蛋白之功能性變體包含親本蛋白經缺失及/或插入一或更多個胺基酸者。例如，成熟 GDF15 蛋白之功能性變體可包括成熟 GDF15 蛋白經缺失及/或插入 1、2、3、4、5、6、7、8、9、10、11、

12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30 或更多個胺基酸者，較佳的是成熟 GDF15 蛋白在 N 端處經缺失 1 至 30 個胺基酸者。

【0071】 根據本發明之又其他實施例，親本蛋白之功能性變體包含親本蛋白經取代（較佳的是保守型胺基酸取代）者及經缺失及/或插入（較佳的是胺基酸之微小缺失及/或插入）者。

【0072】 根據本發明之實施例，本發明之融合蛋白包含 GDF15 蛋白，該 GDF15 蛋白之胺基酸序列與成熟 GDF15 之胺基酸序列具有至少 90%同一性，後者係諸如 GDF15(197-308)（SEQ ID NO: 6）；或者該 GDF15 蛋白之胺基酸序列與 N 端截短成熟 GDF15 之胺基酸序列具有至少 90%同一性，後者係諸如 GDF15(200-308)（SEQ ID NO: 7）、GDF15(201-308)（SEQ ID NO: 8）、GDF15(202-308)（SEQ ID NO: 9)、GDF15(203-308)（SEQ ID NO: 10）、或 GDF15(211-308)（SEQ ID NO: 11)。GDF15 蛋白可具有 SEQ ID NO: 6、7、8、9、10、或 11 經取代、插入、及缺失之至少一者的序列，只要其維持該 GDF15 蛋白之至少一種生物活性，諸如其對於攝食量、血糖水平、胰島素抗性、及體重等的效果。

【0073】 在具體實施例中，本發明之融合蛋白包含具有 SEQ ID NO: 11 之胺基酸序列的 GDF15 蛋白，該蛋白包括（但不限於）SEQ ID NO: 6、7、8、9、10、或 11 之胺基酸序列。

【0074】 任何合適的半衰期延長蛋白均可用於根據本發明之實施例的融合蛋白。如本文中所使用，用語「半衰期延長蛋白(half life extension protein)」可係任何蛋白或其片段已知可延長其經融合而成之蛋白質之半衰期者。此類半衰期延長蛋白之實例包括（但不限於）：人類血清白蛋白(HSA)、免疫球蛋白(Ig)之穩定片段域(Fc)、或輸鐵蛋白(Tf)。在本發明之實施例中，半衰期延長蛋白包

含 HSA 或其功能性變體。在本發明之具體實施例中，半衰期延長蛋白包含與 SEQ ID NO: 1 具有至少 90%同一性的胺基酸序列。在本發明之較佳實施例中，半衰期延長蛋白包含 HSA 或其功能性變體，其中在該 HSA 之位置 34 處的半胱胺酸殘基已經絲胺酸或丙胺酸置換。

【0075】 在具體實施例中，本發明之融合蛋白包含半衰期延長蛋白，該半衰期延長蛋白具有選自由 SEQ ID NO: 1 至 3 所組成之群組的胺基酸序列。

【0076】 任何合適的連接子均可用於根據本發明之實施例的融合蛋白。如本文中所使用，用語「連接子(linker)」係指連接部分，其包含胜肽連接子。較佳的是，連接子有助於確保摺疊正確，盡量減少空間障礙，且不會對融合蛋白內各功能性組分的結構帶來顯著干擾。在本發明之一些實施例中，胜肽連接子包含 2 至 120 個胺基酸。例如，胜肽連接子包含 2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30、31、32、33、34、35、36、37、38、39、40、41、42、43、44、45、46、47、48、49、50、51、52、53、54、55、56、57、58、59、60、61、62、63、64、65、66、67、68、69、70、71、72、73、74、75、76、77、78、79、80、81、82、83、84、85、86、87、88、89、90、91、92、93、94、95、96、97、98、99、100、101、102、103、104、105、106、107、108、109、110、111、112、113、114、115、116、117、118、119、或 120 個胺基酸。

【0077】 在本發明之實施例中，連接子增加融合蛋白組分的柔性。在本發明之具體實施例中，連接子可係包含序列(GGGGS)n 之柔性連接子，其包括（但不限於）GS-(GGGGS)n 或 AS-(GGGGS)n-GT，其中 n 係 2 至 20，諸如 2、3、4、5、6、7、8、9、10、11、12、13、14 或 15。

【0078】 在本發明之其他實施例中，連接子係經結構化。在本發明之具體實施例中，連接子可係包含序列(AP)n 或(EAAAK)n 之結構化連接子，其包括（但

不限於）AS-(AP)n-GT 或 AS-(EAAAK)n-GT，其中 n 係 2 至 20，諸如 2、3、4、5、6、7、8、9、10、11、12、13、14 或 15。在本發明之其他實施例中，連接子包含序列 $(GGGGA)_n$、$(PGGGS)_n$、$(AGGGS)_n$、或 GGS-$(EGKSSGSGSESKST)_n$-GGS，其中 n 係 2 至 20。

【0079】 在本發明之實施例中，融合蛋白包含與 SEQ ID NO: 5、25 至 30、36 至 37、40、48、55 至 56、59 至 60、或 64 至 75 具有至少 90%序列同一性的胺基酸序列。在本發明之具體實施例中，融合蛋白包含選自由 SEQ ID NO: 5、25 至 30、36 至 37、40、48、55 至 56、59 至 60、及 64 至 75 所組成之群組的胺基酸序列。在本發明之更多具體實施例中，融合蛋白包含選自由 SEQ ID NO: 5、25 至 30、40、55 至 56、59 至 60、及 70 所組成之群組的胺基酸序列。在本發明之進一步更多具體實施例中，融合蛋白包含 SEQ ID NO: 92、SEQ ID NO: 60、或 SEQ ID NO: 26 之胺基酸序列。融合蛋白亦可在蛋白質之胺基或羧基末端處包括微小延伸，諸如促進純化進行的標籤，諸如多組胺酸標籤、抗原表位、或結合域。

【0080】 在本文中所揭示之融合蛋白可在 GDF15 生物活性方面經表徵或評估，其包括（但不限於）對下列之效果：攝食量、口服葡萄糖耐受性試驗、血糖水平測量、胰島素抗性分析、體重變化、藥物動力學分析、毒物動力學分析、全長融合蛋白之水平與穩定性的免疫檢定與質譜分析、以及人類血漿離體穩定性分析。

【0081】 本發明亦提供一種編碼本發明之融合蛋白的單離核酸分子。在本發明之實施例中，單離核酸分子編碼融合蛋白，該融合蛋白包含與 SEQ ID NO: 5、25 至 30、36 至 37、40、48、55 至 56、59 至 60、或 64 至 75 具有至少 90%序列同一性的胺基酸序列。在具體實施例中，單離核酸分子編碼融合蛋白，該融合蛋白包含選自由 SEQ ID NO: 5、25 至 31、36 至 37、40、48、55 至 56、59 至

60、及 64 至 75 所組成之群組的胺基酸序列。在更多具體實施例中，單離核酸分子編碼融合蛋白，該融合蛋白包含選自由 SEQ ID NO: 5、25 至 30、40、55 至 56、59 至 60、及 70 所組成之群組的胺基酸序列。在進一步更多具體實施例中，單離核酸分子包含 SEQ ID NO: 76 至 91 之核苷酸序列。

【0082】 根據本發明之其他實施例，編碼融合蛋白之核酸分子可位於表現載體中。表現載體包括（但不限於）用於重組蛋白表現之載體、及用於輸送核酸進入對象體內以於該對象的組織中表現的載體（諸如病毒載體）。適合用於本發明的病毒載體之實例包括（但不限於）腺病毒載體、腺相關病毒載體、慢病毒載體等。載體亦可係非病毒載體。非病毒載體之實例包括（但不限於）質體、細菌人工染色體、酵母菌人工染色體、噬菌體等。載體可包括任何用以建立表現載體之習知功能的元件，例如啟動子、核糖體結合區、終止子、增強子、篩選標記、或複製起始序列。

【0083】 根據本發明之其他實施例，編碼融合蛋白之核酸分子可在考量到本揭露內容下利用所屬技術領域中已知方法，經密碼子最佳化以改善自所欲求宿主細胞（諸如人類腎臟胚胎上皮(HEK)細胞或中國倉鼠卵巢(CHO)細胞）的重組表現。

【0084】 本發明亦提供一種宿主細胞，該宿主細胞包含編碼本發明之融合蛋白的核酸分子。宿主細胞包括（但不限於）用於重組蛋白表現之宿主細胞、及用於輸送核酸進入對象體內以於該對象的組織中表現的宿主細胞。適用於本發明之宿主細胞的實例包括（但不限於）HEK 或 CHO 細胞。

【0085】 在另一通常態樣中，本發明係關於一種獲得本發明之融合蛋白之方法。在一通常態樣中，該方法包含：(1)在產生融合蛋白的條件下培養宿主細胞，該宿主細胞包含編碼該融合蛋白的核酸分子；及(2)回收由該宿主細胞產生的該融合蛋白。可進一步利用所屬技術領域中已知的方法，純化融合蛋白。

【0086】在一些實施例中，融合蛋白可在宿主細胞中表現且自該等宿主細胞純化，純化方式是利用一或多種標準純化技術之組合，該等技術包括（但不限於）親和性層析、尺寸篩除層析、超過濾、及透析。較佳的是，融合蛋白經純化而不含任何蛋白酶。

【0087】本發明亦提供一種醫藥組成物，其包含本發明之融合蛋白及醫藥上可接受之載劑。

【0088】本發明進一步提供一種組成物，該組成物包含編碼本發明之融合蛋白的核酸分子及醫藥上可接受之載劑。當組成物包含編碼本發明之融合蛋白的核酸分子時，該等組成物可包含輸送載體，該載體用於引入核酸分子於細胞內以表現融合蛋白。核酸輸送載體之實例包括微脂體、生物相容性聚合物（包括天然聚合物及合成聚合物）、脂蛋白、多肽、多醣、脂多醣、人工病毒套膜、金屬粒子，以及細菌、病毒（諸如桿狀病毒、腺病毒、及反轉錄病毒）、噬菌體、黏質體、質體、真菌載體、及其他所屬技術領域中一般使用之經描述用於各種真核宿主中表現的重組載體。

【0089】醫藥上可接受之載劑可包括下列之一或多者：醫藥上可接受之賦形劑、緩衝液、穩定劑、或其他所屬技術領域中具有通常知識者已知的材料。醫藥上可接受之載劑之實例包括（但不限於）下列之一或多者：水、鹽水、緩衝液、等張劑（諸如糖）、多元醇、輔助物質（諸如濕潤劑或乳化劑）、保存劑、以及其組合。此類材料應不具毒性，且應不會干擾活性成分於所使用劑量及濃度上之療效。載劑或其他材料的確切本質，取決於投予途徑，例如肌內、皮下、口服、靜脈內、皮膚、黏膜內（例如，消化道）、鼻內、或腹膜內途徑。例如，液體醫藥組成物通常包括液體載劑，諸如水、石油、動物或蔬菜油、礦物油或合成油。亦可包括生理鹽水溶液、葡萄糖（右旋）或其他醣類溶液、或二醇（例如乙二醇、丙二醇或聚乙二醇）。用於非經腸投予的組成物可以凍乾

形式或於溶液中儲存，且通常放入具有無菌出入孔的容器，諸如靜脈內注射溶液袋或所具栓塞可由皮下注射針頭刺穿的藥瓶。

【0090】 根據本發明之實施例，醫藥組成物可包含一或多種額外組分，諸如另一種活性成分。

【0091】 本發明亦關於一種包含本發明之醫藥組成物的套組。套組可含有一第一容器及一第二容器，該第一容器具有本發明之經乾燥融合蛋白，且該第二容器具有在投予至對象前要與該經乾燥融合蛋白混合之水溶液，或者套組可含有單個容器，該容器含有本發明之液體醫藥組成物。套組可含有本發明之醫藥組成物的單次劑量投予單元或多重劑量投予單元。套組亦可包括一或多個預填注射器（例如液體注射器及冷凍注射器）。套組亦可包含其使用說明書。該等說明書可說明套組所提供材料的用途與本質，且可依正在治療之確切代謝病症加以調整。

【0092】 本發明亦關於本文中所描述之醫藥組成物的用途，其係用於治療或預防代謝疾病、病症、或病況，諸如第 2 型糖尿病、升高葡萄糖水平、升高胰島素水平、肥胖、異常血脂症、糖尿病性腎病變、心肌缺血性損傷、充血性心臟衰竭、或類風濕性關節炎。根據本發明之實施例，一種治療或預防有治療需要之對象的代謝疾病、病症、或病況之方法包含向該對象投予治療或預防有效量的本發明之醫藥組成物。在本發明之方法中，可使用本文中所述之任何醫藥組成物，其包括包含本發明之融合蛋白的醫藥組成物、或包含編碼該融合蛋白之核酸的醫藥組成物。

【0093】 如本文中所使用，「對象(subject)」意指將會或已經藉由根據本發明之實施例的方法受到治療的任何動物，具體的是哺乳動物，最具體的是人類。如本文中所使用的用語「哺乳動物(mammal)」，其涵蓋任何哺乳動物。哺

乳動物之實例包括（但不限於）牛、馬、羊、豬、貓、狗、小鼠、兔、天竺鼠、非人類靈長類(NHP)（諸如猴或猿）、人類等，更具體的是人類。

【0094】「代謝疾病、病症、或病況(metabolic disease, disorder or condition)」係指任何與異常代謝相關的病症。可根據本發明之方法治療的代謝疾病、病症、或病況之實例，包括（但不限於）第 2 型糖尿病、升高葡萄糖水平、升高胰島素水平、肥胖、異常血脂症、糖尿病性腎病變、心肌缺血性損傷、充血性心臟衰竭、或類風濕性關節炎。

【0095】如本文中所使用的用語「治療/處理(treat/treating/treatment)」係指投予組成物至對象以在該對象中達到所欲求之治療或臨床成果。在一個實施例中，用語「治療/處理(treat/treating/treatment)」係指投予本發明之醫藥組成物以減少、減輕或減緩代謝病症的進展或發展，該代謝病症係諸如第 2 型糖尿病、升高葡萄糖水平、升高胰島素水平、肥胖、異常血脂症、糖尿病性腎病變、心肌缺血性損傷、充血性心臟衰竭、或類風濕性關節炎。

【0096】用語「治療有效量(therapeutically effective amount)」意指用於引發所欲生物或臨床效果的所需治療活性化合物之量。根據本發明之實施例，「治療有效量(a therapeutically effective amount)」係足以實現有利或所欲結果（包括臨床結果）之量。可採取一或多次投予來投予治療有效量。在疾病狀態方面，有效量係足以改善、穩定、或延遲疾病發展之量。根據本發明之特定實施例，治療有效量係用於治療或預防下列代謝疾病、病症、或病況的所需融合蛋白之量：諸如第 2 型糖尿病、升高葡萄糖水平、升高胰島素水平、肥胖、異常血脂症、糖尿病性腎病變、心肌缺血性損傷、充血性心臟衰竭、或類風濕性關節炎。

【0097】根據本發明之實施例，可在考量到本揭露內容下利用所屬技術領域中具有通常知識者已知的任何方法，諸如肌內、皮下、口服、靜脈內、皮膚、黏膜內（例如，消化道）、鼻內、或腹膜內投予途徑，將本發明之醫藥組成物

投予至對象。在具體實施例中，本發明之醫藥組成物係經由靜脈內注射或皮下注射投予至對象。

【0098】 根據本發明之實施例投予醫藥組成物至對象的參數，諸如劑量、投予頻率、及投予持續時間，未受限於任何具體方式。此類參數的最佳化數值可取決於各種因素，諸如要治療的對象、要治療的具體代謝疾病、疾病的嚴重性、投予途徑等，且所屬技術領域中具有通常知識者將能夠判定適合此類參數的最佳化數值以達到所欲求之治療或臨床成果。例如，可每日一次，或者每日超過一次（諸如二次、三次、四次等），投予醫藥組成物。一般劑量範圍係自約 0.1 μg/kg 至高達約 100 mg/kg 或更多的融合蛋白，此取決於各種因素，諸如上文所提及者。

具體實施例

【0099】 具體實施例 1 係一種融合蛋白，其包含：(a)半衰期延長蛋白、(b)連接子、及(c)GDF15 蛋白；其中該融合蛋白係以(a)-(b)-(c)之順序自 N 端至 C 端配置。

【0100】 具體實施例 2 係根據具體實施例 1 之融合蛋白，其中該 GDF15 蛋白係人類 GDF15 蛋白或其功能性變體。

【0101】 具體實施例 3 係根據具體實施例 1 之融合蛋白，其中該 GDF15 蛋白所包含的胺基酸序列與選自由 SEQ ID NO: 6 至 11 所組成之群組的胺基酸序列具有至少 90%同一性。

【0102】 具體實施例 4 係根據具體實施例 1 之融合蛋白，其中該 GDF15 蛋白包含 SEQ ID NO: 11 之胺基酸序列。

【0103】 具體實施例 5 係根據具體實施例 4 之融合蛋白，其中該 GDF15 蛋白包含選自由 SEQ ID NO: 6 至 11 所組成之群組的胺基酸序列。

【0104】 具體實施例 6 係根據具體實施例 1 至 5 中任一者之融合蛋白，其中該半衰期延長蛋白包含人類血清白蛋白(HSA)或其功能性變體。

【0105】 具體實施例 7 係根據具體實施例 6 之融合蛋白，其中該半衰期延長蛋白包含與 SEQ ID NO: 1 具有至少 90%同一性的胺基酸序列。

【0106】 具體實施例 8 係根據具體實施例 7 之融合蛋白，其中該半衰期延長蛋白包含選自由 SEQ ID NO: 1 至 3 所組成之群組的胺基酸序列。

【0107】 具體實施例 9 係根據具體實施例 1 至 8 中任一者之融合蛋白，其中該連接子係柔性連接子。

【0108】 具體實施例 10 係根據具體實施例 9 之融合蛋白，其中該連接子包含序列(GGGGS)n，其中 n 係 2 至 20，諸如 GS-(GGGGS)x8 或 AS-(GGGGS)x8-GT。

【0109】 具體實施例 11 係根據具體實施例 1 至 9 中任一者之融合蛋白，其中該連接子係結構化連接子。

【0110】 具體實施例 12 係根據具體實施例 11 之融合蛋白，其中該連接子包含序列(AP)n 或(EAAAK)n，其中 n 係 2 至 20，諸如 AS-(AP)n-GT 或 AS-(EAAAK)n-GT。

【0111】 具體實施例 13 係一種融合蛋白，其包含與 SEQ ID NO: 5、25 至 31、36 至 37、40、48、55 至 60、或 64 至 75 具有至少 90%序列同一性的胺基酸序列。

【0112】 具體實施例 14 係根據具體實施例 13 之融合蛋白，其包含選自由 SEQ ID NO: 5、25 至 31、36 至 37、40、48、55 至 60、及 64 至 75 所組成之群組的胺基酸序列。

【0113】 具體實施例 15 係根據具體實施例 14 之融合蛋白，其包含選自由 SEQ ID NO: 5、25 至 3 係、40、55 至 60、及 70 所組成之群組的胺基酸序列。

【0114】 具體實施例 16 係一種單離核酸分子，其編碼具體實施例 1 至 15 中任一者之融合蛋白。

【0115】 具體實施例 17 係一種單離核酸分子，其包含 SEQ ID NO: 76 至 91 之核苷酸序列。

【0116】 具體實施例 18 係一種表現載體，其包含具體實施例 16 或 17 之核酸分子。

【0117】 具體實施例 19 係一種宿主細胞，其包含具體實施例 16 或 17 之核酸分子。

【0118】 具體實施例 20 係產生具體實施例 1 至 15 中任一者之融合蛋白的方法，其包含(1)在產生該融合蛋白的條件下培養宿主細胞，該宿主細胞包含編碼該融合蛋白的核酸分子；及(2)回收由該宿主細胞產生的該融合蛋白。

【0119】 具體實施例 21 係根據具體實施例 20 之方法，其中該回收步驟包含純化該融合蛋白以去除蛋白酶。

【0120】 具體實施例 22 係一種醫藥組成物，其包含治療有效量的具體實施例 1 至 15 中任一者之融合蛋白及醫藥上可接受之載劑。

【0121】 具體實施例 23 係一種醫藥組成物，其包含治療有效量的編碼具體實施例 1 至 15 中任一者之融合蛋白的核酸分子及醫藥上可接受之載劑。

【0122】 具體實施例 24 係一種套組，其包含根據具體實施例 22 或 23 之醫藥組成物。

【0123】 具體實施例 25 係一種治療或預防代謝病症之方法，其包含向有需要之對象投予有效量的根據具體實施例 22 及 23 中任一者之醫藥組成物。

【0124】 具體實施例 26 係根據具體實施例 25 之方法，其中該代謝病症係選自由第 2 型糖尿病、升高葡萄糖水平、升高胰島素水平、肥胖、異常血脂症、

糖尿病性腎病變、心肌缺血性損傷、充血性心臟衰竭、或類風濕性關節炎所組成之群組。

【0125】 具體實施例 27 係根據具體實施例 25 或 26 之方法，其中該醫藥組成物係經皮下或靜脈內投予至該對象。

【0126】 具體實施例 28 係一種治療有需要之對象的代謝病症之方法，該代謝病症係選自由第 2 型糖尿病、升高葡萄糖水平、升高胰島素水平、肥胖、異常血脂症、糖尿病性腎病變、心肌缺血性損傷、充血性心臟衰竭、或類風濕性關節炎所組成之群組，該方法包含向該對象皮下或靜脈內投予治療有效量的醫藥組成物，該醫藥組成物包含：融合蛋白，其包含選自由 SEQ ID NO: 5、25 至 30、40、55 至 60、及 70 所組成之群組的胺基酸序列；及醫藥上可接受之載劑。

【0127】 具體實施例 29 係一種治療有需要之對象的代謝病症之方法，該代謝病症係選自由第 2 型糖尿病、升高葡萄糖水平、升高胰島素水平、肥胖、異常血脂症、糖尿病性腎病變、心肌缺血性損傷、充血性心臟衰竭、或類風濕性關節炎所組成之群組，該方法包含向該對象投予治療有效量之包含含 SEQ ID NO: 60 胺基酸序列之融合蛋白及醫藥上可接受之載劑的醫藥組成物。

【0128】 具體實施例 30 係根據具體實施例 25 至 29 中任一者之方法，其中該醫藥組成物係經皮下或靜脈內投予至該對象。

【0129】 具體實施例 31 係具體實施例 1 至 15 中任一者之融合蛋白，其係用於治療或預防代謝病症，該代謝病症係選自由第 2 型糖尿病、升高葡萄糖水平、升高胰島素水平、肥胖、異常血脂症、糖尿病性腎病變、心肌缺血性損傷、充血性心臟衰竭、或類風濕性關節炎所組成之群組。

實例

【0130】本發明的下列實例是要進一步說明本發明的本質。應了解的是，下文實例不會對本發明加以限制，且本發明之範疇應藉由附加之申請專利範圍來判斷。

實例 1：包含 GDF15 之融合分子的設計–GDF15 截短的效果

【0131】如同其他 TGFβ 家族成員，GDF15 經過合成為前原蛋白，該前原蛋白在內質網中形成二聚體且經歷弗林裂解以產生分泌成熟 GDF15（胺基酸 197 至 308）。分泌成熟 GDF15 同二聚體係約 25k 道耳吞，且各單體有潛力形成高達 4 個分子內雙硫鍵，其中以單個分子內雙硫鍵連接該同二聚體組分。

【0132】GDF15 之晶體結構已於本發明中判定，且描繪於圖 1A 及 1B 中。如晶體結構所示，成熟 GDF15 的 C 端埋入二聚體界面，而 N 端則露出。此露出端可允許融合蛋白連接，諸如半衰期延長蛋白與 GDF15 之 N 端的連接。

【0133】晶體結構亦呈現 GDF15 半胱胺酸殘基的新穎雙硫鍵配對型態。當 TGFβ1 具有 C1-C3 與 C2-C7 配對（即，其第一與第三半胱胺酸殘基之間，以及其第二與第七半胱胺酸殘基之間的配對）時，GDF15 具有 C1-C2 與 C3-C7 配對（參見圖 1A 及 1B）。此獨特的雙硫鍵配對使得 C1-C2 配對形成環圈，該環圈位於蛋白之 N 端且遠離含有其他雙硫鍵的半胱胺酸結。該結構預測，GDF15 之 N 端對於二聚體形成或整體蛋白摺疊可能不重要，且 GDF15 及其 N 端融合分子可承受屬於 C1 及 C2 缺失的 N 端缺失、C1-C2 環圈內的殘基、或甚至 C 端至 C2 的殘基。

實例 2：包含 GDF15 之融合分子的設計–連接子的效果

【0134】已評估 HSA 分子與 GDF15 分子之間的不同連接子。柔性連接子與結構化連接子兩者皆經過評估，該柔性連接子含有序列(GGGGS)n，且該結構化連接子含有序列(AP)n 或(EAAAK)n，其中 n 係 2 至 20。

【0135】將包含不同連接子之融合蛋白，就彼等之生物物理特性、彼等對於瘦小小鼠攝食量之療效上效果、彼等之小鼠藥物動力學(PK)值、及彼等於人類血液中的離體穩定性方面，作出比較。所測試連接子變體的結果列示於表 1。包含 SEQ ID NO: 31（其含有$(EAAAK)_8$連接子）之分子，藉由 HPLC 顯示出聚集現象。表 1 中其餘七種連接子變體未展示出聚集現象。

【0136】表 1：連接子變體分析概要

SEQ ID NO*	**連接子**	**聚集**	**良好小鼠 PK (WT)**	**在人類血液中的離體穩定性**
25	$AS(GGGGS)_2GT$	否	是	是
5	$GS(GGGGS)_4$	否	是	是
26	$AS(GGGGS)_8GT$	否	是	是
27	$AS(AP)_5GT$	否	是	是
28	$AS(AP)_{10}GT$	否	是	是
29	$AS(AP)_{20}GT$	否	是	是
30	$AS(EAAAK)_4GT$	否	是	是
31	$AS(EAAAK)_8GT$	是	未測試	未測試

*- 6xHis 標籤附接至 N 端，以達純化目的

【0137】亦藉由小鼠體內研究，並藉由人類全血及血漿樣本中的離體穩定性研究，評估此等變體的連接子穩定性。二種檢測形式係用來分析自此等研究得到的結果。採用抗 GDF15 捕捉與抗 HSA 檢測抗體配對的免疫檢定，測量位於連接子任一側的兩者分子存在情形，藉以評估該連接子的完整程度。藉由液相

層析質譜術(LC-MS)分析，使用來自 HSA 與 GDF15 的不同代表性胜肽(surrogate peptide)序列，分析較為廣泛的整體分子完整性狀況。經過 48 小時觀察，免疫檢定展示出所有連接子變體皆呈現穩定 PK 曲線，而且並未有任何連接子變體出現加標(spiked)血漿樣本濃度損失。LC-MS 結果與免疫檢定一致，此顯示來自 HSA 與 GDF15 分子之不同部分的代表性胜肽係屬完整。由 LC-MS 利用代表性胜肽分析的連接子變體之 PK 曲線，其顯示出不同連接子變體的類似趨勢，其中彼等皆在第 7 天具有可檢測出之水平。表 1 中的所有變體，除了 SEQ ID 31 以外，皆具有所欲生物物理特性及 PK 值。

【0138】 連接子變體的體內活性，是藉由進行瘦小小鼠的攝食量研究來評估。表 2 顯示連接子變體對於融合蛋白減少攝食量之療效上的影響。連接子對於療效存在了明確影響。就柔性(GGGGS)n 連接子而言，其從 2 延長至 4 至 8 的連接子長度，即以驚人程度增加了融合蛋白療效。就更為剛性的(AP)n 連接子而言，其趨勢較不明顯，這意味著融合蛋白內的 GDF15 分子自由度在其療效上扮演關鍵角色。

【0139】 表 2：連接子對於瘦小小鼠中 HSA-GDF15 融合蛋白之體內療效上的效果

SEQ ID NO*	**連接子**	**攝食量減少幅度%（平均值）**
25	$AS(GGGGS)_2GT$	28.8
5	$GS(GGGGS)_4$	40.5
26	$AS(GGGGS)_8GT$	60.7
27	$AS(AP)_5GT$	48.2
28	$AS(AP)_{10}GT$	66.2
29	$AS(AP)_{20}GT$	55.1

SEQ ID NO*	連接子	攝食量減少幅度%（平均值）
30	$AS(EAAAK)_4GT$	51.9

*- 6xHis 標籤附接至 N 端，以達純化目的

實例 3：包含 GDF15 之融合分子的設計–HSA 突變的效果

【0140】 已設計重組蛋白，該重組蛋白的半衰期延長蛋白人類血清白蛋白經由連接子與 GDF15 之 N 端融合。此設計應可讓 GDF15 二聚化界面持續不受干擾，且可形成自然的鏈間雙硫鍵連接，使得 GDF15 同二聚體與 HSA 的融合延伸自各 GDF15 分枝。利用此方法，僅需要單一基因來產生 HSA-GDF15 同二聚體。

【0141】 天然人類血清白蛋白含有 35 個半胱胺酸(Cys, C)殘基，該等殘基形成 17 個雙硫鍵，其中 Cys-34 殘基係分子中僅有的游離殘基。此游離 Cys-34 已顯示可捕獲多種反應性氧物種(ROS)及反應性氮物種(RNS)，以作為自由基清除劑使用。因此，此游離 Cys 經過突變而將因氧化作用所招致的異質性風險降到最低。

【0142】 HSA 之位置 34 處的游離半胱胺酸經過突變而成為絲胺酸或丙胺酸，且具有 HSA(C34S)或 HSA(C34A)突變的 GDF15 融合分子經過了分析。兩者分子皆利用三步驟純化方法純化：(i)離子交換層析法、(ii)疏水性交互作用層析、及(iii)尺寸篩除層析。彼等開始產生時，HPLC 分析顯示兩者分子已純化且沒有聚集（表 3）。

【0143】 然而，其產生後二週，含有 HSA(C34A)突變的融合蛋白（包含 SEQ ID NO: 48）經由 HPLC 顯示有聚集，而含有 HSA(C34S)突變的融合蛋白（SEQ ID NO: 40）在四週後仍沒有聚集。

【0144】 表 3：突變 HSA C34 對於融合蛋白聚集的影響

SEQ ID NO	HSA 突變	純化時聚集%	純化後 2 週聚集%
40	C34S	0	0
48	C34A	0	33.29

實例 4：蛋白酶對於 GDF15 的裂解傾向

【0145】 發明人所觀察到的是，在 GDF15 之胺基酸位置 198 的精胺酸殘基(R198)易在 HSA-GDF15 融合分子內受到蛋白酶降解。此類裂解結果會在異質群體中產生，且對治療組成物來說係非所欲。裂解現象可藉由混合的蛋白酶抑制劑預防。純化方法已經過蛋白酶去除方面的探討。表 4 列出了二種類型的 HSA 親和性管柱，該等管柱經過了關於 HSA-GDF15 融合蛋白純化的測試，利用 HPLC 進行測量。進行純化時，藉由兩種方法所純化的 HSA-GDF15 融合蛋白具有 100% 純度及完整性。呈低濃度(2-5 mg/ml)時，藉由兩種方法所純化的蛋白質可持續整個 4 週測試時期維持完整。然而，呈高濃度(40-50 mg/ml)時，僅有抗體性 HSA 樹脂(CaptureSelect)所產生的不含蛋白酶之蛋白質，可持續整個 4 週測試時期維持完整。HSA-配體性樹脂(Albupure)所產生的蛋白質，其最初具完整性，但於高濃度儲存時則展示出會隨時間降解。當高濃度 HSA-GDF15 融合蛋白批次係利用 Albupure 樹脂純化時，則添加混合的蛋白酶抑制劑(PI)及 EDTA，會完全抑制該批次的降解。因此，在產生穩定的治療組成物時，純化方法扮演了關鍵角色。在體內或離體情形下，並未觀察到對應的降解現象，此意味著，一旦製得不含蛋白酶的治療組成物，融合蛋白的降解不會成為體內情形下的問題。因此，可在生產期間有效去除潛在蛋白酶之純化方法，諸如該等使用 CaptureSelect 樹脂之方法，是成功製造均質、完整且穩定之 GDF15 治療劑的關鍵所在。

【0146】 表 4：HSA-GDF15 融合蛋白的蛋白酶裂解作用可藉由樣本純化方

法消除

條件			HSA-GDF15 (SEQ ID 60)之降解群體%				
濃度	**樹脂**	**+PI /EDTA**	第 0 週	第 1 週	第 2 週	第 3 週	第 4 週
低	Capture Select	否	0	0	0	0	0
低	Albupure	否	0	0	0	0	0
高	Capture Select	否	0	0	0	0	0
高	Albupure	否	0	3.04	9.47	11.57	13.89
高	Capture Select	是	0	0	0	0	0
高	Albupure	是	0	0	0	0	0

實例 5：GDF15 的 N 端缺失變體

【0147】 圖 1A 及 1B 中所描繪的 GDF15 晶體結構，其預測涉入缺失變體之 GDF15 之 N 端對於二聚體形成與整體蛋白摺疊並不重要。其亦預測到的是，此類 N 端缺失應不會影響到任何潛在的受體交互作用。包含各種 GDF15 之 N 端缺失的 HSA-GDF15 融合蛋白經過了關於體內活性的測試。

【0148】 GDF15N 端缺失變體在經過設計下，移除了於 GDF15 處的蛋白酶裂解位置(R198)。緊接在殘基 R198 之後，殘基 N199- G200 處有潛在脫醯胺位置，而且受質脫醯胺亦不利於治療組成物。GDF15 之 N 端缺失可同時移除蛋白酶裂解位置與脫醯胺位置兩者。與 HSA 合併成為融合蛋白的所得 GDF15 缺失變體，其包括 GDF15（201-308；SEQ ID NO: 8）、GDF15（202-308；SEQ ID NO: 9）、及 GDF15（211-308；SEQ ID NO: 11）。小鼠的體內研究顯示，GDF15 之 N 端缺失變體在減少攝食量方面仍具活性（圖 17）。經過實驗結果確認，此類 GDF15 之 N 端缺失變體具有恰當表現，形成適當二聚體，且於體內具有活性。

實例 6：GDF15 的非活性突變體

【0149】表 5 列出 GDF15 的十二種突變體，該等突變體係經製造以消除 GDF15 的體內活性且識別 GDF15 的功能性表位。突變體包括五種單突變體、二種雙突變體、及五種三突變體。包含此等突變之 HSA-GDF15 融合蛋白係在其等生物物理特性及活性方面經表徵（表 5）。在 12 種突變體中，有一種並未表現，且有四種隨時間形成聚集，其指示突變中斷了蛋白摺疊及生物物理特性。在其餘七種突變體中，其中四種含有 GDF15 的單一突變，且在小鼠中測試此等突變體在相較於野生型下的攝食量減少情形。有三種單一突變體（I89R、I89W、及 W32A）失去體內活性，而其餘突變體(Q60W)的活性同於野生型。此等結果指出，I89R、I89W、或 W32A 突變中斷了受體/輔受體與 GDF15 之交互作用，其意味著 GDF15 之功能性表位係位在殘基 I89 與 W32 周圍。突變是根據融合蛋白中存在的成熟 GDF15 加以編號，例如，「1」係指成熟 GDF15（SEQ ID NO: 6）的第 1 個胺基酸，且「89」係指成熟 GDF15 的第 89 個胺基酸。

【0150】表 5：包含 GDF15 突變體之融合蛋白的生物物理特性及活性概要

SEQ ID NO	GDF15 中的突變	生物物理特性	活性
5	野生型	表現良好，穩定	野生型活性
64	I89R	表現良好，穩定	完全失去活性
65	I89W	表現良好，穩定	完全失去活性
66	L34A、S35A、R37A	表現良好，穩定	
67	V87A、I89A、L98A	表現良好，不穩定	
68	L34A、S35A、I89A	表現良好，穩定	
69	V87A、I89A	表現良好，穩定	
70	Q60W	表現良好，穩定	活性同於野生型
71	W32A	表現良好，穩定	完全失去活性

SEQ ID NO	GDF15 中的突變	生物物理特性	活性
72	W29A	表現良好，不穩定	
73	Q60A、S64A、R67A	表現良好，不穩定	
74	W29A、Q60A、I61A	未表現	
75	W29A、W32A	表現良好，不穩定	

*- 6xHis 標籤附接至 N 端，以達純化目的

實例 7：表現與純化方法

【0151】 表現

【0152】 對於 20 ml 及更多量的表現，表現過程是利用在 Expi293™ Expression 培養基中生長的 HEK Expi293™細胞進行。細胞是在 37℃下生長，同時在 125RPM 與 8% CO2 的條件下振盪。使用 Expi293™ Expression 套組，以 2.5 × 106 個細胞/ml 進行細胞轉導。以每公升的轉導細胞而言，將 1 mg 的總 DNA 稀釋於 25 ml 的 Opti-MEM 中，並將 2.6 ml 的 Expi293™試劑稀釋於 25 ml 的 Opti-MEM 中且在室溫下培養 5 分鐘。將稀釋 DNA 與稀釋 Expi293 試劑組合，並在室溫下培養 20 分鐘。然後，將 DNA 錯合物加至該些細胞。將細胞置入振盪培養箱整夜。經過轉導之後的該天，將來自套組的 5 ml 之 Enhancer 1 稀釋於來自套組的 50 ml 之 Enhancer 2，然後將總體積的二者 Enhancer 加至細胞。將轉導細胞放回培養箱 4 天，直到彼等經過收穫為止。將細胞在 6,000 g 下離心 30 分鐘，藉此濃縮細胞，然後在進行純化步驟前用 0.2 um 過濾器加以過濾。

【0153】 亦在 CHO 細胞中完成表現。將質體純化並加以表徵。進行轉導前，將 1 等分試樣的 200 µg 含 HSA-GDF15 之編碼區的質體 DNA，藉由採 AclI 之限制酶分解加以線性化。利用限制內核酸酶進行分解，確保胺苄青黴素抗性

基因的移除。使用 BTX ECM 830 Electro Cell Manipulator (Harvard Apparatus, Holliston, MA)，將二份 15 μg DNA 等分試樣轉導入二份 1 × 107CHO 細胞（分配轉導儲集 A 與 B）。在 4 mm 間隙透光管中，在 250 伏特下，使用 15 毫秒脈衝長度與 5 秒脈衝間隔，對細胞進行電穿孔 3 次。使用搖瓶將轉導細胞轉移至 MACH-1 + L-麩醯胺酸，並將該等細胞培養 1 天。將轉導儲集 A 與轉導儲集 B 離心，重新懸浮於 MACH-1 + MSX，且轉移至搖瓶以培養 6 天。在電穿孔後第 8 天，將來自轉導儲集 A 與轉導儲集 B 的轉導 HSA-融合蛋白產生細胞加以儲集且鍍覆於甲基纖維素中。

純化

【0154】採用二步驟純化（使用 CaptureSelect 樹脂）及尺寸篩除層析。以每 ml 樹脂 10 mg 蛋白質的大約交換容量，將來自短時間轉導 Expi293™細胞的細胞上清液裝載於經預平衡(PBS, pH 7.2)的 HSA CaptureSelect 管柱（購自 ThermoFisher Scientific 的 CaptureSelect Human Albumin Affinity Matrix）。經過裝載之後，用 10 倍管柱體積(CV)的 PBS (pH7.2)清洗管柱，藉以去除未結合的蛋白質。用 10 CV 的 2M $MgCl_2$ 溶液（於 20 mM Tris 中，pH 7.0），洗提結合於管柱的 HSA-GDF15。將峰值流份加以儲集、過濾(0.2 μ)，且在 4℃下以 PBS (pH 7.2)透析。經過透析之後，在裝載於 26/60 Superdex 200 管柱(GE Healthcare)之前，再次將蛋白質過濾(0.2 μ)且濃縮成適當體積。當自尺寸篩除層析(SEC)管柱洗提的蛋白質流份具有高純度(由 SDS-PAGE 判定)時，將該等流份儲集。利用 BioTek Synergy HTTM 分光光度計於 280 nm 之吸光度來測定蛋白質的濃度。利用 SDS-PAGE 與分析性尺寸篩除 HPLC (SE-HPLC, Dionex HPLC system)，評估經純化之蛋白質品質。利用 LAL 分析法(Pyrotell®-T, Associates of Cape Cod)，測量內毒素水平。

【0155】 採用二步驟純化（使用 Albupure 樹脂）及 SEC。在室溫下純化 HSA-GDF15 融合蛋白，其過程使用了 AlbuPure 樹脂(ProMetic BioSciences Ltd)，該樹脂利用固定化合成三吡配體以選擇性結合 HSA。將表現上清液施加於 AlbuPure 樹脂。然後，先用 4 CV PBS (pH 7.2)清洗樹脂，隨後用 4 CV 的緩衝液 (50 mM Tris pH 8.0, 150 mM NaCl)清洗該樹脂。用 4 CV 的 PBS pH 7.2 緩衝液（含有 100 mM 辛酸 Na），洗提結合於管柱的 HSA-GDF15。使用 30,000 kDa 截留分子量旋轉濃縮器(Amicon)，將含蛋白質流份濃縮成 10 mL 體積，然後將該流份施加於 26/60 Superdex S200pg 管柱(GE)，其以 PBS (pH 7.2)緩衝液平衡。含有 HSA-GDF15 同二聚體之 SEC 流份，係經由 SDS-PAGE 識別，且經儲集以進行分析。利用 SDSPAGE 及 SE-HPLC 評估蛋白質純度。

【0156】 實例 8 至 14、及 19 涉及本發明之例示性融合蛋白的表徵，該融合蛋白具有 SEQ ID NO: 60 之胺基酸序列。此融合蛋白係完全重組蛋白，其存在的是 HSA 與成熟人類 GDF15 經由 42 個胺基酸連接子所融合的同二聚體，該連接子由甘胺酸與絲胺酸殘基(GS-$(GGGGS)_8$)所組成。所預測的融合蛋白分子量係 162,696 道耳吞，且在 HSA 的位置 34 處之單個自然游離半胱胺酸已突變為絲胺酸。具體 HSA-GDF15 融合蛋白將僅以「FP1」表示於下文實例中，以求簡化。FP1 之 6xHis 標記變體（6xHis-FP1，SEQ ID NO: 26）含有 AS-(GGGGS)x8-GT 連接子，該變體係於下文一些實例中供比較使用。

實例 8：FP1 對於 C57Bl/6 小鼠攝食量的效果

【0157】 此實驗目的是要證實 FP1 對於 C57Bl/6 小鼠攝食量抑制的劑量反應效果。

【0158】 雄性 C57Bl/6 小鼠持續最短 72 小時在 BioDAQ 籠中適應。然後，將小鼠基於先前 24 小時的攝食量分為六組，每組八隻。在 4:00 與 5:00 pm 之間，將動物稱重，並經由皮下注射給予媒劑或包含 FP1 之組成物。在注射後 48 小時

期間，利用 BioDAQ 系統連續記錄各籠的食物重量變化。6xHis-FP1 係於本研究中供比較使用。

【0159】結果（圖 2 及表 6）以給定時間間隔的累積攝食量平均值表示。該等結果指出，在所有測試劑量與時間點上，FP1 對 C57Bl/6 小鼠的皮下投予在相對於媒劑處理動物下，顯著地抑制攝食量。6xHis-FP1 在 8 nmol/kg 劑量下減少攝食量。

【0160】表 6：FP1 的皮下投予對 C57BL/6 小鼠攝食量的效果；其顯示投予後 12、24、及 48 小時的累積攝食量

累積攝食量(g)			
處理	12 小時	24 小時	48 小時
PBS	3.7±0.2	4.3 ± 0.1	8.4 ± 0.3
FP1, 1 nmol/kg	2.9 ± 0.1*	3.4 ± 0.2**	7.0 ± 0.3**
FP1, 4 nmol/kg	2.3 ± 0.2****	3.1 ± 0.1****	6.6 ± 0.3***
FP1, 8 nmol/kg	2.1 ± 0.2****	3.2 ± 0.1***	6.4 ± 0.2****
FP1, 16 nmol/kg	1.7 ± 0.2****	2.7 ± 0.2****	6.2 ± 0.3****
6xHis-FP1, 8 nmol/kg	1.8 ± 0.2****	2.6 ± 0.2****	6.0 ± 0.2****

數據以平均值± SEM 表示。

*p≤0.05，與 PBS 比較；**p≤0.01，與 PBS 比較；***p≤0.001，與 PBS 比較；****p≤0.0001，與 PBS 比較。

單向 ANOVA-杜凱多重比較檢定；*n*=8/組。

實例 9：FP1 對於 SD 大鼠攝食量的效果

【0161】 此實驗目的是要證實 FP1 對於 SD 大鼠攝食量抑制的劑量反應效果。

【0162】 雄性 SD 大鼠持續最短 72 小時在 BioDAQ 籠中適應。然後，將大鼠基於先前 24 小時的攝食量分為六組，每組八隻。在 4:00 與 5:00 pm 之間，將動物稱重，並經由皮下注射給予媒劑或包含融合蛋白之組成物。在注射後 48 小時期間，利用 BioDAQ 系統連續記錄各籠的食物重量變化。6xHis-FP1 係於本研究中供比較使用。

【0163】 結果示於圖 3 及表 7。相較於媒劑處理動物，FP1 在 2.5 nmol/kg 與 10 nmol/kg 之劑量下的皮下投予抑制了攝食量。只有在最高測試劑量(10 nmol/kg)下，於投予後 24 與 48 小時，抑制現象才達到統計顯著性。FP1 在 8 nmol/kg 劑量下減少攝食量，且其在 24 與 48 小時的效果具有顯著性。

【0164】 表 7：FP1 的皮下投予對 SD 大鼠攝食量的效果；其顯示投予後 12、24、及 48 小時的累積攝食量

累積攝食量(g)			
處理	12 小時	24 小時	48 小時
PBS	20.6 ± 1.3	25.3 ± 1.3	49.1 ± 2.1
FP1, 0.1 nmol/kg	23.3 ± 1.4	26.9 ± 0.8	52.8 ± 1.3
FP1, 0.5 nmol/kg	22.6 ± 1.7	25.1 ± 1.0	48.3 ± 1.8
FP1, 2.5 nmol/kg	20.0 ± 1.4	22.0 ± 1.0	44.6 ± 1.4
FP1, 10 nmol/kg	18.7 ± 0.9	19.9 ± 1.0*	39.9 ± 2.3*
6xHis-FP1, 8 nmol/kg	17.0 ± 1.5	18.8 ± 1.4**	38.4 ± 2.5**

數據以平均值± SEM 表示。

*p≤0.05，與 PBS 比較；**p≤0.01，與 PBS 比較。

單向 ANOVA-杜凱多重比較檢定；*n*=8/組。

實例 10：FP1 對於膳食誘發肥胖(DIO)小鼠之葡萄糖恆定與體重的效果

【0165】 此實驗目的是要評估 FP1 對於 DIO C57Bl/6 小鼠在治療二週期間之攝食量、體重、及葡萄糖恆定的效果。

【0166】 將雄性 DIO 小鼠稱重，且在第 0、3、6、9、及 12 天，將 FP1 每三天(q3d)以 2 mL/kg 進行皮下給藥。採類似方案，對媒劑與羅格列酮(Rosiglitazone)治療組進行 PBS 的給藥。對照組羅格列酮係以 0.015%提供於膳食中任食。每日記錄小鼠體重及食物重量。使用血糖儀(One Touch®Ultra®, Lifescan, Milpitas, CA)測量葡萄糖。使用 Bruker Mini-Spec LF110，進行時域 NMR (TD-NMR)，藉以對有意識的小鼠定量其脂肪與瘦肉質量。進行口服葡萄糖耐受性試驗(OGTT)時，使小鼠空腹 4 小時。在 2 g/kg 葡萄糖以 10 mL/kg 餵食管口服投予後 0、30、60、90、及 120 分鐘，經由剪尾巴來測量血糖。在葡萄糖投予後 0、30、及 90 分鐘，測量胰島素。

【0167】 在研究結束時，經由 CO2 吸入將小鼠安樂死，然後收集最終血液樣本。將血清置入濕冰上的 96 孔盤內，然後儲存於-80℃下。取出肝臟，根據製造商之說明書操作 Bruker MiniSpec mq60 以利用 TD-NMR 來評估在相對於肝臟切片之總質量下的脂肪含量。

【0168】 根據空腹葡萄糖（以 mg/dL 表示）與胰島素（以 mU/L 表示）之乘積除以因子 405，計算空腹的胰島素抗性之平衡模型評估(HOMA-IR)。

【0169】 DIO 小鼠經過 1 nmol/kg 與 10 nmol/kg 下的 FP1 q3d 治療，其減輕了體重（表 8）且減少了攝食量（表 9）。如下文所述，減少情形僅在某些時間點達到了統計顯著性。

【0170】對 DIO 小鼠給予 1 nmol/kg（第 2 至 14 天）與 10 nmol/kg（第 1 至 14 天）的劑量時，FP1 減輕了體重（表 8 及圖 4）。在 1 nmol/kg 劑量下的第 1 及 2 天，以及在 10 nmol/kg 劑量下的第 1、8、及 9 天，出現顯著減少的攝食量（表 9）。

【0171】表 8：DIO 小鼠用 FP1 治療期間的體重變化（開始體重的%）

處理	**媒劑**	**FP1 (nmol/kg)**			**羅格列酮**
日	n/a	0.1	1	10	10 mpk/天
-2	0.1 ± 0.2	-0.1 ± 0.4	0.6 ± 0.4	0.2 ± 0.3	0.1 ± 0.2
-1	-0.8 ± 0.3	-0.2 ± 0.3	0.4 ± 0.3	-0.3 ± 0.4	-0.9 ± 0.2
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
1	0.1 ± 0.2	-0.1 ± 0.4	-1.5 ± 0.5	-2.8 ± 0.4*	1.9 ± 0.2
2	0.0 ± 0.3	-0.8 ± 0.5	-3.2 ± 0.4*	-3.1 ± 0.5*	2.2 ± 0.5
3	-0.2 ± 0.4	-0.4 ± 0.4	-3.2 ± 0.6*	-4.0 ± 0.7*	2.6 ± 0.5
4	-0.4 ± 0.5	-0.7 ± 0.5	-3.8 ± 0.6*	-4.4 ± 0.8*	3.0 ± 0.5*
5	-0.5 ± 0.4	-1.0 ± 0.3	-4.0 ± 0.5*	-4.6 ± 0.9*	3.8 ± 0.6*
6	-0.4 ± 0.6	-0.5 ± 0.5	-3.8 ± 0.4*	-5.6 ± 0.9*	4.0 ± 0.7*
7	-0.3 ± 0.5	-0.5 ± 0.5	-4.3 ± 0.6*	-6.1 ± 0.9*	5.5 ± 0.8*
8	-0.6 ± 0.5	-0.5 ± 0.5	-4.2 ± 0.6*	-6.7 ± 1.1*	6.1 ± 0.9*
9	-0.4 ± 0.5	-0.2 ± 0.5	-4.5 ± 0.6*	-7.2 ± 1.2*	7.0 ± 1.0*
10	-0.3 ± 0.5	0.3 ± 0.5	-4.4 ± 0.8*	-7.8 ± 1.2*	7.8 ± 1.1*
11	-0.5 ± 0.5	0.5 ± 0.4	-4.4 ± 0.8*	-7.9 ± 1.4*	8.2 ± 1.2*
12	-0.8 ± 0.6	0.8 ± 0.5	-4.3 ± 1.0*	-7.9 ± 1.5*	8.5 ± 1.2*
13	-0.8 ± 0.6	0.5 ± 0.5	-3.9 ± 0.9*	-8.7 ± 1.6*	8.6 ± 1.3*

14	-1.7 ± 0.6	-0.4 ± 0.5	-4.6 ± 1.0*	-9.0 ± 1.7*	7.6 ± 1.3*
數據以平均值± SEM 表示。n =8/組。					
* = p<0.05，相較於媒劑處理組的體重變化。					

【0172】表 9：DIO 小鼠用 FP1 治療期間的每日攝食量(gm)

處理	**媒劑**	**FP1 (nmol/kg)**			**羅格列酮**
日	n/a	0.1	1	10	10 mpk/天
-2	2.9 ± 0.1	3.0 ± 0.2	2.9 ± 0.1	2.8 ± 0.1	2.8 ± 0.1
0	3.0 ± 0.1	3.0 ± 0.1	2.8 ± 0.1	2.8 ± 0.1	3.0 ± 0.1
1	2.9 ± 0.1	3.1 ± 0.1	2.1 ± 0.2*	1.5 ± 0.1*	3.6 ± 0.1*
2	3.0 ± 0.1	3.0 ± 0.1	2.3 ± 0.1*	2.6 ± 0.2	3.9 ± 0.2*
3	2.8 ± 0.1	3.0 ± 0.1	2.6 ± 0.1	2.4 ± 0.2	3.5 ± 0.1*
4	2.3 ± 0.1	2.6 ± 0.1	2.2 ± 0.1	2.3 ± 0.1	3.3 ± 0.1*
5	2.8 ± 0.1	3.0 ± 0.1	2.8 ± 0.1	2.6 ± 0.1	3.7 ± 0.2*
6	2.8 ± 0.1	3.1 ± 0.1	2.9 ± 0.1	2.4 ± 0.2	3.7 ± 0.2*
7	2.7 ± 0.1	2.9 ± 0.1	2.6 ± 0.1	2.4 ± 0.1	3.8 ± 0.2*
8	2.7 ± 0.1	2.9 ± 0.1	2.6 ± 0.1	2.1 ± 0.1*	3.5 ± 0.2*
9	3.0 ± 0.1	3.3 ± 0.1	2.8 ± 0.1	2.5 ± 0.2*	4.3 ± 0.2*
10	2.6 ± 0.1	3.0 ± 0.1	2.6 ± 0.1	2.2 ± 0.1	3.6 ± 0.1*
11	2.9 ± 0.1	3.1 ± 0.1	2.7 ± 0.2	2.6 ± 0.2	3.4 ± 0.1*
12	2.7 ± 0.1	3.1 ± 0.1	3.0 ± 0.1	3.0 ± 0.2	3.6 ± 0.2*
13	2.6 ± 0.1	2.8 ± 0.1	2.8 ± 0.1	2.2 ± 0.2	3.2 ± 0.1*
數據以平均值± SEM 表示。n =8/組。					
* = p<0.05，相較於媒劑處理組的體重變化。					

【0173】在研究的第 14 天所進行的 OGTT 中，在所測試的全部三種劑量下，於時間 0 後所有時間點，FP1 在相較於媒劑處理動物下顯著降低葡萄糖水平（表 10）。以總曲線下面積(AUC)及 ΔAUC 對此進一步定量，則全部三種測試劑量在相較於媒劑下有顯著降低情形（表 10，以及圖 5A 與 5B）。

【0174】表 10：DIO 小鼠經過為期十四天的 FP1 q3d 給藥後進行 OGTT 期間的血糖(mg/dL)水平

處理	劑量 (nmol/kg)	葡萄糖挑激(challenge)後的時間(min) 0	30	60	90	120	總 AUC (mg/dL/120 min)	ΔAUC (mg/dL/120 min)
媒劑	NA	209.6±16.5	399.4±46.4	338.5±46.3	297.5±38.0	269.3±36.6	38244.4±4308.2	13089.4±3573.0
FP1	0.1	196.6±7.6	319.0 ± 21.5*	241.6 ± 14.4*	196.0 ± 12.8*	184.0 ± 6.3*	28408.1 ± 1236.1*	4885.5 ± 955.1*
	1	164.0±7.2	251.4 ± 13.0*	227.6 ± 12.6*	191.9 ± 9.4*	180.6 ± 13.1*	25295.6 ± 1026.7*	5615.6 ± 647.6*
	10	146.6±5.9	195.6 ± 14.5*	197.1 ± 6.9*	172.1 ± 6.3*	174.9 ± 13.8*	21768.8 ± 603.0*	4211.4 ± 425.8*
羅格列酮	10 mpk/天	130.8±6.0	199.1 ± 12.9*	204.4 ± 8.5*	184.1 ± 10.9*	169.1 ± 5.7*	22115.6 ± 671.9*	6425.6 ± 599.6

數據以平均值± SEM 表示。n =8/組。

* = $p<0.05$，相較於媒劑處理組的體重變化。

【0175】 在研究開始時（第 0 天）、第 7 天、及第 13 天，測量餐後血糖水平（表 11 及圖 6）。在研究的第 13 天，在 1 nmol/kg 與 10 nmol/kg 劑量下的 FP1 降低了血糖，其具統計顯著性。

【0176】 表 11：DIO 小鼠用 FP1 q3d 治療之治療期間的餐後血糖

		治療開始後時間（天數）		
處理	**劑量 (nmol/kg)**	**0**	**7**	**13**
媒劑	NA	177.6±10.9	173.6±10.6	225.3±23.0
FP1	0.1	174.1±8.5	171.8±16.3	196.4±8.1
	1	167.5±7.8	135.1±11.2	165.3±10.3*
	10	165.3±13.7	145.3±4.9	153.8±7.5*
羅格列酮	10 mpk/day	189.6±17.3	122.6±8.1*	154.8±6.5*
數據以平均值± SEM 表示。n =8/組。				
* = p<0.05，相較於媒劑處理組的體重變化。				

【0177】 就 0.1 nmol/kg 劑量之 FP1 組而言，其 OGTT 期間的血漿胰島素水平於 30 分鐘時係顯著高於對應媒劑組，而 1 與 10 nmol/kg 劑量之 FP1 組於相同時間點上則低於該媒劑組（表 12）。如總 AUC 所測得，相較於媒劑組，0.1 nmol/kg 劑量之 FP1 組具較高的 OGTT 期間胰島素變化（表 12），而 1 與 10 nmol/kg 劑量之 FP1 組則具較低變化。在兩者情況中，僅有在最低劑量下才達到統計顯著性。在 90 分鐘之時間點，經過 1 及 10 nmol/kg 之 FP1 治療的小鼠具有較低的胰島素水平；然而，此效果並未達到統計顯著性。在研究的第 14 天測量 HOMA-IR，其可作為胰島素敏感性的衡量指標。在此時間點，FP1 在 10 nmol/kg 下降低了 HOMA-IR，或者改善了胰島素敏感性（表 13 及圖 7）。

【0178】表 12：DIO 小鼠經過為期十四天的 FP1 q3d 給藥後進行 OGTT 期間的血漿胰島素(pg/mL)水平

處理	劑量 (nmol/kg)	葡萄糖挑激後的時間(min) 0	30	90	總 AUC (pg/mL/90min)
媒劑	NA	6096.0 ± 774.3	14660.0 ± 3031.2	5034.4 ± 405.1	902151.9 ± 143123.2
FP1	0.1	7861.0 ± 779.5	33825.8 ± 7902.0*	6494.4 ± 797.0	1834808.8 ± 381276.1*
	1	4808.1 ± 795.8	13061.8 ± 2226.3	3443.5 ± 342.5	763218.1 ± 119766.8
	10	3478.3 ± 634.6	7147.0 ± 823.8	2958.0 ± 414.0	462528.8 ± 44653.1
羅格列酮	10 mpk/day	2965.6 ± 524.2	2203.1 ± 193.5*	1180.0 ± 57.1	179025.0 ± 9970.7

數據以平均值± SEM 表示。n =8/組。

* = $p<0.05$，相較於媒劑處理組的體重變化。

【0179】表 13：DIO 小鼠在經過 FP1 q3d 治療十四天後的空腹 HOMA-IR

處理	劑量(nmol/kg)	HOMA-IR
媒劑	NA	93.5 ± 15.3
FP1	0.1	112.4 ± 14.6
	1	56.7 ± 9.7

處理	劑量(nmol/kg)	HOMA-IR
	10	37.7 ± 8.2*
羅格列酮	10 mpk/day	27.3 ± 4.7*

數據以平均值± SEM 表示。

n =8/組。

* = p<0.05，相較於媒劑處理組的體重變化。

【0180】無論在任何劑量下，第 13 天所達到的體重減輕幅度，並未在絕對脂肪質量或脂肪質量百分比上得到可測量的變化（表 14）。在 10 nmol/kg 劑量下，絕對瘦肉質量有顯著減少。以瘦肉質量百分比表示時，並未觀察到此減少現象。在研究第 15 天進行最終屍體剖檢時，測量肝臟重量（表 15）。在 10 nmol/kg 劑量下，FP1 減輕了絕對肝臟重量，以及以體重之百分比表示的肝臟重量。在 1 nmol/kg 劑量下，已觀察到減輕情形，但此情形並未有任一參數達到統計顯著性。利用 NMR 進行活檢，藉此測量肝臟脂肪（表 16）。在 1 與 10 nmol/kg 劑量下，FP1 融合蛋白減少了肝臟脂肪含量，其以肝臟活檢重量的百分比表示。在較高劑量下，該減少現象具有顯著性。

【0181】表 14：DIO 小鼠經過 FP1 q3d 治療十三天後的體組成

處理	劑量 (nmol/kg)	脂肪質量 (g)	瘦肉質量 (g)	脂肪質量（身體的%）	瘦肉質量（身體的%）
媒劑	NA	11.6±0.5	29.6±0.4	23.4±0.8	59.6±0.9
FP1	0.1	12.2±0.4	29.7±0.4	24.1±0.6	58.5±0.6
	1	12.1±0.3	28.0±0.4	25.1±0.3	58.3±0.6
	10	10.6±0.3	27.7±0.4*	23.1±0.3	60.6±0.6

羅格列酮	10 mpk/天	14.9±0.6*	30.0±0.5	27.2±0.4*	55.0±0.6*

數據以平均值± SEM 表示。n =8/組。

* = p<0.05，相較於媒劑處理組的體重變化。

【0182】

【0183】表 15：DIO 小鼠經過 FP1 q3d 治療十五天後的肝臟重量

處理	**劑量(nmol/kg)**	**肝臟重量(g)**	**肝臟重量（身體的%）**
媒劑	NA	2.6 ± 0.1	5.4 ± 0.2
FP1	0.1	2.9 ± 0.2	5.8 ± 0.2
	1	2.2 ± 0.1	4.6 ± 0.2
	10	1.9 ± 0.1*	4.2 ± 0.1*
羅格列酮	10 mpk/天	2.5 ± 0.2	4.6 ± 0.2

數據以平均值± SEM 表示。n =8/組。

* = p<0.05，相較於媒劑處理組的體重變化。

【0184】表 16：DIO 小鼠經過 FP1 q3d 治療十五天後所測量的肝臟脂肪含量

處理	**劑量(nmol/kg)**	**脂肪(%)**
媒劑	NA	27.3 ± 2.1
FP1	0.1	26.0 ± 1.4
	1	22.5 ± 1.4
	10	17.8 ± 1.6*
羅格列酮	10 mpk/天	25.9 ± 0.8

數據以平均值± SEM 表示。n =8/組。

* = p<0.05，相較於媒劑處理組的體重變化。

實例 11：FP1 對於 ob/ob 小鼠之血糖水平與體重的效果

【0185】 此實驗目的是要在肥胖、高血糖、瘦素殘缺的 *ob/ob* 小鼠中，評估 FP1 對於彼等在八天治療期間之血糖水平與體重的效果。

【0186】 將雄性 *ob/ob* 小鼠稱重，且在第 0、3、及 6 天，將 FP1 每三天(q3d)以 2 mL/kg 進行皮下投予。每日記錄小鼠體重及食物重量。每日使用血糖儀來測量葡萄糖。在研究結束時，將小鼠安樂死，然後收集最終血液樣本。

【0187】 相對於媒劑處理小鼠，在 1 nmol/kg 劑量之 FP1 下的 *ob/ob* 小鼠在第 2 天開始直到第 8 天，其顯著減輕了體重（以開始體重的百分比表示）。相對於媒劑處理小鼠，在 10 nmol/kg 劑量之 FP1 下的 *ob/ob* 小鼠在第 1 天開始直到第 8 天，其減輕了體重（以開始體重的百分比表示）（表 17 及圖 8）。

【0188】 表 17：*ob/ob* 小鼠用 FP1 q3d 治療期間的體重變化(開始體重的%)

處理	**媒劑**	**FP1**	
日	n/a	1 nmol/kg	10 nmol/kg
-6	-2.5 ± 0.3	-2.8 ± 0.4	-3.6 ± 0.5
-5	-2.4 ± 0.3	-3.0 ± 0.5	-3.5 ± 0.5
-4	-1.9 ± 0.2	-2.5 ± 0.4	-2.8 ± 0.3
-1	-0.3 ± 0.3	0.1 ± 0.2	-0.3 ± 0.2
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
1	0.5 ± 0.2	-1.6 ± 0.2	-2.3 ± 0.5*
2	1.1 ± 0.2	-1.8 ± 0.4*	-2.0 ± 0.9*
3	1.3 ± 0.3	-2.5 ± 0.4*	-3.1 ± 1.1*

處理	媒劑	FP1	
4	1.8 ± 0.3	-3.3 ± 0.5*	-4.2 ± 1.3*
5	1.8 ± 0.4	-3.5 ± 0.5*	-4.7 ± 1.5*
6	2.0 ± 0.5	-4.0 ± 0.7*	-5.7 ± 1.6*
7	2.8 ± 0.6	-4.8 ± 0.8*	-6.3 ± 1.7*
8	3.5 ± 0.8	-4.5 ± 1.0*	-6.1 ± 1.9*
數據以平均值± SEM 表示。n =8/組。			
* = p<0.05，相較於媒劑處理組的體重變化。			

【0189】 相對於媒劑處理小鼠，FP1 在 10 nmol/kg 劑量下，在研究第 1 及 2 天以及第 4 天直到第 8 天，降低了 *ob/ob* 小鼠的餐後血糖值。在 1 nmol/kg 下，已觀察到血糖下降；然而，此效果並未達到統計顯著性（表 18 及圖 9）。

【0190】 表 18：*ob/ob* 小鼠用 FP1 q3d 治療期間的餐後血糖

處理 日	媒劑 n/a	FP1 1 nmol/kg	 10 nmol/kg
-6	463.6 ± 31.2	395.7 ± 52.0	463.6 ± 41.0
-5	554.9 ± 57.5	609.6 ± 53.6	552.9 ± 53.0
-4	502.9 ± 41.6	517.9 ± 71.6	490.3 ± 54.4
-1	552.1 ± 45.1	567.2 ± 51.2	586.0 ± 42.6
0	468.8 ± 57.3	479.7 ± 61.8	437.0 ± 42.7
1	537.0 ± 42.8	439.0 ± 80.4	336.2 ± 51.0*
2	511.7 ± 43.5	440.0 ± 74.3	293.7 ± 37.6*
3	447.8 ± 54.2	369.6 ± 75.9	279.4 ± 38.8
4	516.3 ± 47.0	384.6 ± 84.0	261.2 ± 43.7*

5	531.0 ± 47.1	410.9 ± 92.2	286.9 ± 55.8*
6	596.1 ± 45.1	451.1 ± 82.6	301.9 ± 49.3*
7	566.7 ± 44.3	425.3 ± 86.9	246.7 ± 43.5*
8	509.9 ± 37.6	337.8 ± 75.1	223.4 ± 34.1*
數據以平均值± SEM 表示。n =8/組。			

實例 12：多物種的藥物動力學

【0191】 小鼠的藥物動力學

【0192】 以於 PBS (pH 7)中的 2 mg/kg IV 與 SC 劑量，將 FP1 投予至雌性 C57Bl/6 小鼠。收集血液樣本，將血清加以處理，並在經過兩者投予途徑後長達 7 天測量藥物濃度。使用免疫檢定方法，測定 FP1 濃度。血清藥物濃度-時間曲線數據總結於表 19 及 20，且描繪於圖 10。

【0193】 表 19：C57Bl/6 雌性小鼠經單次 SC 投予之後隨時間的血清 FP1 濃度(nM)

	FP1 - SC 給藥						
時間點	**動物 56 結果 (nM)**	**動物 57 結果(nM)**	**動物 58 結果 (nM)**	**動物 60 結果(nM)**	**動物 63 結果 (nM)**	**平均結果 (nM)**	**標準偏差**
4 hr	32.299	50.735	42.766	32.407	23.018	36.245	10.698
24 hr	88.822	106.418	88.648	103.841	80.346	93.615	11.093
72 hr	33.563	38.473	32.473	33.625	32.769	34.181	2.451

96 hr	20.639	24.988	21.247	19.356	20.771	21.400	2.124
第 7 天	5.399	6.919	7.234	5.994	5.637	6.237	0.803

【0194】 表 20：C57Bl/6 雌性小鼠經單次 IV 投予之後隨時間的血清 FP1 濃度(nM)

	FP1 - IV 給藥						
時間點	**動物 52 結果(nM)**	**動物 53 結果(nM)**	**動物 65 結果(nM)**	**動物 66 結果(nM)**	**動物 70 結果(nM)**	**平均結果 (nM)**	**標準偏差**
1 hr	240.419	233.318	232.484	276.913	272.727	251.172	21.857
24 hr	86.823	95.774	80.201	93.153	88.853	88.961	6.027
72 hr	33.634	37.447	33.108	41.680	34.034	35.981	3.612
96 hr	22.666	20.588	19.458	33.718	20.361	23.358	5.909
第 7 天	7.401	5.606	4.896	8.556	4.205	6.133	1.803

【0195】 藥物動力學分析顯示，C57Bl/6 小鼠經過 SC 與 IV 投予之後，FP1 的終末半衰期各別係 1.67 與 1.57 天（表 21）。FP1 在經過 SC 投予後展示出~71% 之平均生物利用率。

【0196】 表 21：雌性 C57Bl/6 小鼠經過 2 mg/kg IV 與 SC 投予之後的 FP1 藥物動力學參數平均值(± SD)

途徑		**$t_{1/2}$ (天)**	**CL 或 CL/F （ml/天**	**Vss (ml/kg)**	**C 最大值 (ng/ml)**	**T 最大值* (天)**	**$AUC_{0\text{-最後}}$ （天 *ng/ml）**	**$AUC_{0\text{-無限}}$ （天 *ng/ml）**

			/kg）					
SC	**平均值**	**1.67**	**49.48**		**14994**	**1**	**38315**	**40734**
	(SD)	(0.14)	(4.791)		(1776)		(3851)	(4072)
IV	**平均值**	**1.57**	**35.00**	**69.03**	**40231**	**0.04**	**55263**	**57531**
	(SD)	(0.19)	(3.13)	(5.8)	(3500)		(4853)	(5416)

註：*T 最大值（中位數）

【0197】 大鼠的藥物動力學

【0198】 以於 PBS (pH 7)中的 2 mg/kg IV 與 SC 劑量，將 FP1 投予至雌性 SD 大鼠。收集血液樣本，將血清加以處理，並在經過兩者投予途徑後長達 7 天測量藥物濃度。使用免疫檢定方法，測定 FP1 濃度。血清藥物濃度-時間曲線數據總結於表 22 及 23，且描繪於圖 11。

【0199】 表 22：雌性 SD 大鼠經單次 SC 投予之後隨時間的血清 FP1 濃度 (nM)。

	FP1 -第 3 組（SC 給藥）						
時間點	**動物 53 結果 (nM)**	**動物 55 結果 (nM)**	**動物 67 結果 (nM)**	**動物 68 結果 (nM)**	**動物 69 結果 (nM)**	**平均結果 (nM)**	**標準偏差**
4 hr	4.766	3.500	3.932	3.546	3.250	3.799	0.593
24 hr	45.118	53.192	39.196	39.823	40.804	43.627	5.826
72 hr	18.900	24.102	23.124	23.718	18.933	21.755	2.615
96 hr	12.193	14.333	14.185	14.669	11.256	13.327	1.511

第 7 天	2.805	2.821	2.447	3.438	2.358	2.774	0.426

【0200】表 23：雌性 SD 大鼠經單次 IV 投予之後隨時間的血清 FP1 濃度 (nM)

	FP1 -第 4 組（IV 給藥）						
時間點	**動物 51 結果 (nM)**	**動物 52 結果 (nM)**	**動物 57 結果 (nM)**	**動物 64 結果 (nM)**	**動物 66 結果 (nM)**	**平均結果(nM)**	**標準偏差**
1 hr	43.620*	382.676	403.255	443.080	510.105	356.547	181.560
24 hr	102.665*	142.661	139.066	124.528	126.425	127.069	15.728
72 hr	46.720	60.105	67.090	59.257	70.423	60.719	9.127
96 hr	29.409	39.897	41.225	42.258	48.074	40.173	6.779
第 7 天	6.976	11.251	8.913	9.540	13.006	9.937	2.298

*重複分析確認結果

【0201】藥物動力學分析顯示，SD 大鼠經過 SC 與 IV 投予之後，FP1 的終末半衰期各別係 1.34 與 1.51 天（表 24）。FP1 在經過 SC 投予後展示出~23% 之平均生物利用率。

【0202】表 24：SD 大鼠經過 2 mg/kg IV 與 SC 投予之後的 FP1 藥物動力學參數平均值(± SD)

途徑		**$t_{1/2}$ (天)**	**CL 或 CL/F（ml/天/kg）**	**Vss (ml/kg)**	**C 最大值 (ng/ml)**	**T 最大值* (天)**	**$AUC_{0-最後}$（天*ng/ml）**	**$AUC_{0-無限}$（天*ng/ml）**
SC	平均	**1.34**	**100.09**		**6987**	**1**	**19250**	**20112**

	值							
	(SD)	(0.04)	(3.97)		(417)		(794)	(820)
IV	**平均值**	**1.51**	**24.75**	**53.41**	**59000**	**0.04**	**83028**	**86525**
	(SD)	(0.12)	(8.53)	(17.15)	(25031)		(20126)	(20881)

註：*T 最大值（中位數）

【0203】 猴子的藥物動力學

【0204】 以於 PBS (pH 7)中的 1 mg/kg IV 與 SC 劑量，將 FP1 投予至原態(naïve)雄性石蟹獼猴(*Macaca fascicularis*)。收集血液樣本，將血清加以處理，並在經過兩者投予途徑後長達 21 天利用免疫檢定的生物分析來測量藥物濃度。血清藥物濃度-時間曲線數據總結於表 25 及 26，且描繪於圖 12。

【0205】 表 25：石蟹獼猴經單次 SC 投予之後依免疫檢定測定之隨時間的血清 FP1 濃度(nM)

	FP1（SC 給藥）				
時間點	**動物 110 結果 (nM)**	**動物 111 結果 (nM)**	**動物 112 結果 (nM)**	**平均結果(nM)**	**標準偏差**
給藥前	< LLOQ	< LLOQ	< LLOQ	< LLOQ	N/A
6 hr	49.304	43.784	72.110	55.066	15.017
24 hr	93.368	71.958	96.863	87.396	13.483
48 hr	107.689	97.509	115.144	106.781	8.853
72 hr	113.601	104.190	104.449	107.414	5.360
120 hr	101.490	95.049	91.717	96.085	4.968
168 hr	82.167	75.435	81.569	79.724	3.726

240 hr	71.033	56.732	59.266	62.344	7.631
336 hr	44.380	42.758	42.571	43.236	0.995
432 hr	30.911	29.445	32.839	31.065	1.702
528 hr	21.277	20.404	26.427	22.703	3.255

【0206】 表 26：石蟹獼猴經單次 IV 投予之後依免疫檢定測定之隨時間的血清 FP1 濃度(nM)

	FP1（IV 給藥）				
時間點	**動物 104 結果 (nM)**	**動物 105 結果 (nM)**	**動物 106 結果 (nM)**	**平均結果(nM)**	**標準偏差**
給藥前	< LLOQ	< LLOQ	< LLOQ	< LLOQ	N/A
1 hr	212.661	235.168	189.000	212.276	23.087
6 hr	190.315	185.331	183.575	186.407	3.497
24 hr	141.743	155.943	146.487	148.058	7.229
48 hr	111.765	126.105	120.744	119.538	7.246
72 hr	105.076	106.955	106.441	106.157	0.971
120 hr	92.591	103.882	103.757	100.077	6.483
168 hr	71.368	93.055	87.706	84.043	11.298
240 hr	71.554	65.093	65.685	67.444	3.572
336 hr	46.184	38.961	41.696	42.280	3.647
432 hr	34.589	31.266	19.492	28.449	7.933
528 hr	26.885	24.154	22.422	24.487	2.250

【0207】 藥物動力學分析顯示，石蟹獼猴各別經過 SC 與 IV 投予之後，FP1 的終末半衰期係介於 8.5 與 9.2 天之間，且其在經過 SC 投予之後的平均生物利用率係~88%（表 27）。

【0208】 表 27：石蟹獼猴經過 1 mg/kg IV 與 SC 投予之後的 FP1 藥物動力學參數平均值(± SD)。

途徑		$t_{1/2}$ (天)	CL 或 CL/F （ml/天/kg）	Vss (ml/kg)	C 最大值 (ng/ml)	T 最大值* (天)	$AUC_{0-最後}$ （天*ng/ml）	$AUC_{0-無限}$ （天*ng/ml）
SC	**平均值**	**8.5**	**3.9**		**17776**	**3**	**211030**	**256202**
	(SD)	(1.5)	(0.3)		(950)		(11332)	(20192)
IV	**平均值**	**9.2**	**3.4**	**45.6**	**34001**	**0.04**	**239758**	**292206**
	(SD)	(0.5)	(0.1)	(1.6)	(3698)		(6095)	(11516)

註：*T 最大值（中位數）

【0209】 利用免疫親和性捕捉 LCMS 分析，對石蟹獼猴在經過 IV 與 SC 投予後的血清中所存在的完整二聚體濃度進行定量（表 28 與 29，以及圖 13 與 14）。此方法所測定的濃度與免疫檢定(IA)所測定的濃度類似，其展示出 FP1 在石蟹獼猴中呈完整二聚體下進行循環時，不具可檢測出的代謝傾向。

【0210】 表 28：石蟹獼猴經過單次 IV 投予之後，依免疫親和性捕捉 LCMS 分析所測定之隨時間的呈完整二聚體的血清 FP1 濃度(ng/mL)

日	二聚體完整 MS 數據（儲集樣本）	IA 數據（平均）
0.00	0	0
0.04	33347	34537
0.25	29686	30328
1.00	28787	24089
2.00	17249	19449
3.00	16827	17272
5.00	16159	16282
7.00	11124	13674
10.00	8746	10973
14.00	5328	6879
18.00	3857	4629
22.00	2252	3984

【0211】 表 29：石蟹獼猴經過單次 SC 投予之後，依免疫親和性捕捉 LCMS 分析所測定之隨時間的呈完整二聚體的血清 FP1 濃度(ng/mL)。

日	二聚體完整 MS 數據（儲集樣本）	IA 數據（平均）
0.00	0	0
0.25	9625	8959
1.00	15799	14219
2.00	17671	17373
3.00	19130	17476
5.00	12284	15633
7.00	10808	12971

日	二聚體完整 MS 數據（儲集樣本）	IA 數據（平均）
10.00	8910	10143
14.00	5814	7034
18.00	4074	5054
22.00	2967	3694

【0212】石蟹獼猴經過 IV 與 SC 投予之後的血清中分析物濃度，亦利用免疫親和性捕捉胰蛋白酶分解 LC-MS/MS 分析加以測量（表 30 及 31）。所選胰蛋白酶肽，即 ALV (ALVLIAFAQYLQQSPFEDHVK)、ASL (ASLEDLGWADWVLSPR)、及 TDT (TDTGVSLQTYDDLLAK)，係分別位在 FP1 內接近 HSA 區之 N 端處、GDF15 之 N 端、及 GDF15 之 C 端。該等胜肽係作為 FP1 之代表性胜肽而受到監測。所有代表性胜肽的濃度係彼此相近，且相近於由免疫檢定測量的濃度，其證實了體內 FP1 中的 GDF15 序列保持完整且連接至全 HSA 序列。

【0213】表 30：石蟹獼猴經過單次 IV 投予之後，依免疫親和性捕捉胰蛋白酶分解 LC-MS/MS 分析所測定，代表 FP1 各區之代表性胜肽隨時間的血清濃度(ng/mL)

時間點		**FP1 平均值(ng/mL)**			**標準偏差**			**IA 數據 (ng/mL)**
日	小時	**ALV**	**TDT**	**ASL**	**ALV**	**TDT**	**ASL**	
0.00	0	<LLOQ	<LLOQ	<LLOQ	N/A	N/A	N/A	0.0
0.04	1	32400.0	39766.7	33333.3	2623.0	3162.8	2722.7	34536.9
0.25	6	29100.0	27166.7	30600.0	3439.5	1006.6	2095.2	30328.1
1.00	24	24366.7	23300.0	23800.0	4215.8	3996.2	4100.0	24088.7

時間點		FP1 平均值(ng/mL)			標準偏差			IA 數據 (ng/mL)
2.00	48	19433.3	17733.3	18700.0	1457.2	1193.0	854.4	19448.6
3.00	72	18100.0	17200.0	17166.7	360.6	871.8	1001.7	17271.6
5.00	120	15966.7	14033.3	14233.3	1001.7	642.9	1011.6	16282.3
7.00	168	13733.3	11800.0	12100.0	1115.0	600.0	300.0	13673.6
10.00	240	9303.3	8570.0	8570.0	2290.1	1682.2	1685.9	10973.0
14.00	336	5860.0	5890.0	6056.7	415.8	312.2	388.0	6878.9
18.00	432	4143.3	4400.0	4226.7	374.3	52.9	571.2	4628.6
22.00	528	2830.0	3256.7	2753.3	355.4	420.0	319.0	3984.0

【0214】 表 31：石蟹獼猴經過單次 SC 投予之後，依免疫親和性捕捉胰蛋白酶分解 LC-MS/MS 分析所測定，代表 FP1 各區之代表性胜肽隨時間的血清濃度(ng/mL)

時間點		FP1 平均值(ng/mL)			標準偏差			IA 數據 (ng/mL)
日	小時	ALV	TDT	ASL	ALV	TDT	ASL	
0.00	0	<LLOQ	<LLOQ	<LLOQ	N/A	N/A	N/A	0.0
0.25	6	9323.3	7430.0	8123.3	1900.3	2471.6	1954.1	8959.1
1.00	24	15233.3	13390.0	14533.3	2926.3	3222.0	2683.9	14219.2
2.00	48	15366.7	14000.0	14166.7	2579.4	1646.2	2311.6	17373.0
3.00	72	17300.0	16033.3	15333.3	1571.6	1001.7	986.6	17476.0
5.00	120	15333.3	13366.7	13666.7	1222.0	1692.1	1501.1	15632.9
7.00	168	13333.3	11633.3	11700.0	709.5	472.6	781.0	12970.9

時間點		FP1 平均值(ng/mL)			標準偏差			IA 數據 (ng/mL)
10.00	240	8496.7	7376.7	8343.3	1475.5	189.0	1039.1	10143.2
14.00	336	6046.7	6116.7	6253.3	90.2	118.5	110.6	7034.5
18.00	432	4593.3	5250.0	4636.7	802.6	1157.5	621.7	5054.2
22.00	528	3056.7	3490.0	3116.7	424.5	687.7	220.5	3693.7

【0215】 人類血漿穩定性分析

【0216】 此研究目的是要分析人體血漿中 FP1 的離體穩定性。將取自二名對象（一名男性與一名女性）的肝素抗凝血液，藉由離心方式產生新鮮的非冷凍人類血漿。在 37℃下將 FP1 培養於此基質中，同時輕輕混合，如此持續 0、4、24、及 48 小時。使用免疫檢定方法，測定 FP1 濃度。與開始濃度（0 小時）的平均相差幅度百分比係自-4.1 至-12.9 之範圍，且並未隨時間增加，其證實了 FP1 在人類血漿中持續長達 48 小時具有離體穩定性（表 32 與圖 15）。

【0217】 表 32：在獲自二名人類對象(Sub)的血漿中離體培養 0、4、24、及 48 小時(hr)之後，依免疫檢定測定的 FP1 濃度(μg/mL)

離體樣本	男性對象 1 濃度 (ug/mL)	與 T0 相差幅度%	女性對象 2 濃度 (ug/mL)	與 T0 相差幅度%	平均濃度 (ug/mL)	與 T0 相差幅度%
血漿- T0hr_ FP1	11.503	N/A	12.649	N/A	12.076	N/A
血漿- T4hr_ FP1	10.524	-8.5	10.521	-16.8	10.523	-12.9
血漿- T24hr_ FP1	9.934	-13.6	12.402	-2.0	11.168	-7.5
血漿- T48hr_ FP1	10.582	-8.0	12.575	-0.6	11.578	-4.1

【0218】 在人類血漿中培養之後，利用免疫親和性捕捉 LCMS 定量完整二聚體的濃度。此方法所測定的濃度隨時間（0、4、24、及 48 小時）經過仍具穩定性，其展示出 FP1 在離體人類血漿中長達 48 小時保持完整二聚體（表 33 及圖 16）。

【0219】 表 33：在獲自二名人類對象的血漿中離體培養 0、4、24、及 48 小時(hr)之後，依免疫親和性捕捉 LCMS 分析測定的呈完整二聚體之平均 FP1 濃度(μg/mL)及與開始濃度的相差幅度%

	二聚體濃度(ug/mL)	相差幅度%
0 hr	15.8	100.0
4 hr	15.8	100.1
24 hr	15.9	100.9
48 hr	15.2	96.0

實例 13：IR 計畫

【0220】 將為動物及臨床樣本的抗藥物抗體(ADA)檢測，開發出免疫反應(IR)分析法。IR 分析將會識別 ADA 陽性樣本，以將 ADA 狀態與藥物動力學/毒物動力學(PK/TK)結果作比較，且能夠評估 FP1 暴露量與藥物動力學。臨床 IR 分析法將用來篩選血清樣本，確認 ADA 陽性樣本的特異性，且測定 ADA 效價以確認陽性樣本。隨後的中和抗體(NAb)分析法開發將用於對第 1 期程序中來自 ADA 陽性對象的陽性樣本進行確認。另外，隨後判定 ADA 與內源性 GDF15 的交叉反應，以用於第二期程序。在首次應用於人體(first in human, FIH)的研究之前，將進行免疫原性風險評估，額外的免疫反應表徵分析可在彼等有正當理由時實施。

實例 14：毒物學計畫

【0221】 由於尚未發現關於GDF15的內源性標靶受體，因而缺乏關於FP1的活體外結合與功能性資料。然而，在大鼠、小鼠、及石蟹獼猴中的單次或多重劑量藥理與療效的研究已證實 FP1 在此等物種中的活性，顯示其減少攝食量、減輕體重、及調節口服葡萄糖耐受性的效果。根據療效結果，大鼠與猴子將分別屬於嚙齒與非嚙齒動物毒物學測試物種，且應了解的是，FP1 在此等物種中對於其受體的內在效力（相較於在人類中的內在效力）尚未經過完全表徵。

【0222】 實例 15 至 19 涉及本發明之另一種例示性融合蛋白的表徵，該融合蛋白描述於實例 5，其具有 SEQ ID NO: 92（由核苷酸序列 SEQ ID NO: 92（密碼子最佳化 1）及 110（密碼子最佳化 2）編碼）之胺基酸序列。此融合蛋白係完全重組蛋白，其存在的是 HSA (C34S)與成熟人類 GDF15 之缺失變體（201-308；SEQ ID NO:8）經由 42 個胺基酸連接子所融合的同二聚體，該連接子由甘胺酸與絲胺酸殘基 GS-$(GGGGS)_8$所組成。在 HSA 的位置 34 處之單個自然游離半胱胺酸已突變為絲胺酸。具體 HSA-GDF15 融合蛋白將以「FP2」表示於下文實例中，以求簡化。

實例 15：FP2 對於 C57Bl/6 小鼠攝食量的效果

【0223】 雄性 C57Bl/6 小鼠經過單次給藥後，評估 FP2 對於降低攝食量的能力。本研究使用了獲自 Taconic Biosciences (Hudson, NY)的雄性 C57Bl/6N 小鼠（10 至 12 週齡）。將小鼠單獨飼養在溫控空間內，提供 12 小時光暗循環(6 am/6 pm)，允許小鼠任意採食水及飼料。雄性 C57Bl/6 小鼠持續最短 72 小時在 BioDAQ 籠中適應；然後，將小鼠基於最後 24 小時的攝食量分為六組，每組八隻。在 4:00 至 5:00 pm 之間，將動物稱重，並經由皮下注射給予媒劑或化合物。在化合物投予後 48 小時期間，利用

BioDAQ 系統連續記錄各籠的食物重量變化。6xHis-FP1 係於本研究中作為對照組使用。

【0224】 FP2 對於所有測試劑量水平經過投予後 12、24、及 48 小時的減少攝食量具有顯著效果（表 34）。相對於 PBS，小鼠在所有時間點以及在所有劑量水平下（表 35）皆有以百分比變化表示的攝食量減少。

【0225】 **表 34**：FP2 的單次給藥對 C57Bl/6 小鼠於 48 小時期間攝食量的效果

累積攝食量(g)			
處理	12 小時	24 小時	48 小時
PBS	3.7±0.2	4.4±0.2	8.8±0.4
FP2, 1 nmol/kg	2.8±0.4*	3.0±0.4**	6.9±0.7*
FP2, 4 nmol/kg	2.4±0.2***	3.1±0.2**	7.0±0.3*
FP2, 8 nmol/kg	1.9±0.2****	2.4±0.1****	6.2±0.2***
FP2, 16 nmol/kg	1.8±0.1****	2.7±0.1***	6.3±0.4**
6xHis-FP1, 8 nmol/kg	2.3±0.3***	2.8±0.4**	6.6±0.7**

數據以平均值± SEM 表示。

*p≤0.05，與 PBS 比較

**p≤0.01，與 PBS 比較

***p≤0.001，與 PBS 比較

****p≤0.0001，各別與 PBS 比較

所採用的統計分析：ANOVA 與鄧奈特多重比較檢定。

n=8/組，但以 6xHis-FP1 8 nmol/kg (n=6)為例外。

【0226】 **表 35**：FP2 的單次給藥對 C57Bl/6 小鼠於 48 小時期間攝食量之減

少幅度百分比（相對於媒劑）的效果

相對於 PBS 的抑制百分比			
處理	12 小時	24 小時	48 小時
PBS	0.0±7.9	0.0±7.7	0.0±5.9
FP2, 1 nmol/kg	22.4±12.5*	31.8±10.5**	21.8±8.1*
FP2, 4 nmol/kg	36.6±7.2***	30.4±5.8**	20.2±4.7*
FP2, 8 nmol/kg	47.0±6.2****	45.7±3.8****	29.7±3.9***
FP2, 16 nmol/kg	49.2±4.1****	38.1±4.1***	27.8±5.1**
6xHis-FP1, 8 nmol/kg	36.9±9.9***	36.5±8.8**	24.6±8.2**

FP2 的食慾抑制效果，係以相較於各別 PBS 對照組下攝食量的相對減少幅度表示。

數據以平均值± SEM 表示。

*p≤0.05，與 PBS 比較

**p≤0.01，與 PBS 比較

***p≤0.001，與 PBS 比較

****p≤0.0001，各別與 PBS 比較

所採用的統計分析：ANOVA 與鄧奈特多重比較檢定。

n=8/組，但以 6xHis-FP1 8 nmol/kg (n=6)為例外。

實例 16：FP2 對於 SD 大鼠攝食量的效果

【0227】 雄性 SD 大鼠經過單次給藥後，評估 FP2 對於降低攝食量與體重增加的能力。該等動物是在體重 200-225 g 時獲自 Charles River Labs (Wilmington, MA)，且在到達一週內使用。彼等係以每籠一隻飼養於溫控空間內，且提供 12 小時光暗循環，籠內鋪上 ALPHA-dri 墊草，且設有馴養用塑膠管。允許彼等任意採食水與實驗室嚙齒動物飼料，該飼料即照射過的

Certified PicoLab® Rodent Diet 20, 5K75*（由 Purina Mills, St. Louis, MO.經由 ASAP Quakertown, PA 供應）。給藥前，為各別大鼠測量體重並加以記錄。

【0228】 動物持續最短 72 小時在 BioDAQ 籠中適應；然後，將大鼠基於最後 24 小時的攝食量分為六組，每組八隻。在 4:00 至 5:00 pm 之間，將動物稱重，並經由皮下注射給予媒劑或化合物。在化合物投予後 48 小時期間，利用 BioDAQ 系統連續記錄各籠的食物重量變化。6XHis-FP1 係於本研究中作為對照組使用。

【0229】 經過 FP2 的單次給藥後，已測得攝食量的劑量依賴性減少。在 0.3 nmol/kg 的劑量下，未觀察到攝食量的顯著差異。在 1 nmol/kg 下，已觀察到 12 小時（但未在 24 或 48 小時）的攝食量減少有顯著效果。在 3 及 10 nmol/kg 劑量水平下，已觀察到所有時間點的攝食量皆有顯著減少（表 36、圖 19）。相對於 PBS，在所有時間點以及在所有劑量水平下（表 37）皆有以百分比變化表示的攝食量減少。

【0230】 **表 36：**FP2 的單次給藥對 SD 大鼠於 48 小時期間攝食量的效果。

累積攝食量(g)			
處理	12 小時	24 小時	48 小時
PBS	21.7±0.6	25.0±0.8	53.1±1.6
FP2, 0.3 nmol/Kg	19.5±0.9	22.9±0.7	48.4±1.5
FP2, 1 nmol/Kg	17.5±0.9*	19.8±0.8	47.0±2.6
FP2, 3 nmol/Kg	16.1±1.2**	17.0±1.0**	39.2±3.2**
FP2, 10 nmol/Kg	15.8±0.9***	16.5±0.9**	36.5±3.2**
6XHis-FP1 8 nmol/Kg	15.0±1.4***	15.7±1.2**	37.2±4.5**

數據以平均值± SEM 表示。

*p≤0.05，與 PBS 比較

**p≤0.01，與 PBS 比較

***p≤0.001，各別與 PBS 比較

所採用的統計分析：ANOVA 與鄧奈特多重比較檢定。

n=8/組

【0231】表 37：FP2 的單次給藥對 SD 大鼠於 48 小時期間攝食量之減少幅度百分比（相對於媒劑）的效果。

相對於 PBS 的抑制百分比			
處理	12 小時	24 小時	48 小時
PBS	0.0±4.0	0.0±4.6	0.0±4.3
FP2 0.3 nmol/kg	10.0±4.7	8.5±4.1	8.8±3.9
FP2 1 nmol/kg	19.3±4.7*	20.8±4.1	11.5±5.5
FP2 3 nmol/kg	25.9±6.1**	32.0±4.7**	26.2±6.5**
FP2 10 nmol/kg	27.4±4.8***	33.8±4.1**	31.2±6.4**
6XHis-FP1 8 nmol/kg	30.8±6.6***	37.0±5.4**	29.9±8.8**

FP2 的食慾抑制效果，係以相較於各別 PBS 對照組下攝食量的相對減少幅度表示。

數據以平均值± SEM 表示。

*p≤0.05，與 PBS 比較

**p≤0.01，與 PBS 比較

***p≤0.001，各別與 PBS 比較

所採用的統計分析：ANOVA 與鄧奈特多重比較檢定。

n=8/組

實例 17：FP2 對於膳食誘發肥胖(DIO)C57Bl/6 小鼠之攝食量、體重、及葡萄糖恆定的效果

【0232】 雄性 DIO 之 C57Bl/6 小鼠在 8 天期間經過重複給藥，評估 FP2 對於減少攝食量與體重且改善葡萄糖恆定的能力。本研究使用了獲自 Taconic Biosciences (Hudson, NY)的雄性 DIO 之 C57Bl/6 小鼠(21 週齡，高脂採食 15 週）。將小鼠單獨飼養在溫控空間內，提供 12 小時光暗循環(6 am/6 pm)，允許小鼠任意採食水及 Research Diet D12492 (Research Diets, New Brunswick, NJ)。實驗進行前，讓小鼠在小鼠空間中適應>1 週。研究終點係攝食量、體重、體組成、及血糖終點（OGTT、血糖）的測量值。給藥前一天，將動物稱重，並按體重(BW)分組。藉由皮下注射對小鼠給藥。經過 FP2 給藥的動物是在第 0 天、第 3 天、第 6 天、第 9 天、及第 12 天接受此化合物。媒劑組及羅格列酮組也在這幾天接受無菌 PBS（採 SC）。Rosliglitazone 係以 0.015% w/w 提供於膳食中任食。在十五天期間，每日記錄 BW 及攝食量。在第 0、7、及 13 天，測量血糖。在第 14 天，進行口服葡萄糖耐受性試驗(OGTT)。在 OGTT 期間，在所選時間點上測量胰島素水平。在第 15 天，使用 CO_2 將小鼠安樂死，且經由心臟穿刺收集最終血液樣本以分析暴露量。運行另外的 PK 小組，其中每個劑量組為三隻小鼠，總共 15 隻小鼠。

【0233】 DIO 小鼠的 FP2 暴露反應(E-R)分析

【0234】 在獲得藥物動力學(PK)樣本時的最後一個研究日，藥效學(PD)(療效）小組中的大多數動物不具可檢測出的藥物濃度，這可能歸因於免疫原性。因此，採用 PK 小組的平均 PK 曲線（而不是 PD 小組的個別 PK）來實施在對應劑量水平下，PD 小組自基線之重量變化%的暴露反應（各別自第 3、6、及 9 天起）。此方法假定，PK 小組在藥物暴露方面的表現與 PD 小組類似。

【0235】 使用 E_{max} 模型（GraphPad Prism 6，對數(促效劑)相對於反應）來建立暴露與反應數據的相關性（對數轉換藥物濃度）。Hill Slope（最大斜度）設定為 1。應注意的是，在第 3、6、及 9 天之中模型擬合的 EC_{10} 至 EC_{50} 值係在二倍之內，儘管 E_{max} 估計值有所不同（各別 E_{max} =-4.26%、-8.18%、及-9.85%）。在第 9 天，有些動物亦顯示出藥物暴露喪失，其歸因於潛在 ADA 形成，因此根據第 9 天數據的 E-R 參數估計值應謹慎判讀。

【0236】 在膳食誘發肥胖的雄性 C57Bl/6 小鼠中，已評估二週 FP2 暴露對於攝食量、體重、葡萄糖恆定、及肝臟脂肪含量的效果。在研究的 PK 小組（n = 2 或 3）中，在第 9 天前的谷值暴露量在 0.3 nmol/kg 治療組中維持於 1.7 與 3.3 nM FP2 之間，在 1.0 nmol/kg 治療組中維持於 7.1 與 14 nM 之間，在 3.0 nmol/kg 治療組中維持於 20.8 與 41.6 nM 之間，且在 10 nmol/kg 治療組中維持於 28.5 與 112.9 nM FP2 之間（表 49）。在第 9 天後，大部分動物即使持續接受 q3d 給藥，仍觀察到循環水平降低（表 49）。與此種加快清除現象一致的是，研究中 PD 小組的大部分動物在第 15 天時未達到可檢測出的 FP2 循環水平（表 50）。

【0237】 相較於媒劑處理，DIO 小鼠用 FP2 q3d 治療會減少攝食量（表 38）、體重（表 39、40，以及圖 20）、及餐後血糖（表 43 及圖 23）。在 0.3 nmol/kg 組的第 2 天、第 5 天、及第 8 天，1.0 nmol/kg 組的第 1 天至第 7 天，3.0 nmol/kg 組的第 1 天、第 2 天、第 4 天至第 6 天、及第 8 天，及 10.0 nmol/kg 組的第 1 天、第 3 天至第 6 天、第 8 天、及第 9 天，出現攝食量顯著減少情形。0.3 nmol/kg 組的第 5 天至第 13 天、1.0 nmol/kg 與 10.0 nmol/kg 組的第 3 天至第 13 天、及 3.0 nmol/kg 組的第 4 天至第 13 天，具顯著的體重變化百分比。0.3 nmol/kg 組自第 8 天起，1.0 nmol/kg 自第 6 天起，3.0 nmol/kg 自第 7 天起，及 10.0 nmol/kg 組自第 5 天起，具有顯著的體重克數變化。3.0 nmol/kg 劑量水平下的動物在第 7 天，以及 3.0 與 10.0 nmol/kg 劑量水平下的動物在第 13 天，其餐後血糖水平顯著降低。

【0238】 相較於媒劑處理，在口服葡萄糖挑激期間，用 FP2 q3d 治療的 DIO 小鼠在第 14 天具有改善的葡萄糖耐受性（表 41；圖 21A 及 21B）。0.3 nmol/kg 組在 30 分鐘時，1.0 nmol/kg 組在 60 分鐘及 120 分鐘時，3.0 nmol/kg 組在 120 分鐘時，及 10.0 nmol/kg 組在 30、90、及 120 分鐘時，具有顯著較低的葡萄糖。所有劑量組皆有顯著的總曲線下面積。0.3 及 10.0 nmol/kg 組的葡萄糖挑激期間胰島素水平在 30 分鐘時顯著較低（表 42；圖 22A 及 22B）。此外，相較於媒劑處理動物，DIO 小鼠在經過 10.0 nmol/kg 劑量下 FP2 q3d 治療 14 天後的所計算空腹 HOMA-IR 有顯著減少，此表示胰島素敏感性有所改善（表 44 及圖 24）。

【0239】 在研究開始前的第-1 天，以及第 13 天，利用 MRI 測量體組成（表 47 及表 48）。在 1.0 nmol/kg 下與在 10.0 nmol/kg 下經過 FP2 治療的 DIO 小鼠，其等在第 13 天時的脂肪質量顯著降低；而並未有任何治療組發生瘦肉質量變化。在第 13 天，10.0 nmol/kg 治療組在相較於媒劑處理組下，其瘦肉質量百分比顯著增加，且其脂肪質量百分比顯著減少。在第-1 天至第 13 天，0.3 nmol/kg、1.0 nmol/kg、及 10.0 nmol/kg 治療組具有顯著的瘦肉質量變化，且 1.0、3.0、及 10.0 nmol/kg 治療組具有顯著的瘦肉質量百分比變化。所有治療組在相較於媒劑下，皆在第-1 天至第 13 天有顯著的脂肪質量變化與瘦肉質量百分比變化。

【0240】 媒劑處理動物與 15 天 FP2 q3d 治療小鼠之間，沒有顯著的內源性小鼠 GDF15 血清水平差異（表 46）。

【0241】 結論：結果意味著，在第 3、6、及 9 天，跨及所研究劑量組的群體水平，愈高的藥物暴露量，通常與愈大的自基線的重量變化%有關聯。

【0242】 DIO 小鼠於二周期間暴露於 FP2，導致攝食量減少、體重減輕、血糖降低、葡萄糖耐受性改善、及胰島素敏感性。在 1.0、3.0、及 10.0 nmol/kg q3d 下，經過多天的攝食量可達到顯著減少。研究開始之後三至五天，體重開始顯著減輕。FP2 在 3.0 與 10.0 nmol/kg 下進行 q3d 投予後，第 13 天的餐後血糖顯著

降低。經過 10.0 nmol/kg 下 FP2 q3d 投予後 14 天，達到顯著降低的空腹 HOMA-IR 所表示的胰島素敏感性。在第 13 天，經過 10.0 nmol/kg 下 FP2 q3d 治療的 DIO 小鼠中，已觀察到瘦肉質量百分比顯著增加且脂肪質量顯著減少。

【0243】**表 38**：FP2 對於 13 天治療期間的每日攝食量(g)之效果。

處理	**媒劑**	**FP2 (nmol/kg)**				**羅格列酮**
日	**N/A**	**0.3**	**1.0**	**3.0**	**10.0**	**10 mpk/天**
0	2.0±0.1	1.9±0.1	2.2±0.2	1.9±0.2	1.9±0.2	2.2±0.1
1	2.4±0.2	2.1±0.1	1.6±0.1 *	1.5±0.1 *	1.3±0.1*	2.7±0.1
2	2.5±0.1	1.8±0.1*	1.7±0.2 *	1.9±0.1 *	2.0±0.1	3.0±0.2
3	2.5±0.1	2.1±0.1	1.7±0.1 *	1.9±0.1	1.8±0.1*	2.8±0.2
4	2.6±0.1	2.0±0.1	1.8±0.1 *	1.9±0.1 *	1.9±0.1*	2.9±0.2
5	2.8±0.1	2.1±0.2*	2.2±0.1 *	2.2±0.0 *	1.9±0.1*	2.7±0.2
6	2.8±0.1	2.3±0.2	2.1±0.1 *	2.2±0.1 *	2.0±0.1*	2.8±0.2
7	2.6±0.2	2.3±0.1	2.0±0.1 *	2.0±0.2	2.1±0.1	2.9±0.2
8	2.7±0.2	2.1±0.1*	2.2±0.1	2.0±0.1 *	2.0±0.1*	3.1±0.2

9	2.8±0.1	2.3±0.1	2.3±0.2	2.3±0.2^	2.1±0.2*	3.2±0.1
10	2.6±0.1	2.5±0.1	2.4±0.2	2.3±0.2^	2.1±0.2	3.0±0.2
11	2.9±0.1	2.5±0.1	2.8±0.2	2.6±0.4	2.6±0.1	3.3±0.1
12	2.8±0.1	2.7±0.2	2.8±0.1	2.8±0.2	2.9±0.1	3.1±0.2
13	2.7±0.1	2.5±0.2	2.6±0.1	2.6±0.1	2.2±0.1	3.1±0.2

數值代表每組每時間點 8 隻動物的數據之平均值±SEM，但例外的是以^表示時為 n=7。

*- p<0.05，與媒劑比較。

所採用的統計分析：二因子 ANOVA RM、杜凱多重比較檢定

【0244】**表 39：**FP2 對於 13 天治療期間的體重變化百分比之效果

處理	**媒劑**	**FP2 (nmol/kg)**				**羅格列酮**
日	**N/A**	**0.3**	**1.0**	**3.0**	**10.0**	**10 mpk/天**
-1	-0.1±0.4	0.5±0.2	-0.1±0.1	-0.4±0.2	0.0±0.6	0.1±0.2
0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
1	-0.4±0.5	-1.0±0.3	-2.2±0.4	-1.8±0.6	-2.4±0.5	1.3±0.4
2	-0.4±0.3	-2.2±0.4	-3.4±0.6	-3.0±0.6	-3.1±0.4	1.3±0.5
3	-0.3±0.4	-2.3±0.4	-4.2±0.6*	-3.5±0.6	-4.3±0.5*	1.9±0.5
4	-0.3±0.5	-2.9±0.5	-5.3±0.6*	-4.9±0.7*	-5.8±0.7*	1.8±0.7
5	-0.2±0.4	-4.2±0.7*	-6.2±0.6*	-5.6±0.7*	-6.8±0.7*	1.7±0.8
6	-0.4±0.6	-5.1±0.7*	-7.4±0.8*	-6.9±0.7*	-8.5±0.9*	1.1±0.9
7	0.2±0.8	-5.1±0.7	-7.7±0.9*	-7.4±0.7*	-8.7±0.9*	2.0±1.0

		*				
8	0.2±1.0	-6.1±0.8 *	-7.9±0.9*	-8.0±0.8*	-9.7±0.8*	2.4±1.1
9	0.5±1.1	-6.0±0.9 *	-8.4±0.9*	-8.8±0.9*	-10.1±1.0*	3.1±1.0
10	1.1±1.2	-5.7±0.8 *	-8.1±0.9*	-8.9±0.9*	-10.7±1.2*	3.5±1.2
11	1.2±1.3	-6.1±0.9 *	-8.2±0.8*	-8.6±1.3*	-11.1±1.4*	3.7±1.2
12	1.4±1.3	-6.3±1.2 *	-7.7±0.8*	-8.2±1.4*	-10.9±1.4*	4.1±1.3
13	1.7±0.9	-5.8±1.4 *	-7.1±1.0*	-7.2±1.4*	-10.9±1.4*	4.7±1.3

數值代表取自每組每時間點 8 隻動物的數據之平均值±SEM。

*p<0.05，與媒劑比較。

所採用的統計分析：二因子 ANOVA RM、杜凱多重比較檢定

【0245】**表 40**：FP2 對於 13 天治療期間體重變化(g)之效果

處理	**媒劑**	**FP2 (nmol/kg)**				**羅格列酮**
日	**N/A**	**0.3**	**1.0**	**3.0**	**10.0**	**10 mpk/天**
-1	44.6±0.6	44.5±0.6	44.5±0.6	44.5±0.6	44.5±0.6	44.5±0.6
0	44.6±0.6	44.3±0.6	44.6±0.6	44.7±0.6	44.6±0.7	44.4±0.6
1	44.5±0.7	43.8±0.6	43.6±0.6	43.9±0.7	43.5±0.7	45.0±0.7

2	44.5±0.7	43.3±0.7	43.1±0.6	43.3±0.7	43.2±0.7	45.0±0.7
3	44.5±0.7	43.2±0.7	42.7±0.6	43.1±0.7	42.6±0.6	45.3±0.7
4	44.5±0.7	43.0±0.7	42.2±0.6	42.5±0.7	42.0±0.7	45.2±0.7
5	44.5±0.7	42.4±0.7	41.8±0.5	42.2±0.7	41.5±0.6*	45.2±0.7
6	44.5±0.7	42.0±0.7	41.3±0.6*	41.6±0.7	40.7±0.5*	44.9±0.8
7	44.7±0.7	42.0±0.7	41.1±0.6*	41.4±0.7*	40.6±0.5*	45.3±0.8
8	44.7±0.7	41.6±0.7*	41.1±0.7*	41.1±0.7*	40.2±0.6*	45.5±0.8
9	44.8±0.7	41.6±0.8*	40.8±0.7*	40.8±0.8*	40.0±0.8*	45.8±0.7
10	45.1±0.7	41.8±0.8*	41.0±0.8*	40.8±0.8*	39.8±0.8*	46.0±0.8
11	45.2±0.8	41.6±0.8*	40.9±0.7*	40.8±0.9*	39.6±0.9*	46.1±0.8
12	45.3±0.7	41.5±0.9*	41.2±0.7*	41.0±0.9*	39.7±0.9*	46.3±0.9
13	45.4±0.7	41.7±0.9*	41.4±0.8*	41.5±0.9*	39.7±0.9*	46.5±0.9

數值代表取自每組每時間點 8 隻動物的數據之平均值±SEM。

*- $p<0.05$，與媒劑比較。

統計分析：二因子 ANOVA RM、杜凱多重比較檢定

【0246】 **表 41**：FP2 對於 14 天治療後 OGTT 期間血糖(mg/dL)水平之效果

劑量	**劑量 (nmol/kg)**	**葡萄糖挑激後的時間(min)**					**總 AUC (mg/dL/120min)**	**Δ AUC (mg/dL/120min)**
		0	**30**	**60**	**90**	**120**		

媒劑	NA	161±10	225±17	228±14	208±18	213±19	25429±1228	6094±1430
FP2	0.3	144±4	163±14*	209±11	180±12	171±7	21270±399*	3985±521
	1.0	151±9	179±18	188±7	179±13	163±8*	21096±754*	2972±907
	3.0	149±8	180±18	179±11*	164±6	163±9*	20338±876*	2426±1058
	10.0	134±6	163±7*	190±13	152±7*	163±8*	19599±614*	3539±1198
羅格列酮	10 mpk/天	132±9	152±10*	162±13*	138±9*	159±9*	17904±632*	2139±1179

數值代表取自每組每時間點 8 隻動物的數據之平均值±SEM。

*- $p<0.05$，與媒劑比較。

統計分析：二因子 ANOVA RM、杜凱多重比較檢定，用於葡萄糖值；

單因子 ANOVA、杜凱多重比較檢定，用於 AUC

【0247】**表 42：**FP2 對於 14 天治療後 OGTT 期間胰島素(ng/mL)水平之效果

處理	劑量	葡萄糖挑激後的時間(min)			總 AUC (ng/mL/90min)
		0	30	90	

	(nmol/kg)				
媒劑	NA	4.2±0.7	12.2±2.3	3.6±0.5	716.1±122.0
FP2	0.3	2.9±0.6	5.8±1.8*	2.4±0.4	377.1±97.3
	1.0	2.9±0.4	8.2±2.6	2.6±0.4	491.8±118.2
	3.0	3.0±0.3	8.4±1.5	2.5±0.3	498.6±77.0
	10.0	2.4±0.4	4.3±0.5*	2.1±0.4	295.5±32.0*
羅格列酮	10 mpk/天	0.9±0.1	1.8±0.2*	0.8±0.1	118.5±9.6*

數值代表取自每組每時間點 8 隻動物的數據之平均值±SEM。

*- p<0.05，與媒劑比較。

統計分析：二因子 ANOVA RM、杜凱多重比較檢定，用於胰島素值；

單因子 ANOVA、杜凱多重比較檢定，用於 AUC

【0248】 **表 43：**FP2 對於餐後血糖(mg/dL)水平之效果

處理	**劑量 (nmol/kg)**	**治療開始後時間（天數）**		
		0	**7**	**13**
媒劑	NA	162±5	159±6	180±9
FP2	0.3	143±5	150±9	168±9
	1.0	153±12	135±7	159±7
	3.0	148±3	127±6*	151±8*
	10.0	146±6	136±4	148±3*
羅格列酮	10 mpk/天	137±7	117±4*	134±6*

數值代表取自每組每時間點 8 隻動物的數據之平均值±SEM。

*- p<0.05，與媒劑比較。

統計分析：二因子 ANOVA RM、杜凱多重比較檢定

【0249】表 44：DIO 小鼠在經過 FP2 q3d 治療 14 天後的空腹 HOMA-IR

處理	劑量(nmol/kg)	HOMA-IR
媒劑	NA	48.7±9.2
FP2	0.1	30.1±6.6
	1.0	30.5±3.8
	3.0	31.3±3.2
	10.0	22.7±3.1*
羅格列酮	10 mpk/天	8.7±1.0*

數值代表取自每組每時間點 8 隻動物的數據之平均值±SEM。

*- p<0.05，與媒劑比較。

統計分析：單因子 ANOVA、杜凱多重比較檢定

【0250】表 45：DIO 小鼠經過 FP2 q3d 治療 15 天後的肝臟重量

處理	劑量(nmol/kg)	肝臟重量(g)	肝臟重量（身體的%）
媒劑	NA	1.9±0.1	4.3±0.3
FP2	0.1	1.7±0.1	4.0±0.1
	1.0	1.7±0.0	4.2±0.1
	3.0	1.8±0.1	4.2±0.1
	10.0	1.7±0.1	4.2±0.1
羅格列酮	10 mpk/天	1.9±0.1	4.1±0.2

數值代表取自每組每時間點 8 隻動物的數據之平均值±SEM。

*- p<0.05，與媒劑比較。

統計分析：單因子 ANOVA、杜凱多重比較檢定

【0251】**表 46**：DIO 小鼠經過 FP2 q3d 治療 15 天後的血清小鼠 GDF15 (pg/mL)水平

處理	**劑量(nmol/kg)**	**mGDF15**
媒劑	NA	258.3±21.4
FP2	0.1	214.1±10.3
	1.0	191.6±12.7
	3.0	254.5±28.6
	10.0	202.0±10.0
羅格列酮	10 mpk/天	509.6±26.2*

數值代表取自每組每時間點 8 隻動物的數據之平均值±SEM。

*- p<0.05，與媒劑比較。

統計分析：單因子 ANOVA、杜凱多重比較檢定

【0252】**表 47**：MRI 所測量的 JNJ-64739090 q3d 對於 DIO 小鼠體組成(g)的效果

處理	**劑量 (nmol / kg)**	**脂肪(g) 第-1 天**	**脂肪(g)第 13 天**	**Δ脂肪 (g)**	**瘦肉(g) 第-1 天**	**瘦肉(g) 第 13 天**	**Δ瘦肉(g)**

媒劑	NA	17.4±0.6	18.2±0.6	0.9±0.3	25.4±0.3	25.1±0.3	-0.4±0.2
FP2	0.3	17.0±0.6	15.2±0.8	-1.9±0.6*	25.8±0.7	24.5±0.5	-1.2±0.2*
	1.0	17.0±0.6	14.9±0.6*	-2.1±0.4*	25.8±0.5	24.6±0.4	-1.2±0.2*
	3.0	17.4±0.7	15.1±1.1	-2.3±0.5*	25.3±0.4	24.2±0.4	-1.1±0.1
	10.0	16.7±0.6	13.2±0.8*	-3.6±0.5*	26.1±0.6	24.5±0.6	-1.7±0.2*
羅格列酮	10 mpk/天	17.2±0.6	19.1±0.5	1.9±0.6	25.5±0.7	25.1±0.6	-0.4±0.2

數值代表取自每組每時間點 8 隻動物的數據之平均值±SEM。

*p<0.05，與媒劑比較。

統計分析：單因子 ANOVA、杜凱多重比較檢定

【0253】**表 48**：MRI 所測量的 FP2 q3d 對於 DIO 小鼠體組成(%)的效果

處理	**劑量 (nmol/kg)**	**脂肪(%)第-1天**	**脂肪(%)第 13 天**	**Δ脂肪(%)**	**瘦肉(%)第-1天**	**瘦肉(%)第 13 天**	**Δ瘦肉(%)**
媒劑	NA	38.1±1.0	40.1±1.0	2.1±0.3	55.9±0.9	55.3±0.9	-0.6±0.3

FP2	0.3	37.6±1.2	36.3±1.3	-1.3±0.9*	56.8±1.3	59.0±1.4	2.2±0.8
	1.0	37.2±1.1	35.8±0.9	-1.4±0.5*	56.7±1.1	59.5±1.0	2.8±0.6*
	3.0	38.3±1.4	36.1±2.0	-2.3±0.7*	55.9±1.2	58.7±2.0	2.8±0.8*
	10.0	36.9±1.1	33.1±1.5*	-3.8±0.8*	57.5±1.0	61.7±1.4*	4.2±0.7*
羅格列酮	10 mpk/天	38.0±1.2	41.1±0.9	3.1±0.9	56.2±1.2	53.9±0.8	-2.3±0.8

數值代表取自每組每時間點 8 隻動物的數據之平均值±SEM。

*p<0.05，與媒劑比較。

統計分析：單因子 ANOVA、杜凱多重比較檢定

【0254】 **表 49**：DIO 小鼠進行 q3d 治療期間 PK 小組的 FP2 血清暴露量(nM)

		初始給藥後時間（上次給藥後時間）						
治療組	**對象 ID**	**第 3 天**	**第 6 天**	**第 9 天**	**第 12 天**	**第 14 天 (48hr)**	**第 15 天 (72hr)**	**第 17 天 (120hr)**
0.1 nmol/	9	1.930	2.993	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
	10	1.853	3.369	2.817	< LOQ	< LOQ	< LOQ	< LOQ

kg	11	1.715	2.637	2.568	2.709	3.441	1.313	< LOQ
1.0	9	8.198	9.660	9.645	< LOQ	< LOQ	< LOQ	< LOQ
nmol/	10	7.073	10.595	8.966	< LOQ	< LOQ	< LOQ	< LOQ
kg	11	6.689	13.967	10.802	< LOQ	< LOQ	< LOQ	< LOQ
3.0	9	20.802	26.329	27.863	< LOQ	< LOQ	< LOQ	< LOQ
nmol/	10	23.563	32.020	41.576	1.168	< LOQ	< LOQ	< LOQ
kg	11	21.704	30.101	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
10.0	9	28.495	33.050	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
nmol/	10	70.779	112.898	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
kg	11	70.404	111.767	55.117	< LOQ	< LOQ	< LOQ	< LOQ

數據以各隻動物的濃度表示。

< LOQ =低於定量限值；LOQ 係 0.494 nM。

**第 Day 3、6、9、及 12 的數值係緊接在下次給藥前。

【0255】**表 50**：DIO 小鼠經過 15 天 q3d 治療後的最終血清暴露量(nM)

	治療組(nmol/kg)			
動物 ID	**0.1**	**1.0**	**3.0**	**10.0**
1	2.567	< LOQ	< LOQ	< LOQ
2	< LOQ	< LOQ	< LOQ	44.149
3	< LOQ	< LOQ	< LOQ	< LOQ

4	1.144	0.678	< LOQ	< LOQ
5	< LOQ	< LOQ	< LOQ	< LOQ
6	3.440	< LOQ	< LOQ	< LOQ
7	2.727	< LOQ	< LOQ	< LOQ
8	< LOQ	< LOQ	< LOQ	< LOQ

數據以各隻動物的濃度表示。

< LOQ =低於定量限值；LOQ 係 0.494 nM。

實例 18：FP2 之多物種的藥物動力學及免疫反應

【0256】 小鼠的藥物動力學

【0257】 FP2 在經皮下投予至雌性 C57Bl/6 小鼠時，評估其藥物動力學特性。在於 PBS（pH 7.3 至 7.5）中 2.0 mg/kg 的劑量水平下，將 FP2 分別以皮下（n =每個時間點 5 個樣本）與靜脈內（n =每個時間點 5 個樣本）投予至雌性 C57Bl/6 小鼠(Sage Laboratories, St Louis, MO)。在最後時間點的樣本收集是經由最終出血程序。收集血液樣本，將血清加以處理，並長達 168 小時測量藥物濃度。使用免疫檢定方法，測量 FP2 水平。血漿中的藥物濃度曲線數據總結於表 51 及 52，且描繪於圖 25。

【0258】 在 C57Bl/6 小鼠中的 FP2 之藥物動力學分析展示，經過 IV 與 SC 給藥後的終末半衰期各別係~1.51 及~1.76 天，且在經過 SC 投予之後的平均生物利用率係~61%。

【0259】 **表 51**：C57Bl/6 小鼠經過單次皮下(SC)給藥之後的血清 FP2 濃度 (ng/mL)

FP2 - SC 給藥

時間點	動物 31 結果 (ng/mL)	動物 32 結果 (ng/mL)	動物 33 結果 (ng/mL)	動物 35 結果 (ng/mL)	動物 36 結果 (ng/mL)	平均結果 (nM)	標準偏差 (ng/mL)
4 hr	11310.11	6323.44	23489.21	4357.74	4835.54	10063.21	7995.0
24 hr	12378.58	10896.80	17769.03	15928.14	15404.08	14475.33	2785.0
72 hr	5127.95	5569.27	6727.37	7909.66	7550.32	6576.91	1210.5
96 hr	3059.83	3350.25	4042.04	4095.15	4431.94	3795.84	569.0
168 hr	784.61	1202.66	1364.68	1557.60	1678.02	1317.51	348.9

【0260】 表 52：C57Bl/6 小鼠經過單次靜脈內(IV)給藥之後的血清 FP2 濃度(ng/mL)。

	FP2 - IV 給藥						
時間點	動物 37 結果 (ng/mL)	動物 40 結果 (ng/mL)	動物 41 結果 (ng/mL)	動物 45 結果 (ng/mL)	動物 48 結果 (ng/mL)	平均結果 (nM)	標準偏差 (ng/mL)
1 hr	49573.59	42382.59	40001.18	43085.75	46443.59	44297.34	3742.9
24 hr	22173.85	19120.39	19393.78	19798.29	17459.96	19589.25	1696.7
72 hr	8334.33	7989.10	8573.44	9086.37	8186.68	8433.98	422.5
96 hr	4478.83	4699.80	4749.93	5331.39	4579.08	4767.81	332.3
168 hr	1044.24	1419.64	1393.44	1835.63	979.49	1334.49	343.6

【0261】 **表 53**：C57Bl/6 小鼠經過 2 mg/kg IV 與 2 mg/kg SC 投予之後的 FP2 藥物動力學參數。

途徑		$t_{1/2}$ (天)	CL 或 CL/F	Vz 或 Vz/F	C 最大值 (ng/m	T 最大值 *	$AUC_{0-最後}$ (天*	$AUC_{0-無限}$ (天*

			（ml/天/kg）	(ml/kg)	l)	(天)	ng/ml)	ng/ml)
SC	平均值	1.76	43	108	15619	1	44972	48379
	SD	0.16	8	20	4870		8563	9147
IV	平均值	1.51	25	55	44297	0.042	76269	79253
	SD	0.18	1	6	3743		3788	4051

【0262】 大鼠的藥物動力學

【0263】 在於 PBS（pH 7.3 至 7.5）中的 2.0 mg/kg 劑量水平下，將 FP2 分別以皮下（n =每個時間點 5 個樣本）與靜脈內（n =每個時間點 5 個樣本）投予至雌性 SD 大鼠(Sage Laboratories, St. Louis, MO)。在最後時間點的樣本收集是經由最終出血程序。收集血液樣本，將血清加以處理，並長達 168 小時測量藥物濃度。使用免疫檢定方法，測量 FP2 水平。血漿中的藥物濃度曲線數據總結於表 54 及 55，且描繪於圖 26。自此等數據計算的藥物動力學參數總結於表 56。

【0264】 在 SD 大鼠中的 FP2 之藥物動力學分析展示，經過 IV 與 SC 給藥後的終末半衰期各別係~1.46 及~1.37 天，且在經過 SC 投予之後的平均生物利用率係~28%。

【0265】 **表 54：**SD 大鼠經過單次皮下(SC)給藥之後的血清 FP2 濃度 (ng/mL)。

	FP2 - SC 給藥						
時間點	**動物 01 結果**	**動物 02 結果**	**動物 03 結果**	**動物 04 結果**	**動物 05 結果**	**平均結果**	**標準偏差**

	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml)	(ng/ml)
4 hr	730.95	257.94	469.95	496.34	400.65	471.16	172.2
24 hr	9236.27	6658.79	7728.92	7449.56	6502.60	7515.23	1092.1
72 hr	4559.04	4464.72	5619.82	4287.25	3844.15	4555.00	655.6
96 hr	2791.97	2452.35	3387.55	2316.06	2176.00	2624.79	483.8
168 hr	622.32	606.36	< 80.00	514.19	476.49	554.84	70.7

【0266】 **表 55**：SD 大鼠經過單次靜脈內(IV)給藥之後的血清 FP2 濃度 (ng/mL)。

	FP2 - IV 給藥						
時間點	**動物 06 結果 (ng/ml)**	**動物 07 結果 (ng/ml)**	**動物 08 結果 (ng/ml)**	**動物 09 結果 (ng/ml)**	**動物 10 結果 (ng/ml)**	**平均結果 (ng/ml)**	**標準偏差 (ng/ml)**
1 hr	60785.80	47392.80	43046.54	46014.25	44547.65	48357.41	7134.5
24 hr	25470.36	24729.88	21157.29	20497.32	21459.71	22662.91	2267.1
72 hr	8208.46	9262.13	8866.76	8635.93	8843.83	8763.42	384.1
96 hr	4433.18	4833.22	4995.63	4630.60	4604.13	4699.35	218.1
168 hr	1083.14	1469.35	1614.61	1394.17	1053.89	1323.03	245.7

【0267】 **表 56**：SD 大鼠經過 2 mg/kg IV 與 2 mg/kg SC 投予之後的 FP2 藥物動力學參數。

途徑		**$t_{1/2}$ (天)**	**CL 或 CL/F (ml/天/kg)**	**Vz 或 Vz/F (ml/kg)**	**C 最大值 (ng/ml)**	**T 最大值 * (天)**	**$AUC_{0-最後}$ (天* ng/ml)**	**$AUC_{0-無限}$ (天* ng/ml)**

SC	平均值	1.37	84	165	7515	1	22614	24036
	SD	0.04	10	17	1092		2509	2893
IV	平均值	1.46	23	49	48357	0.042	83271	86089
	SD	0.12	2	6	7135		6081	5820

【0268】 猴子的藥物動力學

【0269】 各組三隻雄性石蟹獼猴，係各別在 1 mg/kg 下經皮下投予與在 1 mg/kg 下經靜脈內投予於 PBS（pH 7.0 至 7.6）中的 FP2。收集血液樣本，將血漿加以處理，並長達 21 天測量藥物濃度。

【0270】 石蟹獼猴經過單次劑量的 IV (1.0 mg/kg)與 SC (1.0 mg/kg)投予後，將 FP2 的藥物動力學(PK)加以表徵。血漿藥物濃度-時間曲線，其在 SC 投予後的免疫檢定及 LCMS 分析之數據各別總結於表 57 及 58，而其在 IV 投予後的免疫檢定及 LCMS 分析數據總結於表 59 及 60。免疫檢定數據以圖形表示於圖 27 中，且 LCMS 數據表示於圖 28 中。

【0271】 使用自免疫檢定得到的結果時，FP2 經過 IV 與 SC 給藥後平均的根據 NCA 之終末半衰期(t1/2)各別係~7.05 與~8.51 天。IV 與 SC 投予後的平均 PK 參數總結於表 61。使用免疫檢定的生物分析結果時，FP2 經過 IV 與 SC 給藥後平均的非房室模型估計之終末半衰期(t1/2)各別係 7.05 與 8.51 天。石蟹獼猴經過 SC 投予後，FP2 之平均生物利用率(F%)在根據 $AUC_{0\text{-最後}}$ 時的估計值係~98.5%，且在根據 $AUC_{0\text{-無限}}$ 時的估計值係~109.2%。

【0272】 **表 57**：石蟹獼猴經過單次 SC 給藥之後藉由免疫檢定測得的血漿 FP2 濃度(ng/mL)。

時間(hr)	免疫檢定				
	動物 704	動物 705	動物 706	SC 平均值	標準偏差
0	< 80.0	< 80.0	< 80.0	< 80.0	N/A
6	7365.3	6128.5	6056.9	6516.9	735.6
24	19716.8	10903.8	10554.7	13725.1	5191.9
48	18191.7	14353.7	14464.7	15670.0	2184.5
72	17813.9	14207.5	12684.0	14901.8	2634.5
120	13823.9	11445.8	10590.8	11953.5	1675.3
168	12359.6	10103.8	9467.8	10643.8	1519.7
240	9457.9	7642.6	8109.1	8403.2	942.7
336	6796.8	5679.8	5235.7	5904.1	804.3
432	5581.3	3830.6	3746.5	4386.1	1035.9
528	4126.2	2613.4	2879.3	3206.3	807.7

N/A =不適用

【0273】 **表58:**石蟹獼猴經過單次SC給藥之後藉由LCMS測得的血漿FP2濃度(ng/mL)。

時間(hr)	LC/MS				
	動物 704	動物 705	動物 706	SC 平均值	SEM
0	< 1000	< 1000	< 1000	< 1000	N/A
6	6110.0	5910	6200.0	6073.3	85.7
24	#	10420.0	11300.0	10860.0	359.3
48	16560.0	13510.0	14960.0	15010.0	880.8

72	13690.0	13450.0	13380.0	13506.7	93.9
120	11040.0	#	#	11040.0	N/A
168	#	8680.0	9400.0	9040.0	293.9
240	6940.0	7070.0	7140.0	7050.0	58.6
336	4400.0	4580.0	4430.0	4470.0	55.7
432	-	2910.0	-	2910.0	N/A
528	< 1000	< 1000	< 1000	< 1000	N/A

- =最初執行失敗，無足夠樣本供重複分析

=試管標示錯誤，樣本排除在分析之外

N/A =不適用

【0274】**表 59：**石蟹獼猴經過單次 IV 給藥之後藉由免疫檢定測得的血漿 FP2 濃度(ng/mL)。

時間(hr)	**免疫檢定**				
	動物 701	**動物 702**	**動物 703**	**IV 平均值**	**標準偏差**
0	< 80.0	< 80.0	< 80.0	< 80.0	N/A
1	29938.3	31139.0	23545.3	28207.6	4082.0
6	24711.9	21173.0	20434.4	22106.4	2286.5
24	19648.4	21420.9	8662.7	16577.3	6911.3
48	17790.1	17107.0	12983.1	15960.0	2600.7
72	17889.4	13871.1	13692.4	15151.0	2373.3
120	15298.6	11982.5	11361.5	12880.9	2116.7
168	11752.0	10982.8	9933.8	10889.5	912.7

240	8921.1	7465.0	6733.4	7706.5	1113.6
336	6572.8	5750.5	4687.6	5670.3	945.1
432	1099.6	3425.0	3458.0	2660.9	1352.2
528	< 80.0	2069.0	2416.2	2242.6	N/A

N/A =不適用

【0275】 **表 60**：:石蟹獼猴經過單次 IV 給藥之後藉由 LCMS 測得的血漿 FP2 濃度(ng/mL)

	LC/MS				
時間(hr)	**動物 701**	**動物 702**	**動物 703**	**IV 平均值**	**SEM**
0	< 1000	< 1000	< 1000	< 1000	N/A
1	25340.0	28820	26220.0	26793.3	1044.7
6	24610.0	26340.0	23810.0	24920.0	746.6
24	18410.0	18680.0	9810.0	15633.3	2912.7
48	16290.0	17370.0	13840.0	15833.3	1044.3
72	15430.0	14920.0	14280.0	14876.7	332.7
120	11180.0	11480.0	11440.0	11366.7	94.0
168	9170.0	#	#	9170.0	N/A
240	6800.0	7380.0	7600.0	7260.0	238.6
336	2870.0	3860.0	3480.0	3403.3	288.3
432	-	-	3030.0	3030.0	N/A
528	1150.0	1680.0	1400.0	1410.0	153.1

- =最初執行失敗，無足夠樣本供重複分析

N/A =不適用

=試管標示錯誤，樣本排除在分析之外

【0276】**表 61**：石蟹獼猴經過 1 mg/kg IV 與 SC 投予之後的 FP2 藥物動力學參數平均值(± SD)。

途徑		$t_{1/2}$ (天)	CL 或 CL/F（ml/天/kg）	Vz 或 Vz/F (ml/kg)	$C_{最大值}$ (ng/ml)	$T_{最大值}$* (天)	$AUC_{0-最後}$（天*ng/ml）	$AUC_{0-無限}$（天*ng/ml）
SC	平均值	8.51	4.6	56	16178	1.67	180792	221032
	SD	1.28	0.8	7	3065		29990	44931
IV	平均值	7.05	4.9	51	28208	0.042	183468	202380
	SD	1.45	0.2	12	4082		18268	9617

PK 參數係基於免疫檢定 PK 資料的 NCA 之平均值。

*$T_{最大值}$（中位數）

【0277】人類血漿穩定性分析

【0278】在 37℃下，持續長達 48 小時，檢查 FP2 在新鮮肝素抗凝血漿中的離體穩定性。將取自二名對象（一名男性與一名女性）的肝素抗凝血液，藉由離心方式產生新鮮的非冷凍人類血漿。在 37℃下將 FP2 培養於此基質中，同時輕輕混合，如此持續 0、4、24、及 48 小時。使用免疫檢定方法，測定 FP2 濃

度。採用獨立的免疫親和性捕捉法，以及隨後的 LCMS 方法，在分析條件下定量此基質中存在的完整二聚體之濃度。

【0279】 採用免疫檢定方法時，佔開始濃度的回復百分比係自 104.8 至 94.1 之範圍，且並未隨時間降低，其證實了 FP2 在人類血漿中持續長達 48 小時具有離體穩定性（圖 29 與表 62）。LCMS 方法顯示，濃度隨時間經過呈穩定狀態，其證實了 JNJ-64739090 在離體人類血漿中長達 48 小時保持完整二聚體（圖 30 與表 63）。

【0280】 **表 62：**由免疫檢定測得的人類血漿中 FP2 (ng/ml)在 48 小時內的離體穩定性（標準化回復百分比）。

化合物	性別	時間(hr)	濃度(ng/mL)	標準化回復%
FP2	女性	0	9104	100.0
		4	9056	99.5
		24	9332	102.5
		48	9374	103.0
	男性	0	9473	100.0
		4	9929	104.8
		24	9081	95.9
		48	8912	94.1

【0281】 **表 63：**由完整 LC/MS 測得的人類血漿中 FP2 (ng/ml)在 48 小時內的離體穩定性（標準化回復百分比）。

化合物	性別	時間(hr)	濃度(ng/mL)	標準化回復%
FP2	女性	0	11090	100.0
		4	10830	97.7

		24	10500	94.7
		48	10030	90.4
	男性	0	10760	100.0
		4	9640	89.6
		24	10190	94.7
		48	8500	79.0

【0282】 **實例 19：FP1 與 FP2 在石蟹獼猴中的療效**

【0283】 在原態石蟹獼猴中，評估單次給藥後 FP1 與 FP2 對其攝食量及體重的效果。

【0284】 以三種劑量水平，將 FP1 皮下投予至原態石蟹獼猴分群(cohort)：1、3、及 10 nmol/kg。亦納入媒劑處理組。該等動物是在盲化條件下接受治療。持續總共 6 週的研究：2 週的基線攝食量測量與數據收集、4 週的化合物單次給藥後數據收集。給藥後，接著在第 1、7、14、21、及 28 天測量血漿藥物暴露量。

【0285】 相較於媒劑處理，石蟹獼猴經過 FP1 單次給藥治療，已減少攝食量及體重（圖 32 至 33）。在 10 nmol/kg 劑量水平下，在第 4、5、6、及 8 至 12 天，每日攝食量出現顯著減少（圖 32）。在 10 nmol/kg 劑量水平下的投予後第 2 週期間，每日攝食量的一週平均值係顯著降低。在 3 nmol/kg 劑量水平下的投予後第 2 週，其較給藥前的平均每週攝食量具有顯著的減少幅度百分比；且在 10 nmol/kg 劑量水平下的投予後第 1 及 2 週中，其較給藥前的平均每週攝食量具有顯著的減少幅度百分比。在 3 nmol/kg 劑量水平下的第 28 天，且在 10 nmol/kg 劑量水平下的第 14、21、及 28 天，出現自第 0 天改變的顯著體重減少幅度百分比（圖 33）。

【0286】 以三種劑量水平，將 FP2 皮下投予至原態石蟹獼猴分群：1、3、及 10 nmol/kg。亦納入媒劑處理組。該等動物是在盲化條件下接受治療。持續總共 11 週的研究：5 週的基線攝食量測量與數據收集、1 週的治療及 5 週的清洗期數據收集。給藥後，接著在第 1、7、14、21、28、35、及 42 天測量血漿藥物暴露量。

【0287】 相較於媒劑處理，石蟹獼猴經過 FP2 單次給藥治療，已減少攝食量及體重（圖 34 至 35）。在 3 nmol/kg 劑量水平下的第 3、5 至 8、10 及 12 天，且在 10 nmol/kg 劑量水平下的第 3 至 38 及 40 天，出現顯著的每日攝食量減少（圖 34）。就每日攝食量之每週平均值來說，其在 3 nmol/kg 劑量水平下投予後第 1 週內顯著降低，且在 10 nmol/kg 劑量水平下第 1 至 6 週顯著降低。在 3 nmol/kg 劑量水平下的投予後第 2 週，其較給藥前該週的每週平均每日攝食量具有顯著的減少幅度百分比；且在 10 nmol/kg 劑量水平下的投予後第 1 及 6 週中，其較給藥前該週的每週平均每日攝食量具有顯著的減少幅度百分比。在 1 nmol/kg 劑量水平下的第 21 至 42 天，在 3 nmol/kg 劑量水平下的第 14 至 42 天，在 10 nmol/kg 劑量水平下的第 7 至 42 天，出現自第 0 天改變的顯著體重減少幅度百分比（圖 34）。

實例 20：HSA-GDF15:GDF15 異二聚體(heterodimer)

【0288】 已探討 HSA-GDF15:GDF15 異二聚體的生物活性。

【0289】 為了產生 HSA-GDF15:GDF15 異二聚體，已設計二種建構體。第一建構體所含有的 HSA 經由甘胺酸-絲胺酸連接子（SEQ ID NO: 93）融合至成熟 GDF15 (AA 203-308)之 N 端。第二建構體所含有的 6x 組胺酸標記 HSA 經由甘胺酸-絲胺酸連接子與 HRV3C 蛋白酶裂解位置（SEQ ID NO: 94）融合至成熟 GDF15 (AA 197-308)之 N 端。根據製造商的規程使用 Expi293™ Expression System

(Thermo Fisher Scientific)，使質體以 1:1 之比例進行共轉導。胜肽經過分泌而成為 HSA-GDF15 蛋白，該蛋白包括異二聚體及同二聚體形式，其中單體係由雙硫鍵連接。

【0290】 自經短時間轉導之 Expi293™細胞而來的細胞上清液，其係在轉導後 5 天經過收穫，經由離心加以澄清，且經過無菌過濾。將澄清的上清液裝載於 Histrap HP 管柱(GE Healthcare)，該管柱係於具有 20 mM 磷酸鈉、500 mM NaCl、pH 7.4 之條件下平衡。經過裝載之後，用平衡緩衝液清洗管柱，藉以去除未結合的蛋白質。結合於管柱的 HSA-GDF15 蛋白，包括異二聚體及同二聚體兩者，係於具有 20 mM 磷酸鈉、150 mM 咪唑、pH 7.4 之條件下洗提。儲集洗出液流份，並將其在 4℃下於 6x 組胺酸標記 HRV3C 酶(Janssen)存在時培養整夜，以產生 HSA-GDF15:GDF15 異二聚體。經過培養之後，使蛋白質溶液透析進入平衡緩衝液，以去除咪唑，之後才能將蛋白質溶液再一次施加於 HisTrap HP 管柱。在利用 20 mM 磷酸鈉、50 mM 咪唑、pH 7.4 的清洗步驟中，洗提 HSA-GDF15:GDF15 異二聚體，同時保留組胺酸標記蛋白。藉由尺寸篩除層析(SEC)，在利用 HiLoad 26/60 Superdex 200 pg 管柱(GE Healthcare)且以 1x DPBS (pH 7.2)平衡的條件下，進一步精製異二聚體。儲集來自 SEC 之具有高純度（由 SDS-PAGE 判定）HSA-GDF15:GDF15 異二聚體的洗出液流份，並將其加以過濾。利用 BioTek SynergyHTTM 分光光度計於 280 nm 之吸光度來測定蛋白質的濃度。利用 SDS-PAGE 與分析性尺寸篩除 HPLC (Ultimate3000 HPLC system)，評估經純化之蛋白質品質。利用 LAL 分析法(Pyrotell®-T, Associates of Cape Cod)，測量內毒素水平。在 4℃下儲存純化蛋白質。

【0291】 將穩定表現 GDF15 受體(GFRAL)的 SK-N-AS 細胞(ATCC)播種於 96 孔盤內的生長培養基(10% FBS)中，於 24 小時後進行分析。24 hrs 後，將培養基更換為 200 µl 的 DMEM 培養基（補充 1% HI 馬血清）以在 37℃培養箱中使

細胞飢餓 3 小時。接著，將 1% HI 馬血清補充培養基更換為 200 µl 的 AB1，然後在 37℃培養箱中再培養額外 2 小時。為了進行分析，抽吸掉所有小孔內的 AB1，並將測試化合物於 AB2 中的溶液以不同濃度加入 100 µl，然後將盤板在 37℃培養箱中培養 15 min。15 分鐘過後，移除測試溶液，並加入 30 µl 的裂解液（提供於檢測套組），然後在室溫下用盤板振盪機使盤板振盪 30 min。為進行檢測，將 16 µl 的裂解樣本轉移至 384 孔分析盤，並添加 4 µl 的 HTRF pAKT 檢測抗體。在室溫下整夜培養盤板，然後在 Envision (Perkin Elmer)上讀取 HTRF 信號。

【0292】 利用 GraphPad Prism®非線性迴歸（曲線擬合），來計算 EC_{50} 值。數據是以取自三項獨立實驗的平均±標準誤差(SE)表示，其中每個數據點採三重複。藉由質譜術來確認 HSA-GDF15:GDF15 異二聚體的分子同一性。異二聚體曲線向左偏移的現象，意味著 HSA-GDF15:GDF15 異二聚體誘導 pAKT 的效力強於具有額外白蛋白的相關同二聚體分子。

實例 21：連接子之熱穩定

【0293】 已探討連接 HSA 與 GDF15 之各種連接子的熱穩定性。為評估形成片段與聚集的可能性，將具有各種連接子的 HSA-GDF15 融合蛋白稀釋成 10 mg/ml。添加 EDTA 與甲硫胺酸之後，將樣本在 40℃下培養 14 天。然後，將樣本稀釋成 1 mg/ml 之濃度，且在尺寸篩除高效液相層析(SE-HPLC)下經過評估。對這些蛋白質定量完整蛋白的百分比，以及片段與聚集的百分比。表 64 顯示，當具有連接子的 HSA-GDF15 蛋白由 AP 重複序列組成時，在熱應力下阻止片段形成的穩定性最高。

【0294】 為了評估此等連接子是否影響 GDF15 與其受體的交互作用，使用針對 GDF15 (Janssen)與 HSA (Kerafast, Inc., Boston, MA)的單株抗體，在 GFRAL-Fc 融合蛋白塗覆於盤板上且利用抗 GDF15 或抗 HSA 檢測的條件下進行

免疫檢定。此分析法顯示表 66 中的所有此等連接子變體皆對受體具有類似結合情形。

【0295】 表 64：熱應力下 14 天之後的 SE-HPLC 結果

SEQ ID NO	連接子	聚集 (%)	完整 (%)	片段 (%)
113	$GS(GGGGS)_8$	3.33	84.44	12.22
115	$GA(GGGGA)_8$	3.51	87.98	8.5
117	$(AP)_{10}$	1.64	98.36	0
119	$(AP)_{12}$	2.36	97.64	0
121	$GGS-(EGKSSGSGSESKST)_3-GGS$	1.67	85.24	13.09
123	$GS(PGGGS)_8$	2.96	88.12	8.91
125	$GS(AGGGS)_8$	3.44	86.22	10.34
127	$GGS-(EGKSSGSGSESKST)_2-GGS$	1.71	91.17	7.12

【0296】 本發明已參照其特定實施例詳加說明，而在未悖離本發明之精神與範疇下可於其中進行各種變更與修改，此對於所屬技術領域中具有通常知識者而言將係顯而易見。

【0297】 本申請案所提序列係提供於下表：

【0298】 WT –野生型

SEQ ID NO	說明	序列
1	人類血清白蛋白，WT (HSA)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ

		NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG L
2	HSA 變體，C34S	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG L
3	HSA 變體，C34A	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG L
5	HSA (C34S)-GS(GGGGS)$_4$-GDF15 (WT)融合	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA

		VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFR AANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKT DTGVSLQTYDDLLAKDCHCI
6	成熟 GDF15 (197-308)	ARNGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPRE VQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPC CVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
7	截短成熟 GDF15 (200-308)	GDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQV TMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVP ASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
8	截短成熟 GDF15 (201-308)	DHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVT MCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPA SYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
9	截短成熟 GDF15 (202-308)	HCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTM CIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASY NPMVLIQKTDTGVSLQTYDDLLAKDCHCI
10	截短成熟 GDF15 (203-308)	CPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMC IGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASY NPMVLIQKTDTGVSLQTYDDLLAKDCHCI
11	截短成熟 GDF15 (211-308)	CRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQF RAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQK TDTGVSLQTYDDLLAKDCHCI
25	HSA (C34S)-AS(GGGGS)$_2$GT --GDF15 融合	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LASGGGGSGGGGSGTARNGDHCPLGPGRCCRLHTVRAS LEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQI KTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQT YDDLLAKDCHCI
26	HSA(C34S)-AS(GGGGS)$_8$GT – GDF15(WT)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK

		TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LASGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS GGGGSGTARNGDHCPLGPGRCCRLHTVRASLEDLGWAD WVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKP DTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDC HCI
27	HSA (C34S)-AS(AP)$_5$GT-GDF15 融合	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LASAPAPAPAPAPGTARNGDHCPLGPGRCCRLHTVRASL EDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIK TSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTY DDLLAKDCHCI
28	HSA (C34S) AS(AP)$_{10}$GT - GDF15 融合	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LASAPAPAPAPAPAPAPAPAPGTARNGDHCPLGPGRC CRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQF RAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQK TDTGVSLQTYDDLLAKDCHCI
29	HSA (C34S) – AS(AP)$_{20}$G	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR

	T-GDF15 融合	PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LASAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPA PAPGTARNGDHCPLGPGRCCRLHTVRASLEDLGWADWV LSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDT VPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHC I
30	HSA (C34S) – AS(EAAAK)$_4$GT - GDF15 融合	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LASEAAAKEAAAKEAAAKEAAAKGTARNGDHCPLGPGR CCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQ FRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQ KTDTGVSLQTYDDLLAKDCHCI
31	HSA (C34S)-AS(EAAAK)$_8$GT-GDF15 融合	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LASEAAAKEAAAKEAAAKEAAAKEAAAKEAAAKEAAA

		KEAAAKGTARNGDHCPLGPGRCCRLHTVRASLEDLGWA DWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLK PDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKD CHCI
36	HSA (C34S)- GS(GGGG S)$_4$- GDF15 融 合 （缺失 13 突變體）	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSCSRLHTVRASLEDLG WADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLH RLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLL AKDCHCI
37	HSA (C34S) – GS(GGGG S)$_4$- GDF15 融 合 （缺失 14 突變體）	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSCRLHTVRASLEDLGW ADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRL KPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAK DCHCI
40	HSA (C34S) – GS(GGGG S)$_4$- GDF15 融 合	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ

		NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFR AANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKT DTGVSLQTYDDLLAKDCHCI
48	HSA(C34A)-GS(GGGGS)$_4$-GDF15融合	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFR AANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKT DTGVSLQTYDDLLAKDCHCI
55	HSA(C34A)-GS(GGGGS)$_8$-GDF15	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS GGGGSARNGDHCPLGPGRCCRLHTVRASLEDLGWADWV LSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDT VPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHC I
56	HSA(C34A)-(AP)$_{10}$-GDF15	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF

		AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LAPAPAPAPAPAPAPAPAPAPARNGDHCPLGPGRCCRLH TVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAAN MHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTG VSLQTYDDLLAKDCHCI
59	HSA(C34S)- $(AP)_{10}$- GDF15	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LAPAPAPAPAPAPAPAPAPAPARNGDHCPLGPGRCCRLH TVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAAN MHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTG VSLQTYDDLLAKDCHCI
60	HSA (C34S)- GS-$(GGG$ $GS)_8$- GDF15(W T)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS GGGGSARNGDHCPLGPGRCCRLHTVRASLEDLGWADWV LSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDT

		VPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHC I
64	HSA (C34S) – GS(GGGG S)$_4$- GDF15 (I89R)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFR AANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLRQKT DTGVSLQTYDDLLAKDCHCI
65	HSA (C34S) – GS(GGGG S)$_4$-GDF15 (I89W)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFR AANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLWQK TDTGVSLQTYDDLLAKDCHCI
66	HSA (C34S) – GS(GGGG S)$_4$- GDF15 (L34A, S35A, R37A)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT

		PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGWADWVAAPAEVQVTMCIGACPSQFR AANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKT DTGVSLQTYDDLLAKDCHCI
67	HSA (C34S) – GS(GGGGS)$_4$-GDF15 (V87A, I89A, L98A)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFR AANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMALAQK TDTGVSAQTYDDLLAKDCHCI
68	HSA (C34S) – GS(GGGGS)$_4$-GDF15 (L34A, S35A, I89A)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGWADWVAAPREVQVTMCIGACPSQFR AANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLAQK TDTGVSLQTYDDLLAKDCHCI
69	HSA (C34S) – GS(GGGGS)$_4$-GDF15 (V87A, I89A)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS

		KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFR AANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMALAQK TDTGVSLQTYDDLLAKDCHCI
70	HSA (C34S) – GS(GGGG S)$_4$- GDF15 (Q60W)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFR AANMHAWIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKT DTGVSLQTYDDLLAKDCHCI
71	HSA (C34S) – GS(GGGG S)$_4$- GDF15 (W32A)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGWADAVLSPREVQVTMCIGACPSQFRA ANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTD TGVSLQTYDDLLAKDCHCI
72	HSA (C34S) –	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA

	GS(GGGGS)$_4$-GDF15 (W29A)	TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGAADWVLSPREVQVTMCIGACPSQFRA ANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTD TGVSLQTYDDLLAKDCHCI
73	HSA (C34S) – GS(GGGGS)$_4$-GDF15 (Q60A, S64A, R67A)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFR AANMHAAIKTALHALKPDTVPAPCCVPASYNPMVLIQKT DTGVSLQTYDDLLAKDCHCI
74	HSA (C34S) – GS(GGGGS)$_4$-GDF15 (W29A, Q60A, I61A)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC

		RLHTVRASLEDLGAADWVLSPREVQVTMCIGACPSQFRA ANMHAAAKTSLHRLKPDTVPAPCCVPASYNPMVLIQKT DTGVSLQTYDDLLAKDCHCI
75	HSA (C34S) – GS(GGGGS)$_4$-GDF15 (W29A, W32A)	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSARNGDHCPLGPGRCC RLHTVRASLEDLGAADAVLSPREVQVTMCIGACPSQFRA ANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTD TGVSLQTYDDLLAKDCHCI
76	核酸編碼 SEQ ID NO:5	gacgcccacaagagcgaggtggcccaccggttcaaggacctgggcgaggagaact tcaaggccctggtgctgatcgccttcgcccagtacctgcagcagtccccttcgagga ccacgtgaagctggtgaacgaggtgaccgagttcgccaagacctgcgtggccgacg agagcgccgagaactgcgacaagagcctgcacaccctgttcggcgacaagctgtgc accgtggccaccctgcgggagacctacggcgagatggccgactgctgcgccaagca ggagcccgagcggaacgagtgcttcctgcagcacaaggacgacaaccccaacctgc cccggctggtgcggcccgaggtggacgtgatgtgcaccgccttccacgacaacgag gagaccttcctgaagaagtacctgtacgagatcgcccggcggcacccctacttctacg ccccccgagctgctgttcttcgccaagcggtacaaggccgccttcaccgagtgctgcca ggccgccgacaaggccgcctgcctgctgcccaagctggacgagctgcgggacgag ggcaaggccagcagcgccaagcagcggctgaagtgcgccagcctgcagaagttcg gcgagcgggccttcaaggcctgggccgtggcccggctgagccagcggttccccaag gccgagttcgccgaggtgagcaagctggtgaccgacctgaccaaggtgcacaccga gtgctgccacggcgacctgctggagtgcgccgacgaccgggccgacctggccaagt acatctgcgagaaccaggacagcatcagcagcaagctgaaggagtgctgcgagaag cccctgctggagaagagccactgcatcgccgaggtggagaacgacgagatgcccgc cgacctgcccagcctggccgccgacttcgtggagagcaaggacgtgtgcaagaact acgccgaggccaaggacgtgttcctgggcatgttcctgtacgagtacgcccggcggc accccgactacagcgtggtgctgctgctgcggctggccaagacctacgagaccaccc tggagaagtgctgcgccgccgccgacccccacgagtgctacgccaaggtgttcgac gagttcaagcccctggtggaggagccccagaacctgatcaagcagaactgcgagct gttcgagcagctgggcgagtacaagttccagaacgccctgctggtgcggtacaccaa gaaggtgccccaggtgagcacccccaccctggtggaggtgagccggaacctgggc aaggtgggcagcaagtgctgcaagcaccccgaggccaagcggatgccctgcgccg aggactacctgagcgtggtgctgaaccagctgtgcgtgctgcacgagaagacccccg tgagcgaccgggtgaccaagtgctgcaccgagagcctggtgaaccggcggccctgc ttcagcgccctggaggtggacgagacctacgtgcccaaggagttcaacgccgagac cttcaccttccacgccgacatctgcaccctgagcgagaaggagcggcagatcaagaa gcagaccgccctggtggagctggtgaagcacaagcccaaggccaccaaggagcag ctgaaggccgtgatggacgacttcgccgccttcgtggagaagtgctgcaaggccgac

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91	核酸編碼 SEQ ID NO:70	gacgcccacaagagcgaggtggcccaccggttcaaggacctgggcgaggagaact tcaaggccctggtgctgatcgccttcgcccagtacctgcagcagtccccttcgagga ccacgtgaagctggtgaacgaggtgaccgagttcgccaagacctgcgtggccgacg agagcgccgagaactgcgacaagagcctgcacaccctgttcggcgacaagctgtgc accgtggccaccctgcgggagacctacggcgagatggccgactgctgcgccaagca ggagcccgagcggaacgagtgcttcctgcagcacaaggacgacaaccccaacctgc cccggctggtgcggcccgaggtggacgtgatgtgcaccgccttccacgacaacgag gagaccttcctgaagaagtacctgtacgagatcgcccggcggcacccctacttctacg cccccgagctgctgttcttcgccaagcggtacaaggccgccttcaccgagtgctgcca ggccgccgacaaggccgcctgcctgctgcccaagctggacgagctgcgggacgag ggcaaggccagcagcgccaagcagcggctgaagtgcgccagcctgcagaagttcg gcgagcgggccttcaaggcctgggccgtggcccggctgagccagcggttccccaag gccgagttcgccgaggtgagcaagctggtgaccgacctgaccaaggtgcacaccga gtgctgccacggcgacctgctggagtgcgccgacgaccgggccgacctggccaagt acatctgcgagaaccaggacagcatcagcagcaagctgaaggagtgctgcgagaag cccctgctggagaagagccactgcatcgccgaggtggagaacgacgagatgcccgc cgacctgcccagcctggccgccgacttcgtggagagcaaggacgtgtgcaagaact acgccgaggccaaggacgtgttcctgggcatgttcctgtacgagtacgcccggcggc accccgactacagcgtggtgctgctgctgcggctggccaagacctacgagaccaccc tggagaagtgctgcgccgccgccgacccccacgagtgctacgccaaggtgttcgac gagttcaagcccctggtggaggagccccagaacctgatcaagcagaactgcgagct gttcgagcagctgggcgagtacaagttccagaacgccctgctggtgcggtacaccaa gaaggtgccccaggtgagcacccccaccctggtggaggtgagccggaacctgggc aaggtgggcagcaagtgctgcaagcaccccgaggccaagcggatgccctgcgccg aggactacctgagcgtggtgctgaaccagctgtgcgtgctgcacgagaagacccccg tgagcgaccgggtgaccaagtgctgcaccgagagcctggtgaaccggcggccctgc ttcagcgccctggaggtggacgagacctacgtgcccaaggagttcaacgccgagac cttcaccttccacgccgacatctgcaccctgagcgagaaggagcggcagatcaagaa gcagaccgccctggtggagctggtgaagcacaagcccaaggccaccaaggagcag ctgaaggccgtgatggacgacttcgccgccttcgtggagaagtgctgcaaggccgac gacaaggagacctgcttcgccgaggagggcaagaagctggtggccgccagccagg

		ccgccctgggcctgggcagcggcggcggcggcagcggcggcggcggatctggtg gaggtggcagtggaggaggggatccgctcgcaacggtgaccactgccctctgggt cctggtcgctgctgccgcctgcacaccgttcgcgcttctctggaagacctgggttggg ctgactgggttctgtctcctcgcgaagttcaggttaccatgtgcatcggtgcttgcccctt ctcagttccgcgctgctaacatgcacgcttggatcaaaacctctctgcaccgcctgaaa cctgacaccgttcctgctccttgctgcgttcctgcttcttacaaccctatggttctgatcc agaaaaccgacaccggtgtttctctgcagacctacgacgacctgctggctaaagactg ccactgcatc
92	HSA (C34S) – GS-(GGG GS)$_8$ – GDF15 （缺失 4）	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS GGGGSDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPR EVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAP CCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
93	HSA (C34S)-GS-(GGG GS)$_8$-GDF15（缺失 5）	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS GGGGSHCPLGPGRCCRLHTVRASLEDLGWADWVLSPRE VQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPC CVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
94	6x 組胺酸標籤-HSA (C34S)-GS-(GGG	EFHHHHHHDAHKSEVAHRFKDLGEENFKALVLIAFAQYL QQSPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLF GDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDD NPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHP YFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELR DEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFP

	GS)$_8$-HRV3C 位置 GDF15	KAEFAEVSKLVTDLTKVHTECCHGDLLECADDRADLAK YICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADL PSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPD YSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKP LVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQV STPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVL NQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDET YVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHK PKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKK LVAASQAALGLGSGGGGSGGGGSGGGGSGGGGSLEVLF QGPARNGDHCPLGPGRCCRLHTVRASLEDLGWADWVLS PREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVP APCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
95	核酸編碼 SEQ ID NO:92（密碼子最佳化 1）	GATGCACACAAGAGTGAGGTTGCTCATCGGTTTAAAGA TTTGGGAGAAGAAAATTTCAAAGCCTTGGTGTTGATTG CCTTTGCTCAGTATCTTCAGCAGTCCCCATTTGAAGATC ATGTAAAATTAGTGAATGAAGTAACTGAATTTGCAAAA ACATGTGTTGCTGATGAGTCAGCTGAAAATTGTGACAA ATCACTTCATACCCTTTTTGGAGACAAATTATGCACAG TTGCAACTCTTCGTGAAACCTATGGTGAAATGGCTGAC TGCTGTGCAAAACAAGAACCTGAGAGAAATGAATGCT TCTTGCAACACAAAGATGACAACCCAAACCTCCCCCGA TTGGTGAGACCAGAGGTTGATGTGATGTGCACTGCTTT TCATGACAATGAAGAGACATTTTTGAAAAAATACTTAT ATGAAATTGCCAGAAGACATCCTTACTTTTATGCCCCG GAACTCCTTTTCTTTGCTAAAAGGTATAAAGCTGCTTTT ACAGAATGTTGCCAAGCTGCTGATAAAGCTGCCTGCCT GTTGCCAAAGCTCGATGAACTTCGGGATGAAGGGAAG GCTTCGTCTGCCAAACAGAGACTCAAGTGTGCCAGTCT CCAAAAATTTGGAGAAAGAGCTTTCAAAGCATGGGCA GTAGCTCGCCTGAGCCAGAGATTTCCCAAAGCTGAGTT TGCAGAAGTTTCCAAGTTAGTGACAGATCTTACCAAAG TCCACACGGAATGCTGCCATGGAGATCTGCTTGAATGT GCTGATGACAGGGCGGACCTTGCCAAGTATATCTGTGA AAATCAAGATTCGATCTCCAGTAAACTGAAGGAATGCT GTGAAAAACCTCTGTTGGAAAAATCCCACTGCATTGCC GAAGTGGAAAATGATGAGATGCCTGCTGACTTGCCTTC ATTAGCTGCTGATTTTGTTGAAAGTAAGGATGTTTGCA AAAACTATGCTGAGGCAAAGGATGTCTTCCTGGGCATG TTTTTGTATGAATATGCAAGAAGGCATCCTGATTACTC TGTCGTGCTGCTGCTGAGACTTGCCAAGACATATGAAA CCACTCTAGAGAAGTGCTGTGCCGCTGCAGATCCTCAT GAATGCTATGCCAAAGTGTTCGATGAATTTAAACCTCT TGTGGAAGAGCCTCAGAATTTAATCAAACAAAATTGTG AGCTTTTTGAGCAGCTTGGAGAGTACAAATTCCAGAAT GCGCTATTAGTTCGTTACACCAAGAAAGTACCCCAAGT GTCAACTCCAACTCTTGTAGAGGTCTCAAGAAACCTAG GAAAAGTGGGCAGCAAATGTTGTAAACATCCTGAAGC AAAAAGAATGCCCTGTGCAGAAGACTATCTATCCGTGG TCCTGAACCAGTTATGTGTGTTGCATGAGAAAACGCCA GTAAGTGACAGAGTCACCAAATGCTGCACAGAATCCTT GGTGAACAGGCGACCATGCTTTTCAGCTCTGGAAGTCG

		ATGAAACATACGTTCCCAAAGAGTTTAATGCTGAAACA TTCACCTTCCATGCAGATATATGCACACTTTCTGAGAA GGAGAGACAAATCAAGAAACAAACTGCACTTGTTGAG CTCGTGAAACACAAGCCCAAGGCAACAAAAGAGCAAC TGAAAGCTGTTATGGATGATTTCGCAGCTTTTGTAGAG AAGTGCTGCAAGGCTGACGATAAGGAGACCTGCTTTGC CGAGGAGGGTAAAAAACTTGTTGCTGCAAGTCAAGCT GCCTTAGGGCTTGGAAGCGGCGGAGGGGGGAGTGGCG GCGGTGGCTCCGGGGGGGGCGGATCCGGCGGAGGGGG CAGCGGGGGTGGAGGGAGTGGCGGGGGAGGATCAGGG GGAGGAGGATCAGGAGGGGGCGGAAGTGATCATTGCC CTCTCGGGCCCGGACGGTGTTGCCGCCTCCACACTGTG AGGGCTTCACTTGAAGACCTTGGATGGGCCGACTGGGT GCTGTCCCCAAGAGAGGTACAAGTCACAATGTGTATTG GCGCCTGCCCCAGCCAGTTTCGCGCCGCTAACATGCAC GCCCAGATAAAAACCAGCCTGCACCGCCTGAAGCCCG ACACGGTGCCAGCGCCCTGCTGCGTGCCCGCCAGCTAC AATCCCATGGTGCTCATTCAAAAGACCGACACCGGGGT GTCGCTCCAGACCTATGATGACTTGTTAGCCAAAGACT GCCACTGCATA
96	核酸編碼 SEQ ID NO:7	GGGGACCACTGTCCGCTCGGGCCCGGGCGTTGCTGCCG TCTGCACACGGTCCGCGCGTCGCTGGAAGACCTGGGCT GGGCCGATTGGGTGCTGTCGCCACGGGAGGTGCAAGT GACCATGTGCATCGGCGCGTGCCCGAGCCAGTTCCGGG CGGCAAACATGCACGCGCAGATCAAGACGAGCCTGCA CCGCCTGAAGCCCGACACGGTGCCAGCGCCCTGCTGCG TGCCCGCCAGCTACAATCCCATGGTGCTCATTCAAAAG ACCGACACCGGGGTGTCGCTCCAGACCTATGATGACTT GTTAGCCAAAGACTGCCACTGCATA
97	核酸編碼 SEQ ID NO:8 （密碼子 最佳化 1）	GACCACTGTCCGCTCGGGCCCGGGCGTTGCTGCCGTCT GCACACGGTCCGCGCGTCGCTGGAAGACCTGGGCTGG GCCGATTGGGTGCTGTCGCCACGGGAGGTGCAAGTGAC CATGTGCATCGGCGCGTGCCCGAGCCAGTTCCGGGCGG CAAACATGCACGCGCAGATCAAGACGAGCCTGCACCG CCTGAAGCCCGACACGGTGCCAGCGCCCTGCTGCGTGC CCGCCAGCTACAATCCCATGGTGCTCATTCAAAAGACC GACACCGGGGTGTCGCTCCAGACCTATGATGACTTGTT AGCCAAAGACTGCCACTGCATA
98	核酸編碼 SEQ ID NO:8 （密碼子 最佳化 2）	GATCATTGCCCTCTCGGGCCCGGACGGTGTTGCCGCCT CCACACTGTGAGGGCTTCACTTGAAGACCTTGGATGGG CCGACTGGGTGCTGTCCCCAAGAGAGGTACAAGTCACA ATGTGTATTGGCGCCTGCCCCAGCCAGTTTCGCGCCGC TAACATGCACGCCCAGATAAAAACCAGCCTGCACCGCC TGAAGCCCGACACGGTGCCAGCGCCCTGCTGCGTGCCC GCCAGCTACAATCCCATGGTGCTCATTCAAAAGACCGA CACCGGGGTGTCGCTCCAGACCTATGATGACTTGTTAG CCAAAGACTGCCACTGCATA
99	核酸編碼 SEQ ID NO:8 （密碼子	GATCATTGTCCCCTTGGACCGGGTAGATGCTGTCGCCT GCACACTGTGCGGGCTTCACTGGAGGACCTCGGCTGGG CTGACTGGGTGCTGTCCCCACGGGAGGTGCAAGTGACC ATGTGCATCGGCGCCTGTCCTTCGCAATTCCGGGCCGC GAATATGCACGCCCAGATCAAGACCTCCCTGCATCGCC

	最佳化 3）	TCAAGCCCGACACTGTGCCTGCTCCATGCTGTGTGCCG GCCTCCTATAACCCCATGGTGCTGATCCAGAAAACCGA TACCGGCGTCAGCCTGCAGACGTATGATGATCTGCTGG CCAAGGACTGCCATTGCATC
100	核酸編碼 SEQ ID NO:9 （密碼子 最佳化 1）	CACTGTCCGCTCGGGCCCGGGCGTTGCTGCCGTCTGCA CACGGTCCGCGCGTCGCTGGAAGACCTGGGCTGGGCCG ATTGGGTGCTGTCGCCACGGGAGGTGCAAGTGACCATG TGCATCGGCGCGTGCCCGAGCCAGTTCCGGGCGGCAAA CATGCACGCGCAGATCAAGACGAGCCTGCACCGCCTG AAGCCCGACACGGTGCCAGCGCCCTGCTGCGTGCCCGC CAGCTACAATCCCATGGTGCTCATTCAAAAGACCGACA CCGGGGTGTCGCTCCAGACCTATGATGACTTGTTAGCC AAAGACTGCCACTGCATA
101	核酸編碼 SEQ ID NO:9 （密碼子 最佳化 2）	CATTGCCCTCTCGGGCCCGGACGGTGTTGCCGCCTCCA CACTGTGAGGGCTTCACTTGAAGACCTTGGATGGGCCG ACTGGGTGCTGTCCCCAAGAGAGGTACAAGTCACAATG TGTATTGGCGCCTGCCCCAGCCAGTTTCGCGCCGCTAA CATGCACGCCCAGATAAAAACCAGCCTGCACCGCCTGA AGCCCGACACGGTGCCAGCGCCCTGCTGCGTGCCCGCC AGCTACAATCCCATGGTGCTCATTCAAAAGACCGACAC CGGGGTGTCGCTCCAGACCTATGATGACTTGTTAGCCA AAGACTGCCACTGCATA
102	核酸編碼 SEQ ID NO:9 （密碼子 最佳化 3）	CATTGTCCCCTTGGACCGGGTAGATGCTGTCGCCTGCA CACTGTGCGGGCTTCACTGGAGGACCTCGGCTGGGCTG ACTGGGTGCTGTCCCCACGGGAGGTGCAAGTGACCATG TGCATCGGCGCCTGTCCTTCGCAATTCCGGGCCGCGAA TATGCACGCCCAGATCAAGACCTCCCTGCATCGCCTCA AGCCCGACACTGTGCCTGCTCCATGCTGTGTGCCGGCC TCCTATAACCCCATGGTGCTGATCCAGAAAACCGATAC CGGCGTCAGCCTGCAGACGTATGATGATCTGCTGGCCA AGGACTGCCATTGCATC
103	核酸編碼 SEQ ID NO:10 （密碼子 最佳化 1）	TGTCCGCTCGGGCCCGGGCGTTGCTGCCGTCTGCACAC GGTCCGCGCGTCGCTGGAAGACCTGGGCTGGGCCGATT GGGTGCTGTCGCCACGGGAGGTGCAAGTGACCATGTGC ATCGGCGCGTGCCCGAGCCAGTTCCGGGCGGCAAACAT GCACGCGCAGATCAAGACGAGCCTGCACCGCCTGAAG CCCGACACGGTGCCAGCGCCCTGCTGCGTGCCCGCCAG CTACAATCCCATGGTGCTCATTCAAAAGACCGACACCG GGGTGTCGCTCCAGACCTATGATGACTTGTTAGCCAAA GACTGCCACTGCATA
104	核酸編碼 SEQ ID NO:10 （密碼子 最佳化 2）	TGCCCTCTCGGGCCCGGACGGTGTTGCCGCCTCCACAC TGTGAGGGCTTCACTTGAAGACCTTGGATGGGCCGACT GGGTGCTGTCCCCAAGAGAGGTACAAGTCACAATGTGT ATTGGCGCCTGCCCCAGCCAGTTTCGCGCCGCTAACAT GCACGCCCAGATAAAAACCAGCCTGCACCGCCTGAAG CCCGACACGGTGCCAGCGCCCTGCTGCGTGCCCGCCAG CTACAATCCCATGGTGCTCATTCAAAAGACCGACACCG GGGTGTCGCTCCAGACCTATGATGACTTGTTAGCCAAA GACTGCCACTGCATA
105	核酸編碼 SEQ ID	TGTCCCCTTGGACCGGGTAGATGCTGTCGCCTGCACAC TGTGCGGGCTTCACTGGAGGACCTCGGCTGGGCTGACT GGGTGCTGTCCCCACGGGAGGTGCAAGTGACCATGTGC

	NO:10（密碼子最佳化 3）	ATCGGCGCCTGTCCTTCGCAATTCCGGGCCGCGAATAT GCACGCCCAGATCAAGACCTCCCTGCATCGCCTCAAGC CCGACACTGTGCCTGCTCCATGCTGTGTGCCGGCCTCC TATAACCCCATGGTGCTGATCCAGAAAACCGATACCGG CGTCAGCCTGCAGACGTATGATGATCTGCTGGCCAAGG ACTGCCATTGCATC
106	核酸編碼 SEQ ID NO:11（密碼子最佳化 1）	TGCCGTCTGCACACGGTCCGCGCGTCGCTGGAAGACCT GGGCTGGGCCGATTGGGTGCTGTCGCCACGGGAGGTGC AAGTGACCATGTGCATCGGCGCGTGCCCGAGCCAGTTC CGGGCGGCAAACATGCACGCGCAGATCAAGACGAGCC TGCACCGCCTGAAGCCCGACACGGTGCCAGCGCCCTGC TGCGTGCCCGCCAGCTACAATCCCATGGTGCTCATTCA AAAGACCGACACCGGGGTGTCGCTCCAGACCTATGATG ACTTGTTAGCCAAAGACTGCCACTGCATA
107	核酸編碼 SEQ ID NO:11（密碼子最佳化 2）	TGCCGCCTCCACACTGTGAGGGCTTCACTTGAAGACCT TGGATGGGCCGACTGGGTGCTGTCCCCAAGAGAGGTAC AAGTCACAATGTGTATTGGCGCCTGCCCCAGCCAGTTT CGCGCCGCTAACATGCACGCCCAGATAAAAACCAGCCT GCACCGCCTGAAGCCCGACACGGTGCCAGCGCCCTGCT GCGTGCCCGCCAGCTACAATCCCATGGTGCTCATTCAA AAGACCGACACCGGGGTGTCGCTCCAGACCTATGATGA CTTGTTAGCCAAAGACTGCCACTGCATA
108	核酸編碼 SEQ ID NO:11（密碼子最佳化 3）	TGTCGCCTGCACACTGTGCGGGCTTCACTGGAGGACCT CGGCTGGGCTGACTGGGTGCTGTCCCCACGGGAGGTGC AAGTGACCATGTGCATCGGCGCCTGTCCTTCGCAATTC CGGGCCGCGAATATGCACGCCCAGATCAAGACCTCCCT GCATCGCCTCAAGCCCGACACTGTGCCTGCTCCATGCT GTGTGCCGGCCTCCTATAACCCCATGGTGCTGATCCAG AAAACCGATACCGGCGTCAGCCTGCAGACGTATGATG ATCTGCTGGCCAAGGACTGCCATTGCATC
109	核酸編碼 SEQ ID NO:60（密碼子最佳化 2）	GATGCGCACAAGTCGGAAGTGGCCCATCGCTTTAAGGA CCTGGGAGAAGAGAACTTCAAGGCCCTGGTCCTGATCG CGTTCGCCCAGTACCTCCAGCAGTCCCCGTTTGAGGAC CACGTCAAGCTTGTGAACGAAGTGACCGAGTTCGCAAA GACTTGTGTGGCCGATGAGTCCGCCGAAAACTGCGACA AGTCCCTGCACACCTTGTTCGGAGACAAGCTGTGCACC GTCGCGACTTTGCGGGAGACTTACGGCGAAATGGCGG ACTGCTGCGCAAAGCAGGAGCCCGAAAGGAACGAGTG CTTCCTGCAACACAAGGACGACAACCCGAACCTTCCGA GACTCGTGCGGCCTGAGGTCGACGTGATGTGCACTGCA TTCCATGATAACGAAGAAACATTCCTGAAGAAGTACCT GTATGAAATTGCCAGACGCCACCCGTACTTCTACGCCC CCGAACTGCTGTTCTTCGCCAAGAGATACAAGGCCGCC TTTACCGAATGTTGTCAAGCCGCCGATAAGGCAGCGTG CCTGCTGCCGAAGTTGGACGAGCTCAGGGACGAAGGA AAGGCCTCGTCCGCCAAGCAGAGGCTGAAGTGCGCGT CGCTCCAGAAGTTTGGAGAGCGGGCTTTTAAGGCCTGG GCAGTGGCTAGGTTGAGCCAGAGGTTCCCCAAGGCGG AGTTTGCCGAAGTGTCCAAGCTCGTGACTGACCTGACT AAAGTCCATACCGAATGCTGCCACGGCGATCTGCTCGA ATGCGCAGATGACCGGGCGGATTTGGCCAAGTACATTT GCGAAAACCAAGACTCCATAAGCTCCAAGCTGAAGGA

		GTGCTGTGAAAAGCCTCTGCTCGAGAAGTCCCACTGTA TCGCCGAGGTGGAGAACGACGAAATGCCGGCAGACCT CCCTAGCCTGGCAGCCGACTTCGTCGAATCCAAGGACG TGTGCAAGAACTACGCCGAAGCGAAGGACGTGTTCCTG GGAATGTTCCTGTACGAGTACGCCAGACGGCATCCAGA CTACTCCGTGGTGCTTCTCTTGCGGCTGGCCAAGACTT ATGAAACGACCCTGGAGAAATGTTGCGCTGCTGCTGAC CCACACGAGTGCTACGCCAAAGTGTTCGACGAGTTTAA GCCTCTCGTGGAGGAACCCCAGAACCTCATCAAGCAGA ACTGCGAACTTTTCGAGCAGCTCGGGGAGTACAAGTTC CAAAACGCGCTGCTTGTCCGCTACACCAAGAAAGTGCC GCAAGTGTCCACACCGACCCTCGTGGAAGTGTCCAGGA ACCTGGGCAAAGTCGGAAGCAAATGTTGCAAGCACCC CGAAGCCAAGCGCATGCCGTGCGCAGAGGACTACCTTT CGGTGGTGTTGAACCAGCTCTGCGTCCTGCACGAAAAG ACCCCGGTGTCAGACCGCGTGACCAAGTGCTGTACCGA AAGCCTCGTGAATCGGCGCCCCTGCTTCTCGGCCCTGG AGGTGGACGAAACTTACGTGCCGAAAGAGTTCAACGC GGAAACCTTCACCTTTCATGCCGATATCTGCACCCTGT CCGAGAAGGAGCGGCAGATCAAGAAGCAGACCGCCCT GGTGGAGCTTGTGAAACACAAGCCGAAGGCCACTAAG GAACAGCTGAAGGCCGTCATGGACGATTTCGCTGCCTT CGTCGAGAAGTGCTGCAAGGCCGACGACAAGGAGACT TGCTTCGCTGAAGAAGGGAAGAAGCTTGTGGCCGCTAG CCAGGCTGCACTGGGACTGGGTAGCGGTGGAGGGGGA TCAGGGGGTGGTGGATCGGGAGGAGGAGGATCAGGAG GTGGCGGCTCAGGAGGAGGCGGATCAGGCGGTGGAGG ATCCGGAGGCGGAGGATCGGGTGGAGGAGGCTCAGCG AGGAACGGGGATCATTGTCCCCTTGGACCGGGTAGATG CTGTCGCCTGCACACTGTGCGGGCTTCACTGGAGGACC TCGGCTGGGCTGACTGGGTGCTGTCCCCACGGGAGGTG CAAGTGACCATGTGCATCGGCGCCTGTCCTTCGCAATT CCGGGCCGCGAATATGCACGCCCAGATCAAGACCTCCC TGCATCGCCTCAAGCCCGACACTGTGCCTGCTCCATGC TGTGTGCCGGCCTCCTATAACCCCATGGTGCTGATCCA GAAAACCGATACCGGCGTCAGCCTGCAGACGTATGAT GATCTGCTGGCCAAGGACTGCCATTGCATC
110	核酸編碼 SEQ ID NO:92（密碼子最佳化 2）	GATGCGCACAAGTCGGAAGTGGCCCATCGCTTTAAGGA CCTGGGAGAAGAGAACTTCAAGGCCCTGGTCCTGATCG CGTTCGCCCAGTACCTCCAGCAGTCCCCGTTTGAGGAC CACGTCAAGCTTGTGAACGAAGTGACCGAGTTCGCAAA GACTTGTGTGGCCGATGAGTCCGCCGAAAACTGCGACA AGTCCCTGCACACCTTGTTCGGAGACAAGCTGTGCACC GTCGCGACTTTGCGGGAGACTTACGGCGAAATGGCGG ACTGCTGCGCAAAGCAGGAGCCCGAAAGGAACGAGTG CTTCCTGCAACACAAGGACGACAACCCGAACCTTCCGA GACTCGTGCGGCCTGAGGTCGACGTGATGTGCACTGCA TTCCATGATAACGAAGAAACATTCCTGAAGAAGTACCT GTATGAAATTGCCAGACGCCACCCGTACTTCTACGCCC CCGAACTGCTGTTCTTCGCCAAGAGATACAAGGCCGCC TTTACCGAATGTTGTCAAGCCGCCGATAAGGCAGCGTG CCTGCTGCCGAAGTTGGACGAGCTCAGGGACGAAGGA

		AAGGCCTCGTCCGCCAAGCAGAGGCTGAAGTGCGCGT CGCTCCAGAAGTTTGGAGAGCGGGCTTTTAAGGCCTGG GCAGTGGCTAGGTTGAGCCAGAGGTTCCCCAAGGCGG AGTTTGCCGAAGTGTCCAAGCTCGTGACTGACCTGACT AAAGTCCATACCGAATGCTGCCACGGCGATCTGCTCGA ATGCGCAGATGACCGGGCGGATTTGGCCAAGTACATTT GCGAAAACCAAGACTCCATAAGCTCCAAGCTGAAGGA GTGCTGTGAAAAGCCTCTGCTCGAGAAGTCCCACTGTA TCGCCGAGGTGGAGAACGACGAAATGCCGGCAGACCT CCCTAGCCTGGCAGCCGACTTCGTCGAATCCAAGGACG TGTGCAAGAACTACGCCGAAGCGAAGGACGTGTTCCTG GGAATGTTCCTGTACGAGTACGCCAGACGGCATCCAGA CTACTCCGTGGTGCTTCTCTTGCGGCTGGCCAAGACTT ATGAAACGACCCTGGAGAAATGTTGCGCTGCTGCTGAC CCACACGAGTGCTACGCCAAAGTGTTCGACGAGTTTAA GCCTCTCGTGGAGGAACCCCAGAACCTCATCAAGCAGA ACTGCGAACTTTTCGAGCAGCTCGGGGAGTACAAGTTC CAAAACGCGCTGCTTGTCCGCTACACCAAGAAAGTGCC GCAAGTGTCCACACCGACCCTCGTGGAAGTGTCCAGGA ACCTGGGCAAAGTCGGAAGCAAATGTTGCAAGCACCC CGAAGCCAAGCGCATGCCGTGCGCAGAGGACTACCTTT CGGTGGTGTTGAACCAGCTCTGCGTCCTGCACGAAAAG ACCCCGGTGTCAGACCGCGTGACCAAGTGCTGTACCGA AAGCCTCGTGAATCGGCGCCCCTGCTTCTCGGCCCTGG AGGTGGACGAAACTTACGTGCCGAAAGAGTTCAACGC GGAAACCTTCACCTTTCATGCCGATATCTGCACCCTGT CCGAGAAGGAGCGGCAGATCAAGAAGCAGACCGCCCT GGTGGAGCTTGTGAAACACAAGCCGAAGGCCACTAAG GAACAGCTGAAGGCCGTCATGGACGATTTCGCTGCCTT CGTCGAGAAGTGCTGCAAGGCCGACGACAAGGAGACT TGCTTCGCTGAAGAAGGGAAGAAGCTTGTGGCCGCTAG CCAGGCTGCACTGGGACTGGGTAGCGGTGGAGGGGGA TCAGGGGGTGGTGGATCGGGAGGAGGAGGATCAGGAG GTGGCGGCTCAGGAGGAGGCGGATCAGGCGGTGGAGG ATCCGGAGGCGGAGGATCGGGTGGAGGAGGCTCAGAT CATTGTCCCCTTGGACCGGGTAGATGCTGTCGCCTGCA CACTGTGCGGGCTTCACTGGAGGACCTCGGCTGGGCTG ACTGGGTGCTGTCCCCACGGGAGGTGCAAGTGACCATG TGCATCGGCGCCTGTCCTTCGCAATTCCGGGCCGCGAA TATGCACGCCCAGATCAAGACCTCCCTGCATCGCCTCA AGCCCGACACTGTGCCTGCTCCATGCTGTGTGCCGGCC TCCTATAACCCCATGGTGCTGATCCAGAAAACCGATAC CGGCGTCAGCCTGCAGACGTATGATGATCTGCTGGCCA AGGACTGCCATTGCATC
111	HSA(C34S)-GS-(GGGGS)$_8$-（缺失 5）GDF15	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK

		DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS GGGGSHCPLGPGRCCRLHTVRASLEDLGWADWVLSPRE VQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPC CVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
112	HSA(C34S)-GS-(GGGGS)$_8$-（缺失 14）GDF15	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS GGGGSCRLHTVRASLEDLGWADWVLSPREVQVTMCIGA CPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPM VLIQKTDTGVSLQTYDDLLAKDCHCI
113	（缺失 2）HSA(C34S)-GS-(GGGGS)$_8$-（缺失 4）GDF15	HKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDHVK LVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPE VDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFA KRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQ RLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLV TDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSK LKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKD VCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKT YETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQN CELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNL GKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTP VSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFT FHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAV MDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL GSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSG GGGSDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPRE VQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPC CVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
114	SEQ ID NO: 113 之 DNA	CACAAGAGTGAGGTTGCTCATCGGTTTAAAGATTTGGG AGAAGAAAATTTCAAAGCCTTGGTGTTGATTGCCTTTG CTCAGTATCTTCAGCAGTCCCCATTTGAAGATCATGTA

	（缺失 2）HSA(C34S)-GS-(GGGGS)$_8$-（缺失 4）GDF15	AAATTAGTGAATGAAGTAACTGAATTTGCAAAAACATG TGTTGCTGATGAGTCAGCTGAAAATTGTGACAAATCAC TTCATACCCTTTTTGGAGACAAATTATGCACAGTTGCA ACTCTTCGTGAAACCTATGGTGAAATGGCTGACTGCTG TGCAAAACAAGAACCTGAGAGAAATGAATGCTTCTTGC AACACAAAGATGACAACCCAAACCTCCCCCGATTGGTG AGACCAGAGGTTGATGTGATGTGCACTGCTTTTCATGA CAATGAAGAGACATTTTTGAAAAAATACTTATATGAAA TTGCCAGAAGACATCCTTACTTTTATGCCCCGGAACTC CTTTTCTTTGCTAAAAGGTATAAAGCTGCTTTTACAGA ATGTTGCCAAGCTGCTGATAAAGCTGCCTGCCTGTTGC CAAAGCTCGATGAACTTCGGGATGAAGGGAAGGCTTC GTCTGCCAAACAGAGACTCAAGTGTGCCAGTCTCCAAA AATTTGGAGAAAGAGCTTTCAAAGCATGGGCAGTAGCT CGCCTGAGCCAGAGATTTCCCAAAGCTGAGTTTGCAGA AGTTTCCAAGTTAGTGACAGATCTTACCAAAGTCCACA CGGAATGCTGCCATGGAGATCTGCTTGAATGTGCTGAT GACAGGGCGGACCTTGCCAAGTATATCTGTGAAAATCA AGATTCGATCTCCAGTAAACTGAAGGAATGCTGTGAAA AACCTCTGTTGGAAAAATCCCACTGCATTGCCGAAGTG GAAAATGATGAGATGCCTGCTGACTTGCCTTCATTAGC TGCTGATTTTGTTGAAAGTAAGGATGTTTGCAAAAACT ATGCTGAGGCAAAGGATGTCTTCCTGGGCATGTTTTTG TATGAATATGCAAGAAGGCATCCTGATTACTCTGTCGT GCTGCTGCTGAGACTTGCCAAGACATATGAAACCACTC TAGAGAAGTGCTGTGCCGCTGCAGATCCTCATGAATGC TATGCCAAAGTGTTCGATGAATTTAAACCTCTTGTGGA AGAGCCTCAGAATTTAATCAAACAAAATTGTGAGCTTT TTGAGCAGCTTGGAGAGTACAAATTCCAGAATGCGCTA TTAGTTCGTTACACCAAGAAAGTACCCCAAGTGTCAAC TCCAACTCTTGTAGAGGTCTCAAGAAACCTAGGAAAAG TGGGCAGCAAATGTTGTAAACATCCTGAAGCAAAAAG AATGCCCTGTGCAGAAGACTATCTATCCGTGGTCCTGA ACCAGTTATGTGTGTTGCATGAGAAAACGCCAGTAAGT GACAGAGTCACCAAATGCTGCACAGAATCCTTGGTGAA CAGGCGACCATGCTTTTCAGCTCTGGAAGTCGATGAAA CATACGTTCCCAAAGAGTTTAATGCTGAAACATTCACC TTCCATGCAGATATATGCACACTTTCTGAGAAGGAGAG ACAAATCAAGAAACAAACTGCACTTGTTGAGCTCGTGA AACACAAGCCCAAGGCAACAAAAGAGCAACTGAAAGC TGTTATGGATGATTTCGCAGCTTTTGTAGAGAAGTGCT GCAAGGCTGACGATAAGGAGACCTGCTTTGCCGAGGA GGGTAAAAAACTTGTTGCTGCAAGTCAAGCTGCCTTAG GGCTTGGAAGCGGCGGAGGGGGGAGTGGCGGCGGTGG CTCCGGGGGGGGCGGATCCGGCGGAGGGGGCAGCGGG GGTGGAGGGAGTGGCGGGGGAGGATCAGGGGGAGGA GGATCAGGAGGGGGCGGAAGTGATCATTGCCCTCTCG GGCCCGGACGGTGTTGCCGCCTCCACACTGTGAGGGCT TCACTTGAAGACCTTGGATGGGCCGACTGGGTGCTGTC CCCAAGAGAGGTACAAGTCACAATGTGTATTGGCGCCT GCCCCAGCCAGTTTCGCGCCGCTAACATGCACGCCCAG ATAAAAACCAGCCTGCACCGCCTGAAGCCCGACACGG

		TGCCAGCGCCCTGCTGCGTGCCCGCCAGCTACAATCCC ATGGTGCTCATTCAAAAGACCGACACCGGGGTGTCGCT CCAGACCTATGATGACTTGTTAGCCAAAGACTGCCACT GCATA
115	HSA(C34S)-GA-(GGGGA)$_8$-(缺失4) GDF15	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGAGGGGAGGGGAGGGGAGGGGAGGGGAGGGGAGGG GAGGGGADHCPLGPGRCCRLHTVRASLEDLGWADWVLS PREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVP APCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
116	SEQ ID NO: 115 之DNA HSA(C34S)-GA-(GGGGA)$_8$-(缺失4) GDF15	GATGCACACAAGAGTGAGGTTGCTCATCGGTTTAAAGA TTTGGGAGAAGAAAATTTCAAAGCCTTGGTGTTGATTG CCTTTGCTCAGTATCTTCAGCAGTCCCCATTTGAAGATC ATGTAAAATTAGTGAATGAAGTAACTGAATTTGCAAAA ACATGTGTTGCTGATGAGTCAGCTGAAAATTGTGACAA ATCACTTCATACCCTTTTTGGAGACAAATTATGCACAG TTGCAACTCTTCGTGAAACCTATGGTGAAATGGCTGAC TGCTGTGCAAAACAAGAACCTGAGAGAAATGAATGCT TCTTGCAACACAAAGATGACAACCCAAACCTCCCCCGA TTGGTGAGACCAGAGGTTGATGTGATGTGCACTGCTTT TCATGACAATGAAGAGACATTTTTGAAAAAATACTTAT ATGAAATTGCCAGAAGACATCCTTACTTTTATGCCCCG GAACTCCTTTTCTTTGCTAAAAGGTATAAAGCTGCTTTT ACAGAATGTTGCCAAGCTGCTGATAAAGCTGCCTGCCT GTTGCCAAAGCTCGATGAACTTCGGGATGAAGGGAAG GCTTCGTCTGCCAAACAGAGACTCAAGTGTGCCAGTCT CCAAAAATTTGGAGAAAGAGCTTTCAAAGCATGGGCA GTAGCTCGCCTGAGCCAGAGATTTCCCAAAGCTGAGTT TGCAGAAGTTTCCAAGTTAGTGACAGATCTTACCAAAG TCCACACGGAATGCTGCCATGGAGATCTGCTTGAATGT GCTGATGACAGGGCGGACCTTGCCAAGTATATCTGTGA AAATCAAGATTCGATCTCCAGTAAACTGAAGGAATGCT GTGAAAAACCTCTGTTGGAAAAATCCCACTGCATTGCC GAAGTGGAAAATGATGAGATGCCTGCTGACTTGCCTTC ATTAGCTGCTGATTTTGTTGAAAGTAAGGATGTTTGCA AAAACTATGCTGAGGCAAAGGATGTCTTCCTGGGCATG TTTTTGTATGAATATGCAAGAAGGCATCCTGATTACTC TGTCGTGCTGCTGCTGAGACTTGCCAAGACATATGAAA CCACTCTAGAGAAGTGCTGTGCCGCTGCAGATCCTCAT

		GAATGCTATGCCAAAGTGTTCGATGAATTTAAACCTCT TGTGGAAGAGCCTCAGAATTTAATCAAACAAAATTGTG AGCTTTTTGAGCAGCTTGGAGAGTACAAATTCCAGAAT GCGCTATTAGTTCGTTACACCAAGAAAGTACCCCAAGT GTCAACTCCAACTCTTGTAGAGGTCTCAAGAAACCTAG GAAAAGTGGGCAGCAAATGTTGTAAACATCCTGAAGC AAAAAGAATGCCCTGTGCAGAAGACTATCTATCCGTGG TCCTGAACCAGTTATGTGTGTTGCATGAGAAAACGCCA GTAAGTGACAGAGTCACCAAATGCTGCACAGAATCCTT GGTGAACAGGCGACCATGCTTTTCAGCTCTGGAAGTCG ATGAAACATACGTTCCCAAAGAGTTTAATGCTGAAACA TTCACCTTCCATGCAGATATATGCACACTTTCTGAGAA GGAGAGACAAATCAAGAAACAAACTGCACTTGTTGAG CTCGTGAAACACAAGCCCAAGGCAACAAAAGAGCAAC TGAAAGCTGTTATGGATGATTTCGCAGCTTTTGTAGAG AAGTGCTGCAAGGCTGACGATAAGGAGACCTGCTTTGC CGAGGAGGGTAAAAAACTTGTTGCTGCAAGTCAAGCT GCCTTAGGGCTTGGTGCTGGAGGAGGCGGGGCGGGCG GCGGGGGTGCCGGTGGGGGTGGCGCAGGGGGAGGTGG TGCGGGTGGTGGTGGGGCTGGTGGGGGAGGTGCAGGC GGTGGCGGTGCCGGGGGGGGTGGCGCGGATCATTGCC CTCTCGGGCCCGGACGGTGTTGCCGCCTCCACACTGTG AGGGCTTCACTTGAAGACCTTGGATGGGCCGACTGGGT GCTGTCCCCAAGAGAGGTACAAGTCACAATGTGTATTG GCGCCTGCCCCAGCCAGTTTCGCGCCGCTAACATGCAC GCCCAGATAAAAACCAGCCTGCACCGCCTGAAGCCCG ACACGGTGCCAGCGCCCTGCTGCGTGCCCGCCAGCTAC AATCCCATGGTGCTCATTCAAAAGACCGACACCGGGGT GTCGCTCCAGACCTATGATGACTTGTTAGCCAAAGACT GCCACTGCATA
117	HSA(C34S)-(AP)$_{10}$-（缺失 4）GDF15	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LAPAPAPAPAPAPAPAPAPAPDHCPLGPGRCCRLHTVRAS LEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQI KTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQT YDDLLAKDCHCI
118	SEQ ID NO: 117 之 DNA	GATGCACACAAGAGTGAGGTTGCTCATCGGTTTAAAGA TTTGGGAGAAGAAAATTTCAAAGCCTTGGTGTTGATTG CCTTTGCTCAGTATCTTCAGCAGTCCCCATTTGAAGATC

	HSA(C34S)-$(AP)_{10}$-（缺失 4）GDF15	ATGTAAAATTAGTGAATGAAGTAACTGAATTTGCAAAA ACATGTGTTGCTGATGAGTCAGCTGAAAATTGTGACAA ATCACTTCATACCCTTTTTGGAGACAAATTATGCACAG TTGCAACTCTTCGTGAAACCTATGGTGAAATGGCTGAC TGCTGTGCAAAACAAGAACCTGAGAGAAATGAATGCT TCTTGCAACACAAAGATGACAACCCAAACCTCCCCCGA TTGGTGAGACCAGAGGTTGATGTGATGTGCACTGCTTT TCATGACAATGAAGAGACATTTTTGAAAAAATACTTAT ATGAAATTGCCAGAAGACATCCTTACTTTTATGCCCCG GAACTCCTTTTCTTTGCTAAAAGGTATAAAGCTGCTTTT ACAGAATGTTGCCAAGCTGCTGATAAAGCTGCCTGCCT GTTGCCAAAGCTCGATGAACTTCGGGATGAAGGGAAG GCTTCGTCTGCCAAACAGAGACTCAAGTGTGCCAGTCT CCAAAAATTTGGAGAAAGAGCTTTCAAAGCATGGGCA GTAGCTCGCCTGAGCCAGAGATTTCCCAAAGCTGAGTT TGCAGAAGTTTCCAAGTTAGTGACAGATCTTACCAAAG TCCACACGGAATGCTGCCATGGAGATCTGCTTGAATGT GCTGATGACAGGGCGGACCTTGCCAAGTATATCTGTGA AAATCAAGATTCGATCTCCAGTAAACTGAAGGAATGCT GTGAAAAACCTCTGTTGGAAAAATCCCACTGCATTGCC GAAGTGGAAAATGATGAGATGCCTGCTGACTTGCCTTC ATTAGCTGCTGATTTTGTTGAAAGTAAGGATGTTTGCA AAAACTATGCTGAGGCAAAGGATGTCTTCCTGGGCATG TTTTTGTATGAATATGCAAGAAGGCATCCTGATTACTC TGTCGTGCTGCTGCTGAGACTTGCCAAGACATATGAAA CCACTCTAGAGAAGTGCTGTGCCGCTGCAGATCCTCAT GAATGCTATGCCAAAGTGTTCGATGAATTTAAACCTCT TGTGGAAGAGCCTCAGAATTTAATCAAACAAAATTGTG AGCTTTTTGAGCAGCTTGGAGAGTACAAATTCCAGAAT GCGCTATTAGTTCGTTACACCAAGAAAGTACCCCAAGT GTCAACTCCAACTCTTGTAGAGGTCTCAAGAAACCTAG GAAAAGTGGGCAGCAAATGTTGTAAACATCCTGAAGC AAAAAGAATGCCCTGTGCAGAAGACTATCTATCCGTGG TCCTGAACCAGTTATGTGTGTTGCATGAGAAAACGCCA GTAAGTGACAGAGTCACCAAATGCTGCACAGAATCCTT GGTGAACAGGCGACCATGCTTTTCAGCTCTGGAAGTCG ATGAAACATACGTTCCCAAAGAGTTTAATGCTGAAACA TTCACCTTCCATGCAGATATATGCACACTTTCTGAGAA GGAGAGACAAATCAAGAAACAAACTGCACTTGTTGAG CTCGTGAAACACAAGCCCAAGGCAACAAAAGAGCAAC TGAAAGCTGTTATGGATGATTTCGCAGCTTTTGTAGAG AAGTGCTGCAAGGCTGACGATAAGGAGACCTGCTTTGC CGAGGAGGGTAAAAAACTTGTTGCTGCAAGTCAAGCT GCCTTAGGGCTTGCACCAGCCCCTGCCCCTGCACCTGC ACCTGCTCCCGCACCGGCTCCAGCCCCAGCTCCGGATC ATTGCCCTCTCGGGCCCGGACGGTGTTGCCGCCTCCAC ACTGTGAGGGCTTCACTTGAAGACCTTGGATGGGCCGA CTGGGTGCTGTCCCCAAGAGAGGTACAAGTCACAATGT GTATTGGCGCCTGCCCCAGCCAGTTTCGCGCCGCTAAC ATGCACGCCCAGATAAAAACCAGCCTGCACCGCCTGA AGCCCGACACGGTGCCAGCGCCCTGCTGCGTGCCCGCC AGCTACAATCCCATGGTGCTCATTCAAAAGACCGACAC

		CGGGGTGTCGCTCCAGACCTATGATGACTTGTTAGCCA AAGACTGCCACTGCATA
119	HSA(C34S)-(AP)$_{12}$-（缺失 4）GDF15	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LAPAPAPAPAPAPAPAPAPAPAPAPDHCPLGPGRCCRLHT VRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANM HAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVS LQTYDDLLAKDCHCI
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121	HSA(C34S)-GGS-(EGKSSGSGSESKST)$_3$-GGS-（缺失 4）GDF15	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGGSEGKSSGSGSESKSTEGKSSGSGSESKSTEGKSSGSGS ESKSTGGSDHCPLGPGRCCRLHTVRASLEDLGWADWVL SPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTV PAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
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	ESKST)3-GGS-（缺失 4）GDF15	TGCTGTGCAAAACAAGAACCTGAGAGAAATGAATGCT TCTTGCAACACAAAGATGACAACCCAAACCTCCCCCGA TTGGTGAGACCAGAGGTTGATGTGATGTGCACTGCTTT TCATGACAATGAAGAGACATTTTTGAAAAAATACTTAT ATGAAATTGCCAGAAGACATCCTTACTTTTATGCCCCG GAACTCCTTTTCTTTGCTAAAAGGTATAAAGCTGCTTTT ACAGAATGTTGCCAAGCTGCTGATAAAGCTGCCTGCCT GTTGCCAAAGCTCGATGAACTTCGGGATGAAGGGAAG GCTTCGTCTGCCAAACAGAGACTCAAGTGTGCCAGTCT CCAAAAATTTGGAGAAAGAGCTTTCAAAGCATGGGCA GTAGCTCGCCTGAGCCAGAGATTTCCCAAAGCTGAGTT TGCAGAAGTTTCCAAGTTAGTGACAGATCTTACCAAAG TCCACACGGAATGCTGCCATGGAGATCTGCTTGAATGT GCTGATGACAGGGCGGACCTTGCCAAGTATATCTGTGA AAATCAAGATTCGATCTCCAGTAAACTGAAGGAATGCT GTGAAAAACCTCTGTTGGAAAAATCCCACTGCATTGCC GAAGTGGAAAATGATGAGATGCCTGCTGACTTGCCTTC ATTAGCTGCTGATTTTGTTGAAAGTAAGGATGTTTGCA AAAACTATGCTGAGGCAAAGGATGTCTTCCTGGGCATG TTTTTGTATGAATATGCAAGAAGGCATCCTGATTACTC TGTCGTGCTGCTGCTGAGACTTGCCAAGACATATGAAA CCACTCTAGAGAAGTGCTGTGCCGCTGCAGATCCTCAT GAATGCTATGCCAAAGTGTTCGATGAATTTAAACCTCT TGTGGAAGAGCCTCAGAATTTAATCAAACAAAATTGTG AGCTTTTTGAGCAGCTTGGAGAGTACAAATTCCAGAAT GCGCTATTAGTTCGTTACACCAAGAAAGTACCCCAAGT GTCAACTCCAACTCTTGTAGAGGTCTCAAGAAACCTAG GAAAAGTGGGCAGCAAATGTTGTAAACATCCTGAAGC AAAAAGAATGCCCTGTGCAGAAGACTATCTATCCGTGG TCCTGAACCAGTTATGTGTGTTGCATGAGAAAACGCCA GTAAGTGACAGAGTCACAAAATGCTGTACTGAGAGCTT GGTCAACAGGCGGCCGTGCTTCAGCGCCCTCGAGGTGG ATGAGACTTATGTCCCAAAGGAGTTTAATGCGGAAACT TTTACTTTCCACGCAGACATTTGCACCTTGTCTGAAAA GGAAAGACAGATTAAGAAACAGACTGCTCTTGTGGAA CTGGTAAAACATAAACCAAAAGCTACGAAGGAGCAGC TTAAGGCTGTTATGGATGATTTCGCCGCGTTTGTCGAG AAGTGCTGCAAAGCGGACGATAAGGAAACTTGCTTTGC AGAGGAAGGTAAGAAACTCGTAGCGGCAAGTCAGGCT GCGCTTGGCCTTGGAGGCAGTGAAGGCAAATCCTCTGG GAGTGGCTCTGAAAGTAAATCCACCGAGGGCAAATCC AGTGGATCTGGGTCTGAATCTAAGTCTACCGAGGGGAA GTCTTCTGGCAGTGGGTCAGAATCTAAATCTACAGGCG GCTCTGACCATTGCCCGTTGGGACCAGGACGCTGCTGT CGCCTTCATACAGTGCGAGCGAGTTTGGAAGACCTGGG CTGGGCTGACTGGGTGCTTAGCCCTCGGGAGGTCCAGG TCACAATGTGCATTGGCGCGTGTCCCAGTCAATTTAGA GCAGCAAATATGCACGCCCAAATAAAAACCTCCCTGCA TAGGCTTAAGCCAGATACTGTCCCCGCACCATGCTGTG TGCCTGCTTCTTACAATCCTATGGTACTCATCCAGAAG ACCGACACGGGAGTTAGCCTCCAGACTTATGACGACCT CTTGGCTAAAGATTGCCATTGTATT

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127	HSA(C34S)-GGS-(EGKSSGSGSESKST)$_2$-GGS-（缺失 4）GDF15	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH VKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA TLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVR PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFF AKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAK QRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKL VTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISS KLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK DVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAK TYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETF TFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA VMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALG LGGSEGKSSGSGSESKSTEGKSSGSGSESKSTGGSDHCPL GPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGA CPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPM VLIQKTDTGVSLQTYDDLLAKDCHCI
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<110> 美商健生生物科技公司(Janssen Biotech, Inc.)

<120> GDF15 融合蛋白及其用途

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Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
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Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser

290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

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<400> 2

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu

100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

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Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

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<211> 585
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<220>
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<400> 3

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

111067-seq

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 4
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 4

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

Gly Gly Gly Ser
20

<210> 5
<211> 719
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 5

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro

85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
625 630 635 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 6
<211> 112
<212> PRT
<213> 人工序列

<220>

<223> GDF15變體

<400> 6

```
Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg
1               5                  10                  15

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp
            20                  25                  30

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys
        35                  40                  45

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser
    50                  55                  60

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro
65                  70                  75                  80

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

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
            100                 105                 110
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<210> 7
<211> 109
<212> PRT
<213> 人工序列

<220>
<223> GDF15變體

<400> 7

```
Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr
1               5                  10                  15

Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser
            20                  25                  30

Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln
        35                  40                  45

Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg
```

50 55 60

Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr
65 70 75 80

Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln
85 90 95

Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
100 105

<210> 8
<211> 108
<212> PRT
<213> 人工序列

<220>
<223> GDF15變體

<400> 8

Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val
1 5 10 15

Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro
20 25 30

Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe
35 40 45

Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu
50 55 60

Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn
65 70 75 80

Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr
85 90 95

Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
100 105

<210> 9
<211> 107

<212> PRT
<213> 人工序列

<220>
<223> GDF15變體

<400> 9

```
His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg
1               5                  10                  15

Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg
            20                  25                  30

Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg
        35                  40                  45

Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys
    50                  55                  60

Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro
65                  70                  75                  80

Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr
                85                  90                  95

Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
            100                 105
```

<210> 10
<211> 106
<212> PRT
<213> 人工序列

<220>
<223> GDF15變體

<400> 10

```
Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala
1               5                  10                  15

Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu
            20                  25                  30

Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala
```

35 40 45

Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro
50 55 60

Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met
65 70 75 80

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

Asp Leu Leu Ala Lys Asp Cys His Cys Ile
100 105

<210> 11
<211> 98
<212> PRT
<213> 人工序列

<220>
<223> GDF15變體

<400> 11

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
1 5 10 15

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
20 25 30

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
35 40 45

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
50 55 60

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
65 70 75 80

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
85 90 95

Cys Ile

<210> 12
<211> 42
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 12

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

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
35 40

<210> 13
<211> 42
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 13

Gly Ala Gly Gly Gly Gly Ala Gly Gly Gly Gly Ala Gly Gly Gly Gly
1 5 10 15

Ala Gly Gly Gly Gly Ala Gly Gly Gly Gly Ala Gly Gly Gly Gly Ala
20 25 30

Gly Gly Gly Gly Ala Gly Gly Gly Gly Ala
35 40

<210> 14
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 14

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
1 5 10 15

Ala Pro Ala Pro
20

<210> 15
<211> 24
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 15

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
1 5 10 15

Ala Pro Ala Pro Ala Pro Ala Pro
20

<210> 16
<211> 48
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 16

Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser
1 5 10 15

Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Glu
20 25 30

Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser
35 40 45

<210> 17
<211> 42
<212> PRT
<213> 人工序列

<220>

<223> 連接子

<400> 17

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

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

Pro Gly Gly Gly Ser Pro Gly Gly Gly Ser
35 40

<210> 18
<211> 42
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 18

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

Ser Ala Gly Gly Gly Ser Ala Gly Gly Gly Ser Ala Gly Gly Gly Ser
20 25 30

Ala Gly Gly Gly Ser Ala Gly Gly Gly Ser
35 40

<210> 19
<211> 34
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 19

Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser
1 5 10 15

Thr Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly
20 25 30

Gly Ser

<210> 20
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 20

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

<210> 21
<211> 44
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 21

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

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Thr
35 40

<210> 22
<211> 14
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 22

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

<210> 23
<211> 24
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 23

Ala Ser Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
1 5 10 15

Ala Pro Ala Pro Ala Pro Gly Thr
20

<210> 24
<211> 44
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 24

Ala Ser Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
1 5 10 15

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
20 25 30

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Gly Thr
35 40

<210> 25
<211> 711
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 25

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln

20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

111067-seq

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Ala Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Thr Ala Arg Asn Gly Asp His Cys Pro Leu
595 600 605

Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu
610 615 620

Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val
625 630 635 640

Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met
645 650 655

His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val
660 665 670

Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile
675 680 685

Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu
690 695 700

Ala Lys Asp Cys His Cys Ile
705 710

<210> 26
<211> 741
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 26

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

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Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365
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Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Ala Ser Gly Gly Gly Gly Ser

580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
595 600 605

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
610 615 620

Gly Gly Ser Gly Thr Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro
625 630 635 640

Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu
645 650 655

Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met
660 665 670

Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala
675 680 685

Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala
690 695 700

Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys
705 710 715 720

Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys
725 730 735

Asp Cys His Cys Ile
740

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Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys

225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Ala Ser Ala Pro Ala Pro Ala
580 585 590

Pro Ala Pro Ala Pro Gly Thr Ala Arg Asn Gly Asp His Cys Pro Leu
595 600 605

Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu
610 615 620

Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val
625 630 635 640

Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met
645 650 655

His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val
660 665 670

Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile
675 680 685

Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu
690 695 700

Ala Lys Asp Cys His Cys Ile
705 710

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Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Ala Ser Ala Pro Ala Pro Ala
580 585 590

Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Gly
595 600 605

Thr Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys
610 615 620

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp
625 630 635 640

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala
645 650 655

Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr
660 665 670

Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val
675 680 685

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly
690 695 700

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys
705 710 715 720

Ile

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His

450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Ala Ser Ala Pro Ala Pro Ala
580 585 590

Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
595 600 605

Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
610 615 620

Pro Ala Pro Gly Thr Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro
625 630 635 640

Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu
645 650 655

Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met
660 665 670

Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala
675 680 685

Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala
690 695 700

Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys
705 710 715 720

Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys
725 730 735

Asp Cys His Cys Ile
740

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Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu

100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Ala Ser Glu Ala Ala Ala Lys
580 585 590

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Gly
595 600 605

Thr Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys
610 615 620

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp
625 630 635 640

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala
645 650 655

Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr
660 665 670

Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val
675 680 685

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly
690 695 700

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys
705 710 715 720

Ile

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<223> 融合蛋白

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
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Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205
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Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Ala Ser Glu Ala Ala Ala Lys
580 585 590

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu
595 600 605

Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala
610 615 620

Ala Ala Lys Gly Thr Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro
625 630 635 640

Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu

645 650 655

Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met
660 665 670

Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala
675 680 685

Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala
690 695 700

Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys
705 710 715 720

Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys
725 730 735

Asp Cys His Cys Ile
740

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<400> 32

Ala Ser Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala
1 5 10 15

Lys Glu Ala Ala Ala Lys Gly Thr
20

<210> 33
<211> 44
<212> PRT
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<223> 連接子

<400> 33

Ala Ser Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala
1 5 10 15

Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys
20 25 30

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Gly Thr
35 40

<210> 34
<211> 10
<212> PRT
<213> 人工序列

<220>
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<400> 34

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

<210> 35
<211> 15
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<213> 人工序列

<220>
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<400> 35

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

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<213> 人工序列

<220>
<223> 融合蛋白

<400> 36

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln

20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

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Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460
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Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys
595 600 605

Ser Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala
610 615 620

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly
625 630 635 640

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys
645 650 655

Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys
660 665 670

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr
675 680 685

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His
690 695 700

Cys Ile
705

<210> 37
<211> 705
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 37

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser

580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys
595 600 605

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp
610 615 620

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala
625 630 635 640

Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr
645 650 655

Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val
660 665 670

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly
675 680 685

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys
690 695 700

Ile
705

<210> 38
<211> 20
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 38

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

Gly Gly Gly Ser
20

<210> 39
<211> 25

<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 39

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

<210> 40
<211> 719
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 40

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His

115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

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Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

```
Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
            580                 585                 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
        595                 600                 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
    610                 615                 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
625                 630                 635                 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
                645                 650                 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
            660                 665                 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
        675                 680                 685

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
    690                 695                 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705                 710                 715
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<210> 41
<211> 30
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 41

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Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1               5                   10                  15
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Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

<210> 42
<211> 35
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 42

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser
35

<210> 43
<211> 40
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 43

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser
35 40

<210> 44
<211> 45
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 44

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
35 40 45

<210> 45
<211> 50
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 45

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser
50

<210> 46
<211> 55
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 46

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Gly Ser
50 55

<210> 47
<211> 60
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 47

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
50 55 60

<210> 48
<211> 719
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 48

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser

465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
625 630 635 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 49
<211> 65
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 49

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
50 55 60

Ser
65

<210> 50
<211> 70
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 50

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
50 55 60

Ser Gly Gly Gly Gly Ser
65 70

<210> 51
<211> 75
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 51

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
50 55 60

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65 70 75

<210> 52
<211> 80
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 52

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
50 55 60

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65 70 75 80

<210> 53
<211> 85
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 53

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
50 55 60

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65 70 75 80

Gly Gly Gly Gly Ser
85

<210> 54
<211> 90
<212> PRT

<213> 人工序列

<220>
<223> 連接子

<400> 54

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
50 55 60

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65 70 75 80

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
85 90

<210> 55
<211> 739
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 55

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His

275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

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Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
595 600 605

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
610 615 620

Gly Gly Ser Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg
625 630 635 640

Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp
645 650 655

Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile
660 665 670

Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile
675 680 685

Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys
690 695 700

Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp
705 710 715 720

Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys
725 730 735

His Cys Ile

<210> 56
<211> 717
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 56

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

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Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Ala Pro Ala Pro Ala Pro Ala
580 585 590

Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Arg Asn
595 600 605

Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr
610 615 620

Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser
625 630 635 640

Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln
645 650 655

Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg
660 665 670

Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr
675 680 685

Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln
690 695 700

Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 57
<211> 719
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 57

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr

485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
625 630 635 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 58
<211> 719
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 58

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ala Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala

165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
625 630 635 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 59
<211> 717
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 59

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Ala Pro Ala Pro Ala Pro Ala
580 585 590

Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Arg Asn
595 600 605

Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr
610 615 620

Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser
625 630 635 640

Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln
645 650 655

Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg
660 665 670

Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr
675 680 685

Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln
690 695 700

Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 60

<211> 739
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 60

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro

405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
595 600 605

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
610 615 620

Gly Gly Ser Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg
625 630 635 640

Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp
645 650 655

Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile
660 665 670

Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile
675 680 685

Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys
690 695 700

Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp
705 710 715 720

Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys
725 730 735

His Cys Ile

<210> 61
<211> 95
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 61

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly

50 55 60

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65 70 75 80

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
85 90 95

<210> 62
<211> 100
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 62

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
50 55 60

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65 70 75 80

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
85 90 95

Gly Gly Gly Ser
100

<210> 63
<211> 10
<212> PRT
<213> 人工序列

<220>

<223> 連接子

<400> 63

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys
1 5 10

<210> 64
<211> 719
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 64

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg

145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
625 630 635 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Val Leu Arg Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 65
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<212> PRT
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<400> 65

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
625 630 635 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Val Leu Trp Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile

705 710 715

<210> 66
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<223> 融合蛋白

<400> 66

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu

385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
625 630 635 640

Ala Ala Pro Ala Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 67
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<400> 67

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu

65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
625 630 635 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Ala Leu Ala Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Ala Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 68
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<212> PRT
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<400> 68

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val

625 630 635 640

Ala Ala Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Val Leu Ala Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 69
<211> 719
<212> PRT
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<223> 融合蛋白

<400> 69

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala

305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
625 630 635 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Ala Leu Ala Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 70
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<212> PRT
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<220>
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<400> 70

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
625 630 635 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Trp Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 71
<211> 719
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 71

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys

545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Ala Val
625 630 635 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 72
<211> 719
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 72

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys

225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Ala Ala Asp Trp Val
625 630 635 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 73
<211> 719
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 73

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

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Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
            580                 585                 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
        595                 600                 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
    610                 615                 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
625                 630                 635                 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
                645                 650                 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Ala Ile Lys Thr Ala Leu
            660                 665                 670

His Ala Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
        675                 680                 685

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
    690                 695                 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705                 710                 715
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<210> 74
<211> 719
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 74

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Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30
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Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser

465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Ala Ala Asp Trp Val
625 630 635 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Ala Ala Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 75
<211> 719
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 75

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg

145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
595 600 605

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
610 615 620

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Ala Ala Asp Ala Val
625 630 635 640

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
645 650 655

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
660 665 670

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
675 680 685

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
690 695 700

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 76
<211> 2157
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 76
gacgcccaca agagcgaggt ggcccaccgg ttcaaggacc tgggcgagga gaacttcaag 60

gccctggtgc tgatcgcctt cgcccagtac ctgcagcagt ccccccttcga ggaccacgtg 120

aagctggtga acgaggtgac cgagttcgcc aagacctgcg tggccgacga gagcgccgag 180

aactgcgaca agagcctgca caccctgttc ggcgacaagc tgtgcaccgt ggccaccctg 240

cgggagacct acggcgagat ggccgactgc tgcgccaagc aggagcccga gcggaacgag 300

tgcttcctgc agcacaagga cgacaacccc aacctgcccc ggctggtgcg gcccgaggtg 360

gacgtgatgt gcaccgcctt ccacgacaac gaggagacct tcctgaagaa gtacctgtac 420

gagatcgccc ggcggcaccc ctacttctac gcccccgagc tgctgttctt cgccaagcgg 480

tacaaggccg ccttcaccga gtgctgccag gccgccgaca aggccgcctg cctgctgccc 540

aagctggacg agctgcggga cgagggcaag gccagcagcg ccaagcagcg gctgaagtgc 600

gccagcctgc agaagttcgg cgagcgggcc ttcaaggcct gggccgtggc ccggctgagc 660

cagcggttcc ccaaggccga gttcgccgag gtgagcaagc tggtgaccga cctgaccaag 720

gtgcacaccg agtgctgcca cggcgacctg ctggagtgcg ccgacgaccg ggccgacctg 780

gccaagtaca tctgcgagaa ccaggacagc atcagcagca agctgaagga gtgctgcgag 840

aagcccctgc tggagaagag ccactgcatc gccgaggtgg agaacgacga gatgcccgcc 900

gacctgccca gcctggccgc cgacttcgtg gagagcaagg acgtgtgcaa gaactacgcc 960

gaggccaagg acgtgttcct gggcatgttc ctgtacgagt acgcccggcg gcaccccgac 1020

tacagcgtgg tgctgctgct gcggctggcc aagacctacg agaccaccct ggagaagtgc 1080

tgcgccgccg ccgaccccca cgagtgctac gccaaggtgt tcgacgagtt caagcccctg 1140

gtggaggagc cccagaacct gatcaagcag aactgcgagc tgttcgagca gctgggcgag 1200

tacaagttcc agaacgccct gctggtgcgg tacaccaaga aggtgcccca ggtgagcacc 1260

cccaccctgg tggaggtgag ccggaacctg ggcaaggtgg gcagcaagtg ctgcaagcac 1320

cccgaggcca agcggatgcc ctgcgccgag gactacctga gcgtggtgct gaaccagctg 1380

tgcgtgctgc acgagaagac ccccgtgagc gaccgggtga ccaagtgctg caccgagagc 1440

ctggtgaacc ggcggccctg cttcagcgcc ctggaggtgg acgagaccta cgtgcccaag 1500

gagttcaacg ccgagacctt caccttccac gccgacatct gcaccctgag cgagaaggag 1560

cggcagatca agaagcagac cgccctggtg gagctggtga agcacaagcc caaggccacc 1620

aaggagcagc tgaaggccgt gatggacgac ttcgccgcct tcgtggagaa gtgctgcaag 1680

gccgacgaca aggagacctg cttcgccgag gagggcaaga agctggtggc cgccagccag 1740

gccgccctgg gcctgggcag cggcggcggc ggcagcggcg gcggcggatc tggtggaggt 1800

ggcagtggag gaggggatc cgctcgcaac ggtgaccact gccctctggg tcctggtcgc 1860

tgctgccgcc tgcacaccgt tcgcgcttct ctggaagacc tgggttgggc tgactgggtt 1920

ctgtctcctc gcgaagttca ggttaccatg tgcatcggtg cttgcccttc tcagttccgc 1980

gctgctaaca tgcacgctca gatcaaaacc tctctgcacc gcctgaaacc tgacaccgtt 2040

cctgctcctt gctgcgttcc tgcttcttac aaccctatgg ttctgatcca gaaaaccgac 2100

accggtgttt ctctgcagac ctacgacgac ctgctggcta aagactgcca ctgcatc 2157

<210> 77
<211> 2133
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 77
gatgctcata agtccgaagt cgcccacaga ttcaaggacc tcggagaaga aaattttaag 60

gccctcgtgc ttatcgcctt cgcccaatac ctccagcagt ccccgttcga ggaccacgtg 120

aagctcgtga acgaagtgac cgagtttgcc aagacttgtg tggcggatga atccgccgag 180

aactgcgaca agagcctcca cacgctgttc ggcgacaagc tgtgcaccgt cgccacgctg 240

agagaaactt acggagagat ggccgactgc tgcgcaaagc aggagccgga acggaacgaa 300

tgcttcctgc aacataagga cgataaccct aacttgcctc gcctggtccg ccctgaggtc 360

gacgtgatgt gcaccgcgtt ccacgacaac gaggaaacct ttcttaagaa gtacctgtac 420

gagattgcgc ggaggcaccc ttatttctac gccccccgaac tgttgttctt cgccaagcgg 480

tacaaggctg cctttaccga atgctgccag gccgccgata aggcggcttg cctgctgccg 540

aagctcgacg agttgcgcga tgaggggaag gcgtcctccg ctaagcagcg gctgaaatgt 600

gcgagcctcc agaagttcgg ggagcgcgcc ttcaaggcct gggccgtggc gcgcctgtct 660

caacggttcc cgaaggccga gttcgccgaa gtgtcgaagc tggtcaccga cctgacgaaa 720

gtgcacaccg aatgttgtca cggcgatctg ctggaatgcg ccgatgacag agccgatttg 780

gccaagtaca tctgcgaaaa ccaggacagc atttcgtcaa agctgaagga atgctgcgaa 840

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gaagccaagg acgtgttcct gggaatgttt ctgtatgagt acgcccgccg ccacccggac 1020

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accatgtgca tcggcgcgtg cccgagccag ttccgggcgg caaacatgca cgcgcagatc 1980

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gatgacttgt tagccaaaga ctgccactgc ata 2133

<210> 78
<211> 2223
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 78
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aagctcgtga acgaagtgac cgagtttgcc aagacttgtg tggcggatga atccgccgag 180

aactgcgaca agagcctcca cacgctgttc ggcgacaagc tgtgcaccgt cgccacgctg 240

agagaaactt acggagagat ggccgactgc tgcgcaaagc aggagccgga acggaacgaa 300

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gacctcccgt ccctggccgc cgatttcgtg gagtcgaagg atgtgtgcaa gaactacgca 960

gaagccaagg acgtgttcct gggaatgttt ctgtatgagt acgcccgccg ccacccggac 1020

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ata 2223

<210> 79
<211> 2133
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 79
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aagctcgtga acgaagtgac cgagtttgcc aagacttgtg tggcggatga atccgccgag 180

aactgcgaca agagcctcca cacgctgttc ggcgacaagc tgtgcaccgt cgccacgctg 240

agagaaactt acggagagat ggccgactgc tgcgcaaagc aggagccgga acggaacgaa 300

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gacgtgatgt gcaccgcgtt ccacgacaac gaggaaacct ttcttaagaa gtacctgtac 420

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aagctcgacg agttgcgcga tgaggggaag gcgtcctccg ctaagcagcg gctgaaatgt 600

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agctacaatc ccatggtgct cattcaaaag accgacaccg gggtgtcgct ccagacctat 2100

gatgacttgt tagccaaaga ctgccactgc ata 2133

<210> 80
<211> 2163
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 80
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aagctcgtga acgaagtgac cgagtttgcc aagacttgtg tggcggatga atccgccgag 180

aactgcgaca agagcctcca cacgctgttc ggcgacaagc tgtgcaccgt cgccacgctg 240

agagaaactt acggagagat ggccgactgc tgcgcaaagc aggagccgga acggaacgaa 300

tgcttcctgc aacataagga cgataaccct aacttgcctc gcctggtccg ccctgaggtc 360

gacgtgatgt gcaccgcgtt ccacgacaac gaggaaacct ttcttaagaa gtacctgtac 420

gagattgcgc ggaggcaccc ttatttctac gcccccgaac tgttgttctt cgccaagcgg 480

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atc 2163

<210> 81
<211> 2223
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 81
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aagctcgtga acgaagtgac cgagtttgcc aagacttgtg tggcggatga atccgccgag 180

aactgcgaca agagcctcca cacgctgttc ggcgacaagc tgtgcaccgt cgccacgctg 240

agagaaactt acggagagat ggccgactgc tgcgcaaagc aggagccgga acggaacgaa 300

tgcttcctgc aacataagga cgataaccct aacttgcctc gcctggtccg ccctgaggtc 360

gacgtgatgt gcaccgcgtt ccacgacaac gaggaaacct ttcttaagaa gtacctgtac 420

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caacggttcc cgaaggccga gttcgccgaa gtgtcgaagc tggtcaccga cctgacgaaa 720

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accgacaccg gggtgtcgct ccagacctat gatgacttgt tagccaaaga ctgccactgc 2220

ata 2223

<210> 82
<211> 2163
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 82
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gccctcgtgc ttatcgcctt cgcccaatac ctccagcagt ccccgttcga ggaccacgtg 120

aagctcgtga acgaagtgac cgagtttgcc aagacttgtg tggcggatga atccgccgag 180

aactgcgaca agagcctcca cacgctgttc ggcgacaagc tgtgcaccgt cgccacgctg 240

agagaaactt acggagagat ggccgactgc tgcgcaaagc aggagccgga acggaacgaa 300

tgcttcctgc aacataagga cgataaccct aacttgcctc gcctggtccg ccctgaggtc 360

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ata 2163

<210> 83
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<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 83
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gccctggtgc tgatcgcctt cgcccagtac ctgcagcagt ccccccttcga ggaccacgtg 120

aagctggtga acgaggtgac cgagttcgcc aagacctgcg tggccgacga gagcgccgag 180

aactgcgaca agagcctgca caccctgttc ggcgacaagc tgtgcaccgt ggccaccctg 240

cgggagacct acggcgagat ggccgactgc tgcgccaagc aggagcccga gcggaacgag 300

tgcttcctgc agcacaagga cgacaacccc aacctgcccc ggctggtgcg gcccgaggtg 360

gacgtgatgt gcaccgcctt ccacgacaac gaggagacct tcctgaagaa gtacctgtac 420

gagatcgccc ggcggcaccc ctacttctac gcccccgagc tgctgttctt cgccaagcgg 480

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gccagcctgc agaagttcgg cgagcgggcc ttcaaggcct gggccgtggc ccggctgagc 660

cagcggttcc ccaaggccga gttcgccgag gtgagcaagc tggtgaccga cctgaccaag 720

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gaggccaagg acgtgttcct gggcatgttc ctgtacgagt acgcccggcg gcaccccgac 1020

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gtggaggagc cccagaacct gatcaagcag aactgcgagc tgttcgagca gctgggcgag 1200

tacaagttcc agaacgccct gctggtgcgg tacaccaaga aggtgcccca ggtgagcacc 1260

cccaccctgg tggaggtgag ccggaacctg ggcaaggtgg gcagcaagtg ctgcaagcac 1320

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gcggcaaaca tgcacgcgca gatcaagacg agcctgcacc gcctgaagcc cgacacggtg 2040

ccagcgccct gctgcgtgcc cgccagctac aatcccatgg tgctcattca aaagaccgac 2100

accggggtgt cgctccagac ctatgatgac ttgttagcca aagactgcca ctgcata 2157

<210> 84
<211> 2217
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 84
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gccttggtgt tgattgcctt tgctcagtat cttcagcagg ccccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

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ctgtcgccac gggaggtgca agtgaccatg tgcatcggcg cgtgcccgag ccagttccgg 2040

gcggcaaaca tgcacgcgca gatcaagacg agcctgcacc gcctgaagcc cgacacggtg 2100

ccagcgccct gctgcgtgcc cgccagctac aatcccatgg tgctcattca aaagaccgac 2160

accggggtgt cgctccagac ctatgatgac ttgttagcca aagactgcca ctgcata 2217

<210> 85
<211> 2151
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 85
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gccttggtgt tgattgcctt tgctcagtat cttcagcagg ccccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

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tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

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tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc 1440

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ccctgctgcg tgcccgccag ctacaatccc atggtgctca ttcaaaagac cgacaccggg 2100

gtgtcgctcc agacctatga tgacttgtta gccaaagact gccactgcat a 2151

<210> 86
<211> 2157
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 86
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gccttggtgt tgattgcctt tgctcagtat cttcagcagt ccccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

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gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

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tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc 1440

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accggggtgt cgctccagac ctatgatgac ttgttagcca aagactgcca ctgcata 2157

<210> 87
<211> 2157
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 87
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gccctggtgc tgatcgcctt cgcccagtac ctgcagcaga gcccttcga ggaccacgtg 120

aagctggtca acgaagtgac cgagttcgcc aagacctgcg tggccgacga gagcgccgag 180

aactgcgaca agagcctgca caccctgttc ggcgacaagc tgtgcaccgt ggccaccctg 240

cgggaaacct acggcgagat ggccgactgc tgcgccaagc aggaacccga gcggaacgag 300

tgcttcctgc agcacaagga cgacaacccc aacctgccca gactcgtgcg gcccgaggtg 360

gacgtgatgt gcaccgcctt ccacgacaac gaggaaacct tcctgaagaa gtacctgtac 420

gagatcgcca gacggcaccc ctacttctac gcccccgagc tgctgttctt cgccaagcgg 480

tacaaggccg ccttcaccga gtgctgccag gccgccgata aggccgcctg cctgctgccc 540

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gaggccaagg atgtgttcct gggcatgttc ctgtatgagt acgcccgcag acaccccgac 1020

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gccgccaaca tgcacgccca gatcaagacc agcctgcacc ggctgaagcc cgacaccgtg 2040

cctgcccctt gttgcgtgcc cgccagctac aaccccatgg tgctgattca gaaaaccgac 2100

accggcgtgt ccctgcagac ctacgacgat ctgctggcca aggactgcca ctgcatc 2157

<210> 88
<211> 2157
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 88
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gccttggtgt tgattgcctt tgctcagtat cttcagcagg ccccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

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gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

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tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

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ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

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gcggcaaaca tgcacgcgca gatcaagacg agcctgcacc gcctgaagcc cgacacggtg 2040

ccagcgccct gctgcgtgcc cgccagctac aatcccatgg tgctcattca aaagaccgac 2100

accggggtgt cgctccagac ctatgatgac ttgttagcca aagactgcca ctgcata 2157

<210> 89
<211> 2151
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 89
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gccttggtgt tgattgcctt tgctcagtat cttcagcagt ccccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

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gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag 1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

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gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag 1560

agacaaatca agaaacaaac tgcacttgtt gagctcgtga aacacaagcc caaggcaaca 1620

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gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc tgcaagtcaa 1740

gctgccttag gcttagcacc tgcccccgct ccagcacccg ccccagcccc tgctcccgca 1800

ccagctcctg caccagcgcg caacggggac cactgtccgc tcgggcccgg gcgttgctgc 1860

cgtctgcaca cggtccgcgc gtcgctggaa gacctgggct gggccgattg ggtgctgtcg 1920

ccacgggagg tgcaagtgac catgtgcatc ggcgcgtgcc cgagccagtt ccgggcggca 1980

aacatgcacg cgcagatcaa gacgagcctg caccgcctga agcccgacac ggtgccagcg 2040

ccctgctgcg tgcccgccag ctacaatccc atggtgctca ttcaaaagac cgacaccggg 2100

gtgtcgctcc agacctatga tgacttgtta gccaaagact gccactgcat a 2151

<210> 90
<211> 2217
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 90
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aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag 1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc 1440

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gcggcaaaca tgcacgcgca gatcaagacg agcctgcacc gcctgaagcc cgacacggtg 2100

ccagcgccct gctgcgtgcc cgccagctac aatcccatgg tgctcattca aaagaccgac 2160

accggggtgt cgctccagac ctatgatgac ttgttagcca aagactgcca ctgcata 2217

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<211> 2157
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 91
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gccctggtgc tgatcgcctt cgcccagtac ctgcagcagt ccccttcga ggaccacgtg 120

aagctggtga acgaggtgac cgagttcgcc aagacctgcg tggccgacga gagcgccgag 180

aactgcgaca agagcctgca caccctgttc ggcgacaagc tgtgcaccgt ggccaccctg 240

cgggagacct acggcgagat ggccgactgc tgcgccaagc aggagcccga gcggaacgag 300

tgcttcctgc agcacaagga cgacaacccc aacctgcccc ggctggtgcg gcccgaggtg 360

gacgtgatgt gcaccgcctt ccacgacaac gaggagacct tcctgaagaa gtacctgtac 420

gagatcgccc ggcggcaccc ctacttctac gcccccgagc tgctgttctt cgccaagcgg 480

tacaaggccg ccttcaccga gtgctgccag gccgccgaca aggccgcctg cctgctgccc 540

aagctggacg agctgcggga cgagggcaag gccagcagcg ccaagcagcg gctgaagtgc 600

gccagcctgc agaagttcgg cgagcgggcc ttcaaggcct gggccgtggc ccggctgagc 660

cagcggttcc ccaaggccga gttcgccgag gtgagcaagc tggtgaccga cctgaccaag 720

gtgcacaccg agtgctgcca cggcgacctg ctggagtgcg ccgacgaccg ggccgacctg 780

gccaagtaca tctgcgagaa ccaggacagc atcagcagca agctgaagga gtgctgcgag 840

aagcccctgc tggagaagag ccactgcatc gccgaggtgg agaacgacga gatgcccgcc 900

gacctgccca gcctggccgc cgacttcgtg gagagcaagg acgtgtgcaa gaactacgcc 960

gaggccaagg acgtgttcct gggcatgttc ctgtacgagt acgcccggcg gcaccccgac 1020

tacagcgtgg tgctgctgct gcggctggcc aagacctacg agaccaccct ggagaagtgc 1080

tgcgccgccg ccgaccccca cgagtgctac gccaaggtgt tcgacgagtt caagcccctg 1140

gtggaggagc cccagaacct gatcaagcag aactgcgagc tgttcgagca gctgggcgag 1200

tacaagttcc agaacgccct gctggtgcgg tacaccaaga aggtgcccca ggtgagcacc 1260

cccaccctgg tggaggtgag ccggaacctg ggcaaggtgg gcagcaagtg ctgcaagcac 1320

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gctgctaaca tgcacgcttg gatcaaaacc tctctgcacc gcctgaaacc tgacaccgtt 2040

cctgctcctt gctgcgttcc tgcttcttac aaccctatgg ttctgatcca gaaaaccgac 2100

accggtgttt ctctgcagac ctacgacgac ctgctggcta aagactgcca ctgcatc 2157

<210> 92
<211> 735
<212> PRT
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 92

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
595 600 605

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
610 615 620

Gly Gly Ser Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
625 630 635 640

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
645 650 655

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
660 665 670

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu

675 680 685

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
690 695 700

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
705 710 715 720

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
725 730 735

<210> 93
<211> 734
<212> PRT
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 93

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr

340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
595 600 605

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
610 615 620

Gly Gly Ser His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His
625 630 635 640

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu
645 650 655

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser
660 665 670

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His
675 680 685

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser
690 695 700

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu
705 710 715 720

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
725 730

<210> 94
<211> 735
<212> PRT
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 94

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111067-seq

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Ile Ala Phe Ala Gln Tyr Leu Gln Gln Ser Pro Phe Glu Asp His Val
        35                  40                  45

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
    50                  55                  60

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
65                  70                  75                  80

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
                85                  90                  95

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
            100                 105                 110

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
        115                 120                 125

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
    130                 135                 140

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
145                 150                 155                 160

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
                165                 170                 175

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
            180                 185                 190

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
        195                 200                 205

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
    210                 215                 220
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Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
225 230 235 240

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
245 250 255

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
260 265 270

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
275 280 285

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
290 295 300

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
305 310 315 320

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
325 330 335

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
340 345 350

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
355 360 365

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
370 375 380

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
385 390 395 400

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
405 410 415

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
420 425 430

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
435 440 445

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
450 455 460

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
465 470 475 480

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
485 490 495

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
500 505 510

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
515 520 525

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
530 535 540

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
545 550 555 560

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
565 570 575

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
580 585 590

Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
595 600 605

Gly Ser Gly Gly Gly Gly Ser Leu Glu Val Leu Phe Gln Gly Pro Ala
610 615 620

Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
625 630 635 640

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
645 650 655

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
660 665 670

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
675 680 685

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
690 695 700

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
705 710 715 720

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
725 730 735

<210> 95
<211> 2205
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 95
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aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

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gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

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tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

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cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

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gaggtacaag tcacaatgtg tattggcgcc tgccccagcc agtttcgcgc cgctaacatg 2040

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tgcgtgcccg ccagctacaa tcccatggtg ctcattcaaa agaccgacac cggggtgtcg 2160

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<211> 327
<212> DNA
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tgcatcggcg cgtgcccgag ccagttccgg gcggcaaaca tgcacgcgca gatcaagacg 180

agcctgcacc gcctgaagcc cgacacggtg ccagcgccct gctgcgtgcc cgccagctac 240

aatcccatgg tgctcattca aaagaccgac accggggtgt cgctccagac ctatgatgac 300

ttgttagcca aagactgcca ctgcata 327

<210> 97
<211> 324
<212> DNA
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atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc 180

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 240

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 300

ttagccaaag actgccactg cata 324

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gaagaccttg gatgggccga ctgggtgctg tccccaagag aggtacaagt cacaatgtgt 120

attggcgcct gccccagcca gtttcgcgcc gctaacatgc acgcccagat aaaaaccagc 180

ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat 240

cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg 300

ttagccaaag actgccactg cata 324

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gaggacctcg gctgggctga ctgggtgctg tccccacggg aggtgcaagt gaccatgtgc 120

atcggcgcct gtccttcgca attccgggcc gcgaatatgc acgcccagat caagacctcc 180

ctgcatcgcc tcaagcccga cactgtgcct gctccatgct gtgtgccggc ctcctataac 240

cccatggtgc tgatccagaa aaccgatacc ggcgtcagcc tgcagacgta tgatgatctg 300

ctggccaagg actgccattg catc 324

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<211> 321
<212> DNA
<213> 人工序列

<220>
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gacctgggct gggccgattg ggtgctgtcg ccacgggagg tgcaagtgac catgtgcatc 120

ggcgcgtgcc cgagccagtt ccgggcggca aacatgcacg cgcagatcaa gacgagcctg 180

caccgcctga agcccgacac ggtgccagcg ccctgctgcg tgcccgccag ctacaatccc 240

atggtgctca ttcaaaagac cgacaccggg gtgtcgctcc agacctatga tgacttgtta 300

gccaaagact gccactgcat a 321

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<211> 321
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gaccttggat gggccgactg ggtgctgtcc ccaagagagg tacaagtcac aatgtgtatt 120

ggcgcctgcc ccagccagtt tcgcgccgct aacatgcacg cccagataaa aaccagcctg 180

caccgcctga agcccgacac ggtgccagcg ccctgctgcg tgcccgccag ctacaatccc 240

atggtgctca ttcaaaagac cgacaccggg gtgtcgctcc agacctatga tgacttgtta 300

gccaaagact gccactgcat a 321

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<211> 321
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ggcgcctgtc cttcgcaatt ccgggccgcg aatatgcacg cccagatcaa gacctccctg 180

catcgcctca agcccgacac tgtgcctgct ccatgctgtg tgccggcctc ctataacccc 240

atggtgctga tccagaaaac cgataccggc gtcagcctgc agacgtatga tgatctgctg 300

gccaaggact gccattgcat c 321

<210> 103
<211> 318
<212> DNA
<213> 人工序列

<220>
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ctgggctggg ccgattgggt gctgtcgcca cgggaggtgc aagtgaccat gtgcatcggc 120

gcgtgcccga gccagttccg ggcggcaaac atgcacgcgc agatcaagac gagcctgcac 180

cgcctgaagc ccgacacggt gccagcgccc tgctgcgtgc ccgccagcta caatcccatg 240

gtgctcattc aaaagaccga caccggggtg tcgctccaga cctatgatga cttgttagcc 300

aaagactgcc actgcata 318

<210> 104
<211> 318
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<213> 人工序列

<220>
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cttggatggg ccgactgggt gctgtcccca agagaggtac aagtcacaat gtgtattggc 120

gcctgcccca gccagtttcg cgccgctaac atgcacgccc agataaaaac cagcctgcac 180

cgcctgaagc ccgacacggt gccagcgccc tgctgcgtgc ccgccagcta caatcccatg 240

gtgctcattc aaaagaccga caccggggtg tcgctccaga cctatgatga cttgttagcc 300

aaagactgcc actgcata 318

<210> 105
<211> 318
<212> DNA
<213> 人工序列

<220>
<223> GDF15變體

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ctcggctggg ctgactgggt gctgtcccca cgggaggtgc aagtgaccat gtgcatcggc 120

gcctgtcctt cgcaattccg ggccgcgaat atgcacgccc agatcaagac ctccctgcat 180

cgcctcaagc ccgacactgt gcctgctcca tgctgtgtgc cggcctccta taaccccatg 240

gtgctgatcc agaaaaccga taccggcgtc agcctgcaga cgtatgatga tctgctggcc 300

aaggactgcc attgcatc 318

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<211> 294
<212> DNA
<213> 人工序列

<220>
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tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg 120

gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca 180

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc 240

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata 294

<210> 107
<211> 294
<212> DNA
<213> 人工序列

<220>
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gctaacatgc acgcccagat aaaaaccagc ctgcaccgcc tgaagcccga cacggtgcca 180

gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc 240

ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg cata 294

<210> 108
<211> 294
<212> DNA
<213> 人工序列

<220>
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<400> 108
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tccccacggg aggtgcaagt gaccatgtgc atcggcgcct gtccttcgca attccgggcc 120

gcgaatatgc acgcccagat caagacctcc ctgcatcgcc tcaagcccga cactgtgcct 180

gctccatgct gtgtgccggc ctcctataac cccatggtgc tgatccagaa aaccgatacc 240

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<210> 109
<211> 2217
<212> DNA

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<213> 人工序列

<220>
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gccctggtcc tgatcgcgtt cgcccagtac ctccagcagt ccccgtttga ggaccacgtc 120

aagcttgtga acgaagtgac cgagttcgca aagacttgtg tggccgatga gtccgccgaa 180

aactgcgaca agtccctgca caccttgttc ggagacaagc tgtgcaccgt cgcgactttg 240

cgggagactt acggcgaaat ggcggactgc tgcgcaaagc aggagcccga aaggaacgag 300

tgcttcctgc aacacaagga cgacaacccg aaccttccga gactcgtgcg gcctgaggtc 360

gacgtgatgt gcactgcatt ccatgataac gaagaaacat tcctgaagaa gtacctgtat 420

gaaattgcca gacgccaccc gtacttctac gcccccgaac tgctgttctt cgccaagaga 480

tacaaggccg cctttaccga atgttgtcaa gccgccgata aggcagcgtg cctgctgccg 540

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cagaggttcc ccaaggcgga gtttgccgaa gtgtccaagc tcgtgactga cctgactaaa 720

gtccataccg aatgctgcca cggcgatctg ctcgaatgcg cagatgaccg ggcggatttg 780

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gacctcccta gcctggcagc cgacttcgtc gaatccaagg acgtgtgcaa gaactacgcc 960

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tgcgctgctg ctgacccaca cgagtgctac gccaaagtgt tcgacgagtt taagcctctc 1140

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ccgaccctcg tggaagtgtc caggaacctg ggcaaagtcg gaagcaaatg ttgcaagcac 1320

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accggcgtca gcctgcagac gtatgatgat ctgctggcca aggactgcca ttgcatc 2217

<210> 110
<211> 2205
<212> DNA
<213> 人工序列

<220>
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aagcttgtga acgaagtgac cgagttcgca aagacttgtg tggccgatga gtccgccgaa 180

aactgcgaca agtccctgca caccttgttc ggagacaagc tgtgcaccgt cgcgactttg 240

cgggagactt acggcgaaat ggcggactgc tgcgcaaagc aggagcccga aaggaacgag 300

tgcttcctgc aacacaagga cgacaacccg aaccttccga gactcgtgcg gcctgaggtc 360

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gaaattgcca gacgccaccc gtacttctac gccccccgaac tgctgttctt cgccaagaga 480

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cagaggttcc ccaaggcgga gtttgccgaa gtgtccaagc tcgtgactga cctgactaaa 720

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gccaagtaca tttgcgaaaa ccaagactcc ataagctcca agctgaagga gtgctgtgaa 840

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tgcgctgctg ctgacccaca cgagtgctac gccaaagtgt tcgacgagtt taagcctctc 1140

gtggaggaac cccagaacct catcaagcag aactgcgaac ttttcgagca gctcggggag 1200

tacaagttcc aaaacgcgct gcttgtccgc tacaccaaga aagtgccgca agtgtccaca 1260

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cacactgtgc gggcttcact ggaggacctc ggctgggctg actgggtgct gtccccacgg 1980

gaggtgcaag tgaccatgtg catcggcgcc tgtccttcgc aattccgggc cgcgaatatg 2040

cacgcccaga tcaagacctc cctgcatcgc ctcaagcccg acactgtgcc tgctccatgc 2100

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<210> 111
<211> 734
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 111

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Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
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Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
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180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
595 600 605

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
610 615 620

Gly Gly Ser His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His
625 630 635 640

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu
645 650 655

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser
660 665 670

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His
675 680 685

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser
690 695 700

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu
705 710 715 720

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
725 730

<210> 112
<211> 725
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 112

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser
580 585 590

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
595 600 605

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
610 615 620

Gly Gly Ser Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu
625 630 635 640

Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met
645 650 655

Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala
660 665 670

Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala
675 680 685

Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys
690 695 700

Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys
705 710 715 720

Asp Cys His Cys Ile

725

<210> 113
<211> 733
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 113

His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn
1 5 10 15

Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Ser
20 25 30

Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala
35 40 45

Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu
50 55 60

His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu
65 70 75 80

Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg
85 90 95

Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg
100 105 110

Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn
115 120 125

Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His
130 135 140

Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys
145 150 155 160

Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu
165 170 175

Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala
180 185 190

Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala
195 200 205

Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala
210 215 220

Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His
225 230 235 240

Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
245 250 255

Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys
260 265 270

Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile
275 280 285

Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala
290 295 300

Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala
305 310 315 320

Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His
325 330 335

Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu
340 345 350

Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr
355 360 365

Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn
370 375 380

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys

385 390 395 400

Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
405 410 415

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
420 425 430

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
435 440 445

Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
450 455 460

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
465 470 475 480

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
485 490 495

Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys
500 505 510

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
515 520 525

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
530 535 540

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
545 550 555 560

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
565 570 575

Ser Gln Ala Ala Leu Gly Leu Gly Ser Gly Gly Gly Gly Ser Gly Gly
580 585 590

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
595 600 605

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
610 615 620

Ser Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr
625 630 635 640

Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser
645 650 655

Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln
660 665 670

Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg
675 680 685

Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr
690 695 700

Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln
705 710 715 720

Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
725 730

<210> 114
<211> 2199
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 114
cacaagagtg aggttgctca tcggtttaaa gatttgggag aagaaaattt caaagccttg 60

gtgttgattg cctttgctca gtatcttcag cagtccccat ttgaagatca tgtaaaatta 120

gtgaatgaag taactgaatt tgcaaaaaca tgtgttgctg atgagtcagc tgaaaattgt 180

gacaaatcac ttcataccct ttttggagac aaattatgca cagttgcaac tcttcgtgaa 240

acctatggtg aaatggctga ctgctgtgca aaacaagaac ctgagagaaa tgaatgcttc 300

ttgcaacaca aagatgacaa cccaaacctc ccccgattgg tgagaccaga ggttgatgtg 360

atgtgcactg cttttcatga caatgaagag acatttttga aaaaatactt atatgaaatt 420

gccagaagac atccttactt ttatgccccg gaactccttt tctttgctaa aaggtataaa 480

gctgctttta cagaatgttg ccaagctgct gataaagctg cctgcctgtt gccaaagctc 540

gatgaacttc gggatgaagg gaaggcttcg tctgccaaac agagactcaa gtgtgccagt 600

ctccaaaaat ttggagaaag agctttcaaa gcatgggcag tagctcgcct gagccagaga 660

tttcccaaag ctgagtttgc agaagtttcc aagttagtga cagatcttac caaagtccac 720

acggaatgct gccatggaga tctgcttgaa tgtgctgatg acagggcgga ccttgccaag 780

tatatctgtg aaaatcaaga ttcgatctcc agtaaactga aggaatgctg tgaaaaacct 840

ctgttggaaa aatcccactg cattgccgaa gtggaaaatg atgagatgcc tgctgacttg 900

ccttcattag ctgctgattt tgttgaaagt aaggatgttt gcaaaaacta tgctgaggca 960

aaggatgtct tcctgggcat gtttttgtat gaatatgcaa gaaggcatcc tgattactct 1020

gtcgtgctgc tgctgagact tgccaagaca tatgaaacca ctctagagaa gtgctgtgcc 1080

gctgcagatc ctcatgaatg ctatgccaaa gtgttcgatg aatttaaacc tcttgtggaa 1140

gagcctcaga atttaatcaa acaaaattgt gagcttttg agcagcttgg agagtacaaa 1200

ttccagaatg cgctattagt tcgttacacc aagaaagtac cccaagtgtc aactccaact 1260

cttgtagagg tctcaagaaa cctaggaaaa gtgggcagca aatgttgtaa acatcctgaa 1320

gcaaaaagaa tgccctgtgc agaagactat ctatccgtgg tcctgaacca gttatgtgtg 1380

ttgcatgaga aaacgccagt aagtgacaga gtcaccaaat gctgcacaga atccttggtg 1440

aacaggcgac catgcttttc agctctggaa gtcgatgaaa catacgttcc caaagagttt 1500

aatgctgaaa cattcacctt ccatgcagat atatgcacac tttctgagaa ggagagacaa 1560

atcaagaaac aaactgcact tgttgagctc gtgaaacaca agcccaaggc aacaaaagag 1620

caactgaaag ctgttatgga tgatttcgca gcttttgtag agaagtgctg caaggctgac 1680

gataaggaga cctgctttgc cgaggagggt aaaaaacttg ttgctgcaag tcaagctgcc 1740

ttagggcttg gaagcggcgg agggggagt ggcggcggtg gctccggggg gggcggatcc 1800

ggcggagggg gcagcggggg tggagggagt ggcgggggag gatcaggggg aggaggatca 1860

ggaggggcg gaagtgatca ttgccctctc gggcccggac ggtgttgccg cctccacact 1920

gtgagggctt cacttgaaga ccttggatgg gccgactggg tgctgtcccc aagagaggta 1980

caagtcacaa tgtgtattgg cgcctgcccc agccagtttc gcgccgctaa catgcacgcc 2040

cagataaaaa ccagcctgca ccgcctgaag cccgacacgg tgccagcgcc ctgctgcgtg 2100

cccgccagct acaatcccat ggtgctcatt caaaagaccg acaccggggt gtcgctccag 2160

acctatgatg acttgttagc caaagactgc cactgcata 2199

<210> 115
<211> 735
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 115

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ala Gly Gly Gly Gly Ala
580 585 590

Gly Gly Gly Gly Ala Gly Gly Gly Gly Ala Gly Gly Gly Gly Ala Gly

595 600 605

Gly Gly Gly Ala Gly Gly Gly Gly Ala Gly Gly Gly Gly Ala Gly Gly
610 615 620

Gly Gly Ala Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
625 630 635 640

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
645 650 655

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
660 665 670

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
675 680 685

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
690 695 700

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
705 710 715 720

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
725 730 735

<210> 116
<211> 2205
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 116
gatgcacaca agagtgaggt tgctcatcgg tttaaagatt tgggagaaga aaatttcaaa 60

gccttggtgt tgattgcctt tgctcagtat cttcagcagt ccccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag 1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc 1440

ttggtgaaca ggcgaccatg cttttcagct ctggaagtcg atgaaacata cgttcccaaa 1500

gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag 1560

agacaaatca agaaacaaac tgcacttgtt gagctcgtga aacacaagcc caaggcaaca 1620

aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag 1680

gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc tgcaagtcaa 1740

gctgccttag ggcttggtgc tggaggaggc ggggcgggcg gcgggggtgc cggtgggggt 1800

ggcgcagggg gaggtggtgc gggtggtggt ggggctggtg ggggaggtgc aggcggtggc 1860

ggtgccgggg ggggtggcgc ggatcattgc cctctcgggc ccggacggtg ttgccgcctc 1920

cacactgtga gggcttcact tgaagacctt ggatgggccg actgggtgct gtccccaaga 1980

gaggtacaag tcacaatgtg tattggcgcc tgccccagcc agtttcgcgc cgctaacatg 2040

cacgcccaga taaaaaccag cctgcaccgc ctgaagcccg acacggtgcc agcgccctgc 2100

tgcgtgcccg ccagctacaa tcccatggtg ctcattcaaa agaccgacac cggggtgtcg 2160

ctccagacct atgatgactt gttagccaaa gactgccact gcata 2205

<210> 117
<211> 713
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 117

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

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Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Ala Pro Ala Pro Ala Pro Ala
580 585 590

Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Asp His Cys
595 600 605

Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser
610 615 620

Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val
625 630 635 640

Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala
645 650 655

Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp
660 665 670

Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val
675 680 685

Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp
690 695 700

Leu Leu Ala Lys Asp Cys His Cys Ile
705 710

<210> 118
<211> 2139
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 118
gatgcacaca agagtgaggt tgctcatcgg tttaaagatt tgggagaaga aaatttcaaa 60

gccttggtgt tgattgcctt tgctcagtat cttcagcagt ccccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag 1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc 1440

ttggtgaaca ggcgaccatg cttttcagct ctggaagtcg atgaaacata cgttcccaaa 1500

gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag 1560

agacaaatca agaaacaaac tgcacttgtt gagctcgtga aacacaagcc caaggcaaca 1620

aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag 1680

gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc tgcaagtcaa 1740

gctgccttag ggcttgcacc agcccctgcc cctgcacctg cacctgctcc cgcaccggct 1800

ccagccccag ctccggatca ttgccctctc gggcccggac ggtgttgccg cctccacact 1860

gtgagggctt cacttgaaga ccttggatgg gccgactggg tgctgtcccc aagagaggta 1920

caagtcacaa tgtgtattgg cgcctgcccc agccagtttc gcgccgctaa catgcacgcc 1980

cagataaaaa ccagcctgca ccgcctgaag cccgacacgg tgccagcgcc ctgctgcgtg 2040

cccgccagct acaatcccat ggtgctcatt caaaagaccg acaccggggt gtcgctccag 2100

acctatgatg acttgttagc caaagactgc cactgcata 2139

<210> 119
<211> 717
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 119

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Ala Pro Ala Pro Ala Pro Ala
580 585 590

Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala

595 600 605

Pro Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr
610 615 620

Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser
625 630 635 640

Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln
645 650 655

Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg
660 665 670

Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr
675 680 685

Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln
690 695 700

Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
705 710 715

<210> 120
<211> 2151
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 120
gatgcacaca agagtgaggt tgctcatcgg tttaaagatt tgggagaaga aaatttcaaa 60

gccttggtgt tgattgcctt tgctcagtat cttcagcagt ccccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag 1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc 1440

ttggtgaaca ggcgaccatg cttttcagct ctggaagtcg atgaaacata cgttcccaaa 1500

gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag 1560

agacaaatca agaaacaaac tgcacttgtt gagctcgtga aacacaagcc caaggcaaca 1620

aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag 1680

gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc tgcaagtcaa 1740

gctgccttag ggcttgcacc agcccctgcc cctgcacctg cacctgctcc cgcaccggct 1800

ccagccccag ctccggctcc agctcctgat cattgccctc tcgggcccgg acggtgttgc 1860

cgcctccaca ctgtgagggc ttcacttgaa gaccttggat gggccgactg ggtgctgtcc 1920

ccaagagagg tacaagtcac aatgtgtatt ggcgcctgcc ccagccagtt tcgcgccgct 1980

aacatgcacg cccagataaa aaccagcctg caccgcctga agcccgacac ggtgccagcg 2040

ccctgctgcg tgcccgccag ctacaatccc atggtgctca ttcaaaagac cgacaccggg 2100

gtgtcgctcc agacctatga tgacttgtta gccaaagact gccactgcat a 2151

<210> 121
<211> 741
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 121

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu

385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Gly Ser Glu Gly Lys Ser
580 585 590

Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Glu Gly Lys Ser Ser Gly
595 600 605

Ser Gly Ser Glu Ser Lys Ser Thr Glu Gly Lys Ser Ser Gly Ser Gly
610 615 620

Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp His Cys Pro Leu Gly Pro
625 630 635 640

Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu
645 650 655

Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met
660 665 670

Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala
675 680 685

Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala
690 695 700

Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys
705 710 715 720

Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys
725 730 735

Asp Cys His Cys Ile
740

<210> 122
<211> 2223
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 122
gatgcacaca agagtgaggt tgctcatcgg tttaaagatt tgggagaaga aaatttcaaa 60

gccttggtgt tgattgcctt tgctcagtat cttcagcagt ccccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc 1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt 1140

gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag 1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact 1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat 1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

tgtgtgttgc atgagaaaac gccagtaagt gacagagtca caaaatgctg tactgagagc 1440

ttggtcaaca ggcggccgtg cttcagcgcc ctcgaggtgg atgagactta tgtcccaaag 1500

gagtttaatg cggaaacttt tactttccac gcagacattt gcaccttgtc tgaaaaggaa 1560

agacagatta agaaacagac tgctcttgtg gaactggtaa aacataaacc aaaagctacg 1620

aaggagcagc ttaaggctgt tatggatgat ttcgccgcgt ttgtcgagaa gtgctgcaaa 1680

gcggacgata aggaaacttg ctttgcagag gaaggtaaga aactcgtagc ggcaagtcag 1740

gctgcgcttg gccttggagg cagtgaaggc aaatcctctg ggagtggctc tgaaagtaaa 1800

tccaccgagg gcaaatccag tggatctggg tctgaatcta agtctaccga ggggaagtct 1860

tctggcagtg ggtcagaatc taaatctaca ggcggctctg accattgccc gttgggacca 1920

ggacgctgct gtcgccttca tacagtgcga gcgagtttgg aagacctggg ctgggctgac 1980

tgggtgctta gccctcggga ggtccaggtc acaatgtgca ttggcgcgtg tcccagtcaa 2040

tttagagcag caaatatgca cgcccaaata aaaacctccc tgcataggct taagccagat 2100

actgtccccg caccatgctg tgtgcctgct tcttacaatc ctatggtact catccagaag 2160

accgacacgg gagttagcct ccagacttat gacgacctct tggctaaaga ttgccattgt 2220

att 2223

<210> 123
<211> 735
<212> PRT
<213> 人工序列

<220>
<223> 融合蛋白

<400> 123

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg

130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Pro Gly Gly Gly Ser
580 585 590

Pro Gly Gly Gly Ser Pro Gly Gly Gly Ser Pro Gly Gly Gly Ser Pro
595 600 605

Gly Gly Gly Ser Pro Gly Gly Gly Ser Pro Gly Gly Gly Ser Pro Gly
610 615 620

Gly Gly Ser Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
625 630 635 640

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
645 650 655

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
660 665 670

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
675 680 685

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
690 695 700

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
705 710 715 720

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
725 730 735

<210> 124
<211> 2205
<212> DNA
<213> 人工序列

<220>
<223> 編碼融合蛋白的序列

<400> 124
gatgcacaca agagtgaggt tgctcatcgg tttaaagatt tgggagaaga aaatttcaaa 60

gccttggtgt tgattgcctt tgctcagtat cttcagcagt ccccatttga agatcatgta 120

aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

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cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

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aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

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gaggtccaag tcacgatgtg tattggagcc tgtccctctc aattccgagc cgcaaatatg 2040

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tgcgtccccg cgagttataa tcccatggtc cttatacaga aaacagacac tggtgtcagc 2160

cttcagacgt atgacgattt gcttgctaaa gactgtcatt gtatt 2205

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<212> PRT
<213> 人工序列

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<223> 融合蛋白

<400> 125

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
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Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr

340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu Gly Ser Ala Gly Gly Gly Ser
580 585 590

Ala Gly Gly Gly Ser Ala Gly Gly Gly Ser Ala Gly Gly Gly Ser Ala
595 600 605

Gly Gly Gly Ser Ala Gly Gly Gly Ser Ala Gly Gly Gly Ser Ala Gly
610 615 620

Gly Gly Ser Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu
625 630 635 640

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val
645 650 655

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro
660 665 670

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu
675 680 685

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala
690 695 700

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser
705 710 715 720

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile
725 730 735

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<212> DNA
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aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

tataaagctg cttttacaga atgttgccaa gctgctgata aagctgcctg cctgttgcca 540

aagctcgatg aacttcggga tgaagggaag gcttcgtctg ccaaacagag actcaagtgt 600

gccagtctcc aaaaatttgg agaaagagct ttcaaagcat gggcagtagc tcgcctgagc 660

cagagatttc ccaaagctga gtttgcagaa gtttccaagt tagtgacaga tcttaccaaa 720

gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

gccaagtata tctgtgaaaa tcaagattcg atctccagta aactgaagga atgctgtgaa 840

aaacctctgt tggaaaaatc ccactgcatt gccgaagtgg aaaatgatga gatgcctgct 900

gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct 960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat 1020

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cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta 1380

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cttgttaata ggcggccatg cttcagtgca ttggaagtcg acgaaaccta tgtaccaaag 1500

gagttcaacg cagaaacatt tacattccat gctgatatct gcacattgag cgagaaagag 1560

agacagatta agaaacagac agcgcttgtt gaactggtta aacacaaacc aaaagctacc 1620

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gccgcactgg gtctcggtag tgcgggcggt ggttcagcgg ggggaggatc tgcaggtggt 1800

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gaagtgcagg tgaccatgtg tattggtgct tgcccaagtc aattccgagc agctaacatg 2040

cacgcccaga tcaagactag cctgcatcgg cttaagcccg acactgttcc tgccccttgc 2100

tgtgttcctg catcttataa tccaatggtc ctgatccaga aaaccgatac gggtgtatca 2160

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<213> 人工序列

<220>
<223> 融合蛋白

<400> 127

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20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
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Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys

545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

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580 585 590

Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Glu Gly Lys Ser Ser Gly
595 600 605

Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp His Cys Pro Leu
610 615 620

Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu
625 630 635 640

Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val
645 650 655

Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met
660 665 670

His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Val
675 680 685

Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile
690 695 700

Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu
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Ala Lys Asp Cys His Cys Ile
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<210> 128
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aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

tgcttcttgc aacacaaaga tgacaaccca aacctccccc gattggtgag accagaggtt 360

gatgtgatgt gcactgcttt tcatgacaat gaagagacat ttttgaaaaa atacttatat 420

gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

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gtccacacgg aatgctgcca tggagatctg cttgaatgtg ctgatgacag ggcggacctt 780

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gagtttaacg ccgagacctt tacttttcat gctgatattt gcacccttc cgaaaaggag 1560

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aaggaacaac ttaaagctgt tatggatgac ttcgcagcct tcgtcgagaa atgttgcaag 1680

gcggatgata aggaaacgtg ttttgctgag gaagggaaga agttggttgc tgcctctcaa 1740

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ggagcttgtc cgagccaatt ccgggcggct aatatgcacg cacagatcaa gacctctttg 2040

caccgcttga agcccgatac cgtgccagca ccgtgttgcg tcccagcatc ttacaaccct 2100

atggttttga tacagaaaac tgacacaggt gtgagcctcc agacatatga tgatttgctg 2160

gctaaggatt gccactgtat a 2181

【發明申請專利範圍】

【請求項1】一種融合蛋白，其包含：

a. 半衰期延長蛋白，其包含SEQ ID NO: 2的胺基酸序列，

b. 連接子，其包含選自由以下所組成之群組的胺基酸序列：

GS-(GGGGS)n 或 AS-(GGGGS)n-GT，其中 n 係 8 至 15；

(AP)n，其中 n 係 2 至 20；

(EAAAK)n，其中 n 係 2 至 15；

(GGGGA)n，其中 n 係 8，

(PGGGS)n，其中 n 係 8，

(AGGGS)n，其中n係8，及

GGS-(EGKSSGSGSESKST)n-GGS，其中n係2或3，

及

c. GDF15蛋白，其包含選自由SEQ ID NO：6、7、8、9、10及11所組成之群組的胺基酸序列；

其中該融合蛋白係以(a)-(b)-(c)之順序自N端至C端配置。

【請求項2】一種融合蛋白，其包含SEQ ID NO: 26至30、55至56、59、113、115、117、119、121、123、125、或127的胺基酸序列。

【請求項3】一種單離之核酸分子，其包含編碼如請求項1所述之融合蛋白的核苷酸序列。

【請求項4】一種載體，其包含編碼如請求項1所述之融合蛋白的核酸分子。

【請求項5】一種產生如請求項1所述之融合蛋白的方法，其包含：

(1) 在產生該融合蛋白的條件下培養宿主細胞，該宿主細胞包含編碼該融合蛋白的核酸分子；及

(2) 回收由該宿主細胞產生的該融合蛋白。

【請求項6】 一種醫藥組成物，其包含如請求項1或請求項2所述之融合蛋白及醫藥上可接受之載劑。

【請求項7】 一種如請求項6所述之醫藥組成物用於製備治療或預防代謝病症之藥物的用途。

【請求項8】 一種如請求項6所述之醫藥組成物用於製備治療代謝病症之藥物的用途，該代謝病症係選自由代謝病症所組成之群組，該代謝病症係選自由有需要之對象的第2型糖尿病、升高葡萄糖水平、升高胰島素水平、肥胖、異常血脂症、糖尿病性腎病變、心肌缺血性損傷、充血性心臟衰竭、及類風濕性關節炎所組成之群組。

【請求項9】 一種二聚體，其包含兩條多肽鏈，其中各鏈自N端至C端包含HSA區、連接子及GDF15區；其中該HSA區包含SEQ ID NO: 2的胺基酸序列，且其中該GDF15區包含SEQ ID NO: 6、7、8、9、10、或11的胺基酸序列，且其中該連接子包含選自由以下所組成之群組的胺基酸序列：

GS-(GGGGS)n 或 AS-(GGGGS)n-GT，其中 n 係 8 至 15；

(AP)n，其中 n 係 2 至 20；

(EAAAK)n，其中 n 係 2 至 15；

(GGGGA)n，其中 n 係 8，

(PGGGS)n，其中 n 係 8，

(AGGGS)n，其中 n 係 8，及

GGS-(EGKSSGSGSESKST)n-GGS，其中 n 係 2 或 3。

【請求項10】 如請求項9所述之二聚體，其中該兩條多肽鏈係藉由雙硫鍵連接。

【請求項11】 如請求項9所述之二聚體，其中該HSA區與該GDF15區係藉由多肽連接子接合。

【發明圖式】

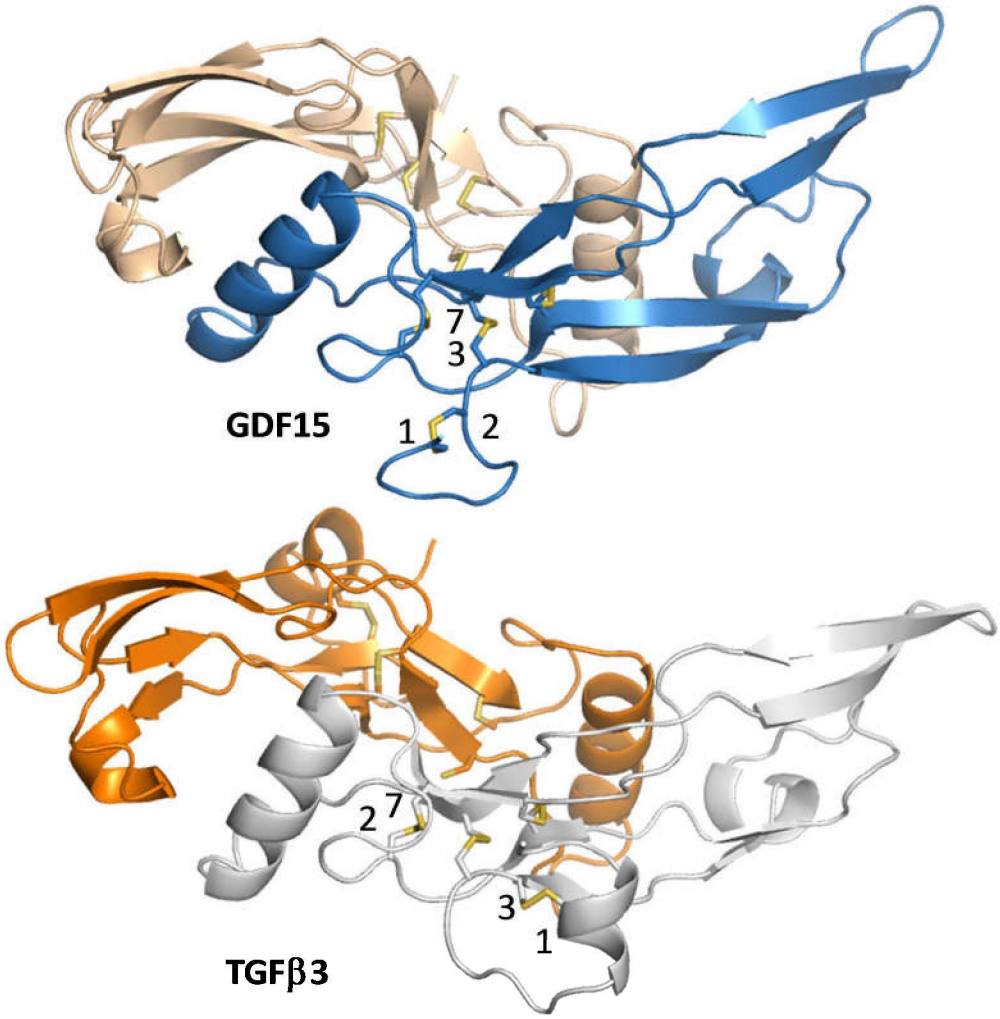
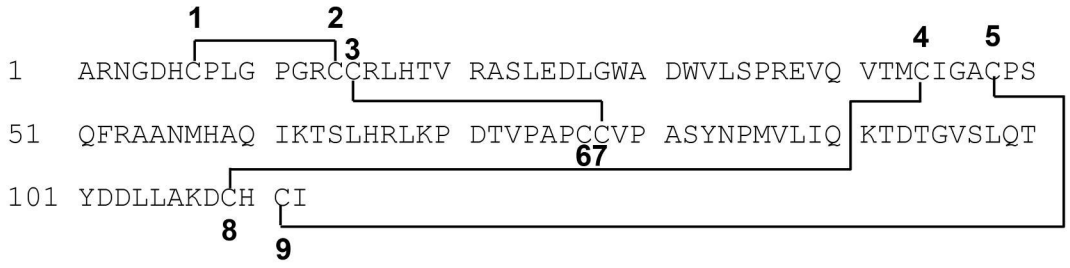


圖 1A

GDF15



TGFβ3

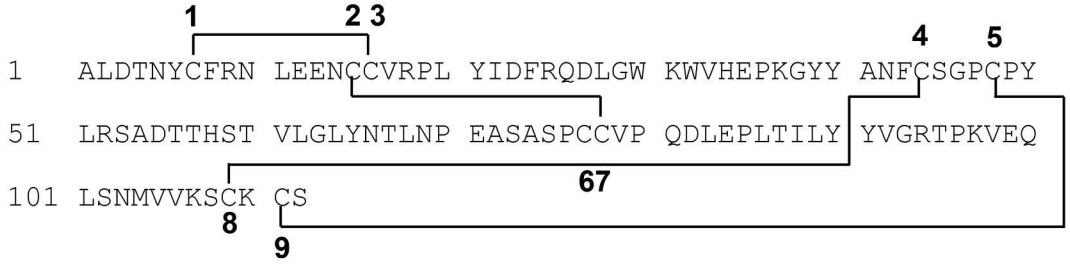


圖1B

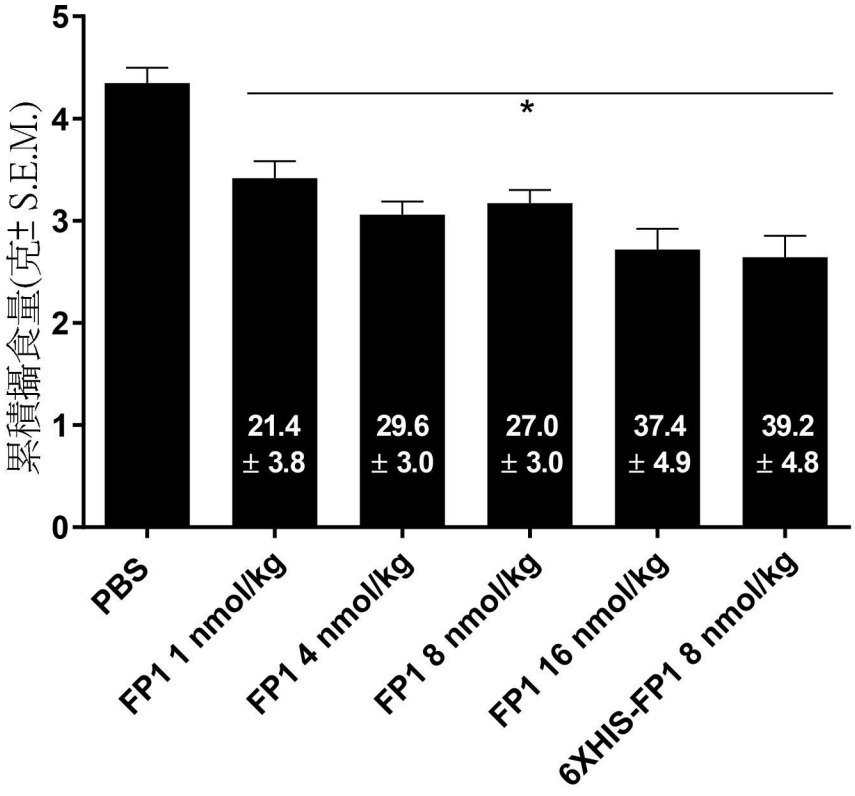

累積攝食量(克± S.E.M.)
5
4
3
2
1
0
*
21.4
± 3.8
29.6
± 3.0
27.0
± 3.0
37.4
± 4.9
39.2
± 4.8
PBS
FP1 1 nmol/kg
FP1 4 nmol/kg
FP1 8 nmol/kg
FP1 16 nmol/kg
6XHIS-FP1 8 nmol/kg

圖2

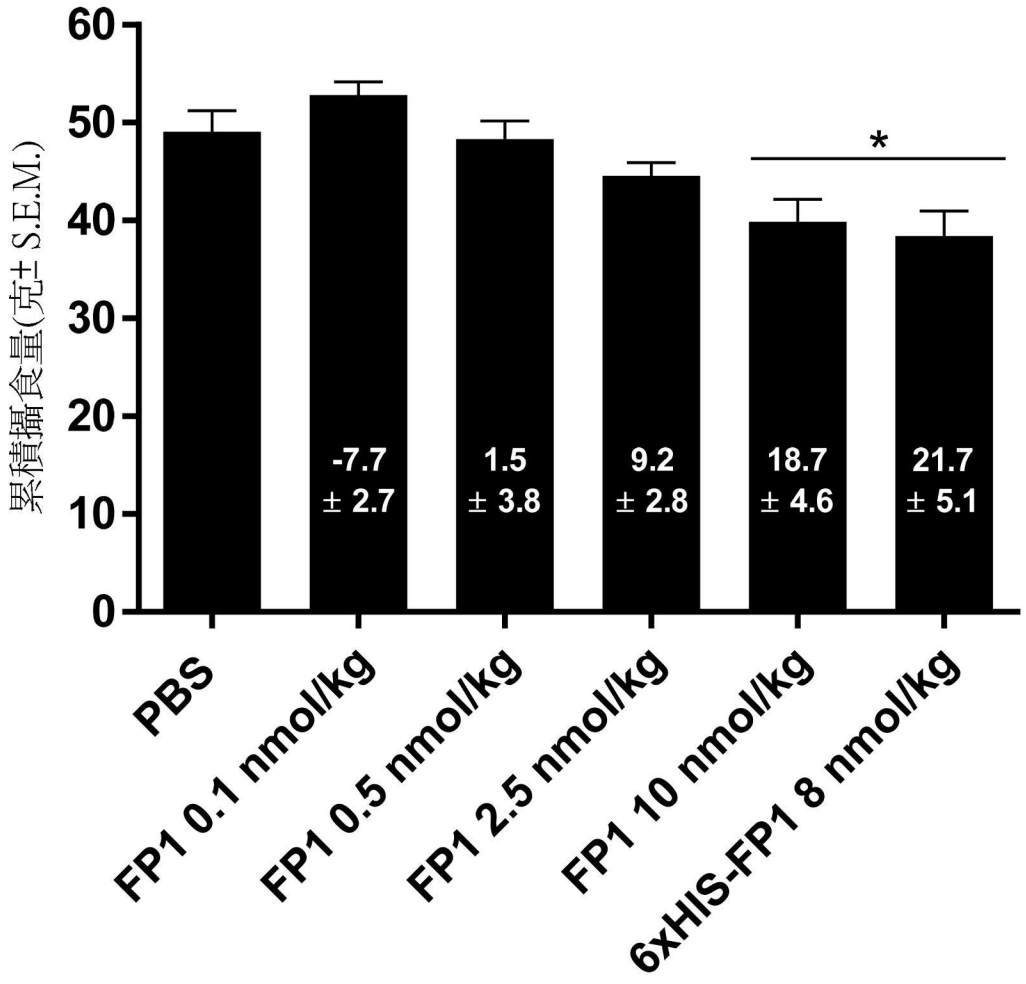

累積攝食量(克± S.E.M.)
60
50
40
30
20
10
0
*
-7.7
± 2.7
1.5
± 3.8
9.2
± 2.8
18.7
± 4.6
21.7
± 5.1
PBS
FP1 0.1 nmol/kg
FP1 0.5 nmol/kg
FP1 2.5 nmol/kg
FP1 10 nmol/kg
6xHIS-FP1 8 nmol/kg

圖3

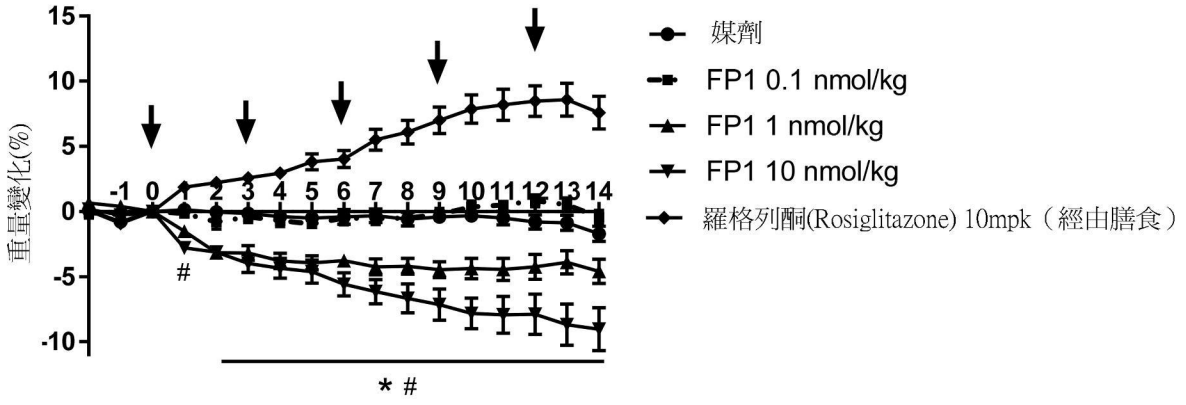

15
10
5
0
-5
-10
重量變化(%)
-1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
#
* #
媒劑
FP1 0.1 nmol/kg
FP1 1 nmol/kg
FP1 10 nmol/kg
羅格列酮(Rosiglitazone) 10mpk（經由膳食）

圖4

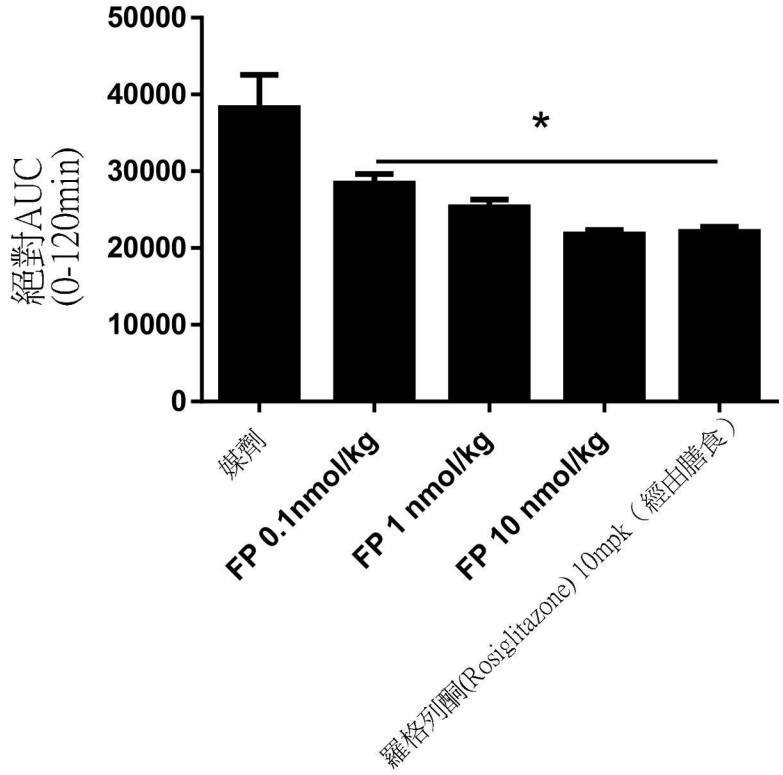

50000
40000
30000
20000
10000
0
絕對AUC
(0-120min)
*
媒劑
FP 0.1nmol/kg
FP 1 nmol/kg
FP 10 nmol/kg
羅格列酮(Rosiglitazone) 10mpk（經由膳食）

圖5A

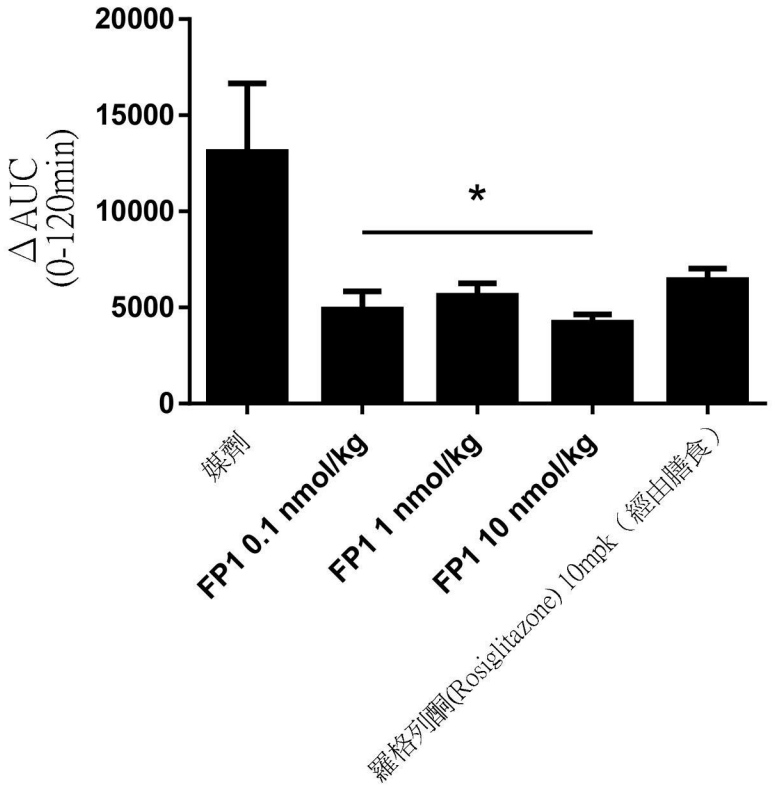

20000
15000
10000
5000
0
ΔAUC
(0-120min)
*
媒劑
FP1 0.1 nmol/kg
FP1 1 nmol/kg
FP1 10 nmol/kg
羅格列酮(Rosiglitazone) 10mpk（經由膳食）

圖5B

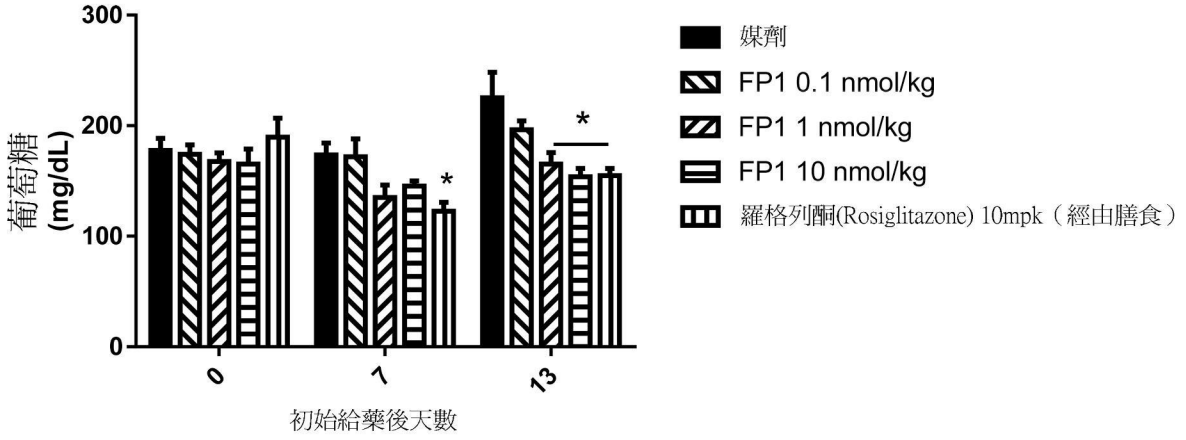

300
200
100
0
葡萄糖
(mg/dL)
0
7
13
初始給藥後天數
*
*
媒劑
FP1 0.1 nmol/kg
FP1 1 nmol/kg
FP1 10 nmol/kg
羅格列酮(Rosiglitazone) 10mpk（經由膳食）

圖6

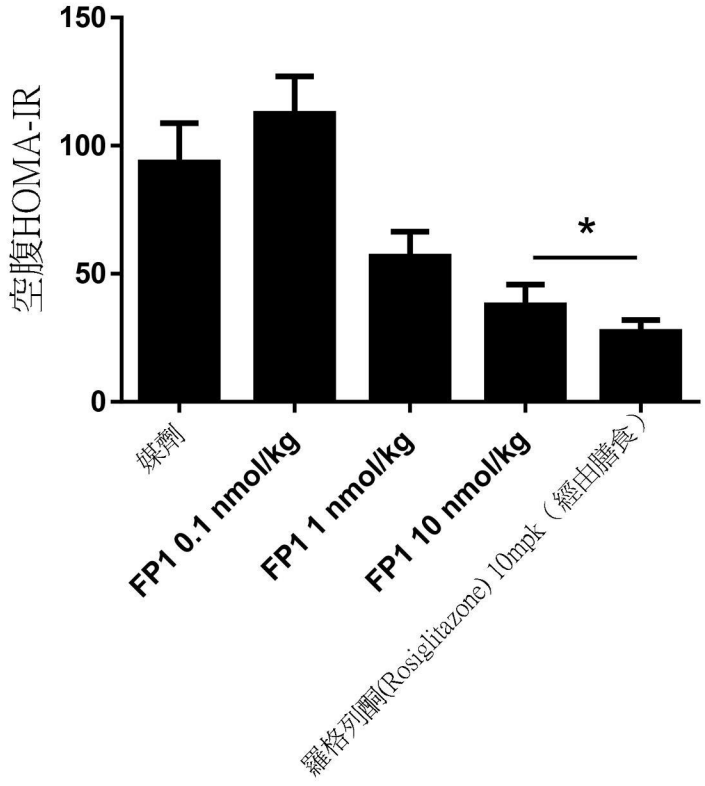

空腹HOMA-IR
150
100
50
0
*
媒劑
FP1 0.1 nmol/kg
FP1 1 nmol/kg
FP1 10 nmol/kg
羅格列酮(Rosiglitazone) 10mpk（經由膳食）

圖7

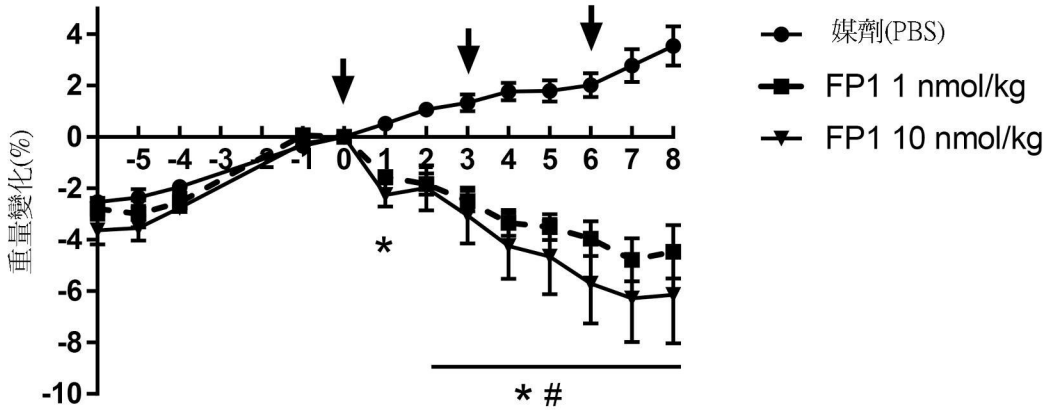

重量變化(%)
4
2
0
-2
-4
-6
-8
-10
-5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8
*
* #
媒劑(PBS)
FP1 1 nmol/kg
FP1 10 nmol/kg

圖8

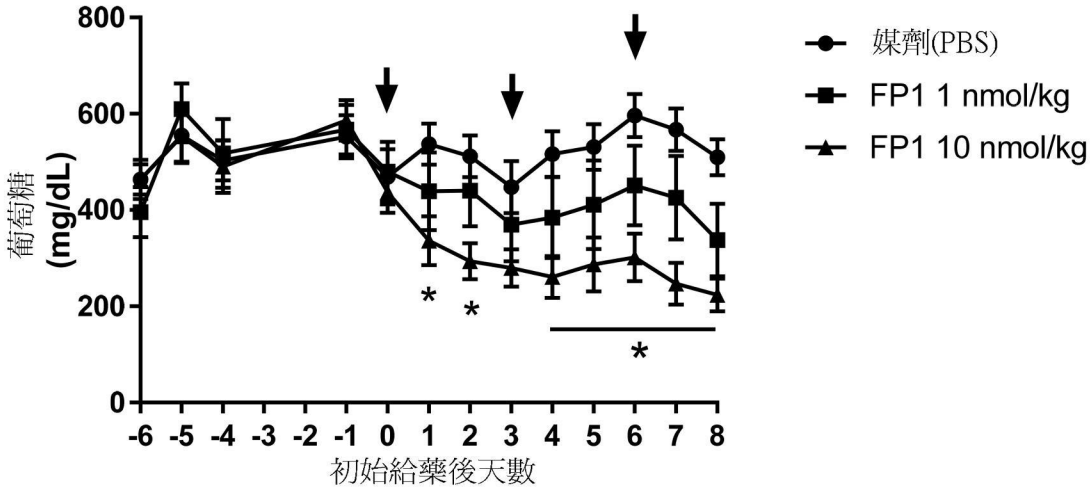

800
600
400
200
0
葡萄糖
(mg/dL)
-6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8
初始給藥後天數
*
*
*
媒劑(PBS)
FP1 1 nmol/kg
FP1 10 nmol/kg

圖9

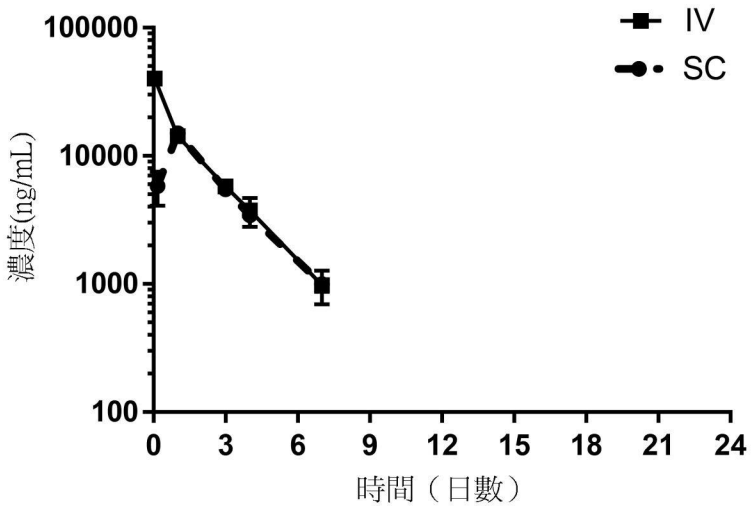


圖10

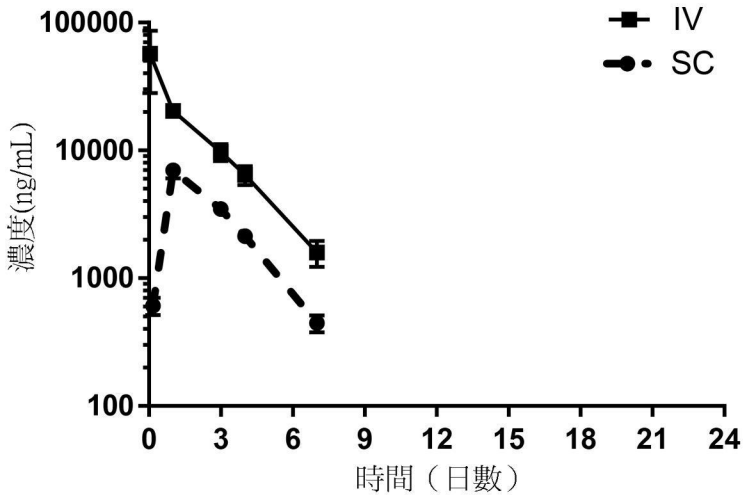


圖11

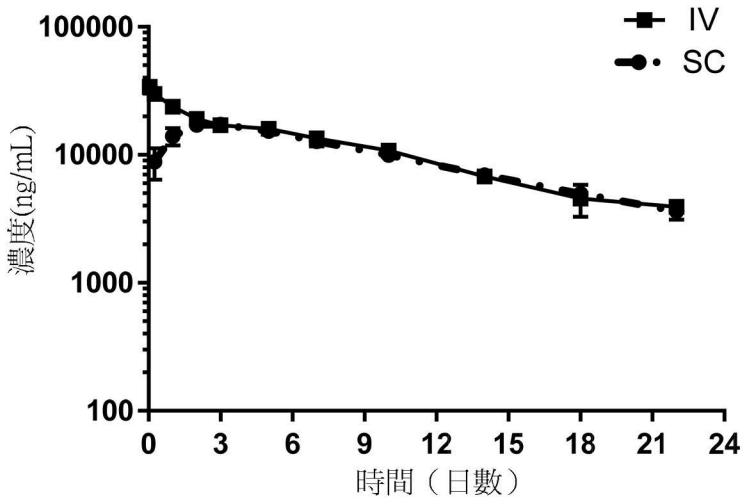


圖12

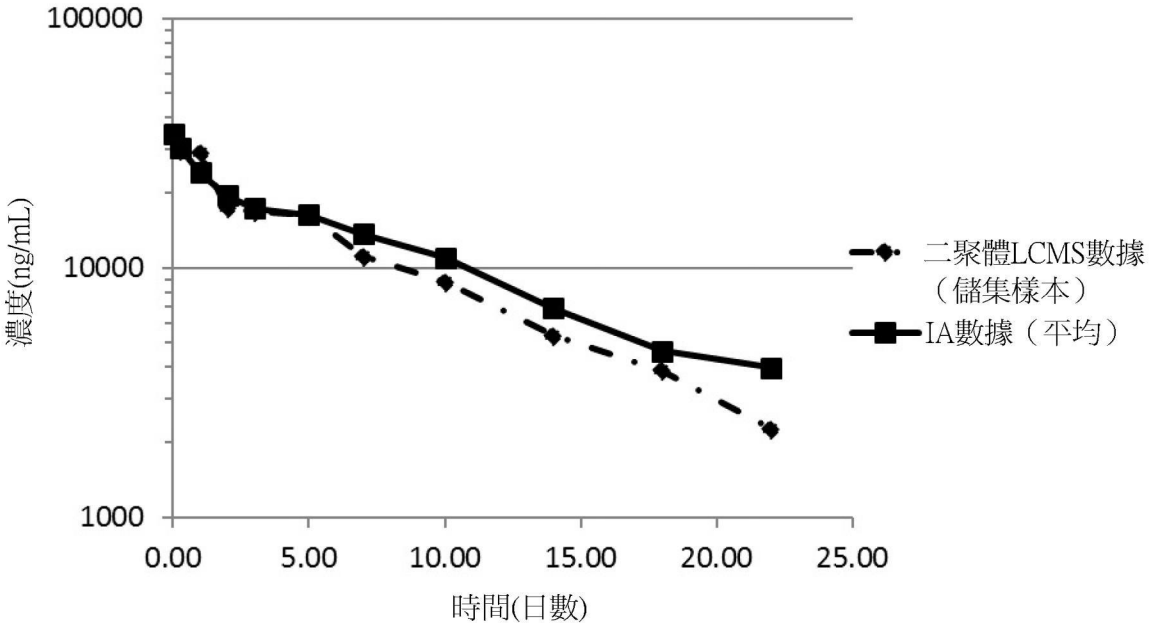

100000
10000
1000
濃度(ng/mL)
0.00
5.00
10.00
15.00
20.00
25.00
時間(日數)
二聚體LCMS數據
（儲集樣本）
IA數據（平均）

圖13

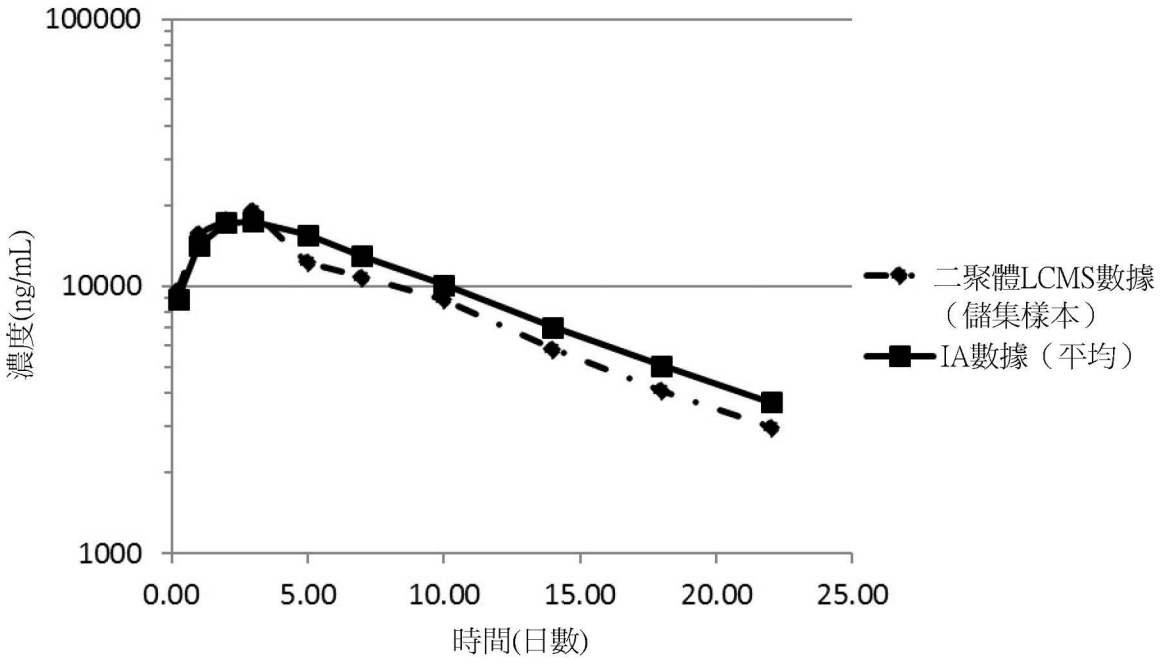

100000
10000
1000
濃度(ng/mL)
0.00
5.00
10.00
15.00
20.00
25.00
時間(日數)
二聚體LCMS數據（儲集樣本）
IA數據（平均）

圖14

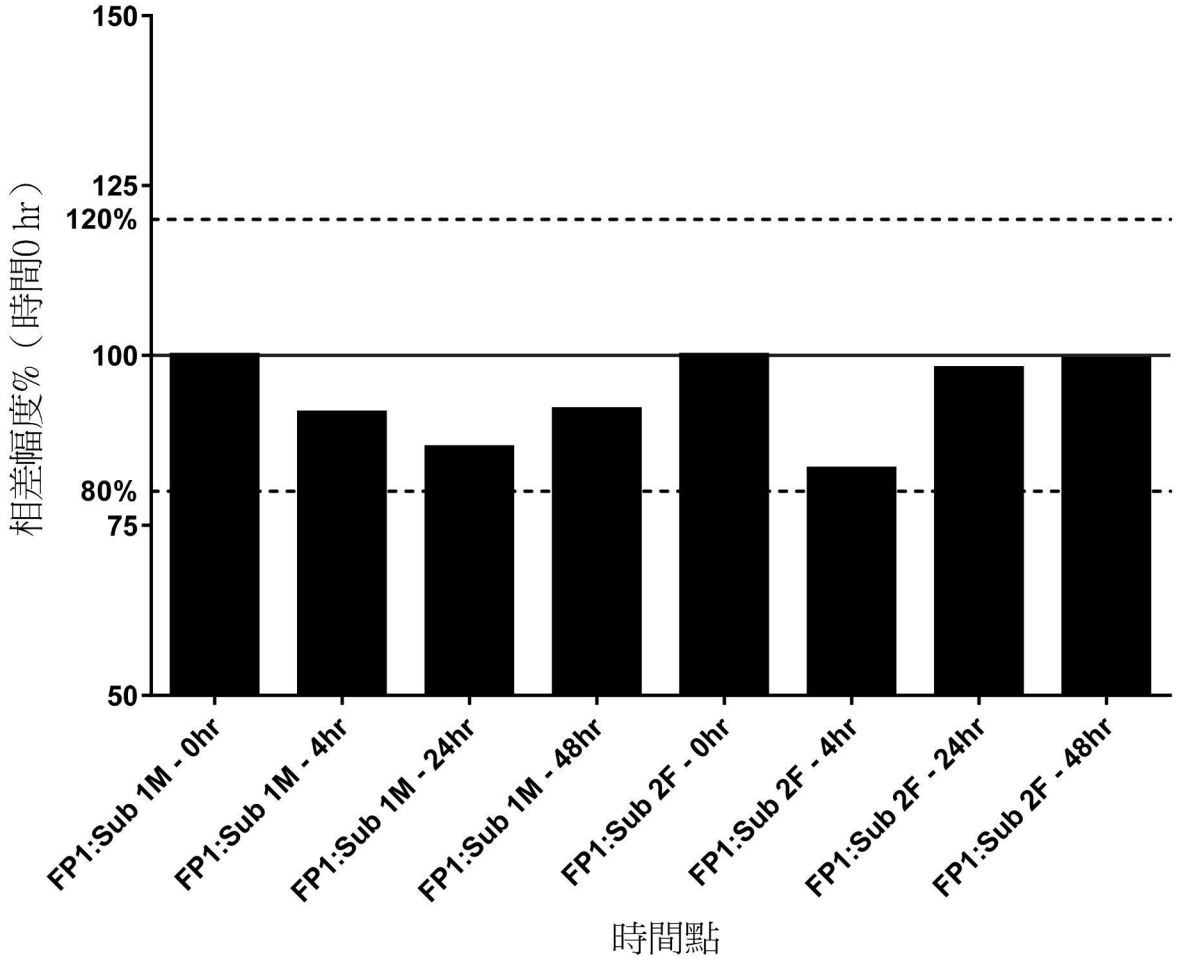

150
125
120%
100
80%
75
50
相差幅度%（時間0 hr）
FP1:Sub 1M - 0hr
FP1:Sub 1M - 4hr
FP1:Sub 1M - 24hr
FP1:Sub 1M - 48hr
FP1:Sub 2F - 0hr
FP1:Sub 2F - 4hr
FP1:Sub 2F - 24hr
FP1:Sub 2F - 48hr
時間點

圖15

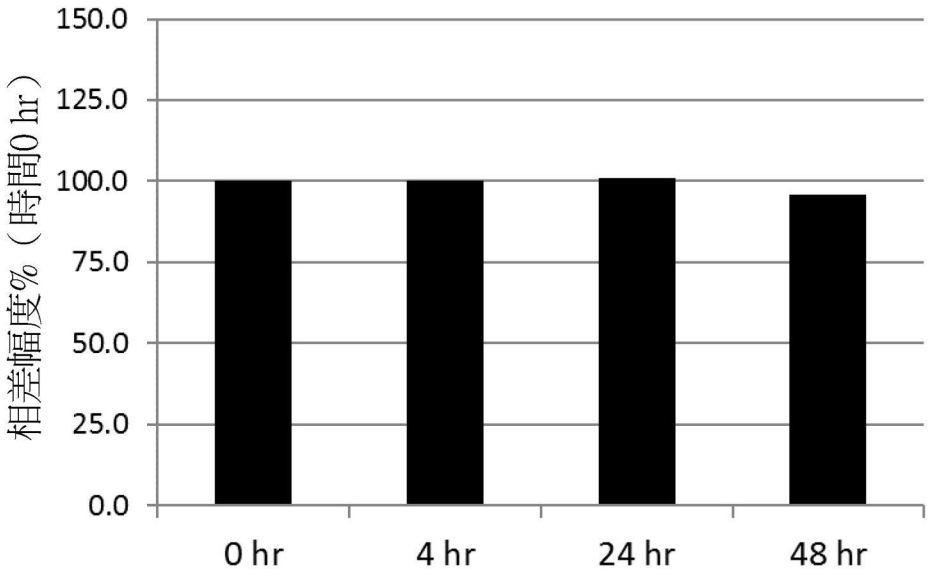


圖16

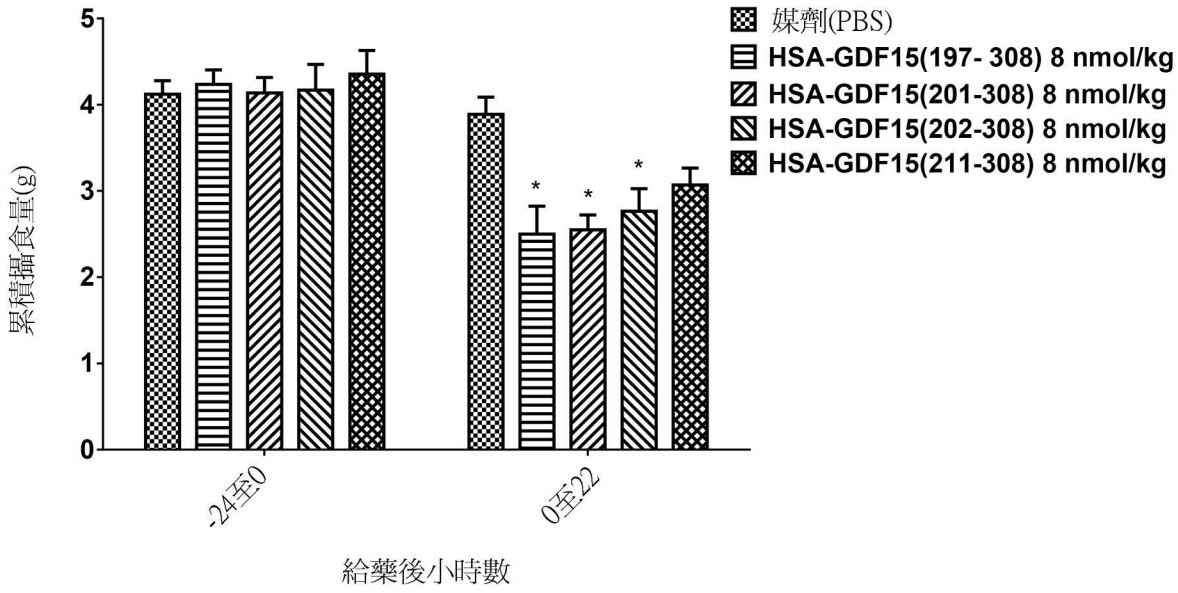

媒劑(PBS)
HSA-GDF15(197- 308) 8 nmol/kg
HSA-GDF15(201-308) 8 nmol/kg
HSA-GDF15(202-308) 8 nmol/kg
HSA-GDF15(211-308) 8 nmol/kg
累積攝食量(g)
0
1
2
3
4
5
*
*
*
-24至0
0至22
給藥後小時數

圖17

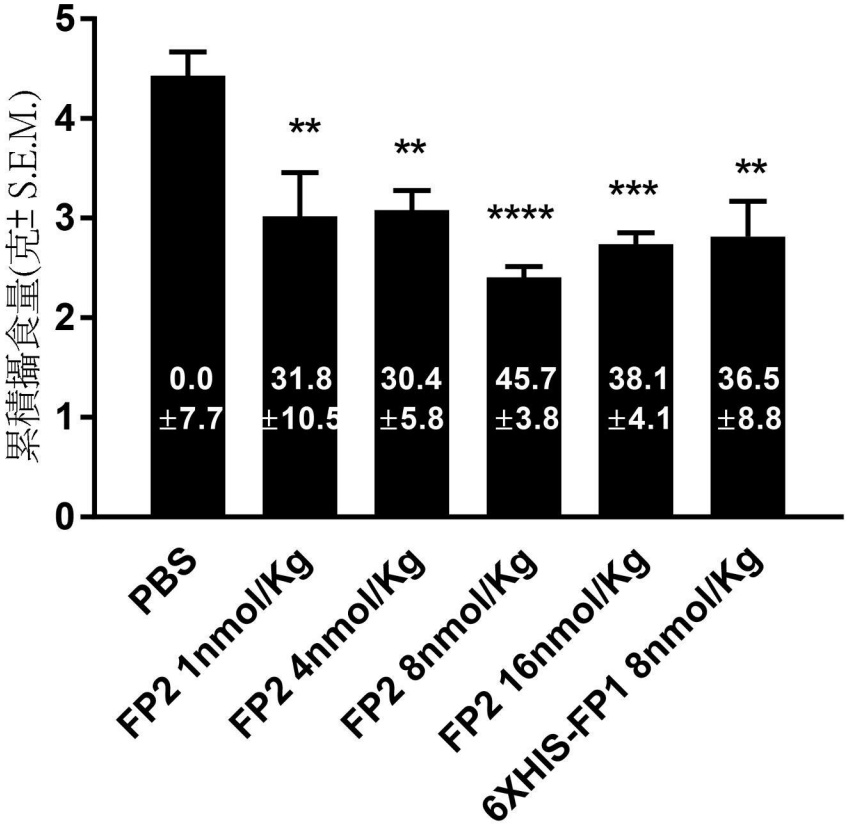

累積攝食量(克± S.E.M.)
5
4
3
2
1
0
**
**
****
***
**
0.0
±7.7
31.8
±10.5
30.4
±5.8
45.7
±3.8
38.1
±4.1
36.5
±8.8
PBS
FP2 1nmol/Kg
FP2 4nmol/Kg
FP2 8nmol/Kg
FP2 16nmol/Kg
6XHIS-FP1 8nmol/Kg

圖18

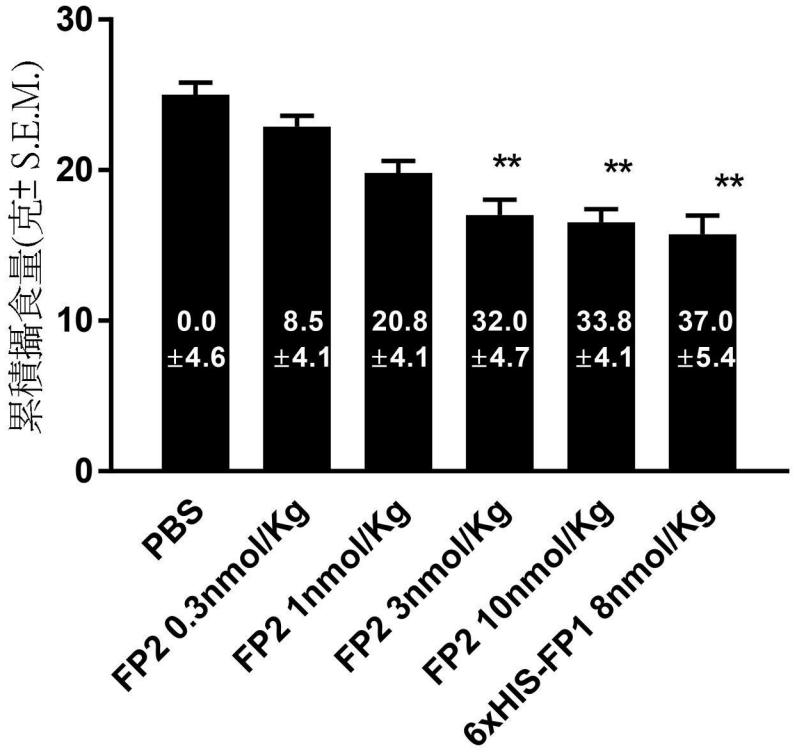

累積攝食量(克± S.E.M.)
30
20
10
0
0.0
±4.6
8.5
±4.1
20.8
±4.1
32.0
±4.7
33.8
±4.1
37.0
±5.4
**
**
**
PBS
FP2 0.3nmol/Kg
FP2 1nmol/Kg
FP2 3nmol/Kg
FP2 10nmol/Kg
6xHIS-FP1 8nmol/Kg

圖19

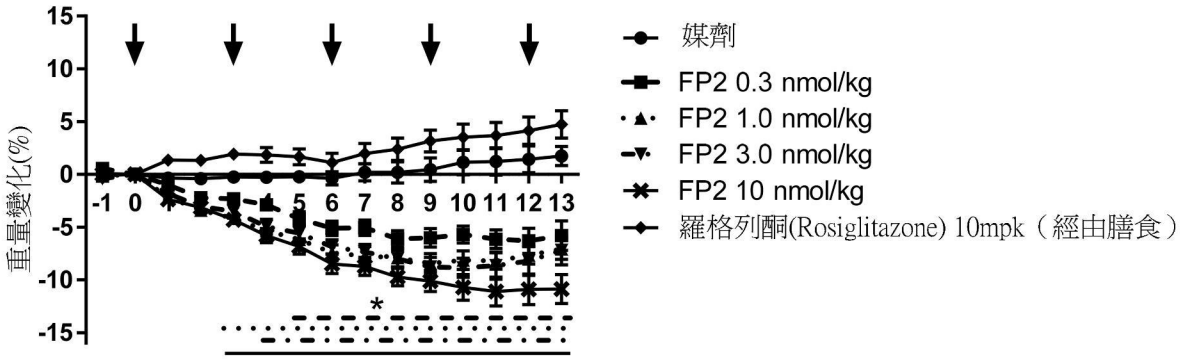

15
10
5
0
-5
-10
-15
重量變化(%)
-1 0 4 5 6 7 8 9 10 11 12 13
*
媒劑
FP2 0.3 nmol/kg
FP2 1.0 nmol/kg
FP2 3.0 nmol/kg
FP2 10 nmol/kg
羅格列酮(Rosiglitazone) 10mpk（經由膳食）

圖20

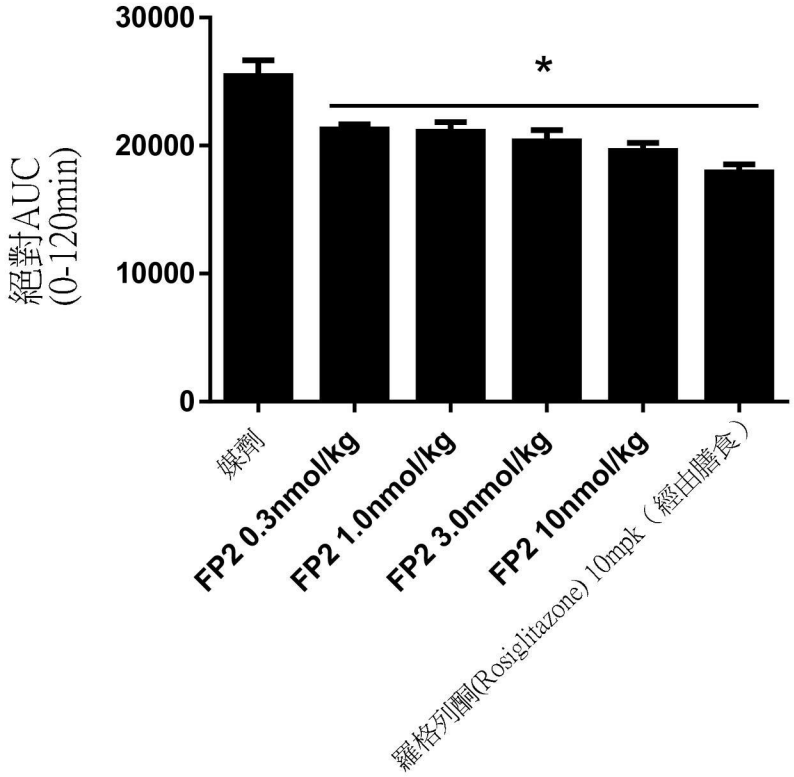

30000
20000
10000
0
絕對AUC
(0-120min)
*
媒劑
FP2 0.3nmol/kg
FP2 1.0nmol/kg
FP2 3.0nmol/kg
FP2 10nmol/kg
羅格列酮(Rosiglitazone) 10mpk（經由膳食）

圖21A

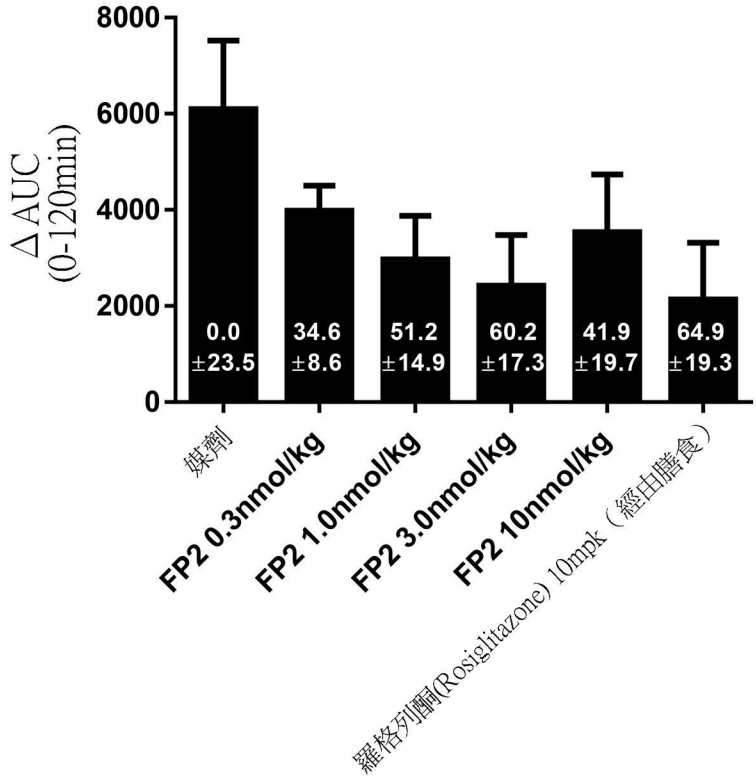

8000
6000
4000
2000
0
ΔAUC
(0-120min)
0.0
±23.5
34.6
±8.6
51.2
±14.9
60.2
±17.3
41.9
±19.7
64.9
±19.3
媒劑
FP2 0.3nmol/kg
FP2 1.0nmol/kg
FP2 3.0nmol/kg
FP2 10nmol/kg
羅格列酮(Rosiglitazone) 10mpk（經由嗜食）

圖21B

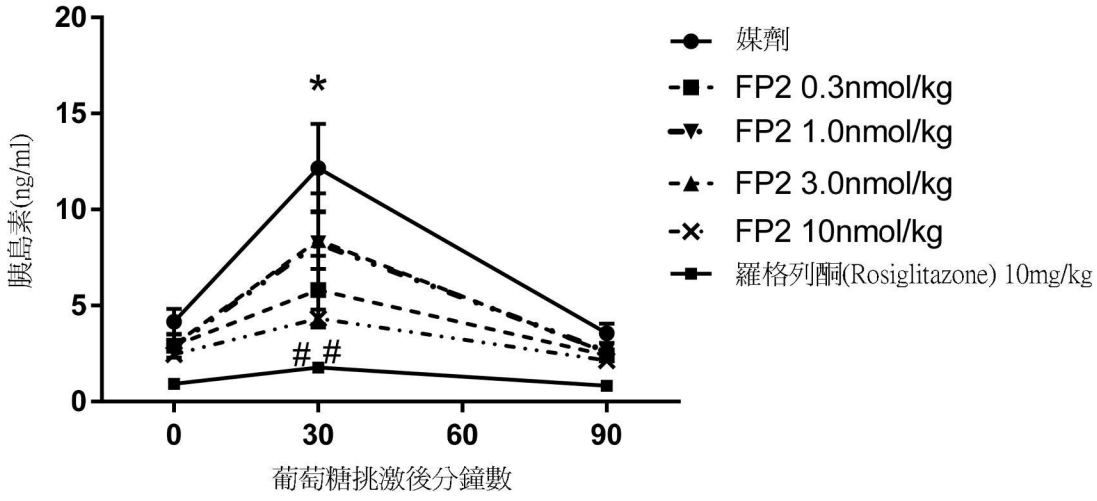

20
15
10
5
0
胰島素(ng/ml)
*
#
#
0
30
60
90
葡萄糖挑激後分鐘數
媒劑
FP2 0.3nmol/kg
FP2 1.0nmol/kg
FP2 3.0nmol/kg
FP2 10nmol/kg
羅格列酮(Rosiglitazone) 10mg/kg

圖22A

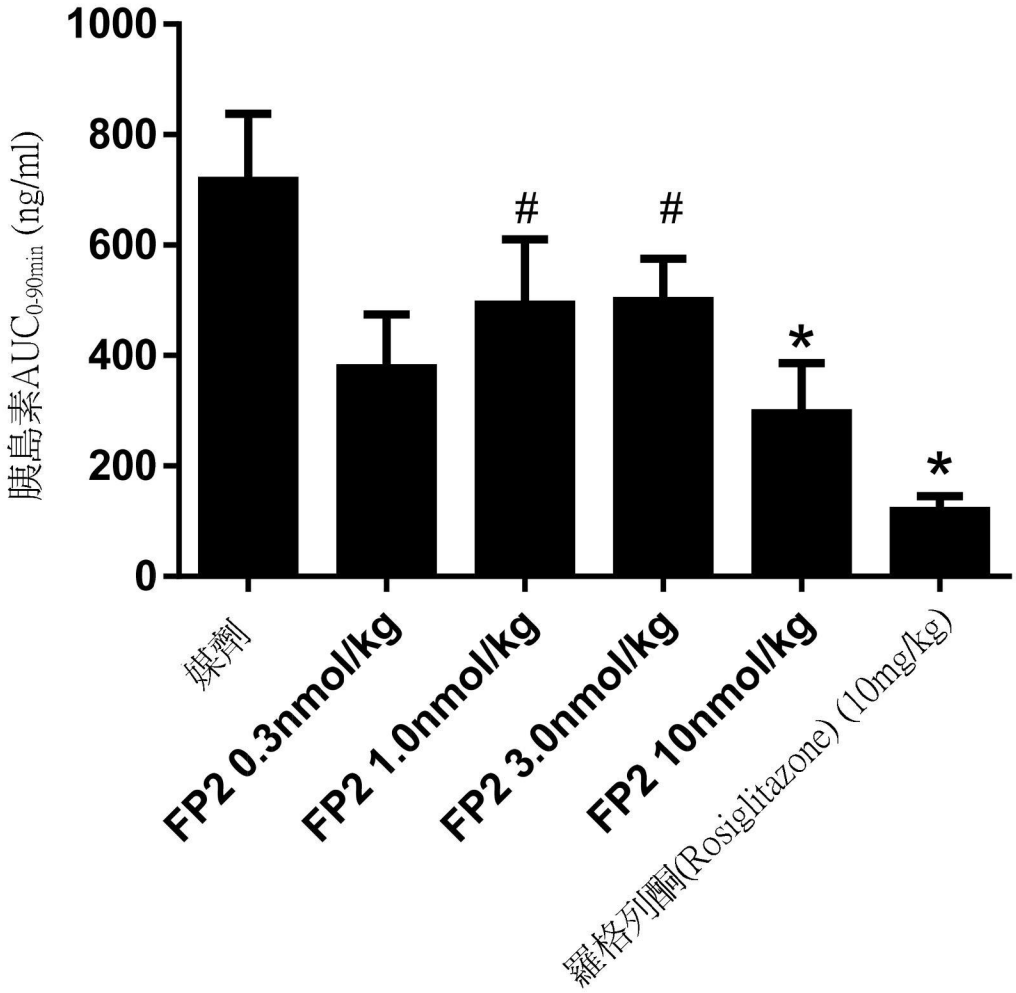

1000
800
600
400
200
0
胰島素AUC0-90min (ng/ml)
#
#
*
*
媒劑
FP2 0.3nmol/kg
FP2 1.0nmol/kg
FP2 3.0nmol/kg
FP2 10nmol/kg
羅格列酮(Rosiglitazone) (10mg/kg)

圖22B

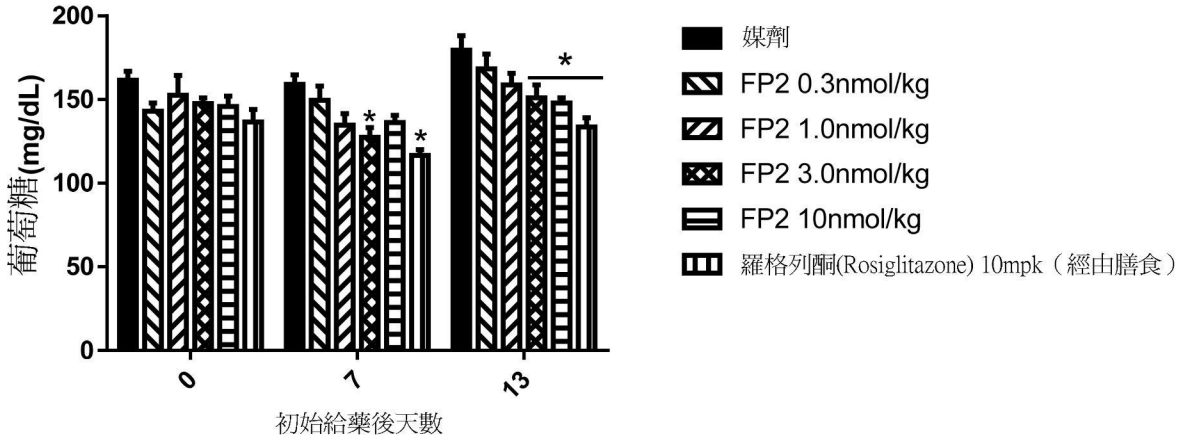

200
150
100
50
0
葡萄糖(mg/dL)
0
7
13
初始給藥後天數
*
*
*
媒劑
FP2 0.3nmol/kg
FP2 1.0nmol/kg
FP2 3.0nmol/kg
FP2 10nmol/kg
羅格列酮(Rosiglitazone) 10mpk（經由膳食）

圖23

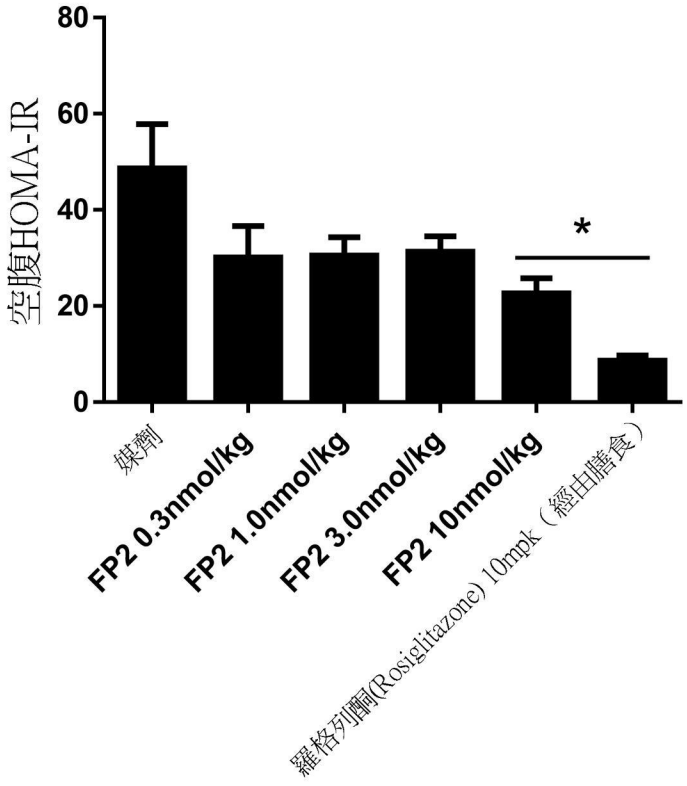

空腹HOMA-IR
80
60
40
20
0
*
媒劑
FP2 0.3nmol/kg
FP2 1.0nmol/kg
FP2 3.0nmol/kg
FP2 10nmol/kg
羅格列酮(Rosiglitazone) 10mpk（經由膳食）

圖24

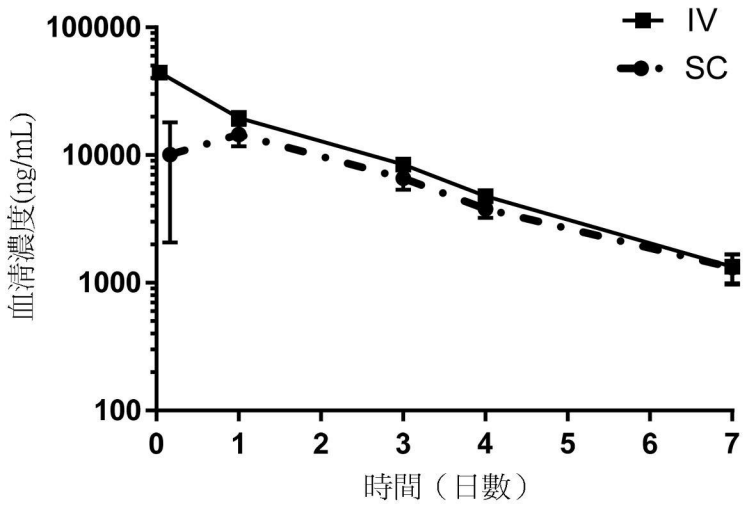


圖25

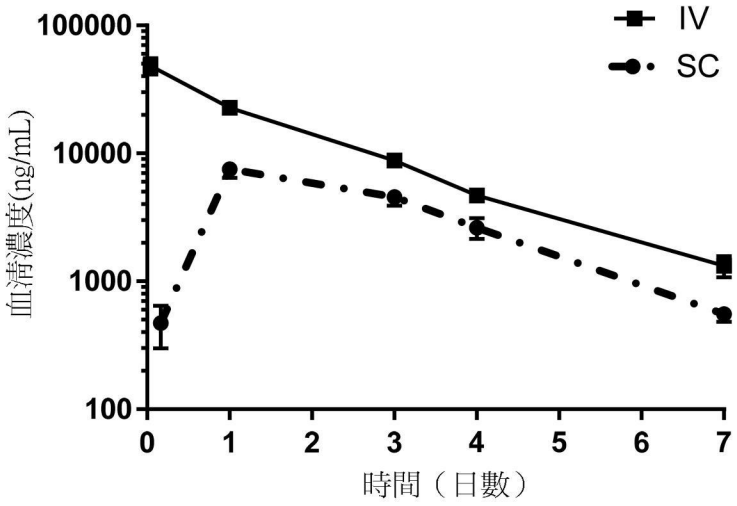


圖26

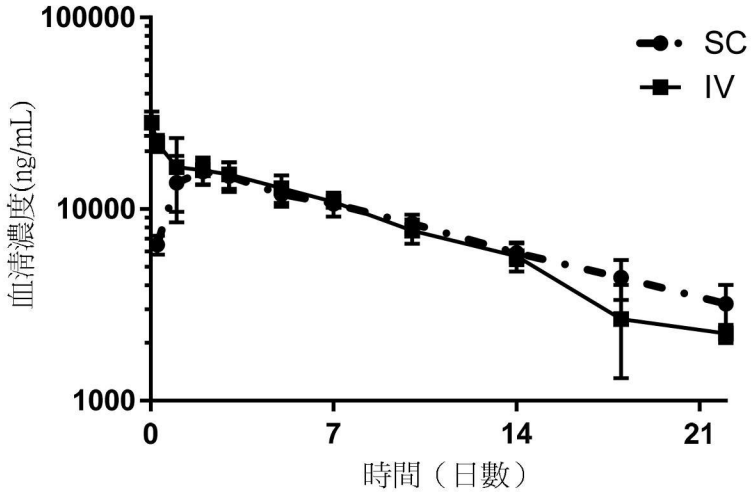


圖27

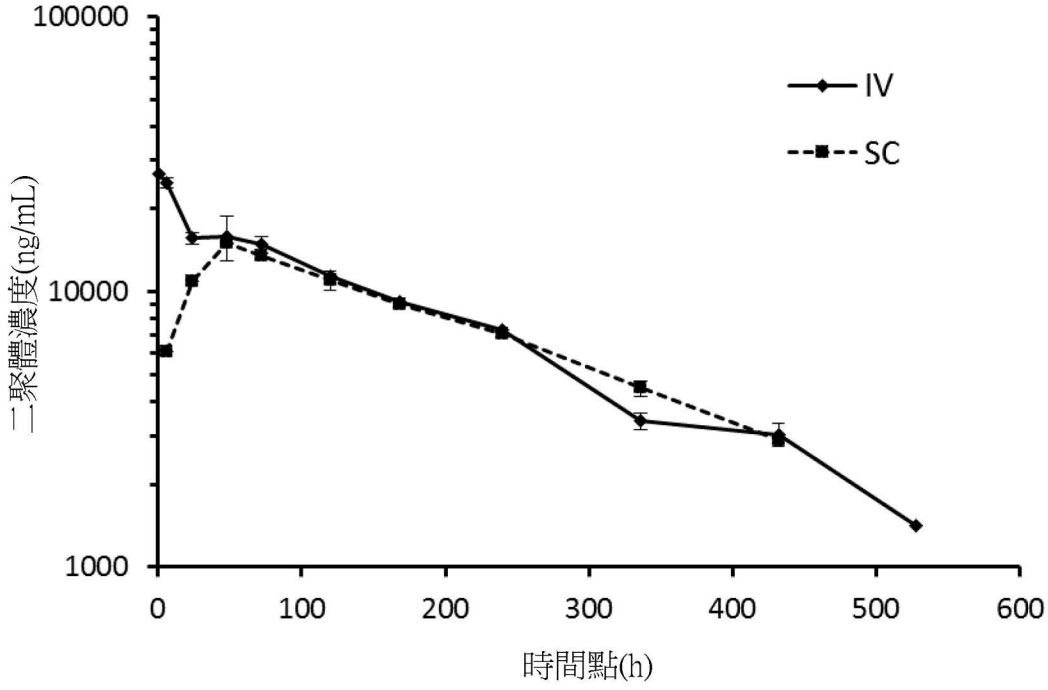

100000
10000
1000
二聚體濃度(ng/mL)
IV
SC
0
100
200
300
400
500
600
時間點(h)

圖28

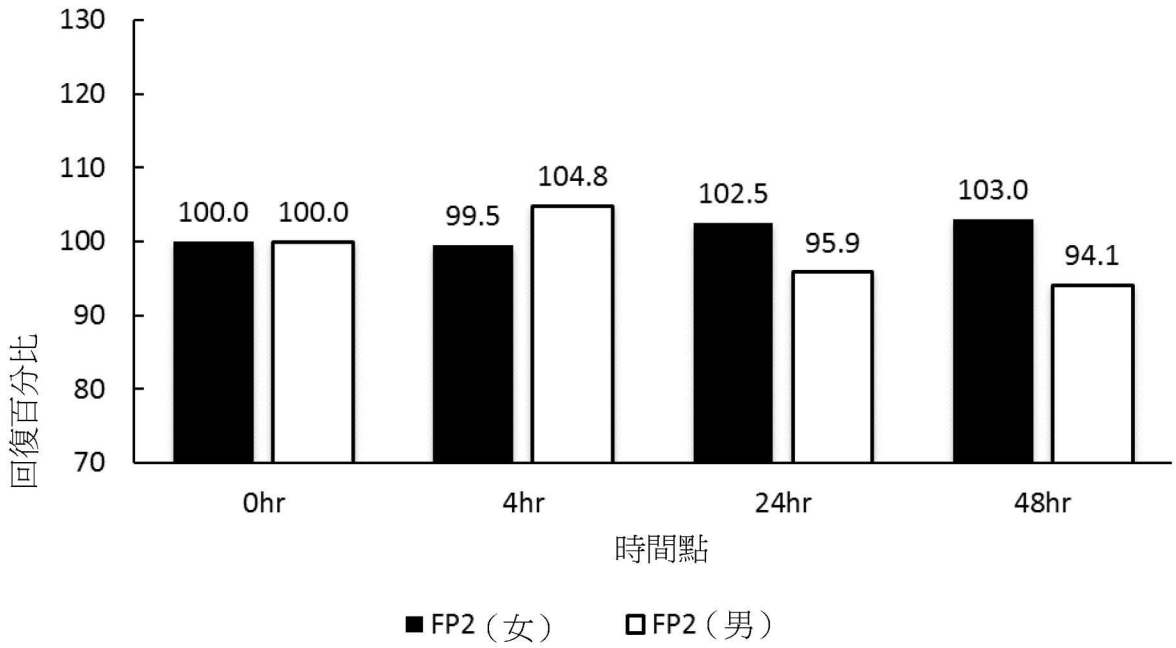

130
120
110
100
90
80
70
回復百分比
100.0
100.0
99.5
104.8
102.5
95.9
103.0
94.1
0hr
4hr
24hr
48hr
時間點
FP2（女）
FP2（男）

圖29

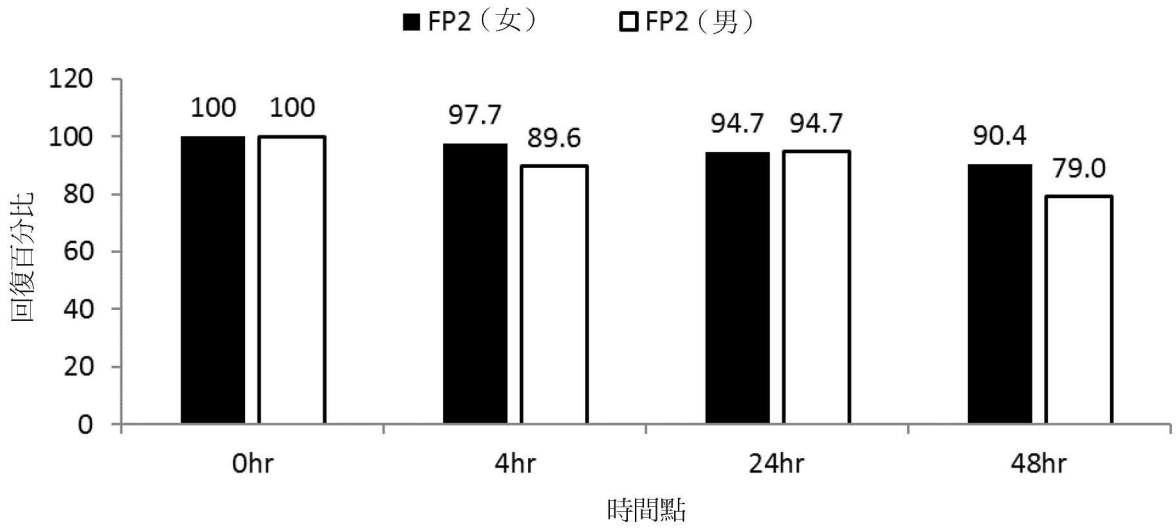

FP2（女）
FP2（男）
回復百分比
120
100
80
60
40
20
0
100
100
97.7
89.6
94.7
94.7
90.4
79.0
0hr
4hr
24hr
48hr
時間點

圖30

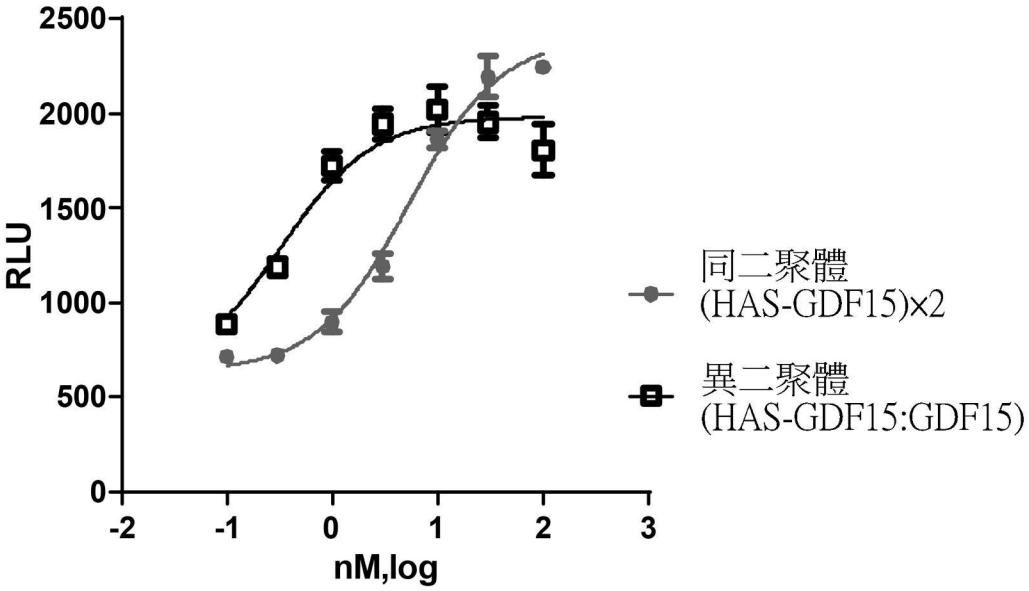

2500
2000
1500
1000
500
0
RLU
-2
-1
0
1
2
3
nM,log
同二聚體
(HAS-GDF15)×2
異二聚體
(HAS-GDF15:GDF15)

圖31

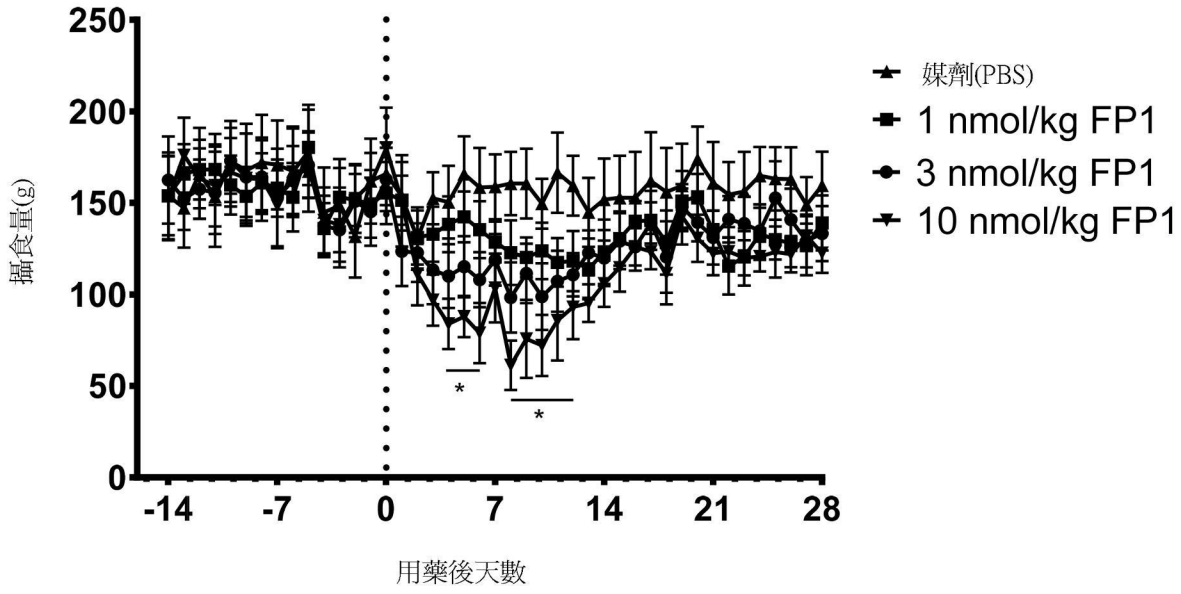

250
200
150
100
50
0
攝食量(g)
-14
-7
0
7
14
21
28
用藥後天數
媒劑(PBS)
1 nmol/kg FP1
3 nmol/kg FP1
10 nmol/kg FP1
*
*

圖32

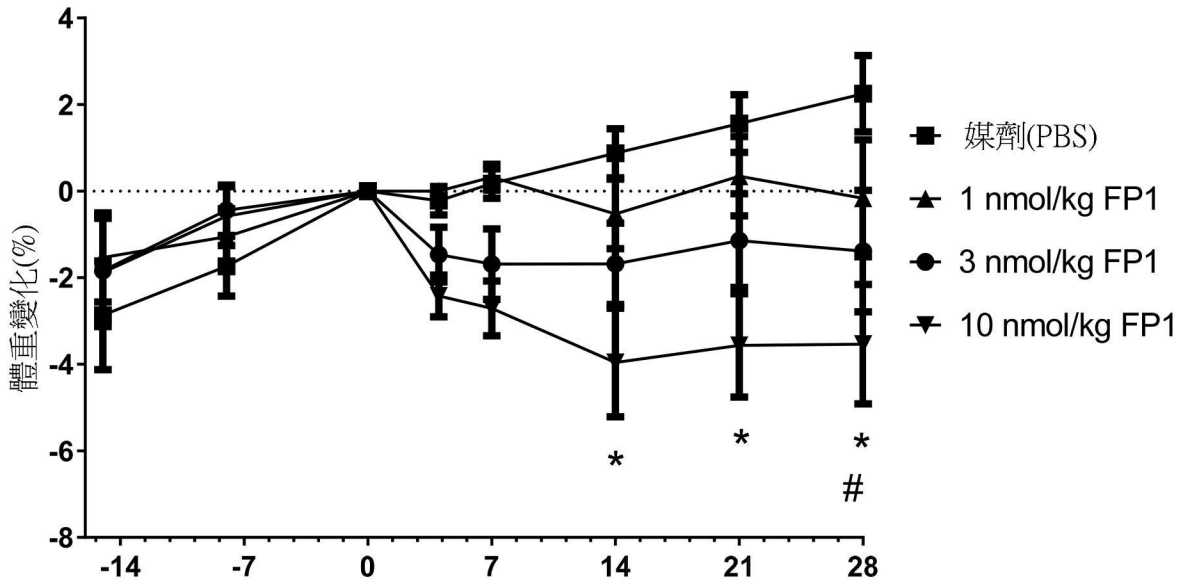

4
2
0
-2
-4
-6
-8
體重變化(%)
-14
-7
0
7
14
21
28
*
*
*
#
媒劑(PBS)
1 nmol/kg FP1
3 nmol/kg FP1
10 nmol/kg FP1
用藥後天數

圖33

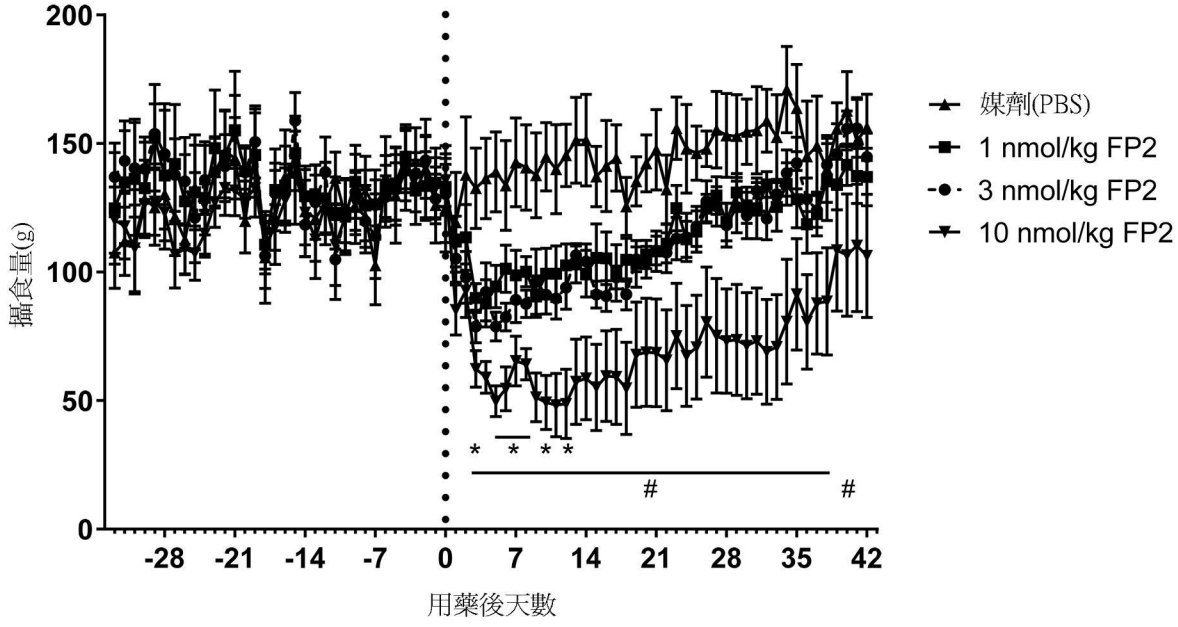

200
150
100
50
0
攝食量(g)
-28
-21
-14
-7
0
7
14
21
28
35
42
用藥後天數
媒劑(PBS)
1 nmol/kg FP2
3 nmol/kg FP2
10 nmol/kg FP2
*
*
*
*
#
#

圖34

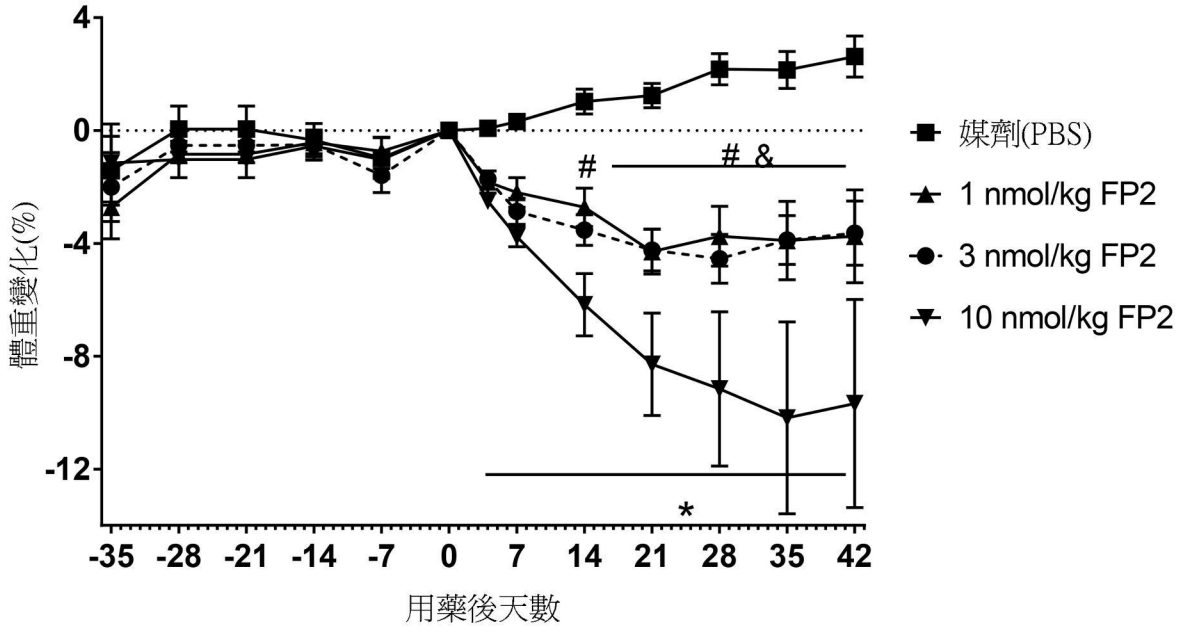

4
0
-4
-8
-12
體重變化(%)
-35 -28 -21 -14 -7 0 7 14 21 28 35 42
用藥後天數
#
&
*
媒劑(PBS)
1 nmol/kg FP2
3 nmol/kg FP2
10 nmol/kg FP2

圖35