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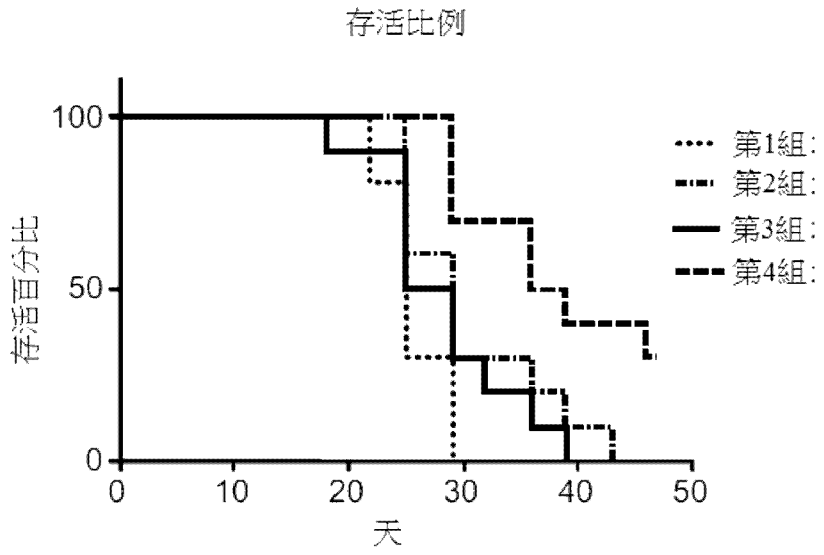
介白素-21 突變蛋白及治療方法

(57)摘要

本文提供供在治療疾病之方法中使用的 IL-21 突變蛋白及包含其之融合蛋白。本文亦提供相關結合物、核酸、載體、宿主細胞、醫藥組合物及套組。本發明提供製造該等 IL-21 突變蛋白及包含其之融合蛋白的方法，以及治療有需要之個體的方法。進一步提供 PD-1 抗原結合蛋白。

Provided herein are IL-21 muteins and fusion proteins comprising the same for use in methods of treating a disease. Related conjugates, nucleic acids, vectors, host cells, pharmaceutical compositions and kits are also provided herein. Methods of making the IL-21 muteins and fusion proteins comprising the same, as well as methods of treating a subject in need thereof, are provided by the present disclosure. Further provided are PD-1 antigen-binding proteins.

指定代表圖：



同型對比IL-21, p=ns, 0.1269
同型對比αPD-1 mAb, p=0.0408
同型組合, p=0.0002
αPD-1 mAb 對比組合, p=0.0143
IL-21對比組合, p=0.0047

【圖 2】

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【發明摘要】

【中文發明名稱】

介白素-21突變蛋白及治療方法

【英文發明名稱】

INTERLEUKIN-21 MUTEINS AND METHODS OF TREATMENT

【中文】

本文提供供在治療疾病之方法中使用的IL-21突變蛋白及包含其之融合蛋白。本文亦提供相關結合物、核酸、載體、宿主細胞、醫藥組合物及套組。本發明提供製造該等IL-21突變蛋白及包含其之融合蛋白的方法，以及治療有需要之個體的方法。進一步提供PD-1抗原結合蛋白。

【英文】

Provided herein are IL-21 muteins and fusion proteins comprising the same for use in methods of treating a disease. Related conjugates, nucleic acids, vectors, host cells, pharmaceutical compositions and kits are also provided herein. Methods of making the IL-21 muteins and fusion proteins comprising the same, as well as methods of treating a subject in need thereof, are provided by the present disclosure. Further provided are PD-1 antigen-binding proteins.

【指定代表圖】

圖2

【代表圖之符號簡單說明】

無

【發明說明書】

【中文發明名稱】

介白素-21突變蛋白及治療方法

【英文發明名稱】

INTERLEUKIN-21 MUTEINS AND METHODS OF TREATMENT

【技術領域】

【先前技術】

【0001】 PD-1/PD-L1軸與癌症中T細胞免疫反應之抑制有關。已在臨床上在許多實體腫瘤適應症中證實此路徑之拮抗劑。納武單抗(Nivolumab)及派姆單抗(pembrolizumab)係靶向PD-1路徑之兩種此類抑制劑，且各已經美國食品與藥物管理局(U.S. Food and Drug Administration，FDA)批准用於治療轉移性黑色素瘤。近來，研究人員已在其他腫瘤類型背景下測試檢查點抑制之範例。雖然已獲得一些進展，但檢查點抑制療法仍然處在其他癌症治療選擇的陰影中。

【0002】 有關檢查點抑制劑與其他藥劑組合之研究正在進行中或近來已完成。舉例而言，在III期臨床試驗中對患有不可切除之III期或IV期黑色素瘤之患者測試納武單抗與伊匹單抗(ipilimumab)(一種CTLA-4受體阻斷抗體)之組合。在此項研究中，在接受納武單抗與伊匹單抗之組合的患者中實現完全反應之患者的百分比最高，打敗在接受任一單獨藥物之組中之患者所展現的結果。當前亦正在探索其他組合。

【0003】 介白素-21 (IL-21)係調節先天性與適應性免疫細胞之活性的T細胞衍生多效性細胞介素。IL-21可加強T細胞存活及效應功能。因為其在抗腫瘤及抗病毒反應中起關鍵作用，所以除對導致自體免疫性疾病及

炎性疾病發生的炎性反應發揮重大作用以外，IL-21已成為若干療法之有吸引力之標靶。

【0004】 但是，基於IL-21之療法的研發係複雜的。展示增強，或令人困惑地，抑制IL-21作用引起治療作用之研究使得研究複雜化。由於IL-21受體(IL-21R)廣泛表現，所以存在額外挑戰。IL-21R不僅在T細胞上表現，且亦在B細胞、NK細胞及骨髓細胞上表現。因此，必須小心地限制白血球中廣泛之IL-21活化且避免毒性可能性。對IL-21信號傳導之限制必須予以權衡且進行選擇。觸發IL-21之作用必須設計成在適當時候及地方進行。

【0005】 實際上，利用IL-21部分作為單一療法或與檢查點抑制劑組合未獲得任何成功，尤其是臨床上之成功。因此，仍然需要利用IL-21之治療模式，包括將IL-21部分與檢查點抑制劑組合之模式。亦仍然需要與免疫檢查點抑制組合之IL-21療法。

【發明內容】

【0006】 本發明提供包含SEQ ID NO: 2之胺基酸序列之IL-21突變蛋白，其中SEQ ID NO: 2為

QGQDX HMXXM XXXXX XVDXL KNXVN DLVPE FLPAP EDVET NCEWS AFSCF QKAQL KSANT GNNEX XIXXX XXXLX XXXXX TNAGR RQKHR LTCPS CDSYE KKPPK EFLXX FXXLL XXMXX QHXSS RTHGS EDS (SEQ ID NO: 2)，且X為任何胺基酸，且其中該IL-21突變蛋白胺基酸序列與人類IL-21之胺基酸序列(SEQ ID NO: 1)的差異在於至少1個胺基酸。

【0007】 因此，在一個態樣中，本發明亦提供相對於在本文中以

SEQ ID NO: 1提供之野生型IL-21胺基酸序列僅僅包含一個胺基酸取代之IL-21突變蛋白。在例示性態樣中，胺基酸取代位於選自由以下組成之群的胺基酸位置處：根據SEQ ID NO: 1之胺基酸位置編號，5、8、9、11、12、13、14、15、16、19、23、65、66、68、69、70、72、73、75、76、77、78、79、80、109、110、112、113、116、117、119、120或123。

【0008】 本發明進一步提供相對於SEQ ID NO: 1僅僅包含兩個胺基酸取代之IL-21突變蛋白。在例示性態樣中，胺基酸取代位於選自由以下組成之群的兩個胺基酸位置處：根據SEQ ID NO: 1之胺基酸位置編號，5、9、15、70、71、72、73及76。

【0009】 在例示性實施例中，IL-21突變蛋白以相對於野生型IL-21對IL-21受體之親和力有所降低之親和力結合於IL-21受體(IL-21R)。在例示性態樣中，IL-21突變蛋白以大於或等於約0.04 nM之K_D結合於人類IL-21R。在例示性態樣中，IL-21突變蛋白以大於或等於約0.055 nM之K_D結合於食蟹獼猴IL-21R。

【0010】 本發明亦提供包含與異源部分連接之本發明之IL-21突變蛋白的結合物。在例示性態樣中，異源部分為多肽，從而使得結合物為融合蛋白。因此，本發明提供包含本發明之IL-21突變蛋白之融合蛋白。在例示性態樣中，融合蛋白包含與諸如抗體或其抗原結合抗體片段之抗原結合蛋白連接的本發明之IL-21突變蛋白。

【0011】 在特定實施例中，融合蛋白包含與本發明之PD-1抗原結合蛋白(例如PD-1抗原結合抗體)連接的IL-21突變蛋白。

【0012】 本發明亦提供PD-1抗原結合蛋白及包含PD-1抗原結合蛋

白之結合物及融合蛋白。

【0013】 本發明進一步提供包含編碼本發明之IL-21突變蛋白、PD-1抗原結合蛋白(例如PD-1抗原結合抗體)或包含IL-21突變蛋白及PD-1抗原結合蛋白(例如PD-1抗原結合抗體)之融合蛋白的核苷酸序列的核酸。在例示性態樣中，核酸分子包含編碼本發明之結合物或融合蛋白之核苷酸序列。此外，本文提供包含本發明之核酸之載體及包含本發明之核酸之宿主細胞。

【0014】 本發明另外提供包含本發明之IL-21突變蛋白、PD-1抗原結合蛋白(例如PD-1抗原結合抗體)、結合物、融合蛋白(例如包含IL-21突變蛋白及PD-1抗原結合蛋白(例如PD-1抗原結合抗體)之融合蛋白)、核酸、載體或宿主細胞或其組合的套組。

【0015】 本文提供包含本發明之IL-21突變蛋白、PD-1抗原結合蛋白(例如PD-1抗原結合抗體)、結合物、融合蛋白(例如包含IL-21突變蛋白及PD-1抗原結合蛋白(例如PD-1抗原結合抗體)之融合蛋白)、核酸、載體或宿主細胞或其組合的醫藥組合物。

【0016】 本文提供製造IL-21突變蛋白、PD-1抗原結合蛋白(例如PD-1抗原結合抗體)及包含IL-21突變蛋白及PD-1抗原結合蛋白(例如PD-1抗原結合抗體)之融合蛋白的方法。在例示性實施例中，該方法包括培養本發明之宿主細胞以表現IL-21突變蛋白、PD-1抗原結合蛋白(例如PD-1抗原結合抗體)或包含IL-21突變蛋白及PD-1抗原結合蛋白(例如PD-1抗原結合抗體)之融合蛋白，且收穫所表現之IL-21突變蛋白、PD-1抗原結合蛋白(例如PD-1抗原結合抗體)或包含IL-21突變蛋白及PD-1抗原結合蛋白(例如PD-1抗原結合抗體)之融合蛋白。

【0017】 本發明另外提供治療方法。在例示性實施例中，該方法為一種治療有需要之個體的方法，其包括向有需要之個體投與有效治療個體之量的本發明之醫藥組合物。在例示性態樣中，個體具有腫瘤(例如實體腫瘤、血液科惡性疾病或淋巴類惡性疾病)且醫藥組合物係以有效治療個體之腫瘤之量投與該個體。在其他例示性態樣中，腫瘤為非小細胞肺癌(NSCLC) (例如III期或IV期NSCLC)、小細胞肺癌(SCLC)、頭頸部癌、腎癌、乳癌、黑色素瘤、卵巢癌、肝癌、胰臟癌、結腸癌、前列腺癌、胃癌、膀胱癌、肝細胞癌、具有高微衛星不穩定性之癌症(亦即高MSI癌症)、淋巴瘤或白血病。

【圖式簡單說明】

【0018】 圖1A表示植入CT26/3E5結腸癌細胞之BALB/c小鼠之腫瘤體積(mm^3)作為時間(天)之函數的圖。在第12天，量測腫瘤，且在第12天、第15天及第18天，向小鼠腹膜內(IP)注射300 μg同型對照抗體(mIgG1)。

【0019】 圖1B表示植入CT26/3E5結腸癌細胞之BALB/c小鼠之腫瘤體積(mm^3)作為時間(天)之函數的圖。在第12天，量測腫瘤，且在第12天、第15天及第18天，向小鼠IP注射300 μg抗PD-1抗體。

【0020】 圖1C表示植入CT26/3E5結腸癌細胞之BALB/c小鼠之腫瘤體積(mm^3)作為時間(天)之函數的圖。在第12天，量測腫瘤，且每週給與小鼠50 μg重組鼠科IL-21 (rmIL-21)三次，歷時3週。在第33天結束給藥。

【0021】 圖1D表示植入CT26/3E5結腸癌細胞之BALB/c小鼠之腫瘤體積(mm^3)作為時間(天)之函數的圖。在第12天，量測腫瘤，且在第12

天、第15天及第18天，給與小鼠300 μg抗PD-1抗體，且每週給與50 μg rmIL-21三次，歷時3週。在第33天結束給藥。

【0022】 圖2表示植入CT26/3E5結腸癌細胞之四組BALB/c小鼠之存活百分比的圖。在第12天、第15天及第18天，向第1組小鼠腹膜內(IP)注射300 μg同型對照抗體(mIgG1)。在第12天、第15天及第18天，向第2組小鼠IP注射300 μg抗PD-1抗體。每週給與第3組小鼠50 μg rmIL-21三次，歷時3週。在第12天、第15天及第18天，給與第4組小鼠300 μg抗PD-1抗體，且每週給與50 μg rmIL-21三次，歷時3週。與單一療法rmIL-21或抗PD-1相比，投與抗PD-1與rmIL-21之組合顯著延長存活。

【0023】 圖3示出包含與IL-21突變蛋白融合之阻斷PD-1抗體之融合蛋白(αPD-1:IL-21突變蛋白)的作用機制之假設。不受特定理論束縛，咸信該融合物結合於CD8+ T細胞上之IL-21R，同時阻斷PD-1與PD-L1之間的信號轉導。

【0024】 圖4A示出包含與IL-21突變蛋白同源二聚體融合之抗PD-1抗體之融合蛋白。該融合蛋白無連接子。該抗體可包含減少或消除Fc相關之效應結合及功能(例如缺乏與Fcγ受體(例如SEFL2-2)相互作用之能力)的恆定區。

【0025】 圖4B示出包含與IL-21突變蛋白同源二聚體融合之抗PD-1抗體之融合蛋白。該融合蛋白可在抗體之重鏈恆定區與IL-21突變蛋白之間包含GGGGS (G4S)連接子。抗體亦可包含SEFL2-2修飾。

【0026】 圖4C示出包含與IL-21突變蛋白單體融合之抗PD-1抗體之融合蛋白。該融合蛋白可在抗體之重鏈恆定區與IL-21突變蛋白之間包含G4S連接子。抗體重鏈包含電荷對突變(cpm；例如V1、V4、V103或

V131)以幫助異源二聚體Fc區優先締合。抗體亦可包含SEFL2-2修飾。

【0027】 圖5A表示暴露於以下之PD-1^{-ve} Hut78 T細胞中STAT3信號傳導之圖：(i)單獨重組人類IL-21 (rhIL-21)(具有實心圓之實線)；(ii)單獨抗PD-1 mAb (具有實心菱形之實線)；(iii)在無連接子下與IL-21同源二聚體融合之抗PD-1 mAb (具有實心三角形之實線)；(iv)在連接子下與IL-21同源二聚體融合之抗PD-1 mAb (具有空心三角形之虛線)；(v)在無連接子下與IL-21單體融合之抗PD-1 mAb (具有實心正方形之實線)；或(vi)在連接子下與IL-21單體融合之抗PD-1 mAb (具有空心正方形之虛線)。

【0028】 圖5B表示暴露於以下之PD-1^{+ve} Hut78 T細胞中STAT3信號傳導之圖：(i)單獨重組人類IL-21 (rhIL-21)(具有實心圓之實線)；(ii)單獨抗PD-1 mAb (具有實心菱形之實線)；(iii)在無連接子下與IL-21同源二聚體融合之抗PD-1 mAb (具有實心三角形之實線)；(iv)在連接子下與IL-21同源二聚體融合之抗PD-1 mAb (具有空心三角形之虛線)；(v)在無連接子下與IL-21單體融合之抗PD-1 mAb (具有實心正方形之實線)；或(vi)在連接子下與IL-21單體融合之抗PD-1 mAb (具有空心正方形之虛線)。

【0029】 圖6表示以低劑量(250 μg/kg)或高劑量(1000 μg/kg)靜脈內投與6隻動物的包含與抗PD-1 mAb融合之WT IL-21之同源二聚體融合蛋白的血清濃度之圖。IgG抗體結構域(150 μg/kg)作為對照物操作。

【0030】 圖7表示暴露於對IL-21Rα之親和力有所降低之IL-21突變蛋白的PD-1^{-ve} Hut78細胞(空心條)或PD-1^{+ve} Hut78細胞(實心條)的IL-21活性之減少倍數(相對於rhIL-21活性)的圖。

【0031】 圖8表示暴露於對IL-21Rγ之親和力有所降低之IL-21突變蛋白的PD-1^{-ve} Hut78細胞(空心條)或PD-1^{+ve} Hut78細胞(實心條)的IL-21

活性之減少倍數(相對於rhIL-21活性)的圖。

【0032】 圖9A表示在暴露於以下之PD-1^{-ve} Hut78 T細胞中STAT3信號傳導之圖：(i)單獨重組人類IL-21 (rhIL-21) (具有實心圓之實線)；(ii)與WT IL-21同源二聚體融合之抗PD-1 mAb (具有空心圓之虛線)；(iii)與WT IL-21單體融合之抗PD-1 mAb (具有實心圓之虛線)；及(iv)與IL-21突變蛋白51同源二聚體(R65P)融合之抗PD-1 mAb (具有實心三角形之點線)。

【0033】 圖9B表示在暴露於以下之PD-1^{+ve} Hut78 T細胞中STAT3信號傳導之圖：(i)單獨重組人類IL-21 (rhIL-21) (具有實心圓之實線)；(ii)與WT IL-21同源二聚體融合之抗PD-1 mAb (具有空心圓之虛線)；(iii)與WT IL-21單體融合之PD-1 mAb (具有實心圓之虛線)；及(iv)與IL-21突變蛋白51同源二聚體(R65P)融合之抗PD-1 mAb (具有實心三角形之點線)。

【0034】 圖10表示包含以下之融合蛋白之血清濃度的圖：(i)與IL-21 R76E突變蛋白同源二聚體融合之抗PD-1 mAb (具有實心圓之點線)；(ii)與IL-21 R76A突變蛋白同源二聚體融合之抗PD-1 mAb (具有實心三角形之虛線)；(iii)與IL-21 D15N突變蛋白同源二聚體融合之抗PD-1 mAb (具有X之虛線)；(iv)抗PD-1抗體(8.25 mg/kg；具有空心菱形之虛線)；及(v)與WT IL-21突變蛋白同源二聚體融合之抗PD-1 mAb (具有實心正方形之實線)。

【0035】 圖11表示藉由混合淋巴細胞反應之細胞分泌之IL-2 (pg/mL)作為以下各者之抗體濃度之函數的圖：(i)抗PD-1抗體(具有實心圓之實線)；(ii)包含IL-21 R5Q/R76E雙重突變蛋白同源二聚體之融合蛋白(具有空心圓之虛線)；(iii)抗PD-1 mAb與rhIL-21之組合(具有空心正方

形之點線)；(iv)包含IL-21 R76E單一突變蛋白同源二聚體之融合蛋白(實心正方形)；(v) IgG對照物(具有空心菱形之點線)及(vi) rhIL-21 (具有空心三角形之摺線)。

【0036】 圖12A表示暴露於以下之細胞之STAT3活性的相對平均螢光強度(MFI)之變化倍數的圖：(i)包含IL-21 R5E/R76A雙重突變蛋白之融合蛋白(具有空心三角形之線)；(ii) IgG1對照物(具有實心菱形之點線)；(iii) rhIL-21 (具有空心正方形之虛線)；(iv)抗PD-1 mAb (具有空心橢圓形之實線)；(v) rhIL-21與抗PD-1 mAb之組合(具有實心橢圓形之虛線)；或(vi)包含IL-21 R76E單一突變蛋白之融合蛋白(具有空心菱形之線)。

【0037】 圖12B表示暴露於以下之細胞之STAT3活性的相對MFI之變化倍數的圖：(i)包含IL-21 R5Q/R76E雙重突變蛋白之融合蛋白(具有空心三角形之線)；(ii) IgG1對照物(具有實心菱形之點線)；(iii) rhIL-21 (具有空心正方形之虛線)；(iv)抗PD-1 mAb (具有空心橢圓形之實線)；(v) rhIL-21與抗PD-1 mAb之組合(具有實心橢圓形之虛線)；或(vi)包含IL-21 R76E單一突變蛋白之融合蛋白(具有空心菱形之線)。

【0038】 圖12C表示暴露於以下之細胞之STAT3活性的相對MFI之變化倍數的圖：(i)包含IL-21 R9E/R76A雙重突變蛋白之融合蛋白(具有空心三角形之線)；(ii) IgG1對照物(具有實心菱形之點線)；(iii) rhIL-21 (具有空心正方形之虛線)；(iv)抗PD-1 mAb (具有空心橢圓形之實線)；(v) rhIL-21與抗PD-1 mAb之組合(具有實心橢圓形之虛線)；或(vi)包含IL-21 R76E單一突變蛋白之融合蛋白(具有空心菱形之線)。

【0039】 圖13A表示藉由暴露於以下之CTL之特異性溶解% (y軸)相

對於效應:標靶細胞比率(x軸)的圖：(i) rhIL-21 (具有實心圓之實線)；(ii) hIgG4對照抗體(具有空心圓之虛線)；(iii)抗PD-1 mAb (具有實心三角形之虛線)；(iv) rhIL-21與抗PD-1 mAb之組合(具有空心三角形之點線)；或(v)包含IL-21 R5E/R76A之融合蛋白(具有X之摺線)。

【0040】 圖13B表示藉由暴露於以下之CTL之特異性溶解%的圖，表示藉由暴露於以下之CTL之特異性溶解%的圖：(i) rhIL-21 (具有實心圓之實線)；(ii) hIgG4對照抗體(具有空心圓之虛線)；(iii)抗PD-1 mAb (具有實心三角形之虛線)；(iv) rhIL-21與抗PD-1 mAb之組合(具有空心三角形之點線)；或(v)包含IL-21 R5Q/R76E之融合蛋白(具有X之摺線)。

【0041】 圖13C表示藉由暴露於以下之CTL之特異性溶解%的圖：(i) rhIL-21 (具有實心圓之實線)；(ii) hIgG4對照抗體(具有空心圓之虛線)；(iii)抗PD-1 mAb (具有實心三角形之虛線)；(iv) rhIL-21與抗PD-1 mAb之組合(具有空心三角形之點線)；或(v)包含IL-21 R9E/R76A之融合蛋白(具有X之摺線)。

【0042】 圖14表示以下各者之血清濃度：(i)抗PD-1 mAb (具有實心正方形之實線)；(ii)包含抗PD-1 mAb及IL-21 R5Q/R76E同源二聚體之融合蛋白(具有實心圓之實線)；(iii)包含抗PD-1 mAb與IL-21 R76E同源二聚體之融合蛋白(實線)；(iv)包含抗PD-1 mAb及IL-21 R5E/R76A同源二聚體之融合蛋白(具有X之虛線)；(v)包含抗PD-1 mAb及IL-21 R76A同源二聚體之融合蛋白(具有實心菱形之虛線)；或(vi)包含抗PD-1 mAb及IL-21 R76E單體之融合蛋白(具有實心三角形之實線)。

【0043】 圖15A表示細胞取樣(空心箭頭)及投與(實心箭頭)之時間線。

【0044】 圖15B表示在給與一定劑量以下各者之動物中如在第7天所量測的PD-1$^+$/CD4$^+$細胞之變化倍數(相對於第-5天)之圖：(i)包含抗PD-1 mAb及IL-21 R76E突變蛋白之融合蛋白(具有水平線之條)；(ii)包含抗PD-1 mAb及IL-21 R76E單一突變蛋白單體之融合蛋白(具有垂直線之條)；或(iii)包含抗PD-1 mAb及IL-21 R5Q/R76E雙重突變蛋白同源二聚體之融合蛋白(空心條) (各在第0天投與)。

【0045】 圖15C表示在給與一定劑量以下各者之動物中如在第7天所量測的PD-1$^+$/CD8$^+$細胞之變化倍數(相對於第-5天)之圖：(i)包含抗PD-1 mAb及IL-21 R76E突變蛋白之融合蛋白(具有水平線之條)；(ii)包含抗PD-1 mAb及IL-21 R76E單一突變蛋白單體之融合蛋白(具有垂直線之條)；或(iii)包含抗PD-1 mAb及IL-21 R5Q/R76E雙重突變蛋白同源二聚體之融合蛋白(空心條) (各在第0天投與)。

【0046】 圖15D表示在給與第一劑量以下各者之動物中如在第21天所量測的PD-1$^+$/CD8$^+$細胞之變化倍數(相對於第-5天)之圖：(i)包含抗PD-1 mAb及IL-21 R76E突變蛋白之融合蛋白(具有水平線之條)；(ii)包含抗PD-1 mAb及IL-21 R76E單一突變蛋白單體之融合蛋白(具有垂直線之條)；或(iii)包含抗PD-1 mAb及IL-21 R5Q/R76E雙重突變蛋白同源二聚體之融合蛋白(空心條) (第一劑量在第0天投與且第二劑量在第8天投與)。

【0047】 圖16表示PD-1$^+$/CD8$^+$細胞之擴增(相對於第-5天)作為PD-1$^+$/CD8$^+$細胞上之PD-1受體佔用率(RO)之函數的圖。IL-21單一突變體(801、802、807及808)顯示在藍色圓內且IL-21雙重突變體(803、804、805及806)顯示在粉紅色圓內。此等資料證明雙重突變體之優良藥物動力學特性允許更佳之標靶覆蓋且與更佳之藥效學反應相關，如藉由PD-1+標

靶群體之擴增所量測。藍線指示單一突變體與雙重突變體之間的總體描繪。

【0048】 圖17表示用單一突變體同源二聚體構築體(動物801及802)、雙重突變體同源二聚體構築體(動物803-806)或單一突變體單體構築體(動物807及808)處理之個別動物的流程圖。PD-1+ T細胞藉由非競爭性或競爭性偵測抗體偵測。標靶覆蓋百分比計算為競爭性與非競爭性PD-1抗體之間的比率百分比。資料顯示所有構築體均在第21天重複給與之後顯示穩固之標靶覆蓋。

【0049】 圖18A表示暴露於包含十種不同抗PD-1 mAb之一及IL-21 R5Q/R76E突變蛋白同源二聚體之融合蛋白的PD-1^{-ve} Hut78 T細胞之STAT3活性之變化倍數(相對於rhIL-21 (具有圓形X之實線))的圖。十種抗PD-1 mAb包括20A2.003 (具有菱形之線)、20C1.006 (紅色正方形)、20C1.009 (具有三角形之線)及22D4.006 (具有空心圓形之線)。

【0050】 圖18B表示暴露於包含十種不同抗PD-1 mAb之一及IL-21 R5Q/R76E突變蛋白同源二聚體之融合蛋白的PD-1+ve Hut78 T細胞之STAT3活性之變化倍數(相對於rhIL-21 (具有圓形X之實線))的圖。十種抗PD-1 mAb包括20A2.003 (具有菱形之線)、20C1.006 (紅色正方形)、20C1.009 (具有三角形之線)及22D4.006 (具有空心圓形之線)。圖18A與圖18B之比較指示pSTAT3信號傳導需要PD-1靶向且當與不同抗PD-1 mAb融合時突變蛋白之活性相似。

【0051】 圖19A表示暴露於包含七種不同抗PD-1 mAb之一及IL-21 R9E/R76A突變蛋白同源二聚體之融合蛋白的PD-1^{-ve} Hut78 T細胞之STAT3活性之變化倍數(相對於rhIL-21 (具有圓形X之實線))的圖。七種抗

PD-1 mAb包括20A2.003 (具有空心三角形之線)、20C1.006 (具有空心正方形之線)、20C1.009 (具有空心菱形之線)及22D4.006 (具有空心圓形之線)。

【0052】 圖19B表示暴露於包含七種不同抗PD-1 mAb之一及IL-21 R9E/R76A突變蛋白同源二聚體之融合蛋白的PD-1^{+ve} Hut78 T細胞之STAT3活性之變化倍數(相對於rhIL-21 (具有圓形X之實線))的圖。圖19A與圖19B之比較指示pSTAT3信號傳導需要PD-1靶向且當與不同抗PD-1 mAb融合時突變蛋白之活性相似。七種抗PD-1 mAb包括20A2.003 (具有空心三角形之線)、20C1.006 (具有空心正方形之線)、20C1.009 (具有空心菱形之線)及22D4.006 (具有空心圓形之線)。

【0053】 圖20A-20D表示在若干抗PD-1 mAb-IL-21單體或二聚雙重突變蛋白融合物下觀察到的pSTAT3信號傳導之量。具有實心圓之實線(圖頂部)為rhIL-21；具有空心圓之虛線(圖底部)為IgG1對照物；具有X之線(圖底部)為IgG2對照物；具有實心正方形之點線(圖底部)為用於IL-21突變蛋白融合物中之22D4.006抗PD-1 mAb (呈mAb存在；亦即不呈融合物)；具有空心正方形之虛線及具有空心菱形之點線(圖底部)為對照抗PD-1 mAb；剩餘線為抗PD-1 mAb (22D4.006)-IL-21單體或二聚雙重突變蛋白融合物(具有多種電荷對突變)，其中雙重突變體為R5E/R76A；R9E/R76A；R5A/R76E或R5Q/R76E。rhIL-21在PD-1^{-ve}與PD-1^{+ve}細胞中顯示活性，單體及同二聚體雙重突變蛋白融合物無法在PD-1^{-ve}細胞中顯示pSTAT3 (基於IL-21)活性，且單體及同二聚體雙重突變蛋白融合物能夠在PD-1^{+ve}細胞中顯示pSTAT3 (基於IL-21)活性。因此，具有IL-21雙重突變體之單體融合物展現與其對應二聚融合物類似水準的在PD-1^{-ve}細胞中

之IL-21活性減弱及PD-1^{+ve}細胞中之IL-21活性拯救。圖20A及20B為PD-1^{-ve}細胞上pSTAT3分析之重複操作。圖20C及20D為PD-1^{+ve}細胞上pSTAT3分析之重複操作。

【0054】 圖21A-21D表示利用在圖20A-20D中評估之相同抗PD-1 mAb (22D4.006)-IL-21單體或二聚雙重突變蛋白融合物的PD-1報導基因分析(RGA；圖21A及21B)及MLR分析(圖21C及21D)之結果。圖21A-21D顯示抗PD-1 mAb (22D4.006)-IL-21單體及二聚雙重突變蛋白融合物能夠誘導PD-1活性。具有實心圓之實線(圖頂部)為rhIL-21；具有空心圓之虛線(圖頂部)為IgG1對照物；具有X之線(圖頂部)為IgG2對照物；具有實心正方形之點線(圖頂部)為用於IL-21突變蛋白融合物中之22D4.006抗PD-1 mAb (呈mAb存在；亦即不呈融合物)；具有空心正方形之虛線及具有空心菱形之點線(圖頂部)為對照抗PD-1 mAb；剩餘線為抗PD-1 mAb-IL-21單體或二聚雙重突變蛋白融合物。圖21A及21B為PD-1 RGA分析之重複操作。圖20C及20D為MLR分析之重複操作。

【0055】 圖22A-22D表示測試與圖20A-20D中之彼等構築體相同之構築體的pSTAT3分析之結果，除了抗PD-1 mAb-IL-21單體及二聚雙重突變蛋白融合物中使用不同抗PD-1 mAb (20A2.003)。圖22A-22D中之結果類似於圖20A-20D中所見之彼等結果。具有實心圓之實線(圖頂部)為rhIL-21；具有空心圓之虛線(圖底部)為IgG1對照物；具有X之線(圖底部)為IgG2對照物；具有實心正方形之點線(圖底部)為用於IL-21突變蛋白融合物中之20A2.003抗PD-1 mAb (呈mAb存在；亦即不呈融合物)；具有空心正方形之虛線及具有空心菱形之點線(圖底部)為對照抗PD-1 mAb；剩餘線為抗PD-1 mAb (20A2.003)-IL-21單體或二聚雙重突變蛋白融合物(具有

多種電荷對突變)，其中雙重突變體為R5E/R76A；R9E/R76A；R5A/R76E或R5Q/R76E。圖22A及22B為PD-1^{-ve}細胞上pSTAT3分析之重複操作。圖22C及22D為PD-1^{+ve}細胞上pSTAT3分析之重複操作。

【0056】 圖23A-23D表示測試與圖21A-21D中之彼等構築體相同之構築體的PD-1報導基因分析(圖23A及23B)及MLR分析(圖23C及23D)之結果，除了抗PD-1 mAb-IL-21單體及二聚雙重突變蛋白融合物中使用不同抗PD-1 mAb (20A2.003)。圖23A-23D中之結果類似於圖21A-21D中所見之彼等結果。具有實心圓之實線(圖頂部)為rhIL-21；具有空心圓之虛線(圖頂部)為IgG1對照物；具有X之虛線(圖頂部)為IgG2對照物；具有實心正方形之點線(圖頂部)為用於IL-21突變蛋白融合物中之20A2.003抗PD-1 mAb (呈mAb存在；亦即不呈融合物)；具有空心正方形之虛線及具有空心菱形之點線(圖頂部)為對照抗PD-1 mAb；剩餘線為抗PD-1 mAb (20A2.003)-IL-21單體或二聚雙重突變蛋白融合物。圖23A及23B為PD-1 RGA分析之重複操作。圖23C及23D為MLR分析之重複操作。

【0057】 圖24表示經純化之抗PD-1抗體之NFAT/螢光素酶活性作為mAb濃度之函數的圖。

【0058】 圖25A為在暴露於融合蛋白[22D4.017]-[R9E:R76A] (單體)或抗PD-1抗體[22D4.017]後Ki67+/CD3+/CD4+細胞數目相對於基線之變化倍數的圖。

【0059】 圖25B為在暴露於融合蛋白[22D4.017]-[R9E:R76A] (單體)或抗PD-1抗體[22D4.017]後Ki67+/CD3+/CD8+細胞數目相對於基線之變化倍數的圖。

【0060】 圖25C為在暴露於融合蛋白[22D4.017]-[R9E:R76A] (單

體)或抗PD-1抗體[22D4.017]後pSTAT3+/CD3+/CD4+細胞數目相對於基線之變化倍數的圖。

【0061】 圖25D為在暴露於融合蛋白[22D4.017]-[R9E:R76A] (單體)或抗PD-1抗體[22D4.017]後pSTAT3+/CD3+/CD8+細胞數目相對於基線之變化倍數的圖。

【0062】 圖25E為在暴露於融合蛋白[22D4.017]-[R9E:R76A] (單體)或抗PD-1抗體[22D4.017]後CD3+/CD4+細胞數目相對於基線之變化倍數的圖。

【0063】 圖25F為在暴露於融合蛋白[22D4.017]-[R9E:R76A] (單體)或抗PD-1抗體[22D4.017]後CD3+/CD8+細胞數目相對於基線之變化倍數的圖。

【0064】 圖25G為在暴露於融合蛋白[22D4.017]-[R9E:R76A] (單體)或抗PD-1抗體[22D4.017]後PD-1+/CD3+/CD4+細胞數目相對於基線之變化倍數的圖。

【0065】 圖25H為在暴露於融合蛋白[22D4.017]-[R9E:R76A] (單體)或抗PD-1抗體[22D4.017]後PD-1+/CD3+/C84+細胞數目相對於基線之變化倍數的圖。

【0066】 圖25I為在暴露於融合蛋白[22D4.017]-[R9E:R76A] (單體)或抗PD-1抗體[22D4.017] 72小時後血清穿孔素之量相對於基線之變化倍數的圖。

【0067】 圖25J為在暴露於融合蛋白[22D4.017]-[R9E:R76A] (單體)或抗PD-1抗體[22D4.017] 72小時後相對於基線之Ki67+細胞%作為穿孔素增加倍數之函數的圖。

【0068】 圖26A為吸光度(nm)作為時間(sec)之函數的圖，其用於確定抗體22D4.017對人類PD-1抗原之指示K_D。

【0069】 圖26B為吸光度(nm)作為時間(sec)之函數的圖，其用於確定抗體20C1.009對人類PD-1抗原之指示K_D。

【0070】 圖26C為吸光度(nm)作為時間(sec)之函數的圖，其用於確定抗體20A2.003對人類PD-1抗原之指示K_D。

【0071】 圖26D為吸光度(nm)作為時間(sec)之函數的圖，其用於確定IgG1抗PD-1 mAb對人類PD-1抗原之指示K_D。

【0072】 圖26E為吸光度(nm)作為時間(sec)之函數的圖，其用於確定IgG4 PD-1 mAb對人類PD-1抗原之指示K_D。

【0073】 圖26F為吸光度(nm)作為時間(sec)之函數的圖，其用於確定抗體22D4.017對食蟹獼猴PD-1抗原之指示K_D。

【0074】 圖26G為吸光度(nm)作為時間(sec)之函數的圖，其用於確定抗體20C1.009對食蟹獼猴PD-1抗原之指示K_D。

【0075】 圖26H為吸光度(nm)作為時間(sec)之函數的圖，其用於確定抗體20A2.003對食蟹獼猴PD-1抗原之指示K_D。

【0076】 圖26I為吸光度(nm)作為時間(sec)之函數的圖，其用於確定IgG1抗PD-1 mAb對食蟹獼猴PD-1抗原之指示K_D。

【0077】 圖26J為吸光度(nm)作為時間(sec)之函數的圖，其用於確定IgG4抗PD-1 mAb對食蟹獼猴PD-1抗原之指示K_D。

【0078】 圖27為抗PD-1抗體22D4.017及20C1.009之Cp (千卡/莫耳/℃)作為溫度函數的圖。

【0079】 圖28為抗PD-1抗體22D4.017及20C1.009之黏度針對剪切

速率繪製之圖。

【0080】 圖29A-29D為一系列繪出以下中信號作為抗體濃度之函數的圖：(圖29A) PD-1陽性之變異Hut78 T細胞株；(圖29B) TIGIT陽性之變異Hut78 T細胞株；(圖29C) LAG3陽性之變異Hut78 T細胞株；及(圖29D)不內源性表現PD-1、TIGIT或LAG3之親本Hut78 T細胞株。

【實施方式】

相關申請案之交叉引用

【0081】 在此依據35 U.S.C.§119 (e)主張2017年8月3日申請之美國臨時專利申請案第62/540,692號及2018年1月12日申請之美國臨時專利申請案第62/616,733號的權益，且其揭示內容在此以引用之方式併入本文中。

以引用之方式併入電子提交之材料

【0082】 以全文引用之方式併入與本文同時提交且如下標識之電腦可讀之核苷酸/胺基酸序列表：命名為「51633_Seqlisting.txt」之975,000位元組ASCII (文本)文件；於2018年7月25日創建。

【0083】 仍然需要新穎的免疫加強方法，其可運用免疫系統以安全且有效之方式抵抗癌細胞，尤其根據以下事實：當前免疫療法僅僅在少數患者中有效，且可能具有顯著且常常不可預知之毒性。在一個態樣中，新穎類別之包含可阻斷PD-1/PD-L1相互作用之PD-1靶向抗體與本文揭示的經工程改造之親和力減弱之介白素-21突變蛋白融合的雙官能融合分子滿足此需求。本文所述之抗體/細胞介素融合物克服與細胞介素治療劑有關之重大障礙，尤其允許IL-21細胞介素以靶向PD-1之方式像抗體般給與及選擇性遞送。當與抗PD-1抗體融合時，IL-21突變蛋白可在活體內選擇性

地活化且擴增表現PD-1之T細胞。因此，本文所述之抗體/細胞介素融合物可改善及延長當前處於臨床測試中之抗PD-1治療劑之效用。

【0084】 細胞介素與共抑制受體促效劑或拮抗劑之組合仍具有挑戰性，因為存在增加毒性之風險且需要複雜之臨床試驗設計(參見例如Ott等人，J Immunother Cancer 5, 16 (2017)；及Hermel等人，Cancer Metastasis Rev 36, 43-50 (2017))。關於細胞介素，亦可能活化抑制反饋路徑，可能引起免疫抑制(參見例如Portielje等人, Clin Cancer Res 9, 76-83 (2003)；Wan等人, Immunity 38, 514-527 (2013)；及Mooradian等人, Oncoimmunology 7, e1423172 (2018))。介白素-21 (IL-21)為一種I型細胞介素及常見細胞介素受體γ鏈(cg鏈)細胞介素家族之一員，其已顯現為有前景之治療癌症之免疫治療劑。IL-21由活化CD4 T細胞及自然殺手T(NKT)細胞產生，且經由由與常見γ鏈相關之離散IL-21受體(IL-21R)次單元構成之異源二聚體受體複合物進行信號傳導(參見例如Spolski等人, Nat Rev Drug Discov 13, 379-395 (2014))。IL-21R複合物之活化引起JAK/STAT信號傳導路徑之活化。IL-21R廣泛地在包括T及B淋巴細胞、自然殺手(NK)細胞及骨髓細胞之造血細胞中表現。雖然並非必需生長或分化因子，但IL-21為NK細胞及活化T細胞之有效有絲分裂原及存活因子。IL-21可支持CD4 (+) T輔助17 (Th17)細胞以及濾泡輔助T細胞(Tfh)之分化且可對抗調節T細胞(Treg)分化。此外，IL-21可加強CD8 T細胞之存活，且保護不太活化但更持久之T細胞表型，此允許增強腫瘤及病毒控制。

【0085】 細胞介素免疫療法之一個挑戰方面為除活化免疫細胞來加強免疫反應外，相同細胞介素亦可活化逆調節路徑。舉例而言，IL-2及

IFNγ可分別活化保護性免疫反應以及調節T細胞反應及抑制路徑(諸如PD-L1)。在樹突狀細胞(DC)中，IL-21可抑制DC成熟與活化，可誘導習知DC之細胞凋亡，可有力地抑制混合培養物中T細胞之激活，且可在耐受性之誘導中起作用。在人類中，IL-21已作為非靶向性游離細胞介素在若干癌症適應症中進行測試，但儘管存在有前景之臨床前資料及早先I期臨床資料，但此方法之發展尚未進展至比II期測試更遠(參見例如Thompson等人, J Clin Oncol 26, 2034-2039 (2008)；及Davis等人, Clin Cancer Res 15, 2123-2129 (2009))。在更近期之臨床前模型中，重組IL-21細胞介素與共抑制受體拮抗體(例如抗CTLA-4及抗PD-1)之組合已證明IL-21可延長此等治療之功效。現在此類組合處於臨床測試中，不過臨床功效尚有待證實(Lewis等人, Oncoimmunology 7, e1377873 (2017))。

【0086】 不受理論束縛，本文所述之抗體/細胞介素融合物經設計以利用IL-21之免疫加強活性(此對於解決毒性及脫靶免疫抑制而言為必要的)、最大化功效及提高臨床中給與之可行性。

IL-21及IL-21突變蛋白

【0087】 介白素-21 (IL-21)為由T細胞、B細胞、NK細胞及骨髓細胞表現之細胞介素，且調節先天性與適應性免疫細胞之活性且改善T細胞存活及效應功能。若干I期及II期臨床試驗包括IL-21作為研究用藥品，用於治療癌症、炎性疾病及自體免疫性疾病，包括黑色素瘤、腎細胞癌、急性骨髓性白血病、非霍奇金氏淋巴瘤(non-Hodgkin's lymphoma)、卵巢癌、結腸直腸癌、全身性紅斑狼瘡、克羅恩氏病(Crohn's disease)及類風濕性關節炎。

【0088】 IL-21具有四螺旋束結構且呈單體存在。在人類中，已知

IL-21之兩種同功型，各來源於前驅分子。第一IL-21同功型包含162個胺基酸(aa)，其中開始29個胺基酸構成信號肽；且第二IL-21同功型包含153 aa，其中如第一同功型中，開始29個胺基酸構成信號肽。第一及第二IL-21同功型之胺基酸序列(包括信號肽)在本文中分別呈SEQ ID NO: 258及SEQ ID NO: 259提供。

【0089】 IL-21結合於在T細胞、B細胞及NK細胞之表面上表現之異源二聚體IL-21受體(IL-21R)。IL-21R之結構與IL-2受體及IL-15受體類似，因為此等細胞介素受體中之每一者均包含常見γ鏈(γc)。除γc外，IL-21R包含對於結合於IL-21而言重要之α鏈。人類IL-21受體α鏈存在兩種同功型：同功型1及同功型2。同功型1及同功型2之胺基酸序列在本文中分別呈SEQ ID NO: 256及261提供。人類常見γ鏈之胺基酸序列在本文中呈SEQ ID NO: 257提供。

【0090】 當IL-21結合於IL-21R時，Jak/STAT信號傳導路徑經活化，從而活化標靶基因。雖然誘導IL-21之信號傳導為治療學上合乎需要的，但考慮到IL-21之廣泛表現概況及由於IL-21能夠加強CD8 T細胞反應以及抑制抗原呈遞及T細胞激活，需要謹慎考慮信號傳導之時機及位置。本文中第一次呈現之資料支持使用小心設計之IL-21突變蛋白在適當時間及地方實現IL-21信號傳導。

【0091】 本發明提供相對於在本文中以SEQ ID NO: 1提供之野生型IL-21胺基酸序列包含至少一個胺基酸取代之IL-21突變蛋白。舉例而言，IL-21突變蛋白包含至少一個且至多34個胺基酸取代。在例示性態樣中，IL-21突變蛋白包含至少一個且至多X個胺基酸取代，其中X為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或34。在例示性實施例中，IL-21突變蛋白包含與人類IL-21之胺基酸序列(SEQ ID NO: 1)的差異在於至多10個胺基酸、15個胺基酸、20個胺基酸或25個胺基酸的胺基酸序列。在例示性實施例中，IL-21突變蛋白包含與人類IL-21之胺基酸序列(SEQ ID NO: 1)的差異在於至多7個胺基酸或至多5個胺基酸的胺基酸序列。在例示性實施例中，IL-21突變蛋白包含與人類IL-21之胺基酸序列(SEQ ID NO: 1)的差異在於3個、4個、5個或6個胺基酸之胺基酸序列。在例示性實施例中，IL-21突變蛋白包含與人類IL-21之胺基酸序列(SEQ ID NO: 1)的差異在於3至6個胺基酸或1至5個胺基酸之胺基酸序列。在例示性實施例中，IL-21突變蛋白包含與人類IL-21之胺基酸序列(SEQ ID NO: 1)的差異在於一或兩個胺基酸的胺基酸序列。

【0092】 在例示性態樣中，IL-21突變蛋白包含SEQ ID NO: 2之胺基酸序列，其中SEQ ID NO: 2為

QGQDX HMXXM XXXXX XVDXL KNXVN DLVPE FLPAP EDVET NCEWS AFSCF QKAQL KSANT GNNEX XIXXX XXXLX XXXXX TNAGR RQKHR LTCPS CDSYE KKPPK EFLXX FXXLL XXMXX QHXSS RTHGS EDS (SEQ ID NO: 2)，其中X表示任何胺基酸，且其中該IL-21突變蛋白胺基酸序列與人類IL-21之胺基酸序列(SEQ ID NO: 1)的差異在於至少1個胺基酸。

【0093】 因此，在例示性態樣中，IL-21突變蛋白包含SEQ ID NO: 2之序列，其中SEQ ID NO: 2與SEQ ID NO: 1的差異在於在SEQ ID NO: 2中由X表示之位置處的至少一個胺基酸。在例示性態樣中，包含SEQ ID NO: 2之IL-21突變蛋白與SEQ ID NO: 1具有至少約30%、至少約40%、

至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性。在例示性態樣中，IL-21突變蛋白包含與SEQ ID NO: 1具有至少約30%、至少約40%、至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。

【0094】 在例示性實施例中，IL-21突變蛋白包含相對於野生型IL-21胺基酸序列包含至少一個胺基酸取代之胺基酸序列，且胺基酸取代出現在胺基酸序列之N端半部內。舉例而言，胺基酸取代出現在根據SEQ ID NO: 1之胺基酸位置編號位置5-25或8-23 (包括端點)內。

【0095】 在例示性實施例中，IL-21突變蛋白包含相對於野生型IL-21胺基酸序列包含至少一個胺基酸取代之胺基酸序列，且胺基酸取代出現在胺基酸序列之C端半部內。舉例而言，胺基酸取代出現在根據SEQ ID NO: 1之胺基酸位置編號位置100-133或109-123 (包括端點)內。

【0096】 在例示性實施例中，IL-21突變蛋白包含相對於野生型IL-21胺基酸序列包含至少一個胺基酸取代之胺基酸序列，且胺基酸取代出現在胺基酸序列之中間三分之一內。舉例而言，胺基酸取代出現在根據SEQ ID NO: 1之胺基酸位置編號位置55-85或65-80 (包括端點)內。

【0097】 本發明亦提供相對於在本文中以SEQ ID NO: 1提供之野生型IL-21胺基酸序列包含僅僅一個胺基酸取代之IL-21突變蛋白。在例示性態樣中，胺基酸取代位於選自由以下組成之群的胺基酸位置處：根據SEQ ID NO: 1之胺基酸位置編號，5、8、9、11、12、13、14、15、16、19、

23、65、66、68、69、70、71、72、73、75、76、77、78、79、80、109、110、112、113、116、117、119、120或123。在其他例示性態樣中，胺基酸取代位於選自由以下組成之群的胺基酸位置處：根據SEQ ID NO: 1之胺基酸位置編號，5、8、9、11、12、13、14、15、16、19、23、65、66、68、69、70、72、73、75、76、77、78、79、80、109、110、112、113、116、117、119、120或123。在其他例示性態樣中，IL-21突變蛋白包含SEQ ID NO: 3-21及23-37之胺基酸序列中之任一者。

【0098】 本發明進一步提供相對於SEQ ID NO: 1僅僅包含兩個胺基酸取代之IL-21突變蛋白。在例示性態樣中，胺基酸取代位於選自由以下組成之群的兩個胺基酸位置處：根據SEQ ID NO: 1之胺基酸位置編號，5、8、9、11、12、13、14、15、16、19、23、65、66、68、69、70、71、72、73、75、76、77、78、79、80、109、110、112、113、116、117、119、120或123。在其他例示性態樣中，胺基酸取代位於選自由以下組成之群的兩個胺基酸位置處：根據SEQ ID NO: 1之胺基酸位置編號，5、9、15、70、71、72、73及76。在其他例示性態樣中，胺基酸取代位於選自由以下組成之群的兩個胺基酸位置處：根據SEQ ID NO: 1之胺基酸位置編號，5、9、73及76。在例示性態樣中，兩個胺基酸取代中之至少一個位於根據SEQ ID NO: 1之胺基酸位置編號位置76處。在例示性態樣中，IL-21突變蛋白包含SEQ ID NO: 199-208及210-212之胺基酸序列中之任一者。

【0099】 在例示性實施例中，IL-21突變蛋白包含相對於野生型IL-21胺基酸包含至少一個胺基酸取代之胺基酸序列，且胺基酸取代為保守胺基酸取代。如本文所用，術語「保守胺基酸取代」係指一個胺基酸經具有

類似性質，例如尺寸、電荷、疏水性、親水性及/或芳香性之另一個胺基酸取代，且包括在以下五組之一內的交換：

I. **小的脂族、非極性或微極性殘基**：Ala、Ser、Thr、Pro、Gly；

II. **極性、帶負電殘基及其醯胺及酯**：Asp、Asn、Glu、Gln、磺基丙胺酸及高磺基丙胺酸；

III. **極性帶正電殘基**：His、Arg、Lys；鳥胺酸(Orn)

IV. **大的脂族非極性殘基**：Met、Leu、Ile、Val、Cys、正白胺酸(Nle)、高半胱胺酸；

V. **大的芳族殘基**：Phe、Tyr、Trp、乙醯基苯丙胺酸。

【0100】在例示性實施例中，IL-21突變蛋白包含相對於野生型IL-21胺基酸包含至少一個胺基酸取代之胺基酸序列，且胺基酸取代為非保守胺基酸取代。如本文所用，術語「非保守胺基酸取代」在本文中定義為一個胺基酸經具有不同性質，例如尺寸、電荷、疏水性、親水性及/或芳香性之另一個胺基酸取代，且包括在以上五組外的交換。

【0101】在例示性態樣中，IL-21突變蛋白包含相對於野生型IL-21胺基酸序列包含至少一個胺基酸取代之胺基酸序列，且取代胺基酸為天然存在之胺基酸。「天然存在之胺基酸」或「標準胺基酸」或「典型胺基酸」意謂在真核生物中發現之直接由通用遺傳密碼之密碼子編碼的20種α胺基酸(Ala、Val、Ile、Leu、Met、Phe、Tyr、Trp、Ser、Thr、Asn、Gln、Cys、Gly、Pro、Arg、His、Lys、Asp、Glu)之一。在例示性態樣中，IL-21突變蛋白包含相對於野生型IL-21胺基酸序列包含至少一個胺基酸取代之胺基酸序列，且取代胺基酸為非標準胺基酸或在轉譯期間未併入

蛋白質中之胺基酸。非標準胺基酸包括(但不限於)：硒代半胱胺酸、吡咯離胺酸、鳥胺酸、正白胺酸、β-胺基酸(例如β-丙胺酸、β-胺基異丁酸、β-苯丙胺酸、β-高苯丙胺酸、β-麩胺酸、β-麩醯胺酸、β-高色胺酸、β-白胺酸、β-離胺酸)、高胺基酸(例如高苯丙胺酸、高絲胺酸、高精胺酸、單半胱胺酸、高胱胺酸)、N-甲基胺基酸 (例如L-紅豆鹼、N-甲基-丙胺酸、N-甲基-異白胺酸、N-甲基-白胺酸)、2-胺基辛酸、7-胺基頭孢黴烷酸、4-胺基肉桂酸、α-胺基環己烷丙酸、胺基-(4-羥苯基)乙酸、4-胺基-菸酸、3-胺基苯乙酸及其類似物。

【0102】 在例示性態樣中，本發明之IL-21突變蛋白包含相對於人類IL-21之胺基酸序列(SEQ ID NO: 1)具有至少一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置5、8、9、12、14、15、65、66、69、70、72、73、75、76、77、80、116及119中之一或多者處，且取代胺基酸為脂族胺基酸。在例示性態樣中，本發明之IL-21突變蛋白包含相對於SEQ ID NO: 1具有僅僅一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置5、8、9、12、14、15、65、66、69、70、72、73、75、76、77、80、116或119中之一或多者處，且取代胺基酸為脂族胺基酸。

【0103】 在例示性態樣中，本發明之IL-21突變蛋白包含相對於人類IL-21之胺基酸序列(SEQ ID NO: 1)具有至少一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置5、8、9、11、12、13、14、15、16、19、23、65、66、69、70、72、73、75、76、77、78、79、110、112、116、117、119、120或123中之一或多者處，且取代胺基酸為酸性胺基酸。在例示性態樣中，本發明之IL-21突變蛋白包含相對於

SEQ ID NO: 1具有僅僅一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置5、8、9、11、12、13、14、15、16、19、23、65、66、69、70、72、73、75、76、77、78、79、110、112、116、117、119、120或123中之一或多者處，且取代胺基酸為酸性胺基酸。

【0104】在例示性態樣中，本發明之IL-21突變蛋白包含相對於人類IL-21之胺基酸序列(SEQ ID NO: 1)具有至少一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置5、9、73、76、109、113或116中之一或多者處，且取代胺基酸為鹼性胺基酸。在例示性態樣中，本發明之IL-21突變蛋白包含相對於SEQ ID NO: 1具有僅僅一個胺基酸取代的胺基酸序列，且在SEQ ID NO: 1之位置5、9、73、76、109、113或116處的胺基酸為鹼性胺基酸。

【0105】在例示性態樣中，本發明之IL-21突變蛋白包含相對於人類IL-21之胺基酸序列(SEQ ID NO: 1)具有至少一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置5、8、9、70或76中之一或多者處，且取代胺基酸為芳族胺基酸。在例示性態樣中，本發明之IL-21突變蛋白包含相對於SEQ ID NO: 1具有僅僅一個胺基酸取代的胺基酸序列，胺基酸取代在SEQ ID NO: 1之位置5、8、9、70或76處，且取代胺基酸為芳族胺基酸。

【0106】在例示性態樣中，本發明之IL-21突變蛋白包含相對於人類IL-21之胺基酸序列(SEQ ID NO: 1)具有至少一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置5、8、9、12、15、73、76、116或119中之一或多者處，且取代胺基酸為包含側鏈醯胺之胺基酸。在例示性態樣中，本發明之IL-21突變蛋白包含相對於SEQ ID NO: 1

具有僅僅一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置5、8、9、12、15、73、76、116或119中之一或多者處，且取代胺基酸為包含側鏈醯胺之胺基酸。

【0107】 在例示性態樣中，本發明之IL-21突變蛋白包含相對於人類IL-21之胺基酸序列(SEQ ID NO: 1)具有至少一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置5、8、9、11、12、14、15、73、76、116或119中之一或多者處，且取代胺基酸為包含側鏈羥基之胺基酸。在例示性態樣中，本發明之IL-21突變蛋白包含相對於SEQ ID NO: 1具有僅僅一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置5、8、9、11、12、14、15、73、76、116或119中之一或多者處，且取代胺基酸為包含側鏈羥基之胺基酸。

【0108】 在例示性態樣中，本發明之IL-21突變蛋白包含相對於人類IL-21之胺基酸序列(SEQ ID NO: 1)具有至少一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置65、66、69、70、72、73、75、76、77或80中之一或多者處，且取代胺基酸為亞胺基酸。在例示性態樣中，本發明之IL-21突變蛋白包含相對於SEQ ID NO: 1具有僅僅一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置65、66、69、70、72、73、75、76、77或80中之一或多者處，且取代胺基酸為包含亞胺基酸之胺基酸。

【0109】 在例示性態樣中，本發明之IL-21突變蛋白包含相對於人類IL-21之胺基酸序列(SEQ ID NO: 1)具有至少一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置5、9、15、76、116或119中之一或多者處，且取代胺基酸為包含含硫側鏈之胺基酸。在例示性態樣

中，本發明之IL-21突變蛋白包含相對於SEQ ID NO: 1具有僅僅一個胺基酸取代的胺基酸序列，該胺基酸取代在SEQ ID NO: 1之位置5、9、15、76、116或119處，且取代胺基酸為包含含硫側鏈之胺基酸。

【0110】 在例示性態樣中，本發明之IL-21突變蛋白包含相對於人類IL-21之胺基酸序列(SEQ ID NO: 1)具有至少一個胺基酸取代之胺基酸序列，其中該至少一個胺基酸取代展示於表A中。

表A

SEQ ID NO: 1 之胺基酸位置	取代胺基酸之實例(按單字母代碼)	例示性 SEQ ID NO:
5	A、D、E、G、H、I、K、L、M、N、Q、S、T、V、Y	38
8	A、D、E、G、N、S	39
9	A、D、E、G、H、I、K、L、M、N、Q、S、T、V、Y	40
11	D、S	41
12	A、D、E、N、S、T、V	42
13	D	43
14	A、D、S	44
15	A、E、I、M、N、Q、S、T、V	45
16	D、E	46
19	D	47
23	D	48
65	D、G、P	49
66	D、G、P	50
68	Q	51
69	D、G、P	52
70	E、G、P、Y、T	53
71	L	54

SEQ ID NO: 1 之胺基酸位置	取代胺基酸之實例(按單字母代碼)	例示性 SEQ ID NO:
72	A、D、G、P	55
73	A、D、E、G、H、I、N、P、Q、S、V	56
75	D、G、P	58
76	A、D、E、G、H、I、K、L、M、N、P、Q、S、T、V、Y	59
77	D、G、P	60
78	D	61
79	D	62
80	G、P	63
109	K	64
110	D	65
112	D	66
113	K	67
116	A、D、E、I、K、L、M、N、S、T、V	68
117	D	69
119	A、D、E、M、N、Q、S、T	70
120	D	71
123	D	72

【0111】在例示性態樣中，本發明之IL-21突變蛋白包含相對於SEQ ID NO: 1具有僅僅一個胺基酸取代之胺基酸序列，且該胺基酸取代為表A中所示之胺基酸取代。在其他實施例中，本發明之IL-21突變蛋白包含相對於SEQ ID NO: 1具有兩個胺基酸取代之胺基酸序列，且該胺基酸取代為表A中所示之胺基酸取代中之兩者。

【0112】在例示性態樣中，本發明之IL-21突變蛋白包含表B中所示之胺基酸序列。

表B

胺基酸取代	SEQ ID NO: 1之胺基酸位置	取代胺基酸	SEQ ID NO:		胺基酸取代	SEQ ID NO: 1之胺基酸位置	取代胺基酸	SEQ ID NO:
R5A	5	A	73		S70E	70	E	136
R5D	5	D	74		S70G	70	G	137
R5E	5	E	75		S70P	70	P	138
R5G	5	G	76		S70Y	70	Y	139
R5H	5	H	77		S70T	70	T	140
R5I	5	I	78		K72D	72	D	141
R5K	5	K	79		K72G	72	G	142
R5L	5	L	80		K72P	72	P	143
R5M	5	M	81		K72A	72	A	144
R5N	5	N	82		K73A	73	A	145
R5Q	5	Q	83		K73D	73	D	146
R5S	5	S	84		K73E	73	E	147
R5T	5	T	85		K73G	73	G	148
R5V	5	V	86		K73H	73	H	149
R5Y	5	Y	87		K73I	73	I	150
I8A	8	A	88		K73N	73	N	151
I8D	8	D	89		K73P	73	P	152
I8E	8	E	90		K73Q	73	Q	153
I8G	8	G	91		K73S	73	S	154
I8N	8	N	92		K73V	73	V	155
I8S	8	S	93		K75D	75	D	156
R9A	9	A	94		K75G	75	G	157
R9D	9	D	95		K75P	75	P	158
R9E	9	E	96		R76A	76	A	159
R9G	9	G	97		R76D	76	D	160
R9H	9	H	98		R76E	76	E	161
R9I	9	I	99		R76G	76	G	162

胺基酸取代	SEQ ID NO: 1之胺基酸位置	取代胺基酸	SEQ ID NO:		胺基酸取代	SEQ ID NO: 1之胺基酸位置	取代胺基酸	SEQ ID NO:
R9K	9	K	100		R76H	76	H	163
R9L	9	L	101		R76I	76	I	164
R9M	9	M	102		R76K	76	K	165
R9N	9	N	103		R76L	76	L	166
R9Q	9	Q	104		R76M	76	M	167
R9S	9	S	105		R76N	76	N	168
R9T	9	T	106		R76P	76	P	169
R9V	9	V	107		R76Q	76	Q	170
R9Y	9	Y	108		R76S	76	S	171
R11D	11	D	109		R76T	76	T	172
R11S	11	S	110		R76V	76	V	173
Q12A	12	A	111		R76Y	76	Y	174
Q12D	12	D	249		K77D	77	D	175
Q12E	12	E	250		K77G	77	G	176
Q12N	12	N	251		K77P	77	P	177
Q12S	12	S	252		P78D	78	D	61
Q12T	12	T	253		P79D	79	D	62
Q12V	12	V	254		S80G	80	G	178
L13D	13	D	112		S80P	80	P	179
I14A	14	A	114		E109K	109	K	64
I14D	14	D	115		R110D	110	D	65
I14S	14	S	116		K112D	112	D	66
D15A	15	A	117		S113K	113	K	67
D15E	15	E	118		Q116A	116	A	180
D15I	15	I	119		Q116D	116	D	181
D15M	15	M	120		Q116E	116	E	182
D15N	15	N	121		Q116I	116	I	183

胺基酸取代	SEQ ID NO: 1之胺基酸位置	取代胺基酸	SEQ ID NO:		胺基酸取代	SEQ ID NO: 1之胺基酸位置	取代胺基酸	SEQ ID NO:
D15Q	15	Q	122		Q116K	116	K	184
D15S	15	S	123		Q116L	116	L	185
D15T	15	T	283		Q116M	116	M	186
D15V	15	V	124		Q116N	116	N	187
I16D	16	D	125		Q116S	116	S	188
I16E	16	E	126		Q116T	116	T	189
Q19D	19	D	47		Q116V	116	V	190
Y23D	23	D	48		K117D	117	D	69
R65D	65	D	127		I119A	119	A	191
R65G	65	G	128		I119D	119	D	192
R65P	65	P	129		I119E	119	E	193
I66D	66	D	130		I119M	119	M	194
I66G	66	G	131		I119N	119	N	195
I66P	66	P	132		I119Q	119	Q	196
N68Q	68	Q	51		I119S	119	S	197
V69D	69	D	133		I119T	119	T	198
V69G	69	G	134		H120D	120	D	71
V69P	69	P	135		L123D	123	D	72

【0113】在例示性實施例中，本發明之IL-21突變蛋白包含SEQ ID NO: 47、48、51、61、62、64-67、69、71-112、114-198、249-254或283中之任一者之胺基酸序列。在例示性態樣中，IL-21突變蛋白包含與SEQ ID NO: 47、48、51、61、62、64-67、69、71-112、114-198、249-254或283中之一者具有至少約30%、至少約40%、至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90%（例如約91%、約92%、約93%、約94%、約95%、約96%、約

97%、約98%或約99%)序列一致性的胺基酸序列。

【0114】本發明進一步提供相對於SEQ ID NO: 1包含僅僅兩個胺基酸取代之IL-21突變蛋白，且兩個胺基酸取代出現在SEQ ID NO: 1之位置5、9、15、70、71、72、73及76中之兩者處。在例示性態樣中，IL-21突變蛋白相對於SEQ ID NO: 1包含僅僅兩個胺基酸取代，且該兩個取代出現在選自由以下組成之群的一對胺基酸位置處：5及76；9及76；15及70；15及71；15及72；15及73；70及73；70及76；71及73；71及76；72及73；72及76；以及73及76。在例示性態樣中，IL-21突變蛋白包含SEQ ID NO: 199-208及210-212之胺基酸序列中之任一者。在其他態樣中，本發明進一步提供相對於SEQ ID NO: 1具有僅僅兩個胺基酸取代的IL-21突變蛋白，且該兩個胺基酸取代出現在SEQ ID NO: 1之位置5、9、73及76中之兩者處。在例示性態樣中，該等取代之一出現在SEQ ID NO: 1之位置76處。在例示性態樣中，在SEQ ID NO: 1之位置76處之取代胺基酸為脂族胺基酸或酸性胺基酸。在例示性態樣中，脂族胺基酸為丙胺酸。在例示性態樣中，酸性胺基酸為天冬胺酸或麩胺酸。在例示性態樣中，酸性胺基酸為麩胺酸。在例示性態樣中，IL-21突變蛋白包含在SEQ ID NO: 1之位置76處之取代胺基酸及在SEQ ID NO: 1之位置5、9或73處之脂族胺基酸或酸性胺基酸。在例示性態樣中，在位置5、9或73處之取代胺基酸為脂族胺基酸、酸性胺基酸或具有側鏈醯胺之胺基酸。在例示性態樣中，脂族胺基酸為丙胺酸，酸性胺基酸為麩胺酸，且具有側鏈醯胺之胺基酸為麩醯胺酸。在例示性態樣中，IL-21突變蛋白包含在SEQ ID NO: 1之位置76處之取代胺基酸(視情況脂族胺基酸或酸性胺基酸)及在位置5或9 (根據SEQ ID NO: 1編號)處之取代胺基酸。

【0115】在例示性態樣中，本發明之IL-21突變蛋白包含表C中所示之SEQ ID NO:中之任一者的胺基酸序列。

表C

胺基酸取代	SEQ ID NO: 1 之第一胺基酸位置	第一取代胺基酸	SEQ ID NO: 1 之第二胺基酸位置	第二取代胺基酸	SEQ ID NO:
R5E、R76E	5	E	76	E	239
R5E、R76A	5	E	76	A	238
R5A、R76A	5	A	76	A	236
R5Q、R76A	5	Q	76	A	240
R5A、R76E	5	A	76	E	237
R5Q、R76E	5	Q	76	E	241
R9E、R76E	9	E	76	E	245
R9A、R76E	9	A	76	E	243
R9E、R76A	9	E	76	A	244
R9A、R76A	9	A	76	A	242
D15N、S70T	15	N	70	T	213
D15N、I71L	15	N	71	L	214
D15N、K72A	15	N	72	A	215
D15N、K73A	15	N	73	A	216
S70T、K73Q	70	T	73	Q	219
S70T、R76A	70	T	76	A	246
S70T、R76D	70	T	76	D	247
S70T、R76E	70	T	76	E	248
I71L、K73Q	71	L	73	Q	217
I71L、R76A	71	L	76	A	227
I71L、R76D	71	L	76	D	228
I71L、R76E	71	L	76	E	229

K72A、K73Q	72	A	73	Q	218
K72A、R76A	72	A	76	A	230
K72A、R76D	72	A	76	D	231
K72A、R76E	72	A	76	E	232
K73A、R76A	73	A	76	A	233
K73A、R76D	73	A	76	D	234
K73A、R76E	73	A	76	E	235

【0116】 在例示性態樣中，IL-21突變蛋白包含選自由SEQ ID NO: 213-219及227-248組成之群的胺基酸序列。在例示性態樣中，IL-21包含與SEQ ID NO: 213-219及227-248中之一者具有至少約30%、至少約40%、至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。

肽長度

【0117】 本文所述之IL-21突變蛋白可包含具有任何數目之胺基酸的肽主鏈，亦即可具有任何肽長度。在一些實施例中，本文所述之肽的長度與SEQ ID NO: 1近乎相同，亦即133 (±約1至約20、±約1至約15、±約1至約10或±約1至約5)個胺基酸長。在一些實施例中，由於與另一多肽鏈，例如包含約400至約600個胺基酸之抗體重鏈、包含約150至約300個胺基酸之抗體輕鏈融合，故本發明之肽長度比133個胺基酸長，如本文中進一步描述。

額外肽修飾

【0118】 在本發明之替代或額外實施例中，IL-21突變蛋白經脂質

化(例如肉豆蔻醯化、棕櫚醯化)、糖基化、醯胺化、羧酸化、磷酸化、酯化、醯化、乙醯化、環化或轉變成酸加成鹽及/或視情況二聚或聚合或結合，如本文進一步描述。

醫藥學上可接受之鹽

【0119】 在例示性態樣中，IL-21突變蛋白呈鹽，例如醫藥學上可接受之鹽的形式。此類鹽可在IL-21突變蛋白之最終分離及純化期間當場製備，或藉由游離鹼官能基與合適酸反應而分開製備。可用以形成醫藥學上可接受之酸加成鹽之酸的實例包括例如無機酸，例如鹽酸、氫溴酸、硫酸及磷酸；及有機酸，例如草酸、順丁烯二酸、丁二酸及檸檬酸。

【0120】 代表性酸加成鹽包括(但不限於)乙酸鹽、己二酸鹽、海藻酸鹽、檸檬酸鹽、天冬胺酸鹽、苯甲酸鹽、苯磺酸鹽、硫酸氫鹽、丁酸鹽、樟腦酸鹽、樟腦磺酸鹽、二葡糖酸鹽、甘油磷酸鹽、半硫酸鹽、庚酸鹽、己酸鹽、反丁烯二酸鹽、鹽酸鹽、氫溴酸鹽、氫碘酸鹽、2-羥基乙烷磺酸鹽(羥基乙磺酸鹽)、乳酸鹽、順丁烯二酸鹽、甲烷磺酸鹽、菸酸鹽、2-萘磺酸鹽、草酸鹽、棕櫚酸鹽、果膠酸鹽、過硫酸鹽、3-苯丙酸鹽、苦味酸鹽、特戊酸鹽、丙酸鹽、丁二酸鹽、酒石酸鹽、硫氰酸鹽、磷酸鹽、麩胺酸鹽、碳酸氫鹽、對甲苯磺酸鹽及十一酸鹽。

【0121】 鹼加成鹽亦可在IL-21突變蛋白之最終分離及純化期間當場製備，或藉由使含羧酸之部分與合適鹼，諸如醫藥學上可接受之金屬陽離子之氫氧化物、碳酸鹽或碳酸氫鹽，或與氨或有機一級胺、二級胺或三級胺反應來製備。醫藥學上可接受之鹽尤其包括(但不限於)基於鹼金屬或鹼土金屬之陽離子，諸如鋰鹽、鈉鹽、鉀鹽、鈣鹽、鎂鹽及鋁鹽及其類似物；及無毒四級氨及胺陽離子，包括銨、四甲銨、四乙銨、甲銨、二甲

銨、三甲銨、三乙銨、二乙銨及乙銨。可用於形成鹼加成鹽之其他代表性有機胺包括例如乙二胺、乙醇胺、二乙醇胺、哌啶、哌嗪及其類似物。

【0122】 此外，含鹼性氮之基團可用諸如以下之活性劑進行四級銨化：低碳烷基鹵化物，諸如甲基、乙基、丙基及丁基氯化物、甲基、乙基、丙基及丁基溴化物及甲基、乙基、丙基及丁基碘化物；長鏈鹵化物，諸如癸基氯、月桂基氯、肉豆寇醯氯及硬脂醯氯、癸基溴、月桂基溴、肉豆寇醯溴及硬脂醯溴以及癸基碘、月桂基碘、肉豆寇醯碘及硬脂醯碘；芳基烷基鹵化物，如苯甲基溴及苯乙基溴及其他。從而獲得水溶性或油溶性或水可分散性或油可分散性產物。

純化

【0123】 可純化本發明之IL-21突變蛋白。如本文所用之術語「純化」意謂增加純度，其中「純度」為相對術語，而不必要視為絕對純度。在例示性態樣中，化合物之純度(例如在組合物中)為至少或約50%、至少或約60%、至少或約70%、至少或約80%、至少或約90%、至少或約95%或至少或約98%或約100%。

肽模擬物

【0124】 在一些態樣中，IL-21突變蛋白為肽模擬物，或突變蛋白之至少一部分為肽模擬物。肽模擬物以及其製造方法為此項技術中已知。參見例如Advances in Amino Acid Mimetics and Peptidomimetics, 第1卷及第2卷, Abell, A.編輯, JAI Press Inc., Greenwich, CT, 2006。在一些態樣中，肽模擬物為包含D-異構體胺基酸之D-肽肽模擬物。在一些態樣中，肽模擬物為類肽，其中胺基酸之側鏈連接至肽主鏈之α氮原子。類肽之製造方法為此項技術中已知。參見例如Zuckermann等人, JACS

114(26): 10646-10647 (1992)及Design, Synthesis, and Evaluation of Novel Peptoids, Fowler, Sarah, University of Wisconsin-Madison, 2008。在一些態樣中，肽模擬物為包含胺基鍵結於β碳而非α碳之β胺基酸的β肽。β-肽之製造方法為此項技術中已知。參見例如Seebach等人, Helvetica Chimica Acta 79(4): 913-941 (1996)。

結合特徵

【0125】在例示性實施例中，IL-21突變蛋白以相對於野生型IL-21對IL-21R之親和力有所降低之親和力結合於IL-21受體(IL-21R)。在例示性實施例中，IL-21突變蛋白以相對於野生型人類IL-21對人類IL-21R之親和力有所降低之親和力結合於人類IL-21R。在例示性實施例中，IL-21突變蛋白以相對於野生型人類IL-21對人類IL-21R之α鏈之親和力有所降低的親和力結合於人類IL-21R之α鏈。在特定實施例中，以相對於野生型人類IL-21對人類IL-21R之α鏈之親和力有所降低的親和力結合於人類IL-21R之α鏈的IL-21突變蛋白含有一個、兩個或更多個位於選自由以下組成之群之胺基酸位置處的取代：根據SEQ ID NO: 1之胺基酸位置編號，5、8、9、12、13、16、19、23、65、66、69、70、72、73、75、76、77、78、79及80。本文中論述可在此類位置處進行之特定胺基酸取代(參見例如表A、B及C)。

【0126】在例示性實施例中，IL-21突變蛋白以相對於野生型人類IL-21對人類IL-21R之γ鏈之親和力有所降低的親和力結合於人類IL-21R之γ鏈。在特定實施例中，以相對於野生型人類IL-21對人類IL-21R之γ鏈之親和力有所降低的親和力結合於人類IL-21R之γ鏈的IL-21突變蛋白含有一個、兩個或更多個位於選自由以下組成之群之胺基酸位置處的取代：根

據SEQ ID NO: 1之胺基酸位置編號，11、14、15、109、110、112、113、116、117、119、120及123。本文中論述可在此類位置處進行之特定胺基酸取代(參見例如表A、B及C)

【0127】在例示性實施例中，IL-21突變蛋白以相對於野生型IL-21對人類IL-21R之α鏈之親和力有所降低的親和力結合於人類IL-21R之γ鏈。在例示性實施例中，IL-21突變蛋白以相對於野生型食蟹獼猴IL-21對食蟹獼猴IL-21R之親和力有所降低之親和力結合於食蟹獼猴IL-21R。在例示性實施例中，IL-21突變蛋白以相對於野生型食蟹獼猴IL-21對食蟹獼猴IL-21R之α鏈之親和力有所降低的親和力結合於食蟹獼猴IL-21R之α鏈。在例示性實施例中，IL-21突變蛋白以相對於野生型食蟹獼猴IL-21對食蟹獼猴IL-21R之γ鏈之親和力有所降低的親和力結合於食蟹獼猴IL-21R之γ鏈。在例示性實施例中，IL-21突變蛋白以相對於野生型食蟹獼猴IL-21對食蟹獼猴IL-21R之α鏈之親和力有所降低的親和力結合於食蟹獼猴IL-21R之γ鏈。

【0128】本文提供之IL-21突變蛋白以非共價及可逆方式結合於IL-21R。在例示性實施例中，突變蛋白對IL-21R之結合強度可根據其親和力描述，親和力為突變蛋白之結合位點與IL-21R之間的相互作用之強度的量度。在例示性態樣中，本文提供之IL-21突變蛋白對IL-21R具有高親和力，且因此將在比低親和力IL-21突變蛋白短的時段內結合更大量之IL-21R。在例示性態樣中，本文提供之IL-21突變蛋白對IL-21R具有低親和力，且因此將在比高親和力IL-21突變蛋白長的時段內結合更少量之IL-21R。在例示性態樣中，IL-21突變蛋白具有平衡締合常數KA，其為至少10^5 M^{-1}、至少10^6 M^{-1}、至少10^7 M^{-1}、至少10^8 M^{-1}、至少10^9 M^{-1}或至少

10^{10} M^{-1}。如普通技術人員所瞭解，KA可受包括pH值、溫度及緩衝液組成之因素影響。

【0129】在例示性實施例中，IL-21突變蛋白與IL-21R之結合強度可根據其敏感性描述。K_D為IL-21突變蛋白與IL-21R之間的平衡解離常數，k_{off}/k_{on}之比率。K_D與KA逆相關。K_D值與突變蛋白之濃度(特定實驗需要之突變蛋白之量)有關，因此K_D值愈低(需要濃度愈低)，突變蛋白之親和力愈高。在例示性態樣中，IL-21突變蛋白與IL-21R之結合強度可根據K_D描述。在例示性態樣中，本文提供之IL-21突變蛋白之K_D為約10^{-1} M、約10^{-2} M、約10^{-3} M、約10^{-4} M、約10^{-5} M、約10^{-6} M或更小。在例示性態樣中，本文提供之IL-21突變蛋白之K_D為微莫耳、奈莫耳、皮莫耳或飛莫耳。在例示性態樣中，本文提供之IL-21突變蛋白之K_D在約10^{-4}至10^{-6} M，或10^{-7}至10^{-9} M，或10^{-10}至10^{-12} M，或10^{-13}至10^{-15} M範圍內。在例示性態樣中，IL-21突變蛋白以大於或等於約0.04 nM之K_D結合於人類IL-21R。在例示性態樣中，IL-21突變蛋白以約0.01 nM至約20 nM、0.02 nM至20 nM、0.05 nM至20 nM、0.05 nM至15 nM、0.1 nM至15 nM、0.1 nM至10 nM、1 nM至10 nM或5 nM至10 nM之K_D結合於人類IL-21R。在例示性態樣中，IL-21突變蛋白以大於或等於約0.055 nM之K_D結合於食蟹獼猴IL-21R。在例示性態樣中，IL-21突變蛋白以約0.01 nM至約20 nM、0.02 nM至20 nM、0.05 nM至20 nM、0.05 nM至15 nM、0.1 nM至15 nM、0.1 nM至10 nM、1 nM至10 nM或5 nM至10 nM之K_D結合於食蟹獼猴IL-21R。

【0130】在例示性實施例中，IL-21突變蛋白展現對IL-21R α-鏈之結合親和力降低。在例示性態樣中，IL-21突變蛋白為展現對IL-21R α-鏈

之結合親和力降低約2倍、5倍、10倍、15倍、20倍、25倍、30倍、35倍、40倍、45倍、50倍、55倍、60倍、65倍、70倍、75倍、80倍、85倍、90倍、95倍、100倍、105倍、110倍、115倍、120倍、125倍、130倍、135倍、140倍、145倍、150倍、175倍、200倍、225倍、250倍、275倍、300倍、325倍、350倍、375倍、400倍、425倍、450倍、475倍、500倍、525倍、550倍、575倍、600倍、625倍、650倍、675倍、700倍、725倍、750倍、775倍、800倍、825倍、850倍、875倍、900倍、925倍、950倍、975倍、1000倍或更多的突變蛋白(例如單一或雙重)。在例示性態樣中，IL-21突變蛋白為展現對IL-21R α-鏈之結合親和力有所降低的雙重突變蛋白。

【0131】 在例示性態樣中，與約0.025 nM之野生型人類IL-21對IL-21R α-鏈之親和力相比，上述IL-21突變蛋白(例如單一或雙重突變蛋白)之結合親和力降低引起對IL-21R α-鏈之親和力降低。因此，如上所論述之親和力降低2倍將引起IL-21突變蛋白對IL-21R α-鏈之親和力為約0.05 nM。因此，在例示性實施例中，IL-21突變蛋白(例如單一或雙重)具有約0.05 nM、0.125 nM、0.25 nM、0.375 nM、0.5 nM、0.625 nM、0.75 nM、0.875 nM、1.0 nM、1.125 nM、1.25 nM、1.375 nM、1.5 nM、1.625 nM、1.75 nM、1.875 nM、2.0 nM、2.125 nM、2.25 nM、2.375 nM、2.5 nM、2.625 nM、2.75 nM、2.875 nM、3.0 nM、3.125 nM、3.25 nM、3.375 nM、3.5 nM、3.625 nM、3.75 nM、4.375 nM、5 nM、5.625 nM、6.25 nM、6.875 nM、7.5 nM、8.125 nM、8.75 nM、9.375 nM、10.0 nM、10.625 nM、11.25 nM、11.875 nM、12.5 nM、13.125 nM、13.75 nM、14.375 nM、15.0 nM、15.625 nM、16.25 nM、16.875

nM、17.5 nM、18.125 nM、18.75 nM、19.375 nM、20.0 nM、20.625 nM、21.25 nM、21.875 nM、22.5 nM、23.125 nM、23.75 nM、24.375 nM、25 nM或更多之對IL-21R α-鏈之親和力。在例示性態樣中，IL-21突變蛋白為展現對IL-21R α-鏈之結合親和力降低的雙重突變蛋白。

【0132】 在例示性實施例中，如藉由活體外STAT3磷酸化分析所量測，IL-21突變蛋白展現活性降低。在例示性態樣中，IL-21突變蛋白為如藉由STAT3磷酸化分析所量測，展現約2倍、5倍、10倍、15倍、20倍、25倍、30倍、35倍、40倍、45倍、50倍、55倍、60倍、65倍、70倍、75倍、80倍、85倍、90倍、95倍、100倍、105倍、110倍、115倍、120倍、125倍、130倍、135倍、140倍、145倍、150倍、175倍、200倍、225倍、250倍、275倍、300倍、325倍、350倍、375倍、400倍、425倍、450倍、475倍、500倍、525倍、550倍、575倍、600倍、625倍、650倍、675倍、700倍、725倍、750倍、775倍、800倍、825倍、850倍、875倍、900倍、925倍、950倍、975倍、1000倍或更多活性降低的突變蛋白(例如單一或雙重)。在例示性態樣中，如藉由STAT3磷酸化分析所量測，IL-21突變蛋白為展現活性降低之雙重突變蛋白。

IL-21突變蛋白結合物

【0133】 本發明亦提供包含與異源部分連接之一或多種本發明之IL-21突變蛋白的結合物。如本文所用，術語「異源部分」與術語「結合部分」同義，且係指與本文所述之IL-21突變蛋白不同之任何分子(化學或生物化學、天然存在或未編碼)。可連接於本文所述之任一IL-21突變蛋白的例示性結合部分包括(但不限於)異源肽或多肽(包括例如免疫球蛋白或其部分(例如可變區、CDR或Fc區))、靶向劑、診斷標記(諸如放射性同位

素、螢光團或酶標記)、包括水溶性聚合物之聚合物或其他治療劑或診斷劑。在一些實施例中，提供包含本發明之IL-21突變蛋白及免疫球蛋白之結合物。在一些實施例中，結合物包含一或多種本文所述之IL-21突變蛋白及以下一或多者：肽(與本文所述之IL-21突變蛋白不同)、多肽、核酸分子、抗體或其片段、聚合物、量子點、小分子、毒素、診斷劑、碳水化合物、胺基酸。

【0134】 在例示性實施例中，本發明之結合物包含如本文所述之IL-21突變蛋白及異源部分，該異源部分為多肽(例如與本文所述之任一IL-21突變蛋白不同之多肽)，且該結合物為融合多肽或融合蛋白或嵌合蛋白或嵌合多肽。本文在「融合蛋白」下提供有關此類結合物之額外描述。

【0135】 在一些實施例中，異源部分經由非共價鍵或共價鍵連接於本發明之IL-21突變蛋白。在例示性態樣中，在IL-21突變蛋白與異源部分之間的鍵經由共價化學鍵，例如肽鍵、二硫鍵及其類似物，或經由物理力，諸如靜電、氫、離子、凡得瓦爾(van der Waal)或疏水性或親水性相互作用實現。可使用多種非共價偶合系統，包括例如生物素-親和素、配位體/受體、酶/受質、核酸/核酸結合蛋白、脂質/脂質結合蛋白、細胞黏附分子搭配物；或對彼此具有親和力之任何結合搭配物或其片段。

【0136】 在例示性實施例中IL-21突變蛋白經由直接共價鍵，藉由使IL-21突變蛋白之靶向胺基酸殘基與能夠與此等靶向胺基酸之所選側鏈或N或C端殘基反應的有機衍生化劑反應來連接於結合部分。IL-21突變蛋白或結合部分上之反應基團包括例如醛、胺基、酯、硫醇、α-鹵乙醯基、順丁烯二醯亞胺基或肼基。衍生化劑包括例如順丁烯二醯亞胺基苯甲醯基磺基丁二醯亞胺酯(經由半胱胺酸殘基結合)、N-羥基丁二醯亞胺(經由離

胺酸殘基)、戊二醛、丁二酸酐或此項技術中已知之其他試劑。可替代地，結合部分可經由中間載劑，諸如多醣或多肽載劑間接連接於IL-21突變蛋白。多醣載劑之實例包括胺基葡聚糖。合適多肽載劑之實例包括聚離胺酸、聚麩胺酸、聚天冬胺酸、其共聚物及此等胺基酸與例如絲胺酸之其他胺基酸的混合聚合物，以比較所得負荷載劑合乎需要之溶解特性。

【0137】 半胱胺醯殘基最常與α-鹵乙酸酯(及對應胺)，諸如氯乙酸、氯乙醯胺反應，得到羧甲基或羧醯胺基甲基衍生物。半胱胺醯殘基亦藉由與溴三氟丙酮、α-溴-β-(5-咪唑基)丙酸、氯乙醯基磷酸酯、N-烷基順丁烯二醯亞胺、3-硝基-2-吡啶基二硫化物、甲基2-吡啶基二硫化物、對氯汞基苯甲酸酯、2-氯汞基-4-硝基酚或氯-7-硝基苯并-2-氧雜-1,3-二唑反應來衍生。

【0138】 組胺醯基殘基藉由與焦碳酸二乙酯在pH 5.5-7.0下反應來衍生，因為此試劑對組胺醯基側鏈具有相對特異性。對溴苯甲醯甲基溴亦適用；較佳在0.1M二甲胂酸鈉中在pH 6.0下進行反應。

【0139】 離胺醯基及胺基端殘基與丁二酸或其他羧酸酐反應。用此等試劑衍生化具有逆轉離胺醯基殘基電荷的作用。其他適用於衍生含α-胺基之殘基的試劑包括亞胺酸酯，諸如吡啶亞胺酸甲酯、磷酸吡哆醛、吡哆醛、氯硼氫化物、三硝基苯磺酸、O-甲基異脲、2,4-戊二酮及轉胺酶催化之與乙醛酸酯之反應。

【0140】 精胺醯基殘基藉由與一種或若干常規試劑反應來修飾，該等試劑尤其為苯甲醯甲醛、2,3-丁二酮、1,2-環己二酮及茚三酮。精胺酸殘基之衍生化需要反應在鹼性條件下進行，因為胍官能基具有高pKa。此外，此等試劑可與離胺酸以及精胺酸ε-胺基之基團反應。

【0141】 可進行酪胺醯基殘基之特定修飾，其中尤其關注藉由與芳族重氮化合物或四硝基甲烷反應而將光譜標記引入酪胺醯基殘基。最通常，N-乙醯基咪唑及四硝基甲烷分別用於形成O-乙醯基酪胺醯基物質及3-硝基衍生物。

【0142】 羧基側基(天冬胺醯基或麩胺醯基)藉由與碳化二亞胺(R-N=C=N-R')反應來選擇性地修飾，其中R及R'為不同烷基，諸如1-環己基-3-(2-嗎啉基-4-乙基)碳化二亞胺或1-乙基-3-(4-氮陽離子-4,4-二甲基苯基)碳化二亞胺。此外，天冬胺醯基及麩胺醯基殘基藉由與銨離子反應而轉變成天冬醯胺醯基及麩醯胺基殘基。

【0143】 其他修飾包括脯胺酸及離胺酸之羥基化、絲胺醯基或蘇胺醯基殘基之羥基之磷酸化、離胺酸、精胺酸及組胺酸側鏈之α-胺基之甲基化(T. E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, 第79-86頁 (1983))、天冬醯胺或麩醯胺酸之脫醯胺化、N端胺之乙醯化及/或C端羧酸基之醯胺化或酯化。

【0144】 另一類型共價修飾包括化學上或藉由酶將糖苷與IL-21突變蛋白偶合。糖可附接於(a)精胺酸及組胺酸；(b)游離羧基；(c)游離硫氫基，諸如半胱胺酸之游離硫氫基；(d)游離羥基，例如絲胺酸、蘇胺酸或羥基脯胺酸之游離羥基；(e)芳族殘基，諸如酪胺酸或色胺酸之芳族殘基；或(f)麩醯胺酸之醯胺基。此等方法描述於1987年9月11日公開之WO87/05330以及Aplin及Wriston, CRC Crit. Rev. Biochem., 第259-306頁 (1981)中。

【0145】 在例示性態樣中，異源部分經由連接子附接於本發明之IL-21突變蛋白。在一些態樣中，連接子包含具有1至約60個或1至30個原子

或更長、2至5個原子、2至10個原子、5至10個原子或10至20個原子長之鏈。在一些實施例中，鏈原子均為碳原子。在一些實施例中，連接子主鏈中之鏈原子係選自由C、O、N及S組成之群。鏈原子及連接子可根據其預期溶解性(親水性)選擇，以便提供更可溶之結合物。在一些實施例中，連接子提供易由在標靶組織或器官或細胞中發現之酶或其他催化劑或水解條件裂解的官能基。在一些實施例中，連接子長度足夠長以減小位阻可能性。若連接子為共價鍵或肽鍵且結合物為多肽，則整個結合物可為融合蛋白。此類肽基連接子可為任何長度。例示性肽基連接子為約1至50個胺基酸長，5至50、3至5、5至10、5至15或10至30個胺基酸長，且為可撓性或剛性。在例示性態樣中，連接子為包含約2至約20個胺基酸之肽。在例示性態樣中，連接子為包含約2至約15個胺基酸、約2至約10個胺基酸或約2至約5個胺基酸之肽。合適肽連接子為此項技術中已知。參見例如Chen等人, Adv Drug Delivery Reviews 65(10): 1357-1369 (2013)；Arai等人, Protein Eng Des Sel 14(8): 529-532 (2001)；及Wriggers等人, Curr Trends in Peptide Science 80(6): 736-746 (2005)。在例示性態樣中，連接子為包含胺基酸序列GGGGS (SEQ ID NO: 262)之肽。

融合蛋白

【0146】在例示性實施例中，IL-21突變蛋白連接於與本文所述之任一IL-21突變蛋白不同之多肽，且結合物為融合多肽或融合蛋白或嵌合蛋白或嵌合多肽。因此，本發明提供包含本發明之IL-21突變蛋白及異源多肽或肽之融合多肽或融合蛋白。在例示性態樣中，本發明之融合蛋白包含連接於抗原結合蛋白之本發明之IL-21突變蛋白。在例示性態樣中，抗原結合蛋白為抗體或免疫球蛋白或其抗原結合抗體片段或抗體蛋白產物。

【0147】 總體上，抗體形成稱為免疫球蛋白之血漿蛋白家族且由免疫球蛋白結構域構成。(Janeway等人, Immunobiology: The Immune System in Health and Disease, 第4版, Elsevier Science Ltd./Garland Publishing, 1999)。如本文所用，術語「抗體」係指具有習知免疫球蛋白格式之蛋白質，包含重鏈及輕鏈且包含可變區及恆定區。舉例而言，抗體可為IgG，其為具有兩對一致多肽鏈之「Y形」結構，每一對具有一條「輕」鏈(通常具有約25 kDa之分子量)及一條「重」鏈(通常具有約50-70 kDa之分子量)。抗體具有可變區及恆定區。在IgG格式中，可變區一般為約100-110個或更多個胺基酸，包含三個互補決定區(CDR)，主要負責抗原識別，在結合於不同抗原之其他抗體中基本上變化。恆定區允許抗體募集免疫系統之細胞及分子。可變區由各輕鏈及重鏈之N端區形成，而恆定區由各重鏈及輕鏈之C端部分形成。(Janeway等人, 「Structure of the Antibody Molecule and the Immunoglobulin Genes」, Immunobiology: The Immune System in Health and Disease, 第4版 Elsevier Science公司/Garland Publishing, (1999))。

【0148】 此項技術中已描述抗體CDR之通用結構及性質。簡言之，在抗體骨架中，CDR包埋在重鏈及輕鏈可變區中之構架內，其中該等CDR構成主要負責抗原結合及識別之區域。可變區通常包含至少三個重鏈或輕鏈CDR (Kabat等人, 1991, Sequences of Proteins of Immunological Interest, Public Health Service N.I.H., Bethesda, Md.；亦參見Chothia及Lesk, 1987, J. Mol. Biol. 196:901-917；Chothia等人, 1989, Nature 342: 877-883)在構架區(稱為構架區1-4，FR1、FR2、FR3及FR4，Kabat等人, 1991；亦參見Chothia及Lesk, 1987, 上述)內。

【0149】 抗體可包含此項技術中已知之任何恆定區。人類輕鏈分成κ及λ輕鏈。重鏈分成μ、δ、γ、α或ε，且將抗體之同型分別定義為IgM、IgD、IgG、IgA及IgE。IgG具有若干子類，包括(但不限於) IgG1、IgG2、IgG3及IgG4。IgM具有子類，包括(但不限於) IgM1及IgM2。本發明之實施例包括抗體之所有此類類別或同型。輕鏈恆定區可為例如κ或λ型輕鏈恆定區，例如人類κ或λ型輕鏈恆定區。重鏈恆定區可為例如α、δ、ε、γ或μ型重鏈恆定區，例如人類α、δ、ε、γ或μ型重鏈恆定區。因此，在例示性實施例中，抗體為同型IgA、IgD、IgE、IgG或IgM之抗體，包括IgG1、IgG2、IgG3或IgG4中之任一者。

【0150】 抗體可為單株抗體或多株抗體。在一些實施例中，抗體包含基本上類似於由哺乳動物，例如小鼠、兔、山羊、馬、雞、倉鼠、人類及其類似動物產生之天然存在之抗體的序列。關於此，抗體可視為哺乳動物抗體，例如小鼠抗體、兔抗體、山羊抗體、馬抗體、雞抗體、倉鼠抗體、人類抗體及其類似動物抗體。在某些態樣中，抗體為人類抗體。在某些態樣中，抗體為嵌合抗體或人類化抗體。術語「嵌合抗體」係指含有來自兩種或更多種不同抗體之結構域的抗體。嵌合抗體可例如含有來自一種物種之恆定域及來自第二物種之可變域，或更一般地，可含有來自至少兩種物種之胺基酸序列之延伸。嵌合抗體亦可含有相同物種內兩種或更多種不同抗體之結構域。術語「人類化」在關於抗體使用時，係指具有至少來自非人類來源之CDR區的抗體，該等抗體經工程改造以具有比原始來源抗體更類似於真實人類抗體的結構及免疫功能。舉例而言，人類化可包括移植來自非人類抗體，諸如小鼠抗體之CDR至人類抗體。人類化亦可包括選擇胺基酸取代以使非人類序列更類似於人類序列。

【0151】 抗體可藉由酶，諸如木瓜蛋白酶及胃蛋白酶裂解成片段。木瓜蛋白酶使抗體裂解，產生兩個Fab片段及單個Fc片段。胃蛋白酶使抗體裂解，產生$F(ab')_2$片段及pFc'片段。在本發明之例示性態樣中，本發明之融合蛋白包含抗原結合抗體片段。如本文所用，術語「抗原結合抗體片段」係指能夠結合於抗體抗原之抗體分子之一部分且亦稱「抗原結合片段」或「抗原結合部分」。在例示性情況下，抗原結合抗體片段為Fab片段或$F(ab')_2$片段。

【0152】 抗體之構造已用於產生日益增大的一系列替代格式，其跨越至少約12-150 kDa分子量範圍且具有在自單體(n = 1)、二聚體(n = 2)、三聚體(n = 3)、四聚體(n = 4)且可能更高之價數(n)範圍；此類替代格式在本文中稱為「抗體蛋白產物」。抗體蛋白產物包括基於完整抗體結構之產物及模擬抗體片段之保留完整抗原結合能力的產物，例如scFv、Fab及VHH/VH (以下論述)。保留完全抗原結合位點之最小抗原結合抗體片段為Fv片段，其完全由可變(V)區組成。可溶之可撓性胺基酸肽連接子用於連接V區至scFv (單鏈片段可變)片段以穩定分子，或將恆定(C)域添加至V區以產生Fab片段[抗原結合片段]。scFv與Fab片段均容易在宿主細胞，例如原核宿主細胞中產生。其他抗體蛋白產物包括經二硫鍵穩定之scFv (ds-scFv)、單鏈Fab (scFab)以及二聚體及多聚體抗體格式，如雙功能抗體、三功能抗體及四功能抗體，或包含由連接於寡聚結構域之scFv組成之不同格式的微型抗體(miniAb)。最小片段為駱駝科重鏈Ab之VHH/VH以及單域Ab (sdAb)。最常用於產生新穎抗體格式之構建基塊為單鏈可變(V)域抗體片段(scFv)，其包含由約15個胺基酸殘基之肽連接子連接的來自重鏈及輕鏈之V結構域(VH及VL結構域)。肽體或肽-Fc融合物

為又一種抗體蛋白產物。肽體之結構由移植至Fc結構域上之生物活性肽組成。此項技術中充分描述肽體。參見例如Shimamoto等人, mAbs 4(5): 586-591 (2012)。

【0153】 其他抗體蛋白產物包括單鏈抗體(single chain antibody，SCA)；雙功能抗體；三功能抗體；四功能抗體；雙特異性或三特異性抗體及其類似物。雙特異性抗體可分成五大類：BsIgG、附加IgG、BsAb片段、雙特異性融合蛋白及BsAb結合物。參見例如Spiess等人, Molecular Immunology 67(2) 部分A: 97-106 (2015)。

【0154】 在例示性態樣中，本發明之融合蛋白包含此等抗體蛋白產物中之任一者。在例示性態樣中，本發明之融合蛋白包含scFv、Fab VHH/VH、Fv片段、ds-scFv、scFab、二聚抗體、多聚抗體(例如雙功能抗體、三功能抗體、四功能抗體)、miniAb、駱駝科重鏈抗體之肽體VHH/VH、sdAb、雙功能抗體；三功能抗體；四功能抗體；雙特異性或三特異性抗體、BsIgG、附加IgG、BsAb片段、雙特異性融合蛋白及BsAb結合物中之任一者。

【0155】 在例示性情況下，本發明之融合蛋白包含呈單體形式或聚合物、寡聚物或多聚體形式之抗體蛋白產物。在抗體包含兩種或更多種不同抗原結合區片段之某些實施例中，抗體視為雙特異性、三特異性或多特異性或者二價、三價或多價，視由抗體識別及結合之不同抗原決定基的數目而定。

【0156】 在例示性實施例中，抗體、抗原結合抗體片段或抗體蛋白產物結合於腫瘤抗原。在例示性態樣中，腫瘤抗原為源自於病毒蛋白之抗原、源自於點突變之抗原或由癌生殖系基因編碼之抗原。在例示性態樣

中，腫瘤抗原為p53、KRAS、NRAS、MAGEA、MAGEB、MAGEC、BAGE、GAGE、LAGE/NY-ESO1、SSX、酪胺酸酶、gp100/pmel17、Melan-A/MART-1、gp75/TRP1、TRP2、CEA、RAGE-1、HER2/NEU、WT1。在例示性態樣中，本發明之融合蛋白的抗體、抗原結合抗體片段或抗體蛋白產物結合於免疫治療劑或為免疫治療劑，如本文所述。在例示性態樣中，本發明之融合蛋白的抗體、抗原結合抗體片段或抗體蛋白產物結合於細胞介素、淋巴激素、生長因子或造血因子，如本文所述。

【0157】 在例示性實施例中，本發明之融合蛋白包含細胞介素(例如本文所述之IL-21突變蛋白)及結合於免疫檢查點路徑之蛋白質、腫瘤抗原、細胞介素、淋巴激素、生長因子或其他造血因子(包括(但不限於)本文所述之彼等物質中之任一者)的抗體、其抗原結合抗體片段或抗體蛋白產物。在例示性實施例中，本發明之融合蛋白包含細胞介素(例如本文所述之IL-21突變蛋白)及結合於選自由以下組成之群的免疫檢查點路徑之蛋白質的抗體、其抗原結合抗體片段或抗體蛋白產物：CTLA-4、PD-1、PD-L1、PD-L2、B7-H3、B7-H4、CEACAM-1、TIGIT、LAG3、CD112、CD112R、CD96、TIM3、BTLA或共刺激受體：ICOS、OX40、41BB、CD27、GITR。

【0158】 在其他實施例中，本發明之融合蛋白包含細胞介素及結合於免疫檢查點路徑之蛋白質的抗體(或其抗原結合抗體片段)。合適細胞介素包括例如增強TH-1型反應之細胞介素；及活化STAT 1、STAT 3、STAT 4或STAT 5之細胞介素。在一些實施例中，細胞介素為介白素。在其他實施例中，細胞介素為增強T細胞活性之介白素，諸如IL-2、IL-7、IL-10、IL-12、IL-15或IL-21。此類細胞介素可經修飾(例如經由突變)以

減弱其對其相應受體之親和力。藉由減少脫靶及不必要之相互作用，此類突變蛋白可展現提高之安全性概況。因此，細胞介素可經修飾以產生IL-2、IL-7、IL-10、IL-12、IL-15或IL-21突變蛋白。在一個特定實施例中，細胞介素為本文所述之IL-21突變蛋白。結合於免疫檢查點路徑之蛋白質的合適抗體(或其抗原結合抗體片段)包括例如結合以下之抗體：CTLA-4、PD-1、PD-L1、PD-L2、B7-H3、B7-H4、TIGIT、LAG3、CD112 TIM3、BTLA或共刺激受體：ICOS、OX40、41BB或GITR。在一個特定實施例中，抗體(或其抗原結合抗體片段)結合於PD-1 (例如人類PD-1)。

【0159】 在其他實施例中，本發明之融合蛋白為包含細胞介素、抗體(或其抗原結合抗體片段)及至少一種額外靶向部分之多特異性融合蛋白。舉例而言，本發明之融合蛋白可為包含細胞介素、抗體(或其抗原結合抗體片段)及至少一種額外靶向部分之三特異性融合蛋白。

【0160】 在例示性實施例中，本發明之融合蛋白包含本文所述之IL-21突變蛋白及結合PD-1之拮抗劑。術語「結合PD-1之拮抗劑」係指減少、阻斷、抑制、消除或干擾由PD-1與其一或多種結合搭配物，諸如PD-L1、PD-L2之相互作用所引起之信號轉導的分子。在一些實施例中，結合PD-1之拮抗劑為抑制PD-1與其一或多種結合搭配物之結合的分子。在一特定態樣中，結合PD-1之拮抗劑抑制PD-1與PD-L1及/或PD-L2之結合。舉例而言，結合PD-1之拮抗劑包括抗PD-1抗體、其抗原結合抗體片段、免疫黏附素、融合蛋白、寡肽及減少、阻斷、抑制、消除或干擾由PD-1與PD-L1及/或PD-L2之相互作用所引起之信號轉導的其他分子。在一個實施例中，結合PD-1之拮抗劑減少由或經由在T淋巴細胞上表現之細胞表面

蛋白介導、經由PD-1介導之信號傳導的負面共刺激信號，使得功能障礙性T細胞較少功能障礙(例如增強效應子對抗原識別之反應)。在一些實施例中，結合PD-1之拮抗劑為抗PD-1抗體。抗PD-1抗體之實例包括納武單抗(BMS-936558)、派姆單抗(MK-3475)、BMS 936558、BMS-936559、TSR-042 (Tesaro)、ePDR001 (Novartis)及皮地利珠單抗(pidilizumab) (CT-011)。在下文提供結合PD-1之拮抗劑之額外特定實例。

【0161】 在例示性實施例中，結合PD-1之拮抗劑包含結合於PD-1之抗原結合蛋白、基本上由其組成或由其組成。在例示性態樣中，抗原結合蛋白為結合於PD-1之抗體、其抗原結合抗體片段或抗體蛋白產物。

【0162】 在例示性態樣中，本發明之融合蛋白包含如本文所述之IL-21突變蛋白及抗PD-1抗體(如本文所述)、其抗原結合抗體片段或抗PD-1抗體蛋白產物。在例示性情況下，抗PD-1抗體為單株IgG。在例示性情況下，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物為單價或二價的。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物結合於人類PD-1，其具有SEQ ID NO: 263之胺基酸序列。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物結合於食蟹獼猴PD-1，其具有SEQ ID NO: 264之胺基酸序列。在例示性情況下，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物結合於人類PD-1與食蟹獼猴PD-1兩者。在例示性情況下，本發明之融合蛋白包含IL-21突變蛋白(如本文所述)及抗PD-1抗體(如本文所述)。

【0163】 在例示性實施例下，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物與PD-1之結合強度可根據K_D來描述。在例示性態樣中，本文提供之抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產

物之K_D為約10^{-1} M、約10^{-2} M、約10^{-3} M、約10^{-4} M、約10^{-5} M、約10^{-6} M、約10^{-7} M、約10^{-8} M、約10^{-9} M或更少。在例示性態樣中，本文提供之抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物之K_D為微莫耳、奈莫耳、皮莫耳或飛莫耳的。在例示性態樣中，本文提供之抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物之K_D在約10^{-4}至10^{-6} M，或10^{-7}至10^{-9} M，或10^{-10}至10^{-12} M，或10^{-13}至10^{-15} M範圍內。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物對人類PD-1、食蟹獼猴PD-1或兩者具有高親和力。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物對人類PD-1之K_D小於100 pM，視情況為約1 pM至約50 pM。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物對人類PD-1之K_D在約1 pM至約20 pM內或小於約10 pM。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物對食蟹獼猴PD-1之K_D小於100 pM，視情況為約1 pM至約75 pM。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物對食蟹獼猴PD-1之K_D在約1 pM至約20 pM內或小於約10 pM。

【0164】 在例示性情況下，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物為減少、阻斷、抑制、消除或干擾由PD-1與其一或多種結合搭配物，諸如PD-L1、PD-L2之相互作用所引起之信號轉導的結合PD-1之拮抗劑。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物阻斷PD-1結合於其配位體PD-L1或PD-L2。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物抑制PD-1與PD-L1或PD-L2之間的結合相互作用至少50%。在例示性態樣

中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物展現PD-1與PD-L1或PD-L2之間的結合相互作用至少約50%、至少約60%或至少約70%抑制。

【0165】 在例示性情況下，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物抑制混合淋巴細胞反應(MLR)中PD-1介導之T細胞之IL-2產生。在例示性態樣中，MLR中抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物之IC_{50}在約0.1 nM至約5 nM內。在例示性態樣中，MLR中抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物之IC_{50}小於2 nM或小於1 nM。在例示性態樣中，MLR中抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物之IC_{50}為約0.5 nM至約2 nM。

【0166】 在例示性情況下，抗PD-1抗體(或其抗原結合抗體片段)包含：(a)選自由SEQ ID NO: 312、322、332、342、352、362、372及382 (參見表D)組成之群的重鏈(HC)互補決定區(CDR) 1胺基酸序列或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(b)選自由SEQ ID NO: 313、323、333、343、353、363、373及383 (參見表D)組成之群的HC CDR2胺基酸序列或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(c)選自由SEQ ID NO: 314、324、334、344、3545、364、374及384 (參見表D)組成之群的HC CDR3胺基酸序列或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(d)選自由SEQ ID NO: 315、325、335、345、355、365、375及385 (參見表D)組成之群的輕鏈(LC) CDR1胺基酸序列或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(e)選自由SEQ ID NO: 316、326、336、346、356、366、376及

386 (參見表D)組成之群的LC CDR2胺基酸序列或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(f)選自由SEQ ID NO: 317、327、337、347、357、367、377及387 (參見表D)組成之群的LC CDR3胺基酸序列或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；或(g) (a)-(f)中之任兩者、三者、四者、五者或六者之組合。在一些實施例中，抗PD-1抗體蛋白產物包含此類CDR。

表D

	20A2	**20C1**	**22D4**	**20C1.006**	**20C1.009**	**20A2.003**	**22D4.006**	**22D4.017**
HC CDR1	312	322	332	342	352	362	372	382
HC CDR2	313	323	333	343	353	363	373	383
HC CDR3	314	324	334	344	354	364	374	384
LC CDR1	315	325	335	345	355	365	375	385
LC CDR2	316	326	336	346	356	366	376	386
LC CDR3	317	327	337	347	357	367	377	387

數字表示相關SEQ ID NO。

【0167】 在例示性態樣中，抗PD-1抗體(或其抗原結合抗體片段)包含表D中闡述之LC CDR1胺基酸序列、LC CDR2胺基酸序列及LC CDR3胺基酸序列以及表D中闡述之HC CDR胺基酸序列中之至少1個或2個。在例示性態樣中，抗PD-1抗體(或其抗原結合抗體片段)包含表D中闡述之HC CDR1胺基酸序列、HC CDR2胺基酸序列及HC CDR3胺基酸序列以

及表D中闡述之LC CDR胺基酸序列中之至少1個或2個。在一些實施例中，抗PD-1抗體蛋白產物包含此類CDR。

【0168】 在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含由表D之單行中之SEQ ID NO:表示的胺基酸序列中之3個、4個、5個或所有6個。在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含由表D之單行之SEQ ID NO:表示的LC CDR胺基酸序列中之每一個，及由表D之同一單行或另一單行中之SEQ ID NO:表示的HC CDR胺基酸序列中之至少1個或2個。在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含由表D之單行之SEQ ID NO:表示的HC CDR胺基酸序列中之每一個，及由表D之同一單行或另一單行中之SEQ ID NO:表示的LC CDR胺基酸序列中之至少1個或2個。在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含選自由以下組成之群的六個CDR胺基酸序列：(a) SEQ ID NO: 312-317；(b) SEQ ID NO: 322-327；(c) SEQ ID NO: 332-337；(d) SEQ ID NO: 342-347；(e) SEQ ID NO: 352-357；(f) SEQ ID NO: 362-367；(g) SEQ ID NO: 372-377；以及(h) SEQ ID NO: 382-387。在特定實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含表D中關於20A2、20C1、22D4、20C1.006、20C1.009、20A2.003、22D4.006或22D4.017抗體中之任一者的所有6個CDR胺基酸序列。在一些實施例中，抗PD-1抗體蛋白產物包含此類CDR。

【0169】 在例示性情況下，表D之胺基酸序列由至少一個或更多個(例如至少2個、3個、4個、5個、6個、7個、8個、9個、10個或更多個)插入胺基酸分開。在例示性情況下，在LC CDR1與LC CDR2之序列之間存在約10個至約20個胺基酸，且在LC CDR2與LC CDR3之序列之間存在約

25個至約40個胺基酸。在例示性情況下，在LC CDR1與LC CDR2之序列之間存在約14個至約16個胺基酸，且在LC CDR2與LC CDR3之序列之間存在約30個至約35個胺基酸。在例示性情況下，在HC CDR1與HC CDR2之序列之間存在約10個至約20個胺基酸，且在HC CDR2與HC CDR3之序列之間存在約25個至約40個胺基酸。在例示性情況下，在HC CDR1與HC CDR2之序列之間存在約14個至約16個胺基酸，且在HC CDR2與HC CDR3之序列之間存在約30個至約35個胺基酸。

【0170】 在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含(a)選自由318、328、338、348、358、368、378及388 (參見表E)組成之群的重鏈可變區胺基酸序列或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之變異序列；或(b)選自由319、329、339、349、359、369、379及389 (參見表E)組成之群的輕鏈可變區胺基酸序列或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之變異序列；或(c) (a)與(b)。在一些實施例中，抗PD-1抗體蛋白產物包含此類可變區。

表E

	20A2	**20C1**	**22D4**	**20C1.006**	**20C1.009**	**20A2.003**	**22D4.006**	**22D4.017**
HC 可變	318	328	338	348	358	368	378	388
LC 可變	319	329	339	349	359	369	379	389
HC (全長)	320	330	340	350	360	370	380	390
LC (全長)	321	331	341	351	361	371	381	391

數字表示相關SEQ ID NO。

【0171】 在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含一對選自由以下組成之群的胺基酸序列：(a) SEQ ID NO: 318及319；(b) SEQ ID NO: 328及329；(c) SEQ ID NO: 338及339；(d) SEQ

ID NO: 348及349；(e) SEQ ID NO: 358及359；(f) SEQ ID NO: 368及369；(g) SEQ ID NO: 378及379；以及(h) SEQ ID NO: 388及389。

【0172】 在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含(a)選自由320、330、340、350、360、370、380及390 (參見表E)組成之群的重鏈可變區胺基酸序列或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之變異序列；或(b)選自由321、331、341、351、361、371、381及391 (參見表E)組成之群的輕鏈可變區胺基酸序列或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之變異序列；或(c) (a)與(b)。在一些實施例中，抗PD-1抗體蛋白產物包含此類可變區。

【0173】 在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含一對選自由以下組成之群的胺基酸序列：(a) SEQ ID NO: 320及321；(b) SEQ ID NO: 330及331；(c) SEQ ID NO: 340及341；(d) SEQ ID NO: 350及351；(e) SEQ ID NO: 360及361；(f) SEQ ID NO: 370及371；(g) SEQ ID NO: 380及381；以及(h) SEQ ID NO: 390及391。在一些實施例中，抗PD-1抗體蛋白產物包含此類區域。

【0174】 在例示性態樣中，抗PD-1抗體(或其抗原結合抗體片段)重鏈胺基酸序列包含一組如本文所述之電荷對突變。在特定態樣中，抗PD-1抗體(或其抗原結合抗體片段)重鏈胺基酸序列包含選自V1、V103及V131電荷對突變之電荷對突變。

【0175】 在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含與以上提及之胺基酸序列類似的胺基酸序列，而抗原結合蛋白基本上保留其生物功能，例如其結合於PD-1、例如人類PD-1、食蟹獼猴PD-1或減少、阻斷、抑制、消除或干擾由PD-1與其一或多種

結合搭配物、諸如PD-L1或PD-L2之相互作用所引起之信號轉導的能力。

【0176】 在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含相對於以上提及之胺基酸序列差異在於僅僅1個、2個、3個、4個、5個、6個或更多個胺基酸的胺基酸序列。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含所提及序列之變異序列，該變異序列相對於所提及序列差異在於僅僅一或兩個胺基酸。在例示性態樣中，抗原結合蛋白包含一或多個出現在CDR外之胺基酸取代，例如該一或多個胺基酸取代出現在重鏈或輕鏈之構架區內。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含一或多個胺基酸取代，而該抗原結合蛋白保留六個CDR之胺基酸序列。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含相對於以上提及之胺基酸序列具有僅僅1個、2個、3個、4個、5個、6個或更多個保守胺基酸取代的胺基酸序列。

【0177】 在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含與以上提及之胺基酸序列具有超過或約30%、超過或約50%或超過或約70%序列一致性的胺基酸序列。在例示性態樣中，抗原結合蛋白包含與以上提及之胺基酸序列具有至少30%、至少40%、至少50%、至少60%、至少70%、至少80%、至少85%、至少90%或具有超過90%序列一致性的胺基酸序列。在例示性態樣中，抗原結合蛋白包含沿以上提及之胺基酸序列全長具有至少70%、至少80%、至少85%、至少90%或具有超過90%序列一致性之胺基酸序列。在例示性態樣中，抗原結合蛋白包含沿以上提及之胺基酸序列全長具有至少95%、96%、97%、98%或99%序列一致性之胺基酸序列。

【0178】在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含所提及序列之變異序列，該變異序列相對於以上提及之序列具有至少或約70%序列一致性。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含所提及序列之變異序列，該變異序列相對於以上提及之序列具有至少或約80%序列一致性。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含所提及序列之變異序列，該變異序列相對於以上提及之序列具有至少或約90%序列一致性。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含所提及序列之變異序列，該變異序列相對於以上提及之序列具有至少或約95%序列一致性。

【0179】在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含表D之單行中之SEQ ID NO.的一個、兩個、三個、四個或五個序列及與SEQ ID NO: 312-387中之任一者具有至少或約70% (例如至少約80%、至少約90%、至少約95%)序列一致性的至少一個變異序列。在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含選自以下之一組序列中的一個、兩個、三個、四個或五個：(a) SEQ ID NO: 312-317；(b) SEQ ID NO: 322-327；(c) SEQ ID NO: 332-337；(d) SEQ ID NO: 342-347；(e) SEQ ID NO: 352-357；(f) SEQ ID NO: 362-367；(g) SEQ ID NO: 372-377；以及(h) SEQ ID NO: 382-387，其中抗體或其片段進一步包含與該組之至少一個序列具有至少或約70% (例如至少約80%、至少約90%、至少約95%)序列一致性的至少一個變異序列。舉例而言，在例示性態樣中，抗PD-1抗體(或其抗原結合抗體片段)包含SEQ ID NO: 312-317之四個序列，亦即SEQ ID NO: 312-315，其中抗體或其片段包含兩個

變異序列：一個變異序列與SEQ ID NO: 316具有至少或約70% (例如至少約80%、至少約90%)序列一致性，且另一個變異序列與SEQ ID NO: 317具有至少或約70% (例如至少約80%、至少約90%、至少約95%)序列一致性。在一些實施例中，抗PD-1抗體蛋白產物包含此類區域。

【0180】 在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)產物包含與SEQ ID NO: 318、319、328、329、338、339、348、349、358、359、368、369、378、379、388及389中之任一者具有至少或約70% (例如至少約80%、至少約90%、至少約95%)序列一致性的一對變異序列。在例示性情況下，抗體或其片段包含與以下具有至少或約70% (例如至少約80%、至少約90%、至少約95%)序列一致性之一對變異序列：(a) SEQ ID NO: 318及319；(b) SEQ ID NO: 328及329；(c) SEQ ID NO: 338及339；(d) SEQ ID NO: 348及349；(e) SEQ ID NO: 358及359；(f) SEQ ID NO: 368及369；(g) SEQ ID NO: 378及379；以及(h) SEQ ID NO: 388及389。在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含一對序列：一個序列為表E之一個序列，且另一個序列為與SEQ ID NO: 318、319、328、329、338、339、348、349、358、359、368、369、378、379、388及389中之任一者具有至少或約70% (例如至少約80%、至少約90%、至少約95%)序列一致性之變異序列。在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含一對序列：一個序列選自(a) SEQ ID NO: 318及319；(b) SEQ ID NO: 328及329；(c) SEQ ID NO: 338及339；(d) SEQ ID NO: 348及349；(e) SEQ ID NO: 358及359；(f) SEQ ID NO: 368及369；(g) SEQ ID NO: 378及379；以及(h) SEQ ID NO: 388及389，且另一個序列為與(a)-(u)之序列具有至少或約70% (例如

至少約80%、至少約90%、至少約95%)序列一致性的變異序列。舉例而言，在例示性態樣中，抗PD-1抗體(或其抗原結合抗體片段)包含SEQ ID NO: 318之序列且進一步包含與SEQ ID NO 319具有至少或約70% (例如至少約80%、至少約90%、至少約95%)序列一致性的變異序列。在一些實施例中，抗PD-1抗體蛋白產物包含此類區域。

【0181】 在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含與SEQ ID NO: 320、321、330、331、340、341、350、351、360、361、370、371、380、381、390及391中之任一者具有至少或約70% (例如至少約80%、至少約90%、至少約95%)序列一致性的一對變異序列。在例示性情況下，抗PD-1抗體(或其抗原結合抗體片段)包含與以下具有至少或約70% (例如至少約80%、至少約90%、至少約95%)序列一致性之一對變異序列：(a) SEQ ID NO: 320及321；(b) SEQ ID NO: 330及331；(c) SEQ ID NO: 340及341；(d) SEQ ID NO: 350及351；(e) SEQ ID NO: 360及361；(f) SEQ ID NO: 370及371；(g) SEQ ID NO: 380及381；以及(h) SEQ ID NO: 390及391。在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含一對序列：一個序列為表E之一個序列，且另一個序列為與SEQ ID NO: 320、321、330、331、340、341、350、351、360、361、370、371、380、381、390及391中之任一者具有至少或約70% (例如至少約80%、至少約90%、至少約95%)序列一致性之變異序列。在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含一對序列：一個序列選自(a) SEQ ID NO: 320及321；(b) SEQ ID NO: 330及331；(c) SEQ ID NO: 340及341；(d) SEQ ID NO: 350及351；(e) SEQ ID NO: 360及361；(f) SEQ ID NO: 370及371；(g) SEQ ID NO: 380及

381；以及(h) SEQ ID NO: 390及391，且另一個序列為與(a)-(u)之序列具有至少或約70% (例如至少約80%、至少約90%、至少約95%)序列一致性的變異序列。舉例而言，在例示性態樣中，抗PD-1抗體(或其抗原結合抗體片段)包含SEQ ID NO: 320之序列且進一步包含與SEQ ID NO 321具有至少或約70% (例如至少約80%、至少約90%、至少約95%)序列一致性的變異序列。在一些實施例中，抗PD-1抗體蛋白產物包含此類區域。

【0182】 在其他例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物相對於天然存在之對應物包含一或多個胺基酸修飾，從而改善半衰期/穩定性或使抗體更適合於表現/製造(例如呈與IL-21突變蛋白之融合蛋白)。在例示性情況下，抗PD-1抗體經設計以預防或減少抗PD-1抗體與Fc受體之間的相互作用。在例示性情況下，抗PD-1抗體為包含缺乏與Fcγ受體相互作用之能力之恆定區的穩定無效應功能(SEFL)抗體。SEFL抗體為此項技術中已知。參見例如Liu等人, J Biol Chem 292: 1876-1883 (2016)；及Jacobsen等人, J. Biol. Chem. 292: 1865-1875 (2017)。在例示性態樣中，SEFL抗體包含以下突變中之一或多種，根據EU系統編號：L242C、A287C、R292C、N297G、V302C、L306C及/或K334C。在例示性態樣中，SEFL抗體包含N297G。在例示性態樣中，SEFL抗體包含A287C、N297G及L306C。在其他例示性態樣中，SEFL抗體包含R292C、N297G及V302C (亦即SEFL2-2)。

【0183】 抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物可包含其他半衰期延長(HLE)修飾。在例示性情況下，HLE修飾存在於重鏈恆定區中且包含以下突變中之一或多種，根據EU系統編號：M252Y、S254T及T256E。在例示性情況下，抗PD-1抗體、其抗原結合

抗體片段或抗PD-1抗體蛋白產物包含M252Y、S254T及T256E中之一或兩種。在例示性情況下，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含M252Y、S254T及T256E中之所有三種。在例示性態樣中，重鏈恆定區包含SEQ ID NO: 545或SEQ ID NO: 547或SEQ ID NO: 549之胺基酸序列或與SEQ ID NO: 545或SEQ ID NO: 547或SEQ ID NO: 549具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。在例示性情況下，HLE修飾存在於重鏈恆定區中且包含以下突變中之一或多種，根據EU系統編號：L309D、Q311H及N434S。在例示性情況下，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含L309D、Q311H及N434S中之一種、兩種或所有三種。在例示性情況下，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含L309D、Q311H及N434S中之所有三種。在例示性態樣中，重鏈恆定區包含SEQ ID NO: 544或SEQ ID NO: 546或SEQ ID NO: 548之胺基酸序列或與SEQ ID NO: 544或SEQ ID NO: 546或SEQ ID NO: 548具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。

【0184】 在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含SEFL2-2修飾及HLE修飾。在一些情況下，HLE修飾包含M252Y、S254T及T256E中之一種或兩種或所有三種。在例示性態樣中，重鏈恆定區包含SEQ ID NO: 551或SEQ ID NO: 553或SEQ ID

NO: 555之胺基酸序列或與SEQ ID NO: 551或SEQ ID NO: 553或SEQ ID NO: 555具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。在一些情況下，HLE修飾包含L309D、Q311H及N434S中之一種或兩種或所有三種。在例示性態樣中，重鏈恆定區包含SEQ ID NO: 550或SEQ ID NO: 552或SEQ ID NO: 554之胺基酸序列或與SEQ ID NO: 550或SEQ ID NO: 552或SEQ ID NO: 554具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。在例示性態樣中，重鏈另外包含如下所述之電荷對突變。

【0185】 在真核細胞中，出現兩類糖基化反應：(1) N連接之糖基化，其中聚糖附接於識別序列Asn-X-Thr/Ser之天冬醯胺，其中「X」為除脯胺酸外之任何胺基酸；及(2) O連接之糖基化，其中聚糖附接於絲胺酸或蘇胺酸。N連接之糖基化開始於內質網(Endoplasmic Reticulum，ER)中，其中一組複雜反應引起基本上由兩個GlcNAc殘基及三個Man殘基形成之核心聚糖結構的附接。在ER中形成之聚糖複合物在高基氏體中在酶作用下修飾。若酶相對難以接近該醣，則其通常保持初始HM形式。若酶可接近該醣，則許多Man殘基裂解且進一步修飾該醣，產生複合型N聚糖結構。舉例而言，位於順面高基氏體中之甘露糖苷酶-1可裂解或水解HM聚糖，而位於中間高基氏體中之岩藻糖基轉移酶FUT-8將聚糖岩藻糖基化(Hanrue Imai-Nishiya (2007), BMC Biotechnology, 7:84)。在例示性

態樣中，抗PD-1抗體經N糖基化，例如包含一或多個共價附接於重鏈之特定胺基酸之糖部分(例如聚糖、醣)。在替代態樣中，抗PD-1抗體未經糖基化，或不包含任何共價附接於重鏈之特定胺基酸之糖部分(例如聚糖、醣)。

【0186】 在例示性態樣中，抗PD-1抗體包含如下重鏈恆定區，該重鏈恆定區包含SEQ ID NO: 284之胺基酸序列或與SEQ ID NO: 284具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。在例示性態樣中，抗PD-1抗體包含如下重鏈恆定區，該重鏈恆定區包含SEQ ID NO: 284之胺基酸序列或與SEQ ID NO: 284具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列，且進一步包含連接子。在例示性情況下，連接子包含SEQ ID NO: 262之胺基酸序列。因此，在一些例示性態樣中，抗PD-1抗體包含SEQ ID NO: 287之重鏈恆定區胺基酸序列或與SEQ ID NO: 287具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。在例示性態樣中，抗PD-1抗體包含如下重鏈恆定區，該重鏈恆定區包含SEQ ID NO: 284之胺基酸序列或與SEQ ID NO: 284具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約

94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列，其中截斷或移除C端Lys。關於此，在一些態樣中，抗PD-1抗體包含缺乏C端Lys之重鏈恆定區，且包含SEQ ID NO: 285之胺基酸序列或與SEQ ID NO: 285具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。一般而言，在表現期間抗體之C端離胺酸藉由羧肽酶進行裂解。缺乏C端Lys之重鏈恆定區有利地預防羧肽酶作用於抗PD-1抗體之重鏈。在例示性態樣中，抗PD-1抗體包含缺乏C端Lys之重鏈恆定區且進一步包含連接子。在例示性情況下，連接子包含SEQ ID NO: 262之胺基酸序列。因此，在一些例示性態樣中，抗PD-1抗體包含SEQ ID NO: 286之重鏈恆定區胺基酸序列或與SEQ ID NO: 286具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。在例示性態樣中，抗PD-1抗體包含如下重鏈恆定區，該重鏈恆定區包含SEQ ID NO: 284之胺基酸序列或與SEQ ID NO: 284具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列，其中具有一或多個預防或減少抗PD-1抗體與Fc受體之間的相互作用的SEFL突變，包括(但不限於) L242C、A287C、R292C、N297G、V302C、L306C及/或K334C。在例示性態樣中，SEFL突變為SEFL2-2突變：R292C、N297G及V302C，使得抗PD-1

抗體包含SEQ ID NO: 265之重鏈恆定區胺基酸序列或與SEQ ID NO: 265具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。在例示性態樣中，抗PD-1抗體包含具有SEFL2-2突變且截斷或移除C端Lys之重鏈恆定區。此類重鏈恆定區可包含SEQ ID NO: 266之序列。在例示性態樣中，抗PD-1抗體包含具有SEFL2-2突變且截斷或移除C端Lys且具有連接子之重鏈恆定區。此類重鏈恆定區可包含SEQ ID NO: 267之序列。在例示性態樣中，抗PD-1抗體包含具有SEFL2-2突變及連接子且未截斷C端Lys之重鏈恆定區。此類重鏈恆定區可包含SEQ ID NO: 282之序列。

【0187】 在例示性態樣中，IL-21突變蛋白附接於抗PD-1抗體之Fc。在例示性態樣中，IL-21突變蛋白附接於抗體之兩個重鏈之一。在例示性態樣中，IL-21突變蛋白附接於抗體之兩個重鏈之一的C端。

【0188】 在例示性態樣中，融合蛋白包含僅僅一個IL-21突變蛋白(亦即融合蛋白包含IL-21突變蛋白單體)。在例示性態樣中，IL-21突變蛋白附接於抗體之兩個重鏈之一的C端。在例示性態樣中，當融合蛋白包含僅僅一個IL-21突變蛋白時，抗體之Fc包含經設計以驅動兩個重鏈(一個重鏈與IL-21突變蛋白融合且一個重鏈缺乏IL-21突變蛋白)之異源二聚化的修飾。此類修飾包括Fc突變，諸如杵-臼、DuoBodies、Azymetric、電荷對、HA-TF、SEEDbody及具有差別蛋白A親和力之修飾。參見例如Spiess等人, Molecular Immunology, 67(2, 部分A), 2015, 第95-106頁。杵-臼突變包括第一重鏈中之T366W，及第二重鏈中之T366S、L368A及/

或Y407V。參見例如Ridgway等人, Protein Eng., 9 (1996), 第617-621頁；及Atwell等人, J. Mol. Biol., 270 (1997), 第26-35頁。DuoBody突變包括第一重鏈中之F405L及第二重鏈中之K409R。參見例如Labrijn等人, Proc. Natl. Acad. Sci. U.S.A., 110 (2013), 第5145-5150頁。Azymetric突變包括第一重鏈中之T350V、L351Y、F405A及/或Y407V及第二重鏈中之T350V、T366L、K392L及/或T394W。參見例如Von Kreudenstein等人, mAbs, 5 (2013), 第646-654頁。HA-TF突變包括第一重鏈中之S364H及/或F405A，及第二重鏈中之Y349T及/或T394F。參見例如Moore等人, mAbs, 3 (2011), 第546-557頁。SEEDbody突變包括第一重鏈中之IgG/A嵌合體突變及第二重鏈中之IgG/A嵌合體突變。參見例如Davis等人, Protein Eng. Des. Sel., 23 (2010), 第195-202頁。差別蛋白A親和力突變在一個重鏈中包括H435R且另一重鏈中無突變。參見例如美國專利第8,586,713號。

【0189】 在一特定實例中，突變為電荷對突變。以下為此類電荷對突變之實例，根據EU系統編號。電荷對突變包括第一重鏈中之K409D及第二重鏈中之D399K；第一重鏈中之K392D及第二重鏈中之E356K；或第一重鏈中之K409D與K392D及第二重鏈中之D399K與E356K (後者在本文中表示為「V1」)。參見例如Gunasekaran等人, J Biol Chem 285: 19637-19646 (2010)。在另一特定實例中，電荷對突變包括第一重鏈中之K439D、K392D及K409D；及第二重鏈中之E356K及D399K (本文中表示為「V103」)。在又一個特定實例中，電荷對突變包括第一重鏈中之K360E、K370E、K392E及K409D；及第二重鏈中之E357K及D399K (本文中表示為「V131」)。電荷對突變亦可包括第一重鏈中之K370D及第二

重鏈中之E357K；或第一重鏈中之K409D、K392D及K370D所有三個及第二重鏈中之D399K、E357K及E356K所有三個(後者在本文中表示為「V4」)。額外電荷對突變亦包括第一重鏈中之D221E、P228E及/或L368E及第二重鏈中之D221R、P228R及/或K409R。參見例如Strop等人, J. Mol. Biol., 420 (2012), 第204-219頁。

【0190】 在融合蛋白包含僅僅一個IL-21突變蛋白(亦即融合蛋白包含IL-21突變蛋白單體)且重鏈含有V1電荷對突變之實施例中，IL-21突變蛋白可附接於含有K409D及K392D突變之重鏈(例如IL-21突變蛋白附接於包含SEQ ID NO: 294、296或298之重鏈)或含有D399K及E356K突變之重鏈(例如IL-21突變蛋白附接於包含SEQ ID NO: 295、297或299之重鏈)。在一特定實施例中，IL-21突變蛋白附接於含有D399K及E356K突變之重鏈。

【0191】 在融合蛋白包含僅僅一個IL-21突變蛋白(亦即融合蛋白包含IL-21突變蛋白單體)且重鏈含有V4電荷對突變之實施例中，IL-21突變蛋白可附接於含有K409D、K392D及K370D突變之重鏈(例如IL-21突變蛋白附接於包含SEQ ID NO: 288、290或292之重鏈)或含有D399K、E357K及E356K突變之重鏈(例如IL-21突變蛋白附接於包含SEQ ID NO: 289、291.或293之重鏈)。在一特定實施例中，IL-21突變蛋白附接於含有D399K、E357K及E356K突變之重鏈。

【0192】 在融合蛋白包含僅僅一個IL-21突變蛋白(亦即融合蛋白包含IL-21突變蛋白單體)且重鏈含有V103電荷對突變之實施例中，IL-21突變蛋白可附接於含有K439D、K392D及K409D突變之重鏈(例如IL-21突變蛋白附接於包含SEQ ID NO: 472、474或476之重鏈)或含有E356K及

D399K突變之重鏈(例如IL-21突變蛋白附接於包含SEQ ID NO: 473、475或477之重鏈)。在一特定實施例中，IL-21突變蛋白附接於含有E356K及D399K突變之重鏈。

【0193】 在融合蛋白包含僅僅一個IL-21突變蛋白(亦即融合蛋白包含IL-21突變蛋白單體)且重鏈含有V131電荷對突變之實施例中，IL-21突變蛋白可附接於含有K360E、K370E、K392E及K409D突變之重鏈(例如IL-21突變蛋白附接於包含SEQ ID NO: 478、480或482之重鏈)或含有E357K及D399K突變之重鏈(例如IL-21突變蛋白附接於包含SEQ ID NO: 479、481或483之重鏈)。在一特定實施例中，IL-21突變蛋白附接於含有E357K及D399K突變之重鏈。

【0194】 因此，在例示性態樣中，抗PD-1抗體(或其抗原結合抗體片段)包含一組如本文所述之電荷對突變。在特定態樣中，抗PD-1抗體(或其抗原結合抗體片段)包含選自V1、V103及V131電荷對突變之電荷對突變。

【0195】 在例示性態樣中，抗PD-1抗體包含如下重鏈恆定區，該重鏈恆定區包含SEQ ID NO: 284之胺基酸序列或與SEQ ID NO: 284具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列，具有一或多個電荷對突變，例如V1、V4、V103或V131電荷對突變。在例示性態樣中，抗PD-1抗體包含如下重鏈恆定區，該重鏈恆定區包含SEQ ID NO: 284之胺基酸序列或與SEQ ID NO: 284具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例

如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列，具有V1電荷對突變，其中第一重鏈恆定區包含K409及K392D突變且第二重鏈恆定區包含D399K及E356K突變。此類第一重鏈恆定區可包含SEQ ID NO: 294之序列且此類第二重鏈恆定區可包含SEQ ID NO: 295之序列。此類第一及第二重鏈恆定區可截斷或移除C端Lys，使得第一及第二重鏈恆定區可分別包含SEQ ID NO: 296及297。此類第一及第二重鏈恆定區可截斷或移除C端Lys且具有連接子，使得第一及第二重鏈恆定區可分別包含SEQ ID NO: 298及299。在例示性態樣中，抗PD-1抗體包含含有V1電荷對突變及SEFL2-2突變之重鏈恆定區。此類包含V1電荷對突變及SEFL2-2突變之第一重鏈恆定區可包含SEQ ID NO: 306之序列且此類包含V1電荷對突變及SEFL2-2突變之第二重鏈恆定區可包含SEQ ID NO: 307之序列。涵蓋此類第一及第二重鏈之額外變化，包括例如截斷或移除C端Lys之重鏈(SEQ ID NO: 308及309)及截斷或移除C端Lys且具有連接子之重鏈(SEQ ID NO: 310及311)。

【0196】 在例示性態樣中，抗PD-1抗體包含如下重鏈恆定區，該重鏈恆定區包含SEQ ID NO: 284之胺基酸序列或與SEQ ID NO: 284具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列，具有V4電荷對，其中第一重鏈恆定區包含K409、K392D及K370D突變，且第二重鏈恆定區包含D399K、E356K及E357K突變。此類第一重鏈恆定區可包含SEQ ID NO: 288之序列且此類第二重鏈恆定區可包含SEQ ID NO: 289之序列。此類第一及第二重鏈恆定區可截斷或移除C端Lys，使得第一及第

二重鏈恆定區可分別包含SEQ ID NO: 290及291。此類第一及第二重鏈恆定區可截斷或移除C端Lys且具有連接子，使得第一及第二重鏈恆定區可分別包含SEQ ID NO: 292及293。在例示性態樣中，抗PD-1抗體包含如下重鏈恆定區，該重鏈恆定區包含V4電荷對突變及SEFL2-2突變。此類包含V4電荷對突變及SEFL2-2突變之第一重鏈恆定區可包含SEQ ID NO: 300之序列且此類包含V4電荷對突變及SEFL2-2突變之第二重鏈恆定區可包含SEQ ID NO: 301之序列。涵蓋此類第一及第二重鏈之額外變化，包括例如截斷C端Lys之重鏈(SEQ ID NO: 302及303)及截斷或移除C端Lys且具有連接子之重鏈(SEQ ID NO: 304及305)。

【0197】 在例示性態樣中，抗PD-1抗體包含如下重鏈恆定區，該重鏈恆定區包含SEQ ID NO: 284之胺基酸序列或與SEQ ID NO: 284具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列，具有V103電荷對突變，其中第一重鏈恆定區包含SEQ ID NO: 484之序列且第二重鏈恆定區包含SEQ ID NO: 485之序列。此類第一及第二重鏈恆定區可截斷或移除C端Lys，使得第一及第二重鏈恆定區可分別包含SEQ ID NO: 486及487。此類第一及第二重鏈恆定區可截斷或移除C端Lys且具有連接子，使得第一及第二重鏈恆定區可分別包含SEQ ID NO: 488及489。在例示性態樣中，抗PD-1抗體包含含有V103電荷對突變及SEFL2-2突變之重鏈恆定區。此類包含V103電荷對突變及SEFL2-2突變之第一重鏈恆定區可包含SEQ ID NO: 484之序列且此類包含V103電荷對突變及SEFL2-2突變之第二重鏈恆定區可包含SEQ ID NO: 485之序列。涵蓋此類第一及第

二重鏈之額外變化，包括例如截斷C端Lys之重鏈(SEQ ID NO: 486及487)及截斷或移除C端Lys且具有連接子之重鏈(SEQ ID NO: 488及489)。

【0198】 在例示性態樣中，抗PD-1抗體包含如下重鏈恆定區，該重鏈恆定區包含SEQ ID NO: 284之胺基酸序列或與SEQ ID NO: 284具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列，具有V131電荷對突變，其中第一重鏈恆定區包含SEQ ID NO: 478之序列且第二重鏈恆定區包含SEQ ID NO: 479之序列。此類第一及第二重鏈恆定區可截斷或移除C端Lys，使得第一及第二重鏈恆定區可分別包含SEQ ID NO: 480及481。此類第一及第二重鏈恆定區可截斷或移除C端Lys且具有連接子，使得第一及第二重鏈恆定區可分別包含SEQ ID NO: 482及483。在例示性態樣中，抗PD-1抗體包含含有V131電荷對突變及SEFL2-2突變之重鏈恆定區。此類包含V131電荷對突變及SEFL2-2突變之第一重鏈恆定區可包含SEQ ID NO: 490之序列且此類包含V131電荷對突變及SEFL2-2突變之第二重鏈恆定區可包含SEQ ID NO: 491之序列。涵蓋此類第一及第二重鏈之額外變化，包括例如截斷C端Lys之重鏈(SEQ ID NO: 492及493)及截斷或移除C端Lys且具有連接子之重鏈(SEQ ID NO: 494及495)。

【0199】 在替代態樣中，融合蛋白包含超過一種IL-21突變蛋白(亦即融合蛋白包含IL-21突變蛋白二聚體或IL-21突變蛋白多聚體)。在例示性替代態樣中，融合蛋白包含2種、3種或4種(或更多種) IL-21突變蛋白。在例示性態樣中，當融合蛋白包含超過一種IL-21突變蛋白時，各IL-21突變蛋白包含相同結構，例如相同胺基酸序列。在例示性情況下，融合蛋白

包含IL-21同源二聚體或IL-21同源多聚體。在替代態樣中，融合蛋白之各IL-21突變蛋白包含不同結構，例如不同胺基酸序列。在例示性情況下，融合蛋白包含IL-21異源二聚體或IL-21異源多聚體。在例示性情況下，融合蛋白包含兩種IL-21突變蛋白，其中第一IL-21突變蛋白連接於第一抗體重鏈之C端，且第二IL-21突變蛋白連接於第二抗體重鏈之C端。在例示性態樣中，各IL-21突變蛋白具有相同胺基酸序列(例如為IL-21突變蛋白同源二聚體)。在例示性態樣中，第一IL-21突變蛋白具有相對於第二IL-21突變蛋白不同之胺基酸序列(例如為IL-21突變蛋白異源二聚體)。

【0200】關於包含一或多種IL-21突變蛋白之融合蛋白，各IL-21突變蛋白可在有或無連接子下附接於抗體之重鏈之一。在例示性態樣中，IL-21突變蛋白經由連接子附接於抗體重鏈之一之C端且該連接子為肽。在例示性情況下，肽包含GGGGS之胺基酸序列(SEQ ID NO: 262)。在替代態樣中，IL-21突變蛋白在無連接子下附接於抗體之重鏈之一的C端。

【0201】在例示性態樣中，融合蛋白包含僅僅一種IL-21突變蛋白，該IL-21突變蛋白直接附接於抗PD-1抗體之重鏈之一的C端。在例示性態樣中，IL-21突變蛋白包含表4中列出之胺基酸取代或表4中列出之SEQ ID NO:之序列。在例示性態樣中，IL-21突變蛋白包含表5中列出之胺基酸取代或表5中列出之SEQ ID NO:之序列。在例示性態樣中，IL-21突變蛋白包含表7中列出之胺基酸取代或表7中列出之SEQ ID NO:之序列。在例示性態樣中，IL-21突變蛋白包含表6及8-14中之任一者中列出之胺基酸取代或此等表中列出之SEQ ID NO:之序列。在例示性態樣中，IL-21突變蛋白包含SEQ ID NO: 159、161、238、241、242或244中之任一者的胺基酸序列。在例示性態樣中，IL-21突變蛋白直接附接於抗PD-1抗

體且不包含肽連接子。

【0202】在例示性態樣中，融合蛋白包含兩種IL-21突變蛋白、各突變蛋白直接附接於抗PD-1抗體之重鏈之C端且各突變蛋白具有相同胺基酸序列。在例示性態樣中，IL-21突變蛋白包含表4中列出之胺基酸取代或表4中列出之SEQ ID NO:之序列。在例示性態樣中，IL-21突變蛋白包含表5中列出之胺基酸取代或表5中列出之SEQ ID NO:之序列。在例示性態樣中，IL-21突變蛋白包含表7中列出之胺基酸取代或表7中列出之SEQ ID NO:之序列。在例示性態樣中，IL-21突變蛋白包含表6及8-14中之任一者中列出之胺基酸取代或此等表中列出之SEQ ID NO:之序列。在例示性態樣中，IL-21突變蛋白包含SEQ ID NO: 159、161、237、238、241及244中之任一者的胺基酸序列。在例示性態樣中，IL-21突變蛋白直接附接於抗PD-1抗體且不包含肽連接子。

【0203】在例示性態樣中，融合蛋白包含與本文所述之任何IL-21突變蛋白之胺基酸序列融合的本文所述之抗體恆定區之胺基酸序列。在例示性態樣中，融合蛋白包含與本文所述之任何IL-21突變蛋白之胺基酸序列融合的未糖基化的本文所述之抗體恆定區之胺基酸序列。在例示性情況下，融合蛋白包含與包含SEQ ID NO: 3-21、23-56、58-112、114-208、210-222、224-255及283中之任一者或與SEQ ID NO: 3-21、23-56、58-112、114-208、210-222、224-255及283具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90%(例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的IL-21突變蛋白融合的恆定區，該恆定區包含SEQ ID NO: 265-267、282、284-311、472-495及544-555中之任一者的

胺基酸序列或與SEQ ID NO: 265-267、282、284-311、472-495及544-555中之任一者具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。在例示性態樣中，融合蛋白包含SEQ ID NO: 268-281中之任一者的胺基酸序列或與SEQ ID NO: 268-281具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。

【0204】 在例示性實施例中，融合蛋白包含如圖4A、4B或4C中所述之構築體。在例示性實施例中，融合蛋白包含(i)本文所述之抗PD-1抗體(或其抗原結合抗體片段)；及(ii)本文所述之IL-21突變蛋白。在其他例示性實施例中，融合蛋白包含(i)本文所述之抗PD-1抗體(或其抗原結合抗體片段)；(ii)本文所述之電荷對突變；及(iii)本文所述之IL-21突變蛋白(參見例如圖4C)。在其他例示性實施例中，融合蛋白包含(i)本文所述之抗PD-1抗體(或其抗原結合抗體片段)，其中該抗PD-1抗體(或其抗原結合抗體片段)之重鏈序列不包含C端離胺酸；(ii)本文所述之電荷對突變；及(iii)本文所述之IL-21突變蛋白。

【0205】 在例示性情況下，抗PD-1抗體(或其抗原結合抗體片段)包含：(a)表D中闡述之重鏈(HC)互補決定區(CDR) 1胺基酸序列，或選自由SEQ ID NO: 312、322、332、342、352、362、372及382組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(b)表D中闡述之HC CDR2胺基酸序列，或選自由SEQ ID NO:

313、323、333、343、353、363、373及383組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(c)表D中闡述之HC CDR3胺基酸序列，或選自由SEQ ID NO: 314、324、334、344、3545、364、374及384組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(d)表D中闡述之輕鏈(LC) CDR1胺基酸序列，或選自由SEQ ID NO: 315、325、335、345、355、365、375及385組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(e)表D中闡述之LC CDR2胺基酸序列，或選自由SEQ ID NO: 316、326、336、346、356、366、376及386組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(f)表D中闡述之LC CDR3胺基酸序列，或選自由SEQ ID NO: 317、327、337、347、357、367、377及387組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；或(g) (a)-(f)中之任兩者或更多者之組合。在例示性態樣中，抗PD-1抗體(或其抗原結合抗體片段)包含表D中闡述之LC CDR1胺基酸序列、LC CDR2胺基酸序列及LC CDR3胺基酸序列以及表D中闡述之HC CDR胺基酸序列中之至少1者或2者。在例示性實施例中，抗原結合蛋白包含由表D之單行中之SEQ ID NO:表示的胺基酸序列中之3個、4個、5個或6個。在例示性實施例中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含選自由以下組成之群的六個CDR胺基酸序列：(a) SEQ ID NO: 312-317；(b) SEQ ID NO: 322-327；(c) SEQ ID NO: 332-337；(d) SEQ ID NO: 342-347；(e) SEQ ID NO: 352-357；(f) SEQ ID NO: 362-367；(g) SEQ ID NO: 372-377；以及(h)

SEQ ID NO: 382-387。在一些實施例中，抗PD-1抗體蛋白產物包含此類區域。

【0206】 在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含(a)表E中闡述之重鏈可變區胺基酸序列，或選自由318、328、338、348、358、368、378及388組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之變異序列；或(b)表E中闡述之輕鏈可變區胺基酸序列，或選自由319、329、339、349、359、369、379及389組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之變異序列；或(c) (a)與(b)。在例示性實施例中，抗PD-1抗體(或其抗原結合抗體片段)包含一對選自由以下組成之群的胺基酸序列：(a) SEQ ID NO: 318及319；(b) SEQ ID NO: 328及329；(c) SEQ ID NO: 338及339；(d) SEQ ID NO: 348及349；(e) SEQ ID NO: 358及359；(f) SEQ ID NO: 368及369；(g) SEQ ID NO: 378及379；以及(h) SEQ ID NO: 388及389。在例示性情況下，抗體恆定區包含SEQ ID NO: 265-267、282及284-311中之任一者的胺基酸序列或與SEQ ID NO: 265-267、282及284-311中之任一者具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列，其與包含SEQ ID NO: 3-21、23-56、58-112、114-208、210-222、224-255及283中之任一者或與SEQ ID NO: 3-21、23-56、58-112、114-208、210-222、224-255及283具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約

96%、約97%、約98%或約99%)序列一致性的胺基酸序列的IL-21突變蛋白融合。在例示性實施例中，抗原結合蛋白包含一對選自由以下組成之群的胺基酸序列：(a) SEQ ID NO: 320及321；(b) SEQ ID NO: 330及331；(c) SEQ ID NO: 340及341；(d) SEQ ID NO: 350及351；(e) SEQ ID NO: 360及361；(f) SEQ ID NO: 370及371；(g) SEQ ID NO: 380及381；以及(h) SEQ ID NO: 390及391。在例示性實施例中，融合蛋白包含(I)一對選自由以下組成之群的胺基酸序列：(a) SEQ ID NO: 320及321；(b) SEQ ID NO: 330及331；(c) SEQ ID NO: 340及341；(d) SEQ ID NO: 350及351；(e) SEQ ID NO: 360及361；(f) SEQ ID NO: 370及371；(g) SEQ ID NO: 380及381；以及(h) SEQ ID NO: 390及391，及(II)包含SEQ ID NO: 3-21、23-56、58-112、114-208、210-222、224-255及283中之任一者或與SEQ ID NO: 3-21、23-56、58-112、114-208、210-222、224-255及283具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列的IL-21突變蛋白。

【0207】 在例示性情況下，融合蛋白包含如圖4A中所示之同源二聚體，其中抗PD-1抗體包含抗體20C1.009之三個輕鏈CDR (SEQ ID NO: 355-357)、抗體20C1.009之三個重鏈CDR (SEQ ID NO: 352-354)，且各重鏈包含含有SEFL2-2突變之恆定區序列(例如SEQ ID NO: 265或266)，其中兩種IL-21突變蛋白中之每一者包含胺基酸取代R9E及R76A (亦即，各包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 358之重鏈可變區及SEQ ID NO: 359之輕鏈可變區。在例示性情

況下，抗PD-1抗體包含SEQ ID NO: 360之重鏈或SEQ ID NO: 361之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 361及562或SEQ ID NO: 361及563之胺基酸序列的同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 361之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 562之胺基酸序列)的同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 361之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 563之胺基酸序列)的同源二聚體。

【0208】 在例示性情況下，融合蛋白包含如圖4A中所示之同源二聚體，其中抗PD-1抗體包含抗體20C1.009之三個輕鏈CDR (SEQ ID NO: 355-357)、抗體20C1.009之三個重鏈CDR (SEQ ID NO: 352-354)，且各重鏈包含含有SEFL2-2突變之恆定區序列(例如SEQ ID NO: 265或266)，其中兩種IL-21突變蛋白中之每一者包含胺基酸取代R9E及R76E (亦即，各包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 358之重鏈可變區及SEQ ID NO: 359之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 360之重鏈或SEQ ID NO: 361之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 361及564或SEQ ID NO: 361及565之胺基酸序列的同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 361之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 564之胺基酸序列)的同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 361之胺基酸序列)及兩條

抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 565之胺基酸序列)的同源二聚體。

【0209】 在例示性情況下，融合蛋白包含如圖4B中所示之同源二聚體，其中抗PD-1抗體包含抗體20C1.009之三個輕鏈CDR (SEQ ID NO: 355-357)、抗體20C1.009之三個重鏈CDR (SEQ ID NO: 352-354)，且各重鏈包含含有SEFL2-2突變及連接子之恆定區序列(例如SEQ ID NO: 267)，其中兩種IL-21突變蛋白中之每一者包含胺基酸取代R9E及R76A(亦即，各包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 358之重鏈可變區及SEQ ID NO: 359之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 360之重鏈或SEQ ID NO: 361之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 361及566之胺基酸序列之同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 361之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 566之胺基酸序列)的同源二聚體。

【0210】 在例示性情況下，融合蛋白包含如圖4B中所示之同源二聚體，其中抗PD-1抗體包含抗體20C1.009之三個輕鏈CDR (SEQ ID NO: 355-357)、抗體20C1.009之三個重鏈CDR (SEQ ID NO: 352-354)，且各重鏈包含含有SEFL2-2突變及連接子之恆定區序列(例如SEQ ID NO: 267)，其中兩種IL-21突變蛋白中之每一者包含胺基酸取代R9E及R76E(亦即，各包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 358之重鏈可變區及SEQ ID NO: 359之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 360之重鏈或SEQ ID NO:

361之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 361及567之胺基酸序列之同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 361之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 567之胺基酸序列)的同源二聚體。

【0211】 在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20C1.009之三個輕鏈CDR (SEQ ID NO: 355-357)、抗體20C1.009之三個重鏈CDR (SEQ ID NO: 352-354)，及包含含有SEFL2-2突變及V1電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 306及307或SEQ ID NO: 308及309)，其中IL-21突變蛋白單體附接於含有E356K及D399K V1電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 309中之任一者之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76A (亦即包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 358之重鏈可變區及SEQ ID NO: 359之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 360之重鏈或SEQ ID NO: 361之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 361及568之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 361之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 568之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 574之胺基酸序列)的單體。

【0212】 在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20C1.009之三個輕鏈CDR (SEQ

ID NO: 355-357)、抗體20C1.009之三個重鏈CDR (SEQ ID NO: 352-354)，及包含含有SEFL2-2突變及V103電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 484及485或SEQ ID NO: 486及487)，其中IL-21突變蛋白單體附接於含有E356K及D399K V103電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 487之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76A (亦即包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 358之重鏈可變區及SEQ ID NO: 359之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 360之重鏈或SEQ ID NO: 361之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 361及569之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 361之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 569之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 575之胺基酸序列)的單體。

【0213】 在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20C1.009之三個輕鏈CDR (SEQ ID NO: 355-357)、抗體20C1.009之三個重鏈CDR (SEQ ID NO: 352-354)，及包含含有SEFL2-2突變及V131電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 490及491或SEQ ID NO: 492及493)，其中IL-21突變蛋白單體附接於含有E357K及D399K V131電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 493之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76A (亦即包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 358之重鏈可變區及

SEQ ID NO: 359之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 360之重鏈或SEQ ID NO: 361之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 361及570之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 361之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 570之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 576之胺基酸序列)的單體。

【0214】 在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20C1.009之三個輕鏈CDR (SEQ ID NO: 355-357)、抗體20C1.009之三個重鏈CDR (SEQ ID NO: 352-354)，及包含含有SEFL2-2突變及V1電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 306及307或SEQ ID NO: 308及309)，其中IL-21突變蛋白單體附接於含有E356K及D399K V1電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 309之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76E (亦即包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 358之重鏈可變區及SEQ ID NO: 359之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 360之重鏈或SEQ ID NO: 361之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 361及571之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 361之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 571之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 574之胺基酸序列)的單體。

【0215】在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20C1.009之三個輕鏈CDR (SEQ ID NO: 355-357)、抗體20C1.009之三個重鏈CDR (SEQ ID NO: 352-354)，及包含含有SEFL2-2突變及V103電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 484及485或SEQ ID NO: 486及487)，其中IL-21突變蛋白單體附接於含有E356K及D399K V103電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 487之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76E (亦即包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 358之重鏈可變區及SEQ ID NO: 359之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 360之重鏈或SEQ ID NO: 361之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 361及572之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 361之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 572之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 575之胺基酸序列)的單體。

【0216】在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20C1.009之三個輕鏈CDR (SEQ ID NO: 355-357)、抗體20C1.009之三個重鏈CDR (SEQ ID NO: 352-354)，及包含含有SEFL2-2突變及V131電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 490及491或SEQ ID NO: 492及493)，其中IL-21突變蛋白單體附接於含有E357K及D399K V1電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 493之重鏈)，且其中該IL-21突

變蛋白包含胺基酸取代R9E及R76E (亦即包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 358之重鏈可變區及SEQ ID NO: 359之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 360之重鏈或SEQ ID NO: 361之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 361及573之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 573之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 576之胺基酸序列)的單體。

【0217】 在例示性情況下，融合蛋白包含如圖4A中所示之同源二聚體，其中抗PD-1抗體包含抗體22D4.017之三個輕鏈CDR (SEQ ID NO: 385-387)、抗體22D4.017之三個重鏈CDR (SEQ ID NO: 382-384)，且各重鏈包含含有SEFL2-2突變之恆定區序列(例如SEQ ID NO: 265或266)，其中兩種IL-21突變蛋白中之每一者包含胺基酸取代R9E及R76A (亦即，各包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 388之重鏈可變區及SEQ ID NO: 389之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 390之重鏈或SEQ ID NO: 391之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 389及496或SEQ ID NO: 389及519之胺基酸序列的同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 496之胺基酸序列)的同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條

抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 519之胺基酸序列)的同源二聚體。

【0218】 在例示性情況下，融合蛋白包含如圖4A中所示之同源二聚體，其中抗PD-1抗體包含抗體22D4.017之三個輕鏈CDR (SEQ ID NO: 385-387)、抗體22D4.017之三個重鏈CDR (SEQ ID NO: 382-384)，且各重鏈包含含有SEFL2-2突變之恆定區序列(例如SEQ ID NO: 265或266)，其中兩種IL-21突變蛋白中之每一者包含胺基酸取代R9E及R76E (亦即，各包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 388之重鏈可變區及SEQ ID NO: 389之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 390之重鏈或SEQ ID NO: 391之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 389及497或SEQ ID NO: 389及498之胺基酸序列的同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且融合重鏈-IL-21突變蛋白包含SEQ ID NO: 497之胺基酸序列)的同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 498之胺基酸序列)的同源二聚體。

【0219】 在例示性情況下，融合蛋白包含如圖4B中所示之同源二聚體，其中抗PD-1抗體包含抗體22D4.017之三個輕鏈CDR (SEQ ID NO: 385-387)、抗體22D4.017之三個重鏈CDR (SEQ ID NO: 382-384)，且各重鏈包含含有SEFL2-2突變及連接子之恆定區序列(例如SEQ ID NO: 267)，其中兩種IL-21突變蛋白中之每一者包含胺基酸取代R9E及R76A

(亦即，各包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 388之重鏈可變區及SEQ ID NO: 389之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 390之重鏈或SEQ ID NO: 391之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 389及499之胺基酸序列之同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 499之胺基酸序列)的同源二聚體。

【0220】 在例示性情況下，融合蛋白包含如圖4B中所示之同源二聚體，其中抗PD-1抗體包含抗體22D4.017之三個輕鏈CDR (SEQ ID NO: 385-387)、抗體22D4.017之三個重鏈CDR (SEQ ID NO: 382-384)，且各重鏈包含含有SEFL2-2突變及連接子之恆定區序列(例如SEQ ID NO: 267)，其中兩種IL-21突變蛋白中之每一者包含胺基酸取代R9E及R76E (亦即，各包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 388之重鏈可變區及SEQ ID NO: 389之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 390之重鏈或SEQ ID NO: 391之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 389及500之胺基酸序列之同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 500之胺基酸序列)的同源二聚體。

【0221】 在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體22D4.017之三個輕鏈CDR (SEQ

ID NO: 385-387)、抗體22D4.017之三個重鏈CDR (SEQ ID NO: 382-384)，及包含含有SEFL2-2突變及V1電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 306及307或SEQ ID NO: 308及309)，其中IL-21突變蛋白單體附接於含有E356K及D399K V1電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 309之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76A (亦即包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 388之重鏈可變區及SEQ ID NO: 389之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 390之重鏈或SEQ ID NO: 391之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 389及501之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 501之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 556之胺基酸序列)的單體。

【0222】 在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體22D4.017之三個輕鏈CDR (SEQ ID NO: 385-387)、抗體22D4.017之三個重鏈CDR (SEQ ID NO: 382-384)，及包含含有SEFL2-2突變及V103電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 484及485或SEQ ID NO: 486及487)，其中IL-21突變蛋白單體附接於含有E356K及D399K V103電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 487之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76A (亦即包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 388之重鏈可變區及

SEQ ID NO: 389之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 390之重鏈或SEQ ID NO: 391之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 389及502之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 502之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 557之胺基酸序列)的單體。

【0223】 在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體22D4.017之三個輕鏈CDR (SEQ ID NO: 385-387)、抗體22D4.017之三個重鏈CDR (SEQ ID NO: 382-384)，及包含含有SEFL2-2突變及V131電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 490及491或SEQ ID NO: 492及493)，其中IL-21突變蛋白單體附接於含有E357K及D399K V131電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 493之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76A (亦即包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 388之重鏈可變區及SEQ ID NO: 389之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 390之重鏈或SEQ ID NO: 391之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 389及503之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 503之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 558之胺基酸序列)的單體。

【0224】在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體22D4.017之三個輕鏈CDR (SEQ ID NO: 385-387)、抗體22D4.017之三個重鏈CDR (SEQ ID NO: 382-384)，及包含含有SEFL2-2突變及V1電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 306及307或SEQ ID NO: 308及309)，其中IL-21突變蛋白單體附接於含有E356K及D399K V1電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 309之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76E (亦即包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 388之重鏈可變區及SEQ ID NO: 389之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 390之重鏈或SEQ ID NO: 391之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 389及504之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 504之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 556之胺基酸序列)的單體。

【0225】在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體22D4.017之三個輕鏈CDR (SEQ ID NO: 385-387)、抗體22D4.017之三個重鏈CDR (SEQ ID NO: 382-384)，及包含含有SEFL2-2突變及V103電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 484及485或SEQ ID NO: 486及487)，其中IL-21突變蛋白單體附接於含有E356K及D399K V103電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 487之重鏈)，且其中該IL-21

突變蛋白包含胺基酸取代R9E及R76E (亦即包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 388之重鏈可變區及SEQ ID NO: 389之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 390之重鏈或SEQ ID NO: 391之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 389及505之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 505之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 557之胺基酸序列)的單體。

【0226】 在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體22D4.017之三個輕鏈CDR (SEQ ID NO: 385-387)、抗體22D4.017之三個重鏈CDR (SEQ ID NO: 382-384)，及包含含有SEFL2-2突變及V131電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 490及491或SEQ ID NO: 492及493)，其中IL-21突變蛋白單體附接於含有E357K及D399K V131電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 493中之任一者之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76E (亦即包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 388之重鏈可變區及SEQ ID NO: 389之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 390之重鏈或SEQ ID NO: 391之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 389及506之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ

ID NO: 506之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 558之胺基酸序列)的單體。

【0227】 在例示性情況下，融合蛋白包含如圖4A中所示之同源二聚體，其中抗PD-1抗體包含抗體20A2.003之三個輕鏈CDR (SEQ ID NO: 365-367)、抗體20A2.003之三個重鏈CDR (SEQ ID NO: 362-364)，且各重鏈包含含有SEFL2-2突變之恆定區序列(例如SEQ ID NO: 265或266)，其中兩種IL-21突變蛋白中之每一者包含胺基酸取代R9E及R76A (亦即，各包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 368之重鏈可變區及SEQ ID NO: 369之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 370之重鏈或SEQ ID NO: 371之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 369及507或SEQ ID NO: 369及508之胺基酸序列的同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 507之胺基酸序列)的同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 508之胺基酸序列)的同源二聚體。

【0228】 在例示性情況下，融合蛋白包含如圖4A中所示之同源二聚體，其中抗PD-1抗體包含抗體20A2.003之三個輕鏈CDR (SEQ ID NO: 365-367)、抗體20A2.003之三個重鏈CDR (SEQ ID NO: 362-364)，且各重鏈包含含有SEFL2-2突變之恆定區序列(例如SEQ ID NO: 265或266)，其中兩種IL-21突變蛋白中之每一者包含胺基酸取代R9E及R76E (亦即，

各包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 368之重鏈可變區及SEQ ID NO: 369之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 370之重鏈或SEQ ID NO: 371之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 369及509或SEQ ID NO: 369及510之胺基酸序列的同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 509之胺基酸序列)的同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 510之胺基酸序列)的同源二聚體。

【0229】 在例示性情況下，融合蛋白包含如圖4B中所示之同源二聚體，其中抗PD-1抗體包含抗體20A2.003之三個輕鏈CDR (SEQ ID NO: 365-367)、抗體20A2.003之三個重鏈CDR (SEQ ID NO: 362-364)，且各重鏈包含含有SEFL2-2突變及連接子之恆定區序列(例如SEQ ID NO: 267)，其中兩種IL-21突變蛋白中之每一者包含胺基酸取代R9E及R76A(亦即，各包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 368之重鏈可變區及SEQ ID NO: 369之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 370之重鏈或SEQ ID NO: 371之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 369及511之胺基酸序列之同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 511之胺

基酸序列)的同源二聚體。

【0230】 在例示性情況下，融合蛋白包含如圖4B中所示之同源二聚體，其中抗PD-1抗體包含抗體20A2.003之三個輕鏈CDR (SEQ ID NO: 365-367)、抗體20A2.003之三個重鏈CDR (SEQ ID NO: 362-364)，且各重鏈包含含有SEFL2-2突變及連接子之恆定區序列(例如SEQ ID NO: 267)，其中兩種IL-21突變蛋白中之每一者包含胺基酸取代R9E及R76E (亦即，各包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 368之重鏈可變區及SEQ ID NO: 369之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 370之重鏈或SEQ ID NO: 371之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 369及512之胺基酸序列之同源二聚體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 512之胺基酸序列)的同源二聚體。

【0231】 在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20A2.003之三個輕鏈CDR (SEQ ID NO: 365-367)、抗體20A2.003之三個重鏈CDR (SEQ ID NO: 362-364)，及包含含有SEFL2-2突變及V1電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 306及307或SEQ ID NO: 308及309)，其中IL-21突變蛋白單體附接於含有E356K及D399K V1電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 309中之任一者之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76A (亦即包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 368之重鏈可變區

及SEQ ID NO: 369之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 370之重鏈或SEQ ID NO: 371之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 369及513之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 513之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 559之胺基酸序列)的單體。

【0232】 在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20A2.003之三個輕鏈CDR (SEQ ID NO: 365-367)、抗體20A2.003之三個重鏈CDR (SEQ ID NO: 362-364)，及包含含有SEFL2-2突變及V103電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 484及485或SEQ ID NO: 486及487)，其中IL-21突變蛋白單體附接於含有E356K及D399K V103電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 487之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76A (亦即包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 368之重鏈可變區及SEQ ID NO: 369之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 370之重鏈或SEQ ID NO: 371之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 369及514之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 514之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 560之胺基酸序列)的單體。

【0233】在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20A2.003之三個輕鏈CDR (SEQ ID NO: 365-367)、抗體20A2.003之三個重鏈CDR (SEQ ID NO: 362-364)，及包含含有SEFL2-2突變及V131電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 490及491或SEQ ID NO: 492及493)，其中IL-21突變蛋白單體附接於含有E357K及D399K V131電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 493之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76A (亦即包含SEQ ID NO: 244之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 368之重鏈可變區及SEQ ID NO: 369之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 370之重鏈或SEQ ID NO: 371之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 369及515之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 515之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 561之胺基酸序列)的單體。

【0234】在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20A2.003之三個輕鏈CDR (SEQ ID NO: 365-367)、抗體20A2.003之三個重鏈CDR (SEQ ID NO: 362-364)，及包含含有SEFL2-2突變及V1電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 306及307或SEQ ID NO: 308及309)，其中IL-21突變蛋白單體附接於含有E356K及D399K V1電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 309之重鏈)，且其中該IL-21突變

蛋白包含胺基酸取代R9E及R76E (亦即包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 368之重鏈可變區及SEQ ID NO: 369之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 370之重鏈或SEQ ID NO: 371之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 369及516之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 516之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 559之胺基酸序列)的單體。

【0235】 在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20A2.003之三個輕鏈CDR (SEQ ID NO: 365-367)、抗體20A2.003之三個重鏈CDR (SEQ ID NO: 362-364)，及包含含有SEFL2-2突變及V103電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 484及485或SEQ ID NO: 486及487)，其中IL-21突變蛋白單體附接於含有E356K及D399K V103電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 487之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76E (亦即包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 368之重鏈可變區及SEQ ID NO: 369之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 370之重鏈或SEQ ID NO: 371之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 369及517之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO:

517之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 560之胺基酸序列)的單體。

【0236】 在例示性情況下，融合蛋白包含如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20A2.003之三個輕鏈CDR (SEQ ID NO: 365-367)、抗體20A2.003之三個重鏈CDR (SEQ ID NO: 362-364)，及包含含有SEFL2-2突變及V131電荷對突變之恆定區序列的一對重鏈(例如SEQ ID NO: 490及491或SEQ ID NO: 492及493)，其中IL-21突變蛋白單體附接於含有E357K及D399K V1電荷對突變之重鏈(例如IL-21突變蛋白單體附接於包含SEQ ID NO: 493之重鏈)，且其中該IL-21突變蛋白包含胺基酸取代R9E及R76E (亦即包含SEQ ID NO: 245之序列)。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 368之重鏈可變區及SEQ ID NO: 369之輕鏈可變區。在例示性情況下，抗PD-1抗體包含SEQ ID NO: 370之重鏈或SEQ ID NO: 371之輕鏈。在例示性情況下，融合蛋白包含含有SEQ ID NO: 369及518之胺基酸序列之單體。在例示性態樣中，融合蛋白包含含有兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 518之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 561之胺基酸序列)的單體。

【0237】 在例示性情況下，融合蛋白包含如圖4A或4B中所示之IL-21突變蛋白同源二聚體或如圖4C中所示之IL-21突變蛋白單體，及抗PD-1抗體，該抗PD-1抗體包含抗體20A2.003之三個輕鏈CDR (SEQ ID NO: 365-367)、抗體20A2.003之三個重鏈CDR (SEQ ID NO: 362-364)，及包含SEQ ID NO 544-555中之任一者之重鏈恆定區序列。在例示性情況下，

融合蛋白包含如圖4A或4B中所示之IL-21突變蛋白同源二聚體或如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20A2.003之三個輕鏈CDR (SEQ ID NO: 365-367)、抗體20A2.003之三個重鏈CDR (SEQ ID NO: 362-364)，及包含SEQ ID NO: 525或527之重鏈恆定區序列。

【0238】 在例示性情況下，融合蛋白包含如圖4A或4B中所示之IL-21突變蛋白同源二聚體或如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體22D4.017之三個輕鏈CDR (SEQ ID NO: 385-387)、抗體22D4.017之三個重鏈CDR (SEQ ID NO: 382-384)，及包含SEQ ID NO: 544-555中之任一者之重鏈恆定區序列。在例示性情況下，融合蛋白包含如圖4A或4B中所示之IL-21突變蛋白同源二聚體或如圖4中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體22D4.017之三個輕鏈CDR (SEQ ID NO: 385-387)、抗體22D4.017之三個重鏈CDR (SEQ ID NO: 382-384)，及包含SEQ ID NO 529或531之重鏈恆定區序列。

【0239】 在例示性情況下，融合蛋白包含如圖4A或4B中所示之IL-21突變蛋白同源二聚體或如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20C1.009之三個輕鏈CDR (SEQ ID NO: 355-357)、抗體20C1.009之三個重鏈CDR (SEQ ID NO: 352-354)，及包含SEQ ID NO: 544-555中之任一者之重鏈恆定區序列。在例示性情況下，融合蛋白包含如圖4A或4B中所示之IL-21突變蛋白同源二聚體或如圖4C中所示之IL-21突變蛋白單體，其中抗PD-1抗體包含抗體20C1.009之三個輕鏈CDR (SEQ ID NO: 355-357)、抗體20C1.009之三個重鏈CDR (SEQ ID NO: 352-354)，及包含SEQ ID NO: 521或523之重鏈恆定區序列。

抗原結合蛋白

【0240】本發明提供PD-1抗原結合蛋白。在例示性態樣中，PD-1抗原結合蛋白為本文所述之抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物。在例示性情況下，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含：(a)表D中闡述之重鏈(HC)互補決定區(CDR) 1胺基酸序列，或選自由SEQ ID NO: 312、322、332、342、352、362、372及382組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(b)表D中闡述之HC CDR2胺基酸序列，或選自由SEQ ID NO: 313、323、333、343、353、363、373及383組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(c)表D中闡述之HC CDR3胺基酸序列，或選自由SEQ ID NO: 314、324、334、344、3545、364、374及384組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(d)表D中闡述之輕鏈(LC) CDR1胺基酸序列，或選自由315、325、335、345、355、365、375及385組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(e)表D中闡述之LC CDR2胺基酸序列，或選自由316、326、336、346、356、366、376及386組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(f)表D中闡述之LC CDR3胺基酸序列，或選自由317、327、337、347、357、367、377及387組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；或(g) (a)-(f)中之任兩者或更多者之組合。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含表D中闡述之LC CDR1胺基酸序列、LC CDR2胺基酸序列及LC CDR3胺

基酸序列，及表D中闡述之HC CDR胺基酸序列中之至少1個或2個。在例示性實施例中，抗原結合蛋白包含由表D之單行中之SEQ ID NO:表示的胺基酸序列中之至少3個、4個或5個。

【0241】 在例示性實施例中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含選自由以下組成之群的六個CDR胺基酸序列：(a) SEQ ID NO: 312-317；(b) SEQ ID NO: 322-327；(c) SEQ ID NO: 332-337；(d) SEQ ID NO: 342-347；(e) SEQ ID NO: 352-357；(f) SEQ ID NO: 362-367；(g) SEQ ID NO: 372-377；以及(h) SEQ ID NO: 382-387。在例示性情況下，表D之胺基酸序列由至少一個或更多個(例如至少2個、3個、4個、5個、6個、7個、8個、9個、10個或更多個)插入胺基酸分開。在例示性實施例中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含(a)表E中闡述之重鏈可變區胺基酸序列，或選自由318、328、338、348、358、368、378及388組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；或(b)圖E中闡述之輕鏈可變區胺基酸序列，或選自由319、329、339、349、359、369、379及389組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；或(c) (a)與(b)。在例示性實施例中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物包含一對選自由以下組成之群的胺基酸序列：(a) SEQ ID NO: 318及319；(b) SEQ ID NO: 328及329；(c) SEQ ID NO: 338及339；(d) SEQ ID NO: 348及349；(e) SEQ ID NO: 358及359；(f) SEQ ID NO: 368及369；(g) SEQ ID NO: 378及379；以及(h) SEQ ID NO: 388及389。在例示性態樣中，抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物

包含：(I)一對選自由以下組成之群的胺基酸序列：(a) SEQ ID NO: 318及319；(b) SEQ ID NO: 328及329；(c) SEQ ID NO: 338及339；(d) SEQ ID NO: 348及349；(e) SEQ ID NO: 358及359；(f) SEQ ID NO: 368及369；(g) SEQ ID NO: 378及379；以及(h) SEQ ID NO: 388及389；及(II)包含SEQ ID NO: 265-267、282、284-311、472-495及544-555中之任一者之恆定區。在例示性實施例中，抗原結合蛋白包含一對選自由以下組成之群的胺基酸序列：(a) SEQ ID NO: 320及321；(b) SEQ ID NO: 330及331；(c) SEQ ID NO: 340及341；(d) SEQ ID NO: 350及351；(e) SEQ ID NO: 360及361；(f) SEQ ID NO: 370及371；(g) SEQ ID NO: 380及381；以及(h) SEQ ID NO: 390及391。在例示性實施例中，抗原結合蛋白包含與以上SEQ ID NO:中之一或多者具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。

【0242】 在一些實施例中，上述抗原結合蛋白為抗PD-1抗體或其抗原結合抗體片段。

【0243】 本發明另外提供包含本文所述之PD-1抗原結合蛋白及異源部分的結合物。異源部分可為與本文所述之PD-1抗原結合蛋白不同的任何分子。在例示性態樣中，異源部分為異源肽或多肽、靶向劑、診斷標記、聚合物、核酸、量子點、小分子、毒素、碳水化合物、胺基酸或其他治療劑或診斷劑。在例示性態樣中，異源部分為如本文所述之IL-21突變蛋白。

【0244】 本發明另外提供包含本文所述之PD-1抗原結合蛋白及異源

多肽或肽的融合蛋白。在例示性態樣中，異源多肽為如本文所述之IL-21突變蛋白。

抗體製備方法

【0245】 製備抗體、抗原結合抗體片段及抗體蛋白質產物之合適方法為此項技術中已知。舉例而言，用於產生抗體之標準雜交瘤方法描述於例如Harlow及Lane (編輯), Antibodies: A Laboratory Manual, CSH Press (1988), 及CA. Janeway等人(編輯), Immunobiology, 第5版, Garland Publishing, New York, NY (2001))中。一種製備本發明之抗PD-1單株抗體的例示性方法提供於本文實例中。

【0246】 視宿主物種而定，多種佐劑可用於增加免疫反應，使宿主產生更大量抗體。此類佐劑包括(但不限於)弗氏佐劑(Freund's)、礦物凝膠(諸如氫氧化鋁)及表面活性物質(諸如溶血卵磷脂)、普朗尼克多元醇(pluronic polyol)、聚陰離子、肽、油乳液、匙孔血藍蛋白及二硝基酚。BCG (卡介苗)及短小棒狀桿菌(Corynebacterium parvum)為可能適用之人類佐劑。

【0247】 其他產生抗體之方法概述於表F中。

表F

技術	例示性參考文獻
EBV-雜交瘤方法及噬菌體載體表現系統	Haskard 及 Archer, J. Immunol. Methods, 74(2), 361-67 (1984)，Roder 等人, Methods Enzymol., 121, 140-67 (1986)，及 Huse 等人, Science, 246, 1275-81 (1989))
非人類動物中產生抗體之方法	美國專利 5,545,806、5,569,825 及 5,714,352，以及美國專利申請公開案第 2002/0197266 號
誘導淋巴細胞群體中活體內產生，或藉由篩選重組免疫球蛋白文庫或高度特異性結合試劑之小組	Orlandi 等人(Proc Natl Acad Sci 86: 3833-3837; 1989)，以及 Winter G 及 Milstein C (Nature 349: 293-299, 1991)

產生重組蛋白之方法	Protein production and purification」 Nat Methods 5(2): 135-146 (2008)
噬菌體呈現	Janeway 等人, 上述，Huse 等人, 上述，及美國專利 6,265,150)。相關方法亦描述於美國專利第 5,403,484 號；美國專利第 5,571,698 號；美國專利第 5,837,500 號；美國專利第 5,702,892 號。以下中描述之技術：美國專利第 5,780,279 號；美國專利第 5,821,047 號；美國專利第 5,824,520 號；美國專利第 5,855,885 號；美國專利第 5,858,657 號；美國專利第 5,871,907 號；美國專利第 5,969,108 號；美國專利第 6,057,098 號；以及美國專利第 6,225,447 號
抗體可藉由轉殖基因小鼠產生	美國專利第 5,545,806 號及第 5,569,825 號，及 Janeway 等人,上述。

【0248】 測試抗體結合於PD-1之能力而不管抗體如何產生的方法為此項技術中已知且包括任何抗體-抗原結合分析，諸如放射免疫分析(RIA)、ELISA、西方墨點法、免疫沈澱法、SPR及競爭性抑制分析(參見例如Janeway等人, 下文，及美國專利申請公開案第2002/0197266號，及以上關於競爭分析之章節)。測試抗體與第二抗體競爭結合於抗原或其抗原決定基之能力的其他結合分析，例如競爭性結合分析或競爭分析，其為此項技術中已知且可用於測試抗體結合於PD-1之能力。參見例如美國專利申請公開案第US20140178905號；Chand等人, Biologicals 46: 168-171 (2017)；Liu等人, Anal Biochem 525: 89-91 (2017)；及Goolia等人, J Vet Diagn Invest 29(2): 250-253 (2017)。比較兩種抗體之其他方法亦為此項技術中已知，且包括例如表面電漿子共振(SPR)。SPR可用於測定抗體及第二抗體之結合常數且可比較兩個結合常數。

異源部分：聚合物、碳水化合物、脂質及治療劑

【0249】 在例示性實施例中，本發明之結合物包含連接於聚合物之IL-21突變蛋白。在一些實施例中，聚合物係選自由以下組成之群：聚醯

胺、聚碳酸酯、聚伸烷基及其衍生物，包括聚烷二醇、聚氧化烯、聚對苯二甲酸伸烷酯、丙烯酸酯與甲基丙烯酸酯之聚合物，包括聚(甲基丙烯酸甲酯)、聚(甲基丙烯酸乙酯)、聚(甲基丙烯酸丁酯)、聚(甲基丙烯酸異丁酯)、聚(甲基丙烯酸己酯)、聚(甲基丙烯酸異癸酯)、聚(甲基丙烯酸月桂酯)、聚(甲基丙烯酸苯酯)、聚(丙烯酸甲酯)、聚(丙烯酸異丙酯)、聚(丙烯酸酸異丁酯)及聚(丙烯酸十八烷酯)；聚乙烯聚合物，包括聚乙烯醇、聚乙烯醚、聚乙烯酯、聚鹵乙烯、聚(乙酸乙烯酯)及聚乙烯吡咯啶酮；聚乙交酯、聚矽氧烷、聚胺酯及其共聚物；纖維素，包括烷基纖維素、羥烷基纖維素、纖維素醚、纖維素酯、硝基纖維素、甲基纖維素、乙基纖維素、羥丙基纖維素、羥丙基甲基纖維素、羥丁基甲基纖維素、乙酸纖維素、丙酸纖維素、乙酸丁酸纖維素、鄰苯二甲酸乙酸纖維素、羧乙基纖維素、三乙酸纖維素及纖維素硫酸鈉鹽；聚丙烯、聚乙烯，包括聚(乙二醇)、聚(氧化乙烯)及聚(對苯二甲酸伸乙酯)及聚苯乙烯。在特定實施例中，聚合物為聚烷二醇，包括例如聚乙二醇(polyethylene glycol，PEG)。

【0250】 在例示性實施例中，本發明之結合物包含連接於碳水化合物之IL-21突變蛋白。在一些實施例中，碳水化合物為單醣(例如葡萄糖、半乳糖、果糖)、二醣(例如蔗糖、乳糖、麥芽糖)、寡醣(例如棉子糖、水蘇糖)或多醣(例如澱粉、澱粉酶、支鏈澱粉、纖維素、幾丁質、胼胝質、昆布多醣、木聚糖、甘露聚糖、褐藻聚醣或半乳甘露聚糖)。

【0251】 在一些實施例中，異源部分為脂質。在一些實施例中，脂質為脂肪酸、類二十烷酸、前列腺素、白細胞三烯、凝血脂素、N-醯基乙醇胺)、甘油脂(例如單取代、二取代、三取代丙三醇)、甘油磷脂(例如磷脂醯膽鹼、磷脂醯肌醇、磷脂醯乙醇胺、磷脂醯絲胺酸)、神經鞘脂(例如

神經鞘胺醇、神經醯胺)、固醇脂質(例如類固醇、膽固醇)、異戊烯醇脂質、醣脂質或聚酮化合物、油、蠟、膽固醇、固醇、脂溶性維生素、單酸甘油酯、二酸甘油酯、三酸甘油酯、磷脂。

【0252】在例示性實施例中，本發明之結合物包含連接於治療劑之IL-21突變蛋白。治療劑可為此項技術中已知之彼等治療劑中之任一者。在例示性態樣中，治療劑為免疫治療劑，只要該治療劑刺激免疫反應即可。在例示性態樣中，免疫治療劑為癌症疫苗。在例示性態樣中，免疫治療劑為單株抗體。在例示性態樣中，免疫治療劑為免疫檢查點抑制劑，例如CTLA4、PD-1、PD-L1之抑制劑。在例示性情況下，單株抗體對免疫檢查點路徑中之蛋白質具有特異性。免疫檢查點路徑之蛋白質可為例如CTLA4、PD-1、PD-L1、B7-H3、B7H4或TIM3。舉例而言，本發明之抗原結合蛋白可結合於阿特珠單抗(atezolizumab)、阿利庫單抗(avelumab)、伊匹單抗、曲美利單抗(tremelimumab)、BMS-936558、MK3475、CT-011、AM-224、MDX-1105、IMP321、MGA271。

【0253】在例示性態樣中，治療劑為有效抑制腫瘤轉移及/或對至少一種細胞群體具有抗增生作用的細胞介素、淋巴激素、生長因子或造血因子。此類細胞介素、淋巴激素、生長因子或其他造血因子包括(但不限於)：M-CSF、GM-CSF、TNF、IL-1、IL-2、IL-3、IL-4、IL-5、IL-6、IL-7、IL-8、IL-9、IL-10、IL-11、IL-12、IL-13、IL-14、IL-15、IL-16、IL-17、IL-18、IFN、TNFα、TNF1、TNF2、G-CSF、Meg-CSF、GM-CSF、血小板生成素、幹細胞因子及促紅細胞生成素。其他用於本文中之生長因子包括血管生成素、骨形態形成性蛋白質-1、骨形態形成性蛋白質-2、骨形態形成性蛋白質-3、骨形態形成性蛋白質-4、骨形態形成性

蛋白質-5、骨形態形成性蛋白質-6、骨形態形成性蛋白質-7、骨形態形成性蛋白質-8、骨形態形成性蛋白質-9、骨形態形成性蛋白質-10、骨形態形成性蛋白質-11、骨形態形成性蛋白質-12、骨形態形成性蛋白質-13、骨形態形成性蛋白質-14、骨形態形成性蛋白質-15、骨形態形成性蛋白質受體IA、骨形態形成性蛋白質受體IB、腦源性神經營養因子、睫狀神經生長因子、睫狀神經生長因子受體α、細胞介素誘導之嗜中性白血球趨化因子1、細胞介素誘導之嗜中性白血球、趨化因子2α、細胞介素誘導之嗜中性白血球趨化因子2β、β內皮細胞生長因子、內皮素1、上皮源性嗜中性白血球引誘劑、膠質細胞株衍生之神經營養因子受體α1、膠質細胞株衍生之神經營養因子受體α2、生長相關蛋白質、生長相關蛋白質α、生長相關蛋白質β、生長相關蛋白質γ、肝素結合表皮生長因子、肝細胞生長因子、肝細胞生長因子受體、胰島素樣生長因子I、胰島素樣生長因子受體、胰島素樣生長因子II、胰島素樣生長因子結合蛋白、角化細胞生長因子、白血病抑制因子、白血病抑制因子受體α、神經生長因子神經生長因子受體、神經營養素-3、神經營養素-4、前B細胞生長刺激因子、幹細胞因子、幹細胞因子受體、轉型生長因子α、轉型生長因子β、轉型生長因子β1、轉型生長因子β1.2、轉型生長因子β2、轉型生長因子β3、轉型生長因子β5、潛在轉型生長因子β1、轉型生長因子β結合蛋白I、轉型生長因子β結合蛋白II、轉型生長因子β結合蛋白III、I型腫瘤壞死因子受體、II型腫瘤壞死因子受體、尿激酶型纖維蛋白溶酶原活化物受體及嵌合蛋白質及其生物或免疫活性片段。在例示性實施例中，治療劑包含對上述細胞介素、淋巴激素、生長因子或其他造血因子中之任一者具有特異性的抗體。

核酸

【0254】本發明進一步提供包含編碼本發明之IL-21突變蛋白、包含IL-21突變蛋白之結合物或包含IL-21突變蛋白之融合蛋白之核苷酸序列的核酸。舉例而言，核酸可包含編碼抗PD-1抗體之重鏈之核苷酸序列，後面為編碼本發明之IL-21突變蛋白之核苷酸序列。編碼重鏈之核苷酸序列及編碼IL-21突變蛋白之核苷酸序列可側接編碼包含GGGGS之胺基酸序列(SEQ ID NO: 262)之肽連接子的核苷酸序列。在替代態樣中，核酸不包含編碼肽連接子之核苷酸序列，且編碼抗PD-1抗體之重鏈的核苷酸序列與編碼本發明之IL-21突變蛋白的核苷酸序列串聯。

【0255】在例示性態樣中，核酸包含編碼IL-21突變蛋白之核苷酸序列，該IL-21突變蛋白包含SEQ ID NO: 3-21、23-56、58-112、114-208、210-222、224-255及283之胺基酸序列或與SEQ ID NO: 3-21、23-56、58-112、114-208、210-222、224-255及283之胺基酸序列具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。

【0256】在例示性態樣中，核酸包含編碼SEQ ID NO: 262或與SEQ ID NO: 262具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列之肽連接子之核苷酸序列。

【0257】在例示性態樣中，核酸包含編碼融合蛋白之核苷酸序列，該融合蛋白包含與本文所述之任何IL-21突變蛋白之胺基酸序列融合的本文所述之抗體恆定區之胺基酸序列。在例示性情況下，核酸包含編碼融合

蛋白之核苷酸序列，該融合蛋白包含與SEQ ID NO: 3-21、23-56、58-112、114-208、210-222、224-255及283中之任一者或與SEQ ID NO: 3-21、23-56、58-112、114-208、210-222、224-255及283具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列融合的SEQ ID NO: 265-267及282中之任一者之胺基酸序列或與SEQ ID NO: 265-267及282中之任一者具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。在例示性態樣中，核酸包含編碼融合蛋白之核苷酸序列，該融合蛋白包含SEQ ID NO: 268-281中之任一者的胺基酸序列或與SEQ ID NO: 268-281具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。

【0258】 在例示性態樣中，核酸包含編碼抗PD-1抗體之核苷酸序列，該抗PD-1抗體包含SEQ ID NO: 265-267、282、284-311、472-495及544-555中之任一者的重鏈恆定區胺基酸序列或與SEQ ID NO: 265-267、282、284-311、472-495及544-555中之任一者具有至少約50%、至少約60%、至少約70%、至少約80%、至少約85%、至少約90%或具有超過約90% (例如約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%)序列一致性的胺基酸序列。

【0259】本發明進一步提供包含編碼本發明之PD-1抗原結合蛋白之核苷酸序列的核酸。在例示性態樣中，核苷酸序列包含編碼重鏈CDR或輕鏈CDR、重鏈可變區或輕鏈可變區或者重鏈序列或輕鏈序列之序列。參見下表G。在例示性情況下，核苷酸序列包含SEQ ID NO: 392-471中之任一者。本發明進一步提供包含以下之成對核苷酸序列：(a) SEQ ID NO: 398及399；(b) SEQ ID NO: 408及409；(c) SEQ ID NO: 418及419；(d) SEQ ID NO: 428及429；(e) SEQ ID NO: 438及439；(f) SEQ ID NO: 448及449；(g) SEQ ID NO: 458及459，或(h) SEQ ID NO: 468及469。本發明另外提供包含以下之成對核苷酸序列：(a) SEQ ID NO: 400及401；(b) SEQ ID NO: 410及411；(c) SEQ ID NO: 420及421；(d) SEQ ID NO: 430及431；(e) SEQ ID NO: 440及441；(f) SEQ ID NO: 450及451；(g) SEQ ID NO: 460及461；或(h) SEQ ID NO: 470及471。

表G

	20A2	**20C1**	**22D4**	**20C1.006**	**20C1.009**	**20A2.003**	**22D4.006**	**22D4.017**
HC CDR1	392	402	412	422	432	442	452	462
HC CDR2	393	403	413	423	433	443	453	463
HC CDR3	394	404	414	424	434	444	454	464
LC CDR1	395	405	415	425	435	445	455	465
LC CDR2	396	406	416	426	436	446	456	466
LC CDR3	397	407	417	427	437	447	457	467
HC可變	398	408	418	428	438	448	458	468
LC可變	399	409	419	429	439	449	459	469
HC全長	400	410	420	430	440	450	460	470
LC全長	401	411	421	431	441	451	461	471

【0260】在例示性態樣中，核酸分子包含編碼本發明之結合物或融合蛋白之核苷酸序列。如本文所用之「核酸」包括「多核苷酸」、「寡核苷酸」及「核酸分子」，且一般意謂DNA或RNA之聚合物或其修飾形式，其可為單鏈或雙鏈、合成或自天然來源獲得(例如分離及/或純化)，其可含有天然產、非天然或改變之核苷酸，且其可含有天然、非天然或改變

之核苷酸間鍵，諸如胺基磷酸酯鍵或硫代磷酸酯鍵，代替在未修飾之寡核苷酸之核苷酸之間發現的磷酸二酯。核酸可包含編碼本發明抗原結合蛋白或多肽中之任一者的任何核苷酸序列。在一些實施例中，核酸不包含任何插入、缺失、倒轉及/或取代。在其他實施例中，核酸包含一或多個插入、缺失、倒位及/或取代。

【0261】 在一些態樣中，本發明之核酸為重組的。如本文所用，術語「重組」係指(i)在活細胞外，藉由將天然或合成核酸區段與可在活細胞中複製之核酸分子接合而構築的分子；或(ii)由以上(i)中所述之分子複製產生的分子。出於本文中之目的，複製可為活體外複製或活體內複製。

【0262】 在一些態樣中，核酸基於化學合成及/或酶連接反應使用此項技術中已知之程序構築。參見例如Sambrook等人, 上述；及Ausubel等人, 上述。舉例而言，核酸可使用天然存在之核苷酸或經不同修飾之核苷酸化學合成，經不同修飾之核苷酸經設計以增加分子之生物穩定性或增加在雜交後形成之雙鏈體的物理穩定性(例如硫代磷酸酯衍生物及吖啶取代之核苷酸)。可用於產生核酸之經修飾之核苷酸的實例包括(但不限於) 5-氟尿嘧啶、5-溴尿嘧啶、5-氯尿嘧啶、5-碘尿嘧啶、次黃嘌呤、黃嘌呤、4-乙醯胞嘧啶、5-(羧基羥基甲基)尿嘧啶、5-羧基甲基胺基甲基-2-硫基尿苷、5-羧基甲基胺基甲基尿嘧啶、二氫尿嘧啶、β-D-半乳糖基辮苷、肌苷、N^6-異戊烯基腺嘌呤、1-甲基鳥嘌呤、1-甲基肌苷、2,2-二甲基鳥嘌呤、2-甲基腺嘌呤、2-甲基鳥嘌呤、3-甲基胞嘧啶、5-甲基胞嘧啶、N取代之腺嘌呤、7-甲基鳥嘌呤、5-甲基胺基甲基尿嘧啶、5-甲氧基胺基甲基-2-硫尿嘧啶、β-D-甘露糖基辮苷、5'-甲氧基羧基甲基尿嘧啶、5-甲氧基尿嘧啶、2-甲基硫基-N^6-異戊烯基腺嘌呤、尿嘧啶-5-氧基乙酸(v)、Y苷

(wybutoxosine)、假尿嘧啶、辮苷、2-硫胞嘧啶、5-甲基-2-硫尿嘧啶、2-硫尿嘧啶、4-硫尿嘧啶、5-甲基尿嘧啶、尿嘧啶-5-氧基乙酸甲酯、3- (3-胺基-3-N-2-羧基丙基)尿嘧啶及2,6-二胺基嘌呤。可替代地，一或多種本發明之核酸可自諸如Macromolecular Resources (Fort Collins, CO)及Synthegen (Houston, TX)之公司購買。

載體

【0263】 在一些態樣中，本發明之核酸併入載體中。關於此，本發明提供包含任一本發明之核酸的載體。在例示性態樣中，載體為重組表現載體。出於本文中之目的，術語「重組表現載體」意謂如下經基因修飾之寡核苷酸或多核苷酸構築體，當該構築體包含編碼mRNA、蛋白質、多肽或肽之核苷酸序列且載體與宿主細胞在足夠使該mRNA、蛋白質、多肽或肽在細胞內表現的條件下接觸時允許細胞表現mRNA、蛋白質、多肽或肽。本發明之載體總體上係非天然存在的。但是，載體之一部分可為天然存在的。本發明之載體可以可包含任一類核苷酸，包括(但不限於) DNA及RNA，其可為單鏈或雙鏈，合成或部分自天然來源獲得，且其可含有天然、非天然或改變之核苷酸。載體可包含天然存在或非天然存在之核苷酸間鍵或兩類鍵。在一些態樣中，改變之核苷酸或非天然存在之核苷酸間鍵不阻礙載體之轉錄或複製。

【0264】 本發明之載體可為任何合適載體，且可用於轉型或轉染任何合適宿主。合適載體包括經設計用於繁殖及擴增或用於表現或兩者的彼等載體，諸如質體及病毒。載體可選自由以下組成之群：pUC系列(Fermentas Life Sciences)、pBluescript系列(Stratagene, LaJoIIa, CA)、pET系列(Novagen, Madison, WI)、pGEX系列(Pharmacia Biotech,

Uppsala, Sweden)及pEX系列(Clontech, Palo Alto, CA)。亦可使用噬菌體載體，諸如λGTIO、λGTl 1、λZapII (Stratagene)、λEMBL4及λNMl149。植物表現載體之實例包括pBIOl、pBI101.2、pBI101.3、pBI121及pBIN19 (Clontech)。動物表現載體之實例包括pEUK-Cl、pMAM及pMAMneo (Clontech)。在一些態樣中，載體為病毒載體，例如逆轉錄病毒載體。

【0265】 本發明之載體可使用例如Sambrook等人, 上述及Ausubel等人, 上述中所述之標準重組DNA技術製備。呈圓形或線性之表現載體之構築體可經製備以含有在原核或真核宿主細胞中發揮功能之複製系統。複製系統可源自例如CoIEl、2μ質體、λ、SV40、牛乳頭狀瘤病毒及其類似物。

【0266】 在一些態樣中，載體包含調節序列，諸如轉錄及轉譯起始及終止密碼子，其對於載體將引入之宿主類型(例如細菌、真菌、植物或動物)為特定的，視情況而定，且考慮載體基於DNA還是基於RNA。

【0267】 載體可包括一或多種標記物基因，其允許選擇轉型或轉染之宿主。標記物基因包括殺生物劑抗性(例如針對抗生素、重金屬等抗性)、營養缺陷型宿主中提供原營養之補充及其類似物。適用於本發明之表現載體的標記物基因包括例如新黴素/G418抗性基因、潮黴素抗性基因(hygromycin resistance gene)、組胺醇抗性基因、四環素抗性基因及安比西林抗性基因(ampicillin resistance gene)。

【0268】 載體可包含可操作地連接於編碼多肽(包括其功能部分及功能變異體)之核苷酸序列或與編碼IL-21、結合物或融合蛋白之核苷酸序列互補或雜交之核苷酸序列的天然或標準啟動子。例如強、弱、誘導型、組

織特異性及發育特異性之啟動子的選擇在技術人員之常規技能範圍內。類似地，核苷酸序列與啟動子組合亦在技術人員之技能範圍內。啟動子可為非病毒啟動子或病毒啟動子，例如巨細胞病毒(CMV)啟動子、SV40啟動子、RSV啟動子及在鼠科幹細胞病毒之長末端重複序列中發現之啟動子。

宿主細胞

【0269】 本文提供包含本發明之核酸或載體之宿主細胞。如本文所用，術語「宿主細胞」係指可含有本發明之載體且能夠產生由核酸編碼之表現產物(例如mRNA、蛋白質)的任一類細胞。在一些態樣中宿主細胞為黏附細胞或懸浮細胞，亦即懸浮生長之細胞。在例示性態樣中，宿主細胞為培養細胞，或初級細胞，亦即直接自生物體，例如人類分離。宿主細胞可屬於任何細胞類型，可來源於任一類組織，且可處於任何發育階段。

【0270】 在例示性態樣中，細胞為真核細胞，包括(但不限於)酵母細胞、絲狀真菌細胞、原生動物細胞、藻類細胞、昆蟲細胞或哺乳動物細胞。此項技術中描述此類宿主細胞。參見例如Frenzel等人, Front Immunol 4: 217 (2013)。在例示性態樣中，真核細胞為哺乳動物細胞。在例示性態樣中，真核細胞為非人類哺乳動物細胞。在一些態樣中，細胞為中國卵巢(CHO)細胞及其衍生物(例如CHO-K1、CHO pro-3、CS9)、小鼠骨髓瘤細胞(例如NS0、GS-NS0、Sp2/0)、經工程改造而缺乏二氫葉酸還原酶(DHFR)活性之細胞(例如DUKX-X11、DG44)、人類胚腎293(HEK293)細胞或其衍生物(例如HEK293T、HEK293-EBNA)、非洲綠猴腎細胞(例如COS細胞、VERO細胞)、人類子宮頸癌細胞(例如HeLa)、人類骨骼骨肉瘤上皮細胞U2-OS、腺癌人類肺泡基底上皮細胞A549、人類纖維肉瘤細胞HT1080、小鼠腦腫瘤細胞CAD、胚胎癌瘤細胞P19、小鼠

胚胎纖維母細胞NIH 3T3、小鼠纖維母細胞L929、小鼠神經母細胞瘤細胞N2a、人類乳癌細胞MCF-7、視網膜母細胞瘤細胞Y79、人類視網膜母細胞瘤細胞SO-Rb50、人類肝癌細胞Hep G2、小鼠B骨髓瘤細胞J558L或幼倉鼠腎(BHK)細胞(Gaillet等人 2007；Khan, Adv Pharm Bull 3(2): 257-263 (2013))。在一個特定實施例中，宿主細胞為CS9 (CHO細胞株)。

【0271】 為擴增或複製載體，在一些態樣中宿主細胞為原核細胞，例如細菌細胞。

【0272】 本發明亦提供包含至少一種本文所述之宿主細胞的細胞群體。在一些態樣中，細胞群體為除至少一種不包含任一載體之其他細胞外亦包含含有所述載體之宿主細胞的異質性群體。可替代地，在一些態樣中，細胞群體為基本上均質群體，其中該群體主要包含含有載體之宿主細胞(例如基本上由其組成)。在一些態樣中，群體為純系細胞群體，其中該群體之所有細胞均為包含載體之單一宿主細胞之純系，使得該群體之所有細胞均包含載體。在本發明之例示性實施例中，細胞群體為包含含有如本文所述之載體之宿主細胞的純系群體。

醫藥組合物

【0273】 本文提供本發明之包含IL-21突變蛋白之組合物、包含IL-21突變蛋白之結合物、包含IL-21突變蛋白及多肽之融合蛋白、PD-1抗原結合蛋白(例如抗PD-1抗體)、包含PD-1抗原結合蛋白(例如抗PD-1抗體)之結合物、包含PD-1抗原結合蛋白(例如抗PD-1抗體)之融合蛋白、核酸、載體或宿主細胞或其組合。在一些態樣中，組合物包含呈分離及/或純化形式的本發明之IL-21突變蛋白、PD-1抗原結合蛋白(例如抗PD-1抗體)、結合物、融合蛋白、核酸、載體或宿主細胞或其組合。在一些態樣

中，組合物包含單一類型(例如結構)之本發明之IL-21突變蛋白、PD-1抗原結合蛋白(例如抗PD-1抗體)、結合物、融合蛋白、核酸、載體或宿主細胞，或包含兩種或更多種不同類型之本發明之IL-21突變蛋白、PD-1抗原結合蛋白、結合物、融合蛋白、核酸、載體或宿主細胞的組合。

【0274】 在例示性態樣中，組合物包含例如經由使例如IL-21突變蛋白或融合蛋白在某些溫度(例如室溫)下穩定，增加例如IL-21突變蛋白或融合蛋白之存放期，減少降解、例如氧化蛋白酶介導之降解，增加半衰期等而增強IL-21突變蛋白、PD-1抗原結合蛋白(例如抗PD-1抗體)、結合物、融合蛋白、核酸、載體或宿主細胞之化學物理特徵的劑。在一些態樣中，組合物包含本文揭示之任一劑作為異源部分或結合物部分，視情況與本發明之IL-21突變蛋白、結合物、融合蛋白、核酸、載體或宿主細胞混合。

【0275】 在本發明之例示性態樣中，組合物另外包含醫藥學上可接受之載劑、稀釋劑或賦形劑。在一些實施例中，如本發明揭示之IL-21突變蛋白、PD-1抗原結合蛋白(例如抗PD-1抗體)、結合物、融合蛋白、核酸、載體或宿主細胞(以下稱為「活性劑」)調配成包含該活性劑以及醫藥學上可接受之載劑、稀釋劑或賦形劑的醫藥組合物。關於此，本發明進一步提供包含活性劑(亦即本發明之IL-21突變蛋白、PD-1抗原結合蛋白(例如抗PD-1抗體)、結合物、融合蛋白、核酸、載體或宿主細胞中之任一者)的醫藥組合物，該醫藥組合物意欲投與個體，例如哺乳動物。

【0276】 在一些實施例中，活性劑以適合於投與患者之純度水準存在於醫藥組合物中。在一些實施例中，活性劑具有至少約90%、約91%、約92%、約93%、約94%、約95%、約96%、約97%、約98%或約99%之

純度水準，及醫藥學上可接受之稀釋劑、載劑或賦形劑。在一些實施例中，組合物含有約0.001至約30.0 mg/ml之濃度的活性劑。

【0277】 在例示性態樣中，醫藥組合物包含醫藥學上可接受之載劑。如本文所用，術語「醫藥學上可接受之載劑」包括任一標準醫藥載劑，諸如磷酸鹽緩衝生理食鹽水溶液、水、乳液(諸如油/水或水/油乳液)及各種類型潤濕劑。該術語亦涵蓋經美國聯邦政府之管理機構批准或在美國藥典中列出之用於包括人類之動物的任一劑。

【0278】 醫藥組合物可包含任何醫藥學上可接受之成分，包括例如酸化劑、添加劑、吸附劑、氣溶膠噴射劑、排氣劑、鹼化劑、防結塊劑、抗凝劑、抗微生物防腐劑、抗氧化劑、殺菌劑、基質、黏合劑、緩衝劑、螯合劑、包覆劑、著色劑、乾燥劑、清潔劑、稀釋劑、消毒劑、崩解劑、分散劑、溶解增強劑、染料、軟化劑、乳化劑、乳液穩定劑、填充劑、成膜劑、風味增強劑、調味劑、流動增強劑、膠凝劑、成粒劑、濕潤劑、潤滑劑、黏膜黏附劑、軟膏基質、軟膏、油質媒劑、有機鹼、軟錠劑基質、顏料、增塑劑、拋光劑、防腐劑、掩蔽劑、皮膚滲透劑、增溶劑、溶劑、穩定劑、栓劑基質、表面活性劑、界面活性劑、懸浮劑、甜味劑、治療劑、增稠劑、張力劑、毒性劑、增黏劑、吸水劑、水可混溶性共溶劑、軟水劑或潤濕劑。參見例如the Handbook of Pharmaceutical Excipients, 第三版, A. H. Kibbe (Pharmaceutical Press, London, UK, 2000)，其以引用之方式整體併入。Remington's Pharmaceutical Sciences, 第十六版, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980)，其以引用之方式整體併入。

【0279】 在例示性態樣中，醫藥組合物包含在所採用之劑量及濃度

下對接受者無毒的調配物質。在特定實施例中，醫藥組合物包含活性劑及一或多種醫藥學上可接受之鹽；多元醇；界面活性劑；滲透平衡劑；張力劑；抗氧化劑；抗生素；抗黴菌劑；增量劑；凍乾保護劑；消泡劑；螯合劑；防腐劑；著色劑；止痛劑；或其他藥劑。在例示性態樣中，視情況除包括(但不限於)醫藥學上可接受之鹽、滲透平衡劑(張力劑)、抗氧化劑、抗生素、抗黴菌劑、增量劑、凍乾保護劑、消泡劑、螯合劑、防腐劑、著色劑及止痛劑之一或多種賦形劑外，醫藥組合物亦包含一或多種多元醇及/或一或多種界面活性劑。

【0280】 在某些實施例中，醫藥組合物可含有用於改變、維持或保持例如組合物之pH值、滲透性、黏性、透明度、顏色、等滲性、氣味、無菌性、穩定性、分解或釋放速率、表面吸收或滲透的調配物質。在此類實施例中，合適調配物質包括(但不限於)胺基酸(諸如甘胺酸、麩醯胺酸、天冬醯胺、精胺酸或離胺酸)；抗微生物劑；抗氧化劑(諸如抗壞血酸、亞硫酸鈉或亞硫酸氫鈉)；緩衝劑(諸如硼酸鹽、碳酸氫鹽、Tris-HCl、檸檬酸鹽、磷酸鹽或其他有機酸)；增量劑(諸如甘露糖醇或甘胺酸)；螯合劑(諸如乙二胺四乙酸(EDTA))；複合劑(諸如咖啡因、聚乙烯吡咯啶酮、β-環糊精或羥丙基-β-環糊精)；填充劑；單醣；二醣；及其他碳水化合物(諸如葡萄糖、甘露糖或糊精)；蛋白質(諸如血清白蛋白、明膠或免疫球蛋白)；著色劑、調味劑及稀釋劑；乳化劑；親水性聚合物(諸如聚乙烯吡咯啶酮)；低分子量多肽；成鹽平衡離子(諸如鈉)；防腐劑(諸如殺藻胺、苯甲酸、水楊酸、硫柳汞、苯乙醇、對羥基苯甲酸甲酯、對羥基苯甲酸丙酯、洛赫西定(chlorhexidine)、山梨酸或過氧化氫)；溶劑(諸如甘油、丙二醇或聚乙二醇)；糖醇(諸如甘露糖醇或山梨糖醇)；懸浮劑；

界面活性劑或潤濕劑(諸如普朗尼克、PEG、脫水山梨糖醇酯、聚山梨酸酯(諸如聚山梨酸酯20)、聚山梨酯、曲通(triton)、緩血酸胺、卵磷脂膽固醇、tyloxapal)；穩定性增強劑(諸如蔗糖或山梨糖醇)；張力增強劑(諸如鹼金屬鹵化物，較佳氯化鈉或氯化鉀、甘露糖醇、山梨糖醇)；遞送媒劑；稀釋劑；賦形劑及/或醫藥佐劑。參見REMINGTON'S PHARMACEUTICAL SCIENCES, 第18版, (A. R. Genrmo編), 1990, Mack Publishing公司。

【0281】 醫藥組合物可經調配以實現生理學上相容之pH值。在一些實施例中，醫藥組合物之pH值可例如介於約4或約5與約8.0之間或約4.5與約7.5之間或約5.0至約7.5。在例示性實施例中，醫藥組合物之pH值介於5.5與7.5之間。

投藥途徑

【0282】 對於本發明，活性劑或包含活性劑之醫藥組合物可經由任何合適投藥途徑投與個體。舉例而言，活性劑可經由非經腸、經鼻、經口、經肺、局部、經陰道或經直腸投與來投與個體。以下關於投藥途徑之論述僅係為說明例示性實施例而提供且不應視為以任何方式限制範疇。

【0283】 適合於非經腸投與之調配物包括水性及非水性之等滲無菌注射溶液，其可含有抗氧化劑、緩衝劑、抑菌劑及使調配物與預期接受者之血液等滲之溶質；及水性及非水性之無菌懸浮液，其可包括懸浮劑、增溶劑、增稠劑、穩定劑及防腐劑。術語「非經腸」意謂不經由消化道，而藉由一些其他途徑，諸如皮下、肌肉、脊柱內或靜脈內。本發明之活性劑可與生理學上可接受之稀釋劑於醫藥載劑(諸如無菌液體或液體混合物，包括水、生理食鹽水、右旋糖水溶液及相關糖溶液、醇(諸如乙醇或十六

醇)、二醇(諸如丙二醇或聚乙二醇)、二甲亞碸、丙三醇、縮酮(諸如2,2-二甲基- 153-二氧戊環-4-甲醇)、醚、聚(乙二醇) 400、油類、脂肪酸、脂肪酸酯或甘油酯或乙醯化脂肪酸甘油酯)中投與，添加或未添加醫藥學上可接受之界面活性劑，諸如脂肪酸鹽或清潔劑、懸浮劑(諸如果膠、卡波姆(carbomer)、甲基纖維素、羥丙基甲基纖維素或羧甲基纖維素)或乳化劑及其他醫藥佐劑。

【0284】 可用於非經腸調配物中之油類包括石油、動物油、植物油或合成油。油類之特定實例包括花生油、大豆油、芝麻油、棉籽油、玉米油、橄欖油、石蠟油及礦物油。合適用於非經腸調配物中之脂肪酸包括油酸、硬脂酸及異硬脂酸。油酸乙酯及肉豆蔻酸異丙酯為合適脂肪酸酯之實例。

【0285】 用於非經腸調配物中之合適脂肪酸鹽包括脂族鹼金屬鹽、銨鹽及三乙醇胺鹽，且合適清潔劑包括(a)陽離子型清潔劑，諸如鹵化二甲基二烷基銨及鹵化烷基吡錠；(b)陰離子型清潔劑，諸如烷基、芳基及烯烴磺酸酯、烷基、烯烴、醚及單酸甘油酯硫酸酯及磺基丁二酸酯；(c)非離子型清潔劑，諸如脂肪胺氧化物、脂肪酸烷醇醯胺及聚氧伸乙基聚伸丙基共聚物；(d)兩性清潔劑，諸如烷基-β-胺基丙酸酯及2-烷基-咪唑啉四級銨鹽；及(e)其混合物。

【0286】 在一些實施例中，非經腸調配物在溶液中含有約0.5重量%至約25重量%之本發明之活性劑。可使用防腐劑及緩衝劑。為最小化或消除對注射部位之刺激，此類組合物可含有一或多種親水親油平衡(HLB)為約12至約17之非離子型界面活性劑。此類調配物中界面活性劑之量通常在約5重量%至約15重量%範圍內。合適界面活性劑包括聚乙二醇脫水山

梨糖醇脂肪酸酯，諸如脫水山梨糖醇單油酸酯及環氧乙烷與由環氧丙烷與丙二醇縮合形成之疏水性基質的高分子量加合物。在一些態樣中非經腸調配物呈單位劑量或多劑量密封容器，諸如安瓿及小瓶呈現，且可儲存在冷凍乾燥(凍乾)條件下，僅僅需要在臨用前添加無菌液體賦形劑，例如注射用水。在一些態樣中，自先前描述之種類的無菌粉末、顆粒及錠劑製備臨用方配製之注射溶液及懸浮液。

【0287】 可注射調配物係根據本發明。對用於可注射組合物之有效醫藥載劑的要求為此項技術之一般技術人員熟知(參見例如Pharmaceutics and Pharmacy Practice, J. B. Lippincott Company, Philadelphia, PA, Banker及Chalmers編輯, 第238-250頁 (1982), 及ASHP Handbook on Injectable Drugs, Toissel, 第4版, 第622-630頁(1986))。

劑量

【0288】 咸信本發明之活性劑可用於如本文所述之抑制PD-1信號傳導，同時提供IL-21信號傳導之方法中，且因此咸信其可用於治療或預防一或多種疾病，例如癌症之方法中。出於本發明之目的，投與之活性劑之量或劑量應足夠在合理時間範圍內在個體或動物中實現例如治療或預防作用。舉例而言，本發明之活性劑之劑量應足夠自投與時間起，在約1至4分鐘、1至4小時或1至4週或更長時間，例如5至20週或更多週的時間內治療如本文所述之癌症。在某些實施例中，時間段可甚至更長。劑量將由特定活性劑之功效及待治療之動物(例如人類)的情況以及待治療之動物(例如人類)的體重決定。

【0289】 用於確定投與劑量之許多分析為此項技術中已知。出於本文中之目的，包含比較在向一組哺乳動物中之一哺乳動物投與既定劑量之

本發明之活性劑後癌症治療程度的分析可用於確定投與哺乳動物之起始劑量，各組哺乳動物給與不同劑量之活性劑。在投與一定劑量後之癌症治療程度可由小鼠異種移植模型中例如活性劑之細胞毒性或用活性劑下實現之腫瘤消退程度表示。量測融合蛋白之細胞毒性之方法及分析腫瘤消退之方法為此項技術中已知。

【0290】 本發明之活性劑之劑量亦由可能伴隨本發明之特定活性劑投與之任何不良副作用的存在、性質及程度決定。通常，主治醫師將考慮多種因素，諸如年齡、體重、整體健康、飲食、性別、待投與之本發明之活性劑、投藥途徑及所治療之病狀之嚴重程度來決定本發明之活性劑之劑量以治療各個別患者。藉助於實例且不意欲限制本發明，本發明之活性劑之劑量可為每天每公斤所治療之個體體重約0.0001至約1 g、約0.0001至約0.001 g或約0.01 mg至約1 g。

控制釋放調配物

【0291】 在一些實施例中，本文所述之活性劑可經修飾成積存形式，使得本發明之活性劑釋放至其投與之身體的方式在體內時間及位置方面得到控制(參見例如美國專利第4,450,150號)。本發明之活性劑之積存形式可為例如包含活性劑及多孔或無孔材料，諸如聚合物之可植入組合物，其中活性劑由該材料囊封或擴散在該材料中及/或無孔材料降解。接著積存物植入個體體內之所需位置，且活性劑以預定速率自植入物釋放。

【0292】 在某些態樣中，包含活性劑之醫藥組合物經修飾以具有任何類型之活體內釋放概況。在一些態樣中，醫藥組合物為立即釋放、控制釋放、持續釋放、延長釋放、延遲釋放或兩相釋放調配物。調配用於控制釋放之肽的方法為此項技術中已知。參見例如Qian等人, J Pharm 374:

46-52 (2009)及國際專利申請公開案第WO 2008/130158號、第WO2004/033036號、第WO2000/032218號及第WO 1999/040942號。

【0293】本發明之組合物可進一步包含例如膠束或脂質體或一些其他囊封形式，或可呈延長釋放形式投與以提供長期儲存及/或遞送作用。

組合

【0294】在一些實施例中，本文所述之融合蛋白或抗原結合蛋白(例如抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物)單獨投與，且在替代實施例中，與另一治療劑，例如不同類型(例如結構)之本發明之另一活性劑組合投與。在一些態樣中，另一治療劑旨在治療或預防癌症。在一些實施例中，另一治療劑為化學治療劑。在一些實施例中，另一治療劑為用於治療癌症之放射療法中之藥劑。因此，在一些態樣中，本文所述之融合蛋白或抗原結合蛋白(例如抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物)與鉑配位化合物、拓撲異構酶抑制劑、抗生素、抗有絲分裂生物鹼及二氟核苷中之一或多種組合投與。在例示性態樣中，本文所述之IL-21融合蛋白(例如與IL-21突變蛋白融合之抗PD-1抗體)與抗原結合蛋白(例如抗PD-1抗體、其抗原結合抗體片段或抗PD-1抗體蛋白產物)組合。

【0295】在特定實施例中，抗體20A2、20C1、22D4、20C1.006、20C1.009、20A2.003、22D4.006、22D4.017中之任一者與本文所述之IL-21融合蛋白組合投與，包括例如：包含選自以下之同源二聚體或單體的融合蛋白：

包含兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ

ID NO: 496之胺基酸序列)的同源二聚體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且融合之重鏈-IL-21突變蛋白包含SEQ ID NO: 497之胺基酸序列)的同源二聚體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 498之胺基酸序列)的同源二聚體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 499之胺基酸序列)的同源二聚體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 500之胺基酸序列)的同源二聚體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 501之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 555之胺基酸序列)的單體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 502之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 556之胺基酸序列)的單體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 503之胺基酸

序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 557之胺基酸序列)的單體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 504之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 555之胺基酸序列)的單體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 505之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 556之胺基酸序列)的單體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 391之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 506之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 557之胺基酸序列)的單體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 507之胺基酸序列)的同源二聚體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 508之胺基酸序列)的同源二聚體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 509之胺基酸序列)的同源二聚體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 510之胺基酸序列)的同源二聚體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 511之胺基酸序列)的同源二聚體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條抗體重鏈(各與IL-21突變蛋白融合且各重鏈-IL-21突變蛋白融合物包含SEQ ID NO: 512之胺基酸序列)的同源二聚體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 513之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 558之胺基酸序列)的單體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 514之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 559之胺基酸序列)的單體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 515之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 560之胺基酸序列)的單體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 516之胺基酸

序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 558之胺基酸序列)的單體；

包含兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 517之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 559之胺基酸序列)的單體；或

包含兩條抗體輕鏈(各包含SEQ ID NO: 371之胺基酸序列)及兩條不同抗體重鏈(一條與IL-21突變蛋白融合且包含SEQ ID NO: 518之胺基酸序列且一條不與IL-21突變蛋白融合且包含SEQ ID NO: 560之胺基酸序列)的單體。

套組

【0296】 本發明另外提供包含本發明之IL-21突變蛋白、PD-1抗原結合蛋白(例如抗PD-1抗體)、結合物、融合蛋白、核酸、載體或宿主細胞或其組合的套組。在例示性態樣中，套組在容器中包含至少一種本發明之IL-21突變蛋白、PD-1抗原結合蛋白(例如抗PD-1抗體)、結合物、融合蛋白、核酸、載體或宿主細胞或其組合。在例示性態樣中，至少一種本發明之IL-21突變蛋白、PD-1抗原結合蛋白(例如抗PD-1抗體)、結合物、融合蛋白、核酸、載體或宿主細胞呈單位劑量提供於套組中。出於本文中之目的，「單位劑量」係指分散在合適載劑中之離散量。在例示性態樣中，單位劑量為足夠向個體提供所需作用，例如治療癌症之量。在例示性態樣中，套組包含若干單位劑量，例如一週或一個月之單位劑量供應，視情況，每一者個別地包裝或以其他方式與其他單位劑量分離。在一些實施例中，套組/單位劑量之組分與關於投與患者之說明書一起包裝。在一些實

施例中，套組包含一或多種用於投與患者之裝置，例如針及注射器及其類似物。在一些態樣中，至少一種本發明之IL-21突變蛋白、PD-1抗原結合蛋白(例如抗PD-1抗體)、結合物、融合蛋白、核酸、載體或宿主細胞或其組合呈備用形式，例如注射器、靜脈內袋等預先包裝。在例示性態樣中，備用形式係一次性使用。在例示性態樣中，套組包含至少一種本發明之IL-21突變蛋白、PD-1抗原結合蛋白(例如抗PD-1抗體)、結合物、融合蛋白、核酸、載體或宿主細胞的多個一次性使用之備用形式。在一些態樣中，套組進一步包含其他治療劑或診斷劑或醫藥學上可接受之載劑(例如溶劑、緩衝劑、稀釋劑等)，包括本文所述之彼等劑中之任一者。

製造方法

【0297】本發明之IL-21突變蛋白可藉由此項技術中已知之方法獲得。重新合成多肽之合適方法描述於例如以下中：Chan等人, Fmoc Solid Phase Peptide Synthesis, Oxford University Press, Oxford, United Kingdom, 2005；Peptide and Protein Drug Analysis, 編輯Reid, R., Marcel Dekker公司, 2000；Epitope Mapping, 編輯Westwood等人, Oxford University Press, Oxford, United Kingdom, 2000；及美國專利第5,449,752號。製造本發明之肽的其他例示性方法闡述於本文中。

【0298】在一些實施例中，本文所述之IL-21突變蛋白由諸如Synpep (Dublin, CA)、Peptide Technologies公司(Gaithersburg, MD)、Multiple Peptide Systems (San Diego, CA)、Peptide 2.0公司(Chantilly, VA)及American Peptide公司(Sunnyvale, CA)之公司商業上合成。在此方面，IL-21突變蛋白可為合成、重組、分離及/或純化的。

【0299】此外，在一些態樣中，IL-21突變蛋白使用編碼肽之胺基

酸序列之核酸，使用標準重組方法重組產生。參見例如Sambrook等人, Molecular Cloning: A Laboratory Manual. 第3版, Cold Spring Harbor Press, Cold Spring Harbor, NY 2001；及Ausubel等人, Current Protocols in Molecular Biology, Greene Publishing Associates及John Wiley & Sons, NY, 1994。

【0300】本文提供製造IL-21突變蛋白之方法。在例示性實施例中，該方法包括培養本發明之宿主細胞以表現IL-21突變蛋白且收穫所表現之IL-21突變蛋白。

【0301】本文亦提供製造包含IL-21突變蛋白之融合蛋白之方法。在例示性實施例中，該方法包括培養本發明之宿主細胞以表現融合蛋白且收穫所表現之融合蛋白。

【0302】在例示性實施例中，該方法包括培養包含編碼如本文所述之IL-21突變蛋白或融合蛋白之核酸的宿主細胞以表現該IL-21突變蛋白或融合蛋白。宿主細胞可為本文所述之宿主細胞中之任一者。在例示性態樣中，宿主細胞係選自由以下組成之群：CHO細胞、NS0細胞、COS細胞、VERO細胞及BHK細胞。在例示性態樣中，培養宿主細胞之步驟包括在生長培養基中培養宿主細胞以支持宿主細胞之生長及擴增。在例示性態樣中，生長培養基以及時方式增加細胞密度、培養活力及生產能力。在例示性態樣中，生長培養基包含胺基酸、維生素、無機鹽、葡萄糖及血清作為生長因子、激素及附著因子之來源。在例示性態樣中，生長培養基為由胺基酸、維生素、微量元素、無機鹽、脂質及胰島素或胰島素樣生長因子組成的化學成分完全確定之培養基。除營養素外，生長培養基亦幫助維持pH值及滲透壓度。若干生長培養基可購得且描述於此項技術中。參見例

如Arora, 「Cell Culture Media: A Review」 MATER METHODS 3:175 (2013)。

【0303】 在例示性態樣中，製造本發明之IL-21突變蛋白或融合蛋白之方法包括在進料培養基中培養宿主細胞。在例示性態樣中，該方法包括在進料培養基中以分批進料模式培養。重組蛋白質產生之方法為此項技術中已知。參見例如Li等人, 「Cell culture processes for monoclonal antibody production」 MAbs 2(5): 466-477 (2010)。

【0304】 製造IL-21突變蛋白或融合蛋白之方法可包括用於自細胞培養物或其上清液純化突變蛋白或蛋白質且較佳回收所純化之蛋白質的一或多個步驟。在例示性態樣中，該方法包括一或多個層析步驟，例如親和層析(例如蛋白A親和層析)、離子交換層析、疏水性相互作用層析。在例示性態樣中，該方法包括使用蛋白A親和層析樹脂純化蛋白質。

【0305】 在例示性實施例中，該方法進一步包括用於調配所純化之蛋白質等，從而獲得包含所純化之蛋白質的調配物的步驟。此類步驟描述於Formulation and Process Development Strategies for Manufacturing, 編輯Jameel及Hershenson, John Wiley & Sons公司(Hoboken, NJ), 2010中。

使用方法

【0306】 本發明另外提供治療方法。在例示性實施例中，該方法為一種治療有需要之個體的方法，其包括向有需要之個體投與有效治療個體之量的本發明之醫藥組合物。

【0307】 本發明之醫藥組合物可用於抑制PD-1信號傳導及/或活化IL-21信號傳導。不限於特定理論，[1]本文提供之組合物之PD-1抑制活性

允許此類實體用於增強T細胞活性及增強免疫反應，及尤其針對腫瘤或癌症之免疫反應的方法中；及/或[2]本文提供之組合物之IL-21活化活性允許此類實體增強T細胞存活及效應功能，限制終末分化及複製潛能喪失，藉由將活化之效應細胞改變成更天然之T細胞表型(例如藉由增強CCR7表現)促進T細胞壽命，且增強針對標靶(例如癌症)細胞之細胞毒性(例如藉由增加IFNγ及顆粒酶B產生)。

【0308】 因此，本文提供增強個體中之T細胞活性、增強T細胞存活及效應功能、限制終末分化及複製潛能喪失、促進T細胞壽命及增強針對標靶(例如癌症)細胞之細胞毒性的方法。在例示性實施例中，該等方法包括向個體投與有效量之本發明之醫藥組合物。在例示性態樣中，T細胞活性或免疫反應係針對癌細胞或癌症組織或腫瘤細胞或腫瘤。在例示性態樣中，免疫反應為體液免疫反應。在例示性態樣中，免疫反應為先天性免疫反應。在例示性態樣中，增強之免疫反應為T細胞介導之免疫反應。

【0309】 如本文所用，術語「增強」及源自其之詞可能不為100%或完全增強或增加。更確切些，存在此項技術之一般技術人員認為具有潛在益處或治療作用的不同程度之增強。在此方面，本發明之醫藥組合物可增強例如T細胞活性或增強免疫反應至任何量或水準。在例示性實施例中，由本發明之方法提供之增強為至少或約10%增強(例如至少或約20%增強、至少或約30%增強、至少或約40%增強、至少或約50%增強、至少或約60%增強、至少或約70%增強、至少或約80%增強、至少或約90%增強、至少或約95%增強、至少或約98%增強)。

【0310】 量測T細胞活性及免疫反應之方法為此項技術中已知。T細胞活性可藉由例如細胞毒性分析，諸如Fu等人, PLoS ONE 5(7): e11867

(2010)中描述之彼等分析量測。其他T細胞活性分析描述於Bercovici等人, Clin Diagn Lab Immunol. 7(6): 859-864 (2000)中。量測免疫反應之方法描述於例如Macatangay等人, Clin Vaccine Immunol 17(9): 1452-1459 (2010)及Clay等人, Clin Cancer Res.7(5):1127-35 (2001)中。

【0311】本文另外提供治療患有癌症之個體之方法及治療具有實體腫瘤之個體之方法。在例示性實施例中，該方法包括向個體投與有效治療個體之癌症或實體腫瘤之量的本發明之醫藥組合物。可由本文揭示之方法治療之癌症可為任何癌症，例如由異常及不受控制之細胞分裂引起的可經由淋巴系統或血流擴散至身體其他部分之任何惡性生長或腫瘤。在一些態樣中，癌症為選自由以下組成之群的癌症：急性淋巴細胞癌、急性骨髓性白血病、腺泡狀橫紋肌肉瘤、骨癌、腦癌、乳癌、肛門、肛管或肛門直腸之癌症、眼癌、肝內膽液管癌、關節癌、頸、膽囊或胸膜之癌症、鼻、鼻腔或中耳之癌症、口腔癌、外陰癌、慢性淋巴細胞性白血病、慢性髓細胞樣癌、結腸癌、食道癌、子宮頸癌、胃腸道類癌腫瘤、霍奇金氏淋巴瘤、舌癌、腎癌、喉癌、肝癌、肺癌、惡性間皮瘤、黑色素瘤、多發性骨髓瘤、鼻咽癌、非霍奇金淋巴瘤、卵巢癌、胰臟癌、腹膜、網膜及腸系膜癌、咽癌、前列腺癌、直腸癌、腎癌(例如腎細胞癌(RCC))、小腸癌、軟組織癌、胃癌、睾丸癌、甲狀腺癌、輸尿管癌及膀胱癌。在特定態樣中，癌症係選自由以下組成之群：頭頸部癌、卵巢癌、子宮頸癌、膀胱及食管癌、胰臟癌、胃腸癌、胃癌、乳癌、子宮內膜癌及結腸直腸癌、肝細胞癌、膠質母細胞瘤、膀胱癌、肺癌(例如非小細胞肺癌(NSCLC))、細支氣管肺泡癌。在特定實施例中，腫瘤為非小細胞肺癌(NSCLC)、頭頸部癌、腎癌、三陰性乳癌及胃癌。在例示性態樣中，個體具有腫瘤(例如實體腫

瘤、血液科惡性疾病或淋巴類惡性疾病)且向該個體投與有效治療個體之腫瘤之量的醫藥組合物。在其他例示性態樣中，腫瘤為非小細胞肺癌(NSCLC)、小細胞肺癌(SCLC)、頭頸部癌、腎癌、乳癌、黑色素瘤、卵巢癌、肝癌、胰臟癌、結腸癌、前列腺癌、胃癌、淋巴瘤或白血病，且向個體投與有效治療個體之腫瘤之量的醫藥組合物。

【0312】 如本文所用，術語「治療」以及與其相關之詞不一定暗示100%或完全治療。更確切些，存在此項技術之一般技術人員認為具有潛在益處或治療作用的不同程度之治療。在此方面，本發明之癌症治療方法可提供任何量或任何水準之治療。此外，由本發明之方法提供之治療可包括治療所治療癌症之一或多種病狀或症狀或徵象。由本發明之方法提供之治療亦可涵蓋減緩癌症之進展。舉例而言，該等方法可藉由增強T細胞活性或針對癌症之免疫反應，減少腫瘤或癌症生長，減少腫瘤細胞轉移，增加腫瘤或癌細胞之細胞死亡及其類似方面而治療癌症。在例示性態樣中，方法藉助於延遲癌症發作或復發1天、2天、4天、6天、8天、10天、15天、30天、兩個月、4個月、6個月、1年、2年、4年或更長時間而進行治療。在例示性態樣中，該等方法藉助於增加個體之存活而治療。

個體

【0313】 在本發明之一些實施例中，個體為哺乳動物，包括(但不限於)嚙齒目哺乳動物，諸如小鼠及倉鼠；及兔目哺乳動物，諸如兔；來自食肉目之哺乳動物，包括貓科動物(貓)及犬科動物(犬)；來自偶蹄目之哺乳動物，包括牛科動物(奶牛)及豬科動物(豬)；或奇蹄目，包括馬科動物(馬)。在一些態樣中，哺乳動物屬於靈長目、闊鼻小目(Ceboid)或猴目(Simoid)(猴)或類人猿目(人類及猿類)。在一些態樣中，哺乳動物為人

類。

示例性實施例

【0314】在例示性實施例中，本發明提供包含SEQ ID NO: 2之胺基酸序列之IL-21突變蛋白，

QGQDX HMXXM XXXXX XVDXL KNXVN DLVPE FLPAP EDVET NCEWS AFSCF QKAQL KSANT GNNEX XIXXX XXXLX XXXXX TNAGR RQKHR LTCPS CDSYE KKPPK EFLXX FXXLL XXMXX QHXSS RTHGS EDS (SEQ ID NO: 2)，其中「X」表示任何胺基酸，且其中該IL-21突變蛋白胺基酸序列與人類IL-21之胺基酸序列(SEQ ID NO: 1)的差異在於至少1個胺基酸。

【0315】在例示性態樣中，IL-21突變蛋白包含與人類IL-21之胺基酸序列(SEQ ID NO: 1)的差異在於至多7個胺基酸的胺基酸序列。在例示性態樣中，IL-21突變蛋白包含與人類IL-21之胺基酸序列(SEQ ID NO: 1)的差異在於3個、4個、5個或6個胺基酸之胺基酸序列。在例示性情況下，IL-21突變蛋白包含與人類IL-21之胺基酸序列(SEQ ID NO: 1)的差異在於1或2個胺基酸的胺基酸序列。在例示性態樣中，IL-21突變蛋白之胺基酸序列與SEQ ID NO: 1之胺基酸序列之間的差異在SEQ ID NO: 2之胺基酸10-15 (包括胺基酸10及15)或胺基酸105-123 (包括胺基酸105及123)內，視情況，其中差異出現在SEQ ID NO: 2之胺基酸11、14、15、109、110、112、113、116、119、120及/或123處。在例示性態樣中，IL-21突變蛋白之胺基酸序列與SEQ ID NO: 1之胺基酸序列之間的差異在SEQ ID NO: 2之胺基酸5-25(包括胺基酸5及25)或胺基酸65-80(包括胺基酸65及80)內，視情況，其中差異出現在SEQ ID NO: 2之胺基酸5、8、9、12、

13、16、19、23、65、66、69、70、72、73、75、76、77、78、79及/或80處。

【0316】在一些態樣中，IL-21突變蛋白包含相對於人類IL-21之胺基酸序列(SEQ ID NO: 1)具有一個胺基酸取代的胺基酸序列。在一些情況下，胺基酸取代出現在SEQ ID NO: 1之位置5、8、9、11、12、13、14、15、16、19、23、65、66、68、69、70、71、72、73、75、76、77、78、79、80、109、110、112、113、116、117、119、120或123處。在例示性態樣中，胺基酸取代出現在SEQ ID NO: 1之位置5、8、9、11、12、13、14、15、16、19、23、65、66、68、69、70、72、73、75、76、77、78、79、80、109、110、112、113、116、117、119、120或123處。在例示性情況下，IL-21突變蛋白包含以下位置處之胺基酸取代：

a. SEQ ID NO: 1之位置5、8、9、12、14、15、65、66、69、70、72、73、75、76、77、80、116或119處，其中取代胺基酸為脂族胺基酸；

b. SEQ ID NO: 1之位置5、8、9、11、12、13、14、15、16、19、23、65、66、69、70、72、73、75、76、77、78、79、110、112、116、117、119、120或123處，其中取代胺基酸為酸性胺基酸；

c. SEQ ID NO: 1之位置5、9、73、76、109、113或116處，其中取代胺基酸為鹼性胺基酸；

d. SEQ ID NO: 1之位置5、8、9、70或76處，其中取代胺基酸為芳族胺基酸；

e. SEQ ID NO: 1之位置5、8、9、12、15、73、76、116或119處，其中取代胺基酸為包含側鏈醯胺之胺基酸；

f. SEQ ID NO: 1之位置5、8、9、11、12、14、15、73、76、116或119處，其中取代胺基酸為包含側鏈羥基之非芳族胺基酸；

g. SEQ ID NO: 1之位置65、66、69、70、72、73、75、76、77或80處，其中取代胺基酸為亞胺基酸；

h. SEQ ID NO: 1之位置5、9、15、76、116或119處，其中取代胺基酸為包含含硫側鏈之胺基酸；或

i. 或其組合。

【0317】 在例示性態樣中，取代胺基酸為天然存在之胺基酸。在一些情況下，IL-21突變蛋白包含胺基酸位於根據表A之位置處的胺基酸取代。表A顯示如下。

表A

SEQ ID NO: 1 之胺基酸位置	胺基酸(按單字母代碼)		SEQ ID NO: 1 之胺基酸位置	胺基酸(按單字母代碼)
5	A、D、E、G、H、I、K、L、M、N、Q、S、T、V或Y		72	D、G或P
8	A、D、E、N、S、T、V或Y		73	A、D、E、G、H、I、N、P、Q、S或V
9	A、D、E、G、H、I、K、L、M、N、Q、S、T、V或Y		75	D、G或P
11	D或S		76	A、D、E、G、H、I、K、L、M、N、P、Q、S、T、V或Y
12	A、D、E、N、S、T 或V		77	D、G或P

13	D		78	D
14	A、D或S		79	D
15	A、E、I、M、N、Q、S、T或V		80	G或P
16	D或E		109	K
19	D		110	D
23	D		112	D
65	D、G或P		113	K
66	D、G或P		116	A、D、E、I、K、L、M、N、S、T或V
68	Q		117	D
69	D、G或P		119	A、D、E、M、N、Q、S或T
70	E、G、P或Y		120	D
71	L		123	D

【0318】在例示性實施例中，本發明提供包含SEQ ID NO: 3-21、23-56、58-112、114-208、210-222、224-255及283中之任一者之胺基酸序列的IL-21突變蛋白。

【0319】在例示性態樣中，IL-21突變蛋白包含相對於人類IL-21之胺基酸序列(SEQ ID NO: 1)具有兩個胺基酸取代的胺基酸序列。在例示性態樣中，胺基酸取代出現在SEQ ID NO: 1之位置5、8、9、11、12、13、14、15、16、19、23、65、66、68、69、70、71、72、73、75、76、77、78、79、80、109、110、112、113、116、117、119、120或123中之兩者處。在例示性情況下，胺基酸取代出現在SEQ ID NO: 1之位置5、9、15、70、71、72、73及76中之兩者處。視情況，胺基酸取代出現在SEQ ID NO: 1之位置5、9、73及76中之兩者處。在一些態樣中，該等取代之一出現在SEQ ID NO: 1之位置76處。在例示性情況下，在SEQ ID

NO: 1之位置76處之取代胺基酸為脂族胺基酸或酸性胺基酸。在例示性態樣中，IL-21突變蛋白包含在SEQ ID NO: 1之位置5、9或73處之胺基酸取代，且取代胺基酸為脂族胺基酸或酸性胺基酸。在一些態樣中，IL-21突變蛋白包含在SEQ ID NO: 1之位置處之胺基酸取代，且取代胺基酸為具有側鏈醯胺之胺基酸。在一些情況下，脂族胺基酸為丙胺酸，酸性胺基酸為麩胺酸，或具有側鏈醯胺之胺基酸為麩醯胺酸。在例示性實施例中，本發明提供包含選自由以下組成之群之胺基酸序列的IL-21突變蛋白：SEQ ID NO: 208、210至222、224至248及255。

【0320】 關於以上態樣中之任一者，IL-21突變蛋白可以相對於野生型IL-21對IL-21受體之親和力有所降低之親和力結合於IL-21受體。在一些態樣中，IL-21受體具有SEQ ID NO: 256或261之胺基酸序列。在一些情況下，IL-21突變蛋白結合於具有SEQ ID NO: 257之胺基酸序列的IL-21受體γ鏈。在例示性情況下，本發明之IL-21突變蛋白以大於或等於約0.04 nM之Kd結合於人類IL-21受體。

【0321】 進一步提供結合物。在例示性態樣中，結合物包含任一前段之IL-21突變蛋白及異源部分。在例示性情況下，IL-21直接附接於異源部分。在替代情況下，IL-21經由連接子附接於異源部分。在一些態樣中，連接子包含例如包含Gly-Gly-Gly-Gly-Ser之胺基酸序列(SEQ ID NO: 262)之肽。在例示性態樣中，異源部分為多肽，視情況其中多肽為抗原結合蛋白。在一些情況下，異源多肽為抗體或其抗原結合抗體片段。在例示性實施例中，抗體為抗PD-1抗體。在一些態樣中，IL-21突變蛋白直接附接於抗體之Fc。在例示性態樣中，IL-21突變蛋白經由連接子附接於抗體之Fc。在一些態樣中，結合物包含單一IL-21突變蛋白，其中該單一

IL-21突變蛋白連接於兩個抗體重鏈中之一者的C端。在例示性情況下，結合物包含兩種IL-21突變蛋白，其中第一IL-21突變蛋白連接於第一抗體重鏈之C端，且第二IL-21突變蛋白連接於第二抗體重鏈之C端。視情況，第一IL-21具有與第二IL-21突變蛋白相同之胺基酸序列。可替代地，第一IL-21具有與第二IL-21突變蛋白不同之胺基酸序列。在例示性態樣中，抗體重鏈包含電荷對突變(例如V1、V4、V103或V131突變)。在任一前段之結合物的例示性態樣中，IL-21突變蛋白包含在SEQ ID NO: 1之位置5、9、73及76中之兩者處的胺基酸取代。在例示性態樣中，結合物包含含有SEQ ID NO: 1之胺基酸序列之IL-21突變蛋白，不同之處為該IL-21突變蛋白在SEQ ID NO: 1之位置5、9、73及76中之任兩者處包含胺基酸取代；及抗PD-1抗體，其中IL-21突變蛋白連接於抗PD-1抗體之C端。在例示性態樣中，結合物包含抗PD-1抗體，該抗PD-1抗體包含：(a)表D中闡述之重鏈(HC)互補決定區(CDR) 1胺基酸序列，或選自由SEQ ID NO: 312、322、332、342、352、362、372及382組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(b)表D中闡述之HC CDR2胺基酸序列，或選自由SEQ ID NO: 313、323、333、343、353、363、373及383組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(c)表D中闡述之HC CDR3胺基酸序列，或選自由SEQ ID NO: 314、324、334、344、3545、364、374及384組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(d)表D中闡述之輕鏈(LC) CDR1胺基酸序列，或選自由315、325、335、345、355、365、375及385組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少

或約70%序列一致性之其變異序列；(e)表D中闡述之LC CDR2胺基酸序列，或選自由316、326、336、346、356、366、376及386組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(f)表D中闡述之LC CDR3胺基酸序列，或選自由317、327、337、347、357、367、377及387組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；或(g) (a)-(f)中之任兩者或更多者之組合。在例示性情況下，抗PD-1抗體包含選自由以下組成之群的六個CDR胺基酸序列：(a) SEQ ID NO: 312-317；(b) SEQ ID NO: 322-327；(c) SEQ ID NO: 332-337；(d) SEQ ID NO: 342-347；(e) SEQ ID NO: 352-357；(f) SEQ ID NO: 362-367；(g) SEQ ID NO: 372-377；以及(h) SEQ ID NO: 382-387。在一些態樣中，抗PD-1抗體包含選自由以下組成之群的一對胺基酸序列：(a) SEQ ID NO: 318及319；(b) SEQ ID NO: 328及329；(c) SEQ ID NO: 338及339；(d) SEQ ID NO: 348及349；(e) SEQ ID NO: 358及359；(f) SEQ ID NO: 368及369；(g) SEQ ID NO: 378及379；以及(h) SEQ ID NO: 388及389。在例示性態樣中，抗PD-1抗體包含含有SEQ ID NO: 265-267、282、284-311中之任一者之胺基酸序列的恆定區。在某些情況下，抗PD-1抗體包含選自由以下組成之群的一對胺基酸序列：(a) SEQ ID NO: 320及321；(b) SEQ ID NO: 330及331；(c) SEQ ID NO: 340及341；(d) SEQ ID NO: 350及351；(e) SEQ ID NO: 360及361；(f) SEQ ID NO: 370及371；(g) SEQ ID NO: 380及381；以及(h) SEQ ID NO: 390及391。

【0322】 在例示性實施例中，本發明提供包含本文所述之IL-21突變蛋白及異源多肽或肽之融合多肽或融合蛋白。在一些態樣中，融合多肽

或融合蛋白包含免疫球蛋白或其抗原結合抗體片段。在例示性實施例中，本發明提供包含編碼本文所述之IL-21突變蛋白之核苷酸序列的核酸。在例示性實施例中，本發明提供包含本文所述之核酸的載體。在例示性實施例中，本發明提供包含本文所述之核酸或載體的宿主細胞。在例示性實施例中，本發明提供一種套組，其包含如本文所述之IL-21突變蛋白、核酸、載體、宿主細胞、結合物、融合蛋白或其組合及容器。

【0323】 進一步提供醫藥組合物，其包含本發明之IL-21突變蛋白、核酸、載體、宿主細胞、結合物、融合蛋白或其組合及醫藥學上可接受之載劑、賦形劑或稀釋劑。

【0324】 亦提供製造IL-21突變蛋白之方法，其包括培養本發明之宿主細胞以表現IL-21突變蛋白且收穫所表現之IL-21突變蛋白。進一步提供一種治療有需要之個體之方法。該方法包括向有需要之個體投與有效治療個體之量的本發明之醫藥組合物。在例示性態樣中，該個體具有實體腫瘤且該醫藥組合物係以有效治療該個體之實體腫瘤之量投與該個體。視情況，實體腫瘤係選自由以下組成之群：頭頸部癌、卵巢癌、子宮頸癌、膀胱及食管癌、胰臟癌、胃腸癌、胃癌、乳癌、子宮內膜癌及結腸直腸癌、肝細胞癌、膠質母細胞瘤、膀胱癌、肺癌(例如非小細胞肺癌(NSCLC))、細支氣管肺泡癌。

【0325】 在例示性實施例中，本發明提供一種PD-1抗原結合蛋白，該PD-1抗原結合蛋白包含：(a)表D中闡述之重鏈(HC)互補決定區(CDR) 1胺基酸序列，或選自由SEQ ID NO: 312、322、332、342、352、362、372及382組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(b)表D中闡述之HC CDR2胺基酸序

列，或選自由SEQ ID NO: 313、323、333、343、353、363、373及383組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(c)表D中闡述之HC CDR3胺基酸序列，或選自由SEQ ID NO: 314、324、334、344、3545、364、374及384組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(d)表D中闡述之輕鏈(LC) CDR1胺基酸序列，或選自由315、325、335、345、355、365、375及385組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(e)表D中闡述之LC CDR2胺基酸序列，或選自由316、326、336、346、356、366、376及386組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；(f)表D中闡述之LC CDR3胺基酸序列，或選自由317、327、337、347、357、367、377及387組成之群的序列，或差異在於僅僅一或兩個胺基酸或具有至少或約70%序列一致性之其變異序列；或(g) (a)-(f)中之任兩者或更多者之組合。在例示性情況下，PD-1抗原結合蛋白包含選自由以下組成之群的六個CDR胺基酸序列：(a) SEQ ID NO: 312-317；(b) SEQ ID NO: 322-327；(c) SEQ ID NO: 332-337；(d) SEQ ID NO: 342-347；(e) SEQ ID NO: 352-357；(f) SEQ ID NO: 362-367；(g) SEQ ID NO: 372-377；以及(h) SEQ ID NO: 382-387。在某些態樣中，PD-1抗原結合蛋白包含選自由以下組成之群的一對胺基酸序列：(a) SEQ ID NO: 318及319；(b) SEQ ID NO: 328及329；(c) SEQ ID NO: 338及339；(d) SEQ ID NO: 348及349；(e) SEQ ID NO: 358及359；(f) SEQ ID NO: 368及369；(g) SEQ ID NO: 378及379；以及(h) SEQ ID NO: 388及389。在例示性情況下，PD-1抗原結合

蛋白包含含有SEQ ID NO: 265-267、282、284-311中之任一者之胺基酸序列的恆定區。在一些態樣中，PD-1抗原結合蛋白包含選自由以下組成之群的一對胺基酸序列：(a) SEQ ID NO: 320及321；(b) SEQ ID NO: 330及331；(c) SEQ ID NO: 340及341；(d) SEQ ID NO: 350及351；(e) SEQ ID NO: 360及361；(f) SEQ ID NO: 370及371；(g) SEQ ID NO: 380及381；以及(h) SEQ ID NO: 390及391。

【0326】 在例示性實施例中，本發明提供包含如上述段落中所述之PD-1抗原結合蛋白及異源部分的結合物。在例示性實施例中，本發明提供包含如上述段落中所述之PD-1抗原結合蛋白及異源多肽或肽的融合多肽或融合蛋白。在例示性實施例中，本發明提供包含編碼如上述段落中所述之PD-1抗原結合蛋白、結合物或融合多肽或融合蛋白之核苷酸序列的核酸。在例示性情況下，核酸包含SEQ ID NO: 392-471中之任一者之序列。在例示性實施例中，本發明提供包含如上所述之核酸的載體以及包含如上所述之核酸或載體的宿主細胞。亦提供一種套組，該套組包含如上述段落中所述之PD-1抗原結合蛋白或結合物、融合多肽、融合蛋白、核酸、載體或宿主細胞或其組合及容器。本發明提供一種醫藥組合物，在例示性實施例中，該醫藥組合物包含如上述段落中所述之PD-1抗原結合蛋白或結合物、融合多肽、融合蛋白、核酸、載體或宿主細胞或其組合，及醫藥學上可接受之載劑、賦形劑或稀釋劑。本發明進一步提供一種製造PD-1抗原結合蛋白之方法，其中在例示性實施例中，該方法包括培養如此段落中所述之宿主細胞，以表現PD-1抗原結合蛋白，且收穫所表現之PD-1抗原結合蛋白。本發明另外提供一種治療有需要之個體的方法，其中在例示性實施例中，該方法包括向有需要之個體投與有效治療個體之量

的如此段落中所述之醫藥組合物。在例示性態樣中，該個體具有實體腫瘤且該醫藥組合物係以有效治療該個體之實體腫瘤之量投與該個體。視情況，實體腫瘤係選自由以下組成之群：頭頸部癌、卵巢癌、子宮頸癌、膀胱及食管癌、胰臟癌、胃腸癌、胃癌、乳癌、子宮內膜癌及結腸直腸癌、肝細胞癌、膠質母細胞瘤、膀胱癌、肺癌(例如非小細胞肺癌(NSCLC))、細支氣管肺泡癌。

【0327】 以下實例僅係為說明本發明而給出，且不以任何方式限制其範疇。

實例

實例1

【0328】 本實例證明包含PD-1阻斷抗體及重組IL-21之組合療法優於相對應之單一療法。

【0329】 在臨床前研究中，將單株PD-1阻斷抗體與重組鼠科IL-21 (rmIL-21)之組合治療的作用與PD-1阻斷抗體或rmIL-21之單一療法治療之作用相比較。

【0330】 在第1天，將CT26/3E5結腸癌細胞植入BALB/c小鼠中以起始腫瘤生長。在第12天，量測腫瘤，且將小鼠隨機化至4組(每組10隻小鼠)：第1組接受300 μg同型對照抗體(mIgG1)之腹膜內(IP)注射，第2組接受300 μg阻斷PD-1抗體之IP注射，第3組接受50 μg rmIL-21，且第4組接受阻斷PD-1抗體(300 μg)與rmIL-21 (50 μg)。第1組、第2組及第4組每3天接受抗體一次，且第3組及第4組每週接受rmIL-21 3次，歷時3週。在第33天結束給藥。

【0331】 在整個研究中監測腫瘤體積。如圖1A-1D所示，第1組之

腫瘤尺寸最大程度增加，且第4組之腫瘤尺寸最小程度增加。

【0332】 如藉由卡普蘭梅耶對數秩曼特爾-考克斯分析(Kaplan Meier log rank mantel cox analysis)所量測之存活率為此研究之主要終點。如圖2及表1所示，第4組之存活率百分比及中值存活期最大。值得注意地，第4組中兩名個體無腫瘤(表1)。

表1

組	中值存活期(天)	無腫瘤之個體
1	25	0
2	29	0
3	27	0
4	37.5	2

【0333】 此等結果證明單株PD-1阻斷抗體與重組mIL-21之組合提供優於作為單一療法單獨投與之任一組分的存活率優點。

實例2

【0334】 本實例說明多平台之設計及構造旨在提供PD-1抑制與IL-21信號傳導之組合。

【0335】 實例1中所得之結果證明IL-21信號傳導及PD-1抑制之組合方法治療具有腫瘤之個體的優點。但是，因為IL-21能夠加強CD8 T細胞反應且抑制抗原呈遞及T細胞激活，所以謹慎考慮IL-21之遞送方式。另外，IL-21R在人類組織中廣泛表現(例如藉由抗原呈遞細胞(APC)、NK細胞、B細胞及T細胞)，因此需要謹慎考慮以避免在不同組織中IL-21結合其受體時之脫靶作用(例如在腫瘤環境外之IL-21活性)及IL-21清除。

【0336】 想出一種雙管齊下之方法以闡明以上考慮。首先，產生經由IL-21突變蛋白與IL-21R之結合減少而具有減弱活性之IL-21突變蛋白。可想像當全身擴散時，此類IL-21突變蛋白將具有減少活性，但若IL-21突變蛋白可集中在標靶(例如癌症) T細胞中，則將「拯救」此類活性。亦

即，IL-21突變蛋白一旦存在及集中在標靶細胞中，則將整體上展現治療IL-21活性。其次，IL-21突變蛋白與諸如單株抗體之標靶臂融合，以使IL-21突變蛋白靶向相關細胞(例如癌細胞)。為將IL-21突變蛋白遞送至標靶癌細胞，將其與抗PD-1 mAb融合。抗PD-1 mAb之使用具有預防經由PD-1/PD-L1信號傳導(因此充當檢查點抑制劑)之額外益處。

【0337】 不受任何具體理論束縛，假定包含抗PD-1抗體與IL-21突變蛋白融合之融合蛋白將提供針對旨在破壞之細胞更持久之反應。舉例而言，[1]表現PD-1之CD8+ T細胞將由融合蛋白之抗PD-1 mAb結合，且[2]同時融合蛋白之IL-21突變蛋白與由CD8+ T細胞表現之IL-21受體的結合將增加T細胞增殖以及T細胞之IFNγ產生及分泌更大，此將提高針對標靶細胞之總體細胞毒性。進一步假設由IL-21活化之細胞內信號傳導路徑將預防終末分化及相關之效應功能喪失及細胞凋亡。參見圖3。

【0338】 其他設計考慮包括mAb之價數(例如單價或二價mAb)、對Fc效應功能之需求、細胞介素融合位點(mAb之C端或N端)、包括連接子及預測之次要修飾或截斷位點之補救。

【0339】 考慮若干融合蛋白格式，且選殖四種融合構築體且表現以用於概念驗證實驗。野生型(WT) IL-21與二價PD-1 mAb之IgG之C端融合成：(1)無任何連接子之IL-21同源二聚體；(2)具有GGGGS (SEQ ID NO: 262)連接子之IL-21同源二聚體；(3)無任何連接子，但在IgG Fc中具有電荷對突變以驅動異源二聚之IL-21單體；及(4)具有GGGGS (SEQ ID NO: 262)連接子及電荷對突變之IL-21單體。所有四種融合蛋白構築體在mAb Fc區中包括以下修飾，根據EU系統編號：N297G、R292C、V302C (SEFL2-2突變)。所用的電荷對突變為V1突變(亦即一條重鏈中之K409D

及K392D及另一條重鏈中之D399K及E356K)。所有四種融合蛋白構築體經設計以移除C端離胺酸從而防止截斷。

【0340】在細胞分析中，使用IL-21R陽性(IL-21R+) Hut78 T細胞株之兩種變異體(PD-1^{+ve}及PD-1^{-ve})，針對IL-21活性篩選融合構築體。在各細胞株中，STAT3磷酸化作為IL-21活性之替代量度量測。兩種Hut78細胞變異體暴露於(i)單獨重組人類IL-21 (rhIL-21)；(ii)單獨抗PD-1 mAb；(iii)抗PD-1 mAb與IL-21同源二聚體融合，具有連接子；(iv)抗PD-1 mAb與IL-21同源二聚體融合，無連接子；(v)抗PD-1 mAb與IL-21單體融合，具有連接子；或(vi)抗PD-1 mAb與IL-21單體融合，無連接子。STAT3磷酸化分析之結果及各分子針對STAT信號傳導之EC50分別展示於圖5A及5B及表2中。

表2

分子	PD-1^{-ve}	PD-1^{+ve}
	EC50 (pM)	EC50 (pM)
rhIL-21	153	204
抗PD-1 mAb	-	-
抗PD-1 mAb + IL-21同源二聚體之融合物，無連接子	1184	97
抗PD-1 mAb + IL-21同源二聚體之融合物，+ 連接子	1822	60
抗PD-1 mAb + IL-21單體之融合物，無連接子	523	70
抗PD-1 mAb + IL-21單體之融合物，+ 連接子	392	58

【0341】如圖5A及表2所示(中間行)，包含抗PD-1 mAb與IL-21同源二聚體之融合蛋白在PD-1^{-ve}細胞中展現相對於rhIL-21低10倍之效力。與包含IL-21單體之融合蛋白相比，rhIL-21亦更有效。儘管僅僅具有一個IL-21部分，但單體融合蛋白顯示相對於具有兩個IL-21部分之同源二聚體

更大的效力。此等結果表明單體在PD-1^{-ve}細胞中展現較高IL-21活性，及/或表明同源二聚體融合蛋白格式可使IL-21活性部分減弱(例如可能經由IL-21部分之間的空間相互作用)。

【0342】 此研究亦允許評估IL-21部分與IgG C端之間的連接子。如表2(中間行)及圖5A及5B (實線=無連接子；點線=連接子)所示，連接子之存在似乎不影響IL-21活性。因此，製造無連接子之所有未來構築體，以減少融合蛋白中非天然序列之量。

【0343】 藉由在PD-1^{-ve}細胞與PD-1^{+ve}細胞之間比較STAT3磷酸化分析之結果，評估PD-1表現對IL-21活性之作用。如圖5B所示，在PD-1^{+ve}細胞中IL-21同源二聚體及單體融合蛋白每一者之IL-21活性基本上相同。

【0344】 總之，此等結果證明在標靶細胞中缺乏PD-1表現時，IL-21信號傳導可藉由IL-21與抗PD-1 mAb融合而減弱。另外，在表現PD-1之細胞中拯救與抗PD-1 mAb融合之IL-21的IL-21信號傳導。

實例3

【0345】 本實例說明多種IL-21突變蛋白之設計、構造及表徵。

【0346】 為獲得對融合蛋白之藥物動力學/藥效學(PK/PD)概況的瞭解，在食蟹獼猴中活體內測試包含與WT IL-21之同源二聚體融合之IgG的融合蛋白。

【0347】 以低劑量(250 μg/kg)或高劑量(1000 μg/kg)向動物靜脈內投與包含與抗PD-1 mAb融合之WT IL-21的同源二聚體融合蛋白。IgG抗體結構域(150 μg/kg)充當對照。隨時間推移量測血清濃度，且測定C_{max}、AUC_{last}、半衰期($t_{1/2}$)、Vss及Cl。結果顯示於圖6及表3中。

表3

動物編號	劑量 (μg/kg)	C_{max} (μg/mL)	AUC_{last} (hr*μg/mL)	半衰期 ($t_{1/2}$) (hr)	Vss (mL/kg)	CL (mL/hr/kg)
979	250	78.5	331	9.99	7400	635
980	250	72.4	463	10.6	7136	521
981	250	101	429	19.6	8904	366
平均低劑量	**250**	**84.0 ± 15.1**	**408 ± 69**	**13.4 ± 5.4**	**7813 ± 954**	**507 ± 135**
982	1000	401	3500	43	6943	281
983	1000	414	2746	21.2	6953	361
984	1000	486	4345	25.0	4996	226
平均高劑量	**1000**	**434 ± 45.8**	**3530 ± 800**	**29.7 ± 11.6**	**6297 ± 1127**	**289 ± 67.9**

【0348】 相對於IgG對照(資料未示)，包含抗PD-1 mAb及WT IL-21之同源二聚體融合蛋白展現增加之清除率及較低暴露。因此確定，為增強融合蛋白之暴露及最小化脫靶IL-21作用(亦即最小化在未表現PD-1受體之免疫細胞的IL-21信號傳導)，將需要誘變IL-21以減弱經由IL-21R之信號傳導。因此，包含突變IL-21之融合蛋白經設計以不太強烈地結合於未表現PD-1之細胞上的IL-21R。假定融合蛋白將首先以高親和力結合PD-1標靶(藉由結合抗PD-1抗體)，接著此將驅動IL-21突變蛋白與IL-21R (α鏈)之間的第二較低親和力相互作用。在缺乏PD-1受體的情況下，假定融合蛋白不會結合於未表現PD-1受體之細胞，無論IL-21R表現如何。

【0349】 結構指導之工程改造用於產生一組141種IL-21突變蛋白，與WT IL-21胺基酸序列相比各具有單一胺基酸取代。各突變蛋白經設計以具有降低之對IL-21R之α子單元(101種突變蛋白)或IL-21R之γ子單元(40種突變蛋白)的親和力。該組中之各突變蛋白可表現為具有PD-1 mAb之融合蛋白(PD-1×IL-21突變蛋白)，且隨後使用FortéBio Octet®系統(Pall FortéBio；Fremont, CA)評定其結合於IL-21R之能力，且使用IL-21R+ T細胞株(Hut78)，使用STAT3磷酸化作為IL-21活性之替代，篩選

活性。為選擇具有最低脫靶活性潛能之突變蛋白，設定選擇標準為在PD-1^{-ve}細胞上對比3.7 nM下rhIL-21，IL-21信號傳導減弱超過20倍。

【0350】 141種突變蛋白之完整清單顯示於表4中。

表4

突變體	IL-21 AA 取代	SEQ ID NO:	IL-21 α鏈或γ鏈突變蛋白	IL-21R-Fc Kd (nM)	親和力降低倍數
1	R5D	74	α	NB	
2	R5E	75	α	NB	
3	R5G	76	α	NB	
4	R5H	77	α	WB	
5	R5I	78	α	WB	
6	R5K	79	α	WB	
7	R5L	80	α	WB	
8	R5M	81	α	WB	
9	R5N	82	α	NB	
11	R5S	84	α	WB	
12	R5T	85	α	WB	
13	R5V	86	α	WB	
14	R5Y	87	α	WB	
15	I8A	88	α	WB	
16	I8D	89	α	WB	
17	I8E	90	α	NB	
18	I8G	91	α	WB	
19	I8N	92	α	WB	
22	R9D	95	α	>100	
23	R9E	96	α	NB	
29	R9M	102	α	WB	
30	R9N	103	α	WB	
31	R9Q	104	α	WB	
32	R9S	105	α	WB	
33	R9T	106	α	WB	
34	R9V	107	α	WB	
24	R9G	97	α	約40	
74	K75D	156	α	19.86	
79	R76E	161	α	18.47	738.8
86	R76N	168	α	15.31	612.4
78	R76D	160	α	約12	
77	R76A	159	α	約11	440
43	L13D	112	α	11	440
59	S70P	138	α	約10	
62	K72P	143	α	8.958	

突變體	IL-21 AA 取代	SEQ ID NO:	IL-21 α鏈或γ鏈突變蛋白	IL-21R-Fc Kd (nM)	親和力降低倍數
53	I66P	132	α	7.11	
21	R9A	94	α	6.836	
20	I8S	93	α	約4	160
52	I66G	131	α	4.552	
95	K77P	177	α	2.056	
26	R9I	99	α	2.2	
42	Q12V	249	α	<2.2	88
70	K73P	152	α	約2	80
80	R76G	162	α	約2	80
81	R76H	163	α	約2	80
56	V69P	135	α	1.989	
10	R5Q	83	α	2.1	
27	R9K	100	α	2	
91	R76V	173	α	1.765	
47	Y23D	48	α	1.7	68
28	R9L	101	α	1.6	
96	P78D	61	α	1.228	
73	K73V	155	α	1.071	
89	R76S	171	α	1.05	42
76	K75P	158	α	約1	40
57	S70E	136	α	0.9481	
50	R65P	129	α	0.9	
88	R76Q	170	α	0.7702	
51	I66D	130	α	0.6773	
94	K77G	176	α	0.658	
85	R76M	167	α	約0.6	24
35	R9Y	108	α	0.63	
58	S70G	137	α	0.5181	
c6	D15A	117	γ	0.4389	
64	K73D	146	α	0.4354	
c1	R11D	109	γ	0.4113	
87	R76P	169	α	約0.4	16
37	Q12D	249	α	0.42	
39	Q12N	251	α	0.38	
82	R76I	164	α	0.3159	12.636
97	P79D	62	α	0.3152	
99	S80P	179	α	0.3089	
40	Q12S	252	α	0.32	
92	R76Y	174	α	0.2651	
98	S80G	178	α	0.265	
66	K73G	148	α	0.2528	
61	K72G	142	α	0.2502	

突變體	IL-21 AA 取代	SEQ ID NO:	IL-21 α鏈或γ鏈突變蛋白	IL-21R-Fc Kd (nM)	親和力降低倍數
c7	D15E	118		0.2492	
41	Q12T	253	α	<0.26	
100	R5A	73	α	0.2375	
101	S70Y	139	α	0.2366	
60	K72D	141	α	0.235	
c3	I14A	114	γ	0.2153	
c8	D15I	119	γ	0.2151	
55	V69G	134	α	0.2148	
36	Q12A	111	α	0.23	
c4	I14D	115	γ	0.2022	
83	R76K	165	α	約0.2	8
84	R76L	166	α	約0.2	8
67	K73H	149	α	0.1901	
72	K73S	154	α	0.1667	
c5	I14S	116	γ	0.1658	
c9	D15M	120	γ	0.1633	
75	K75G	157	α	0.1627	
46	Q19D	47	α	0.17	
c2	R11S	110	γ	0.1346	
49	R65G	128	α	0.13	
90	R76T	172	α	0.105	
44	I16D	125	α	0.094	
抗PD-1 Ab*	--			約0.07-0.092	
48	R65D	127	α	0.088	
25	R9H	98	α	0.084	
69	K73N	151	α	0.07368	
65	K73E	147	α	0.07262	
45	I16E	126	α	0.076	
71	K73Q	153	α	0.06919	
63	K73A	145	α	0.0525	
68	K73I	150	α	0.1724	
54	V69D	133	α	0.03952	
38	Q12E	250	α	0.031	
huIL-21**	--			0.025-0.027	
PD-1 Ab***	--			NB	

NB = 無可偵測之結合

WB = 弱結合 (低於可靠定量極限)

IL-21 AA取代係根據SEQ ID NO: 1之胺基酸位置編號。

* 抗PD-1 mAb與人類IL-21 (無突變)融合

** 不呈融合物；僅僅呈人類IL-21存在

*** 不呈融合物；僅僅呈PD-1 Ab存在

【0351】 使用IL-21突變蛋白之STAT3磷酸化分析的例示性結果顯示於圖7 (對IL-21Rα之親和力降低之突變蛋白)及圖8 (對IL-21Rγ之親和力降低之突變蛋白)中。如此等圖中所示，若干突變蛋白顯示在PD-1-ve細胞中IL-21活性減弱超過20倍，但在PD-1+ve細胞中保留活性。如圖9A-9B中所示，突變體51 (R65P) (藍色圓圈)為顯示在PD^{-ve}細胞中IL-21活性降低超過20倍，但展現與rhIL-21在表現PD-1之細胞中所實現之活性類似的IL-21活性水準的一種突變體。表5中提供針對在PD-1低/陰性細胞上STAT3信號減弱超過20倍進行選擇的例示性突變蛋白的清單。

表5

突變體編號	AA 取代	SEQ ID NO:	對 IL-21R 之親和力 (K_D (nM))	親和力降低倍數 [1]	N1		N2	
					$PD\text{-}1^{-ve}$ 降低倍數 (rhIL-21)	$PD\text{-}1^{+ve}$ 降低倍數 (rhIL-21)	$PD\text{-}1^{-ve}$ 降低倍數 (rhIL-21)	$PD\text{-}1^{+ve}$ 降低倍數 (rhIL-21)
20	I8S	93	約 4	160	38.1	4.4	58.8	5.7
42	Q12V	249	<2.2	88	80	2.4	44	6.9
43	L13D	112	11	440	83.8	2.3	25.7	2.6
47	Y23D	48	1.7	68	35.6	1.4	13.7	1.4
70	K73P	152	約 2	80	46.4	1.8	21	1.7
76	K75P	158	約 1	40	25.1	1.7	36	1.6
77	R76A	159	約 11	440	29.9	2.6	20	3
79	R76E	161	18.47	738.8	40.2	2.6	23.2	2.5
80	R76G	162	約 2	80	31.4	1.5	17	1.6
81	R76H	163	約 2	80	23.4	1.5	38.6	1.8
82	R76I	164	0.3159	12.636	25.1	1.5	28.2	1.6
83	R76K	165	約 0.2	8	19.3	1.7	27.4	1.4
84	R76L	166	約 0.2	8	24.4	1.6	29.1	1.5
85	R76M	167	約 0.6	24	21.8	1.4	28.2	1.4
86	R76N	168	15.31	612.4	30.1	3	21.1	4.2
87	R76P	169	約 0.4	16	26.5	1.7	34.4	1.6
89	R76S	171	1.05	42	32.7	1.3	28.9	1.1
C10	D15N	121	11	87.3	16.9	4.1	39.7	4.7
C12	D15S	123	6.6	52.4	16.4	3.2	36.4	3.5
C14	D15V	124	5.471	43.4	20.1	4.7	35	5.7

突變體編號	AA取代	SEQ ID NO:	對IL-21R之親和力(K_D (nM))	親和力降低倍數[1]	N1		N2	
					PD-1^{-ve}降低倍數 (rhIL-21)	PD-1^{+ve}降低倍數 (rhIL-21)	PD-1^{-ve}降低倍數 (rhIL-21)	PD-1^{+ve}降低倍數 (rhIL-21)
C18	S113K	67	8.098	64.3	20.8	3.2	42	3.9
C21	Q116E	182	7.949	63.1	26.9	5.4	52.1	6.5

[1]對比rhIL-21

實例4

【0352】本實例說明用於融合蛋白構築及其活體內測試之候選IL-21突變蛋白的選擇。

【0353】將最高22種效能之IL-21突變蛋白按比例增大以用於進一步測試。基於此進一步測試(在如本文中論述之Hut78 pSTAT3分析中)，選擇四種候選融合蛋白以便該系列四種融合蛋白將顯示一系列減弱(在Hut78 pSTAT3分析中相對於rhIL-21，效力改變)。突變體C10 (D15N)代表低減弱突變蛋白，突變體77 (R76A)代表中等減弱突變蛋白，且突變體79及78 (分別R76E及R76D)代表高減弱突變蛋白。在四種中，三種按比例擴大以用於食蟹獼猴中之活體內研究，以評估突變蛋白融合蛋白構築體之藥物動力學性質。將單劑量(10 mg / kg)突變體79 (R76E)、突變體77 (R76A)或突變體C10 (D15N)靜脈內投與(推注)未處理食蟹獼猴，且在十天時期內，收集血清濃度。為進行比較，藉由靜脈內推注，將抗PD-1 mAb及包含抗PD-1 mAb及WT IL-21之融合蛋白(個別)給與食蟹獼猴。研究用兩種對照物進行：單獨抗PD-1 mAb及包含抗PD-1 mAb及WT IL-21之融合蛋白構築體。如圖10所示，與親本抗PD-1 mAb (黑色三角形)相比，各抗PD-1 mAb-IL-21突變蛋白融合蛋白展現改變之藥物動力學概況。表6提供藉由非房室分析擬合之藥物動力學性質。

表6

構築體	劑量 (mg/kg)	C_{15min} (μg/mL)	AUC_{last} (hr*μg/mL)	Vss (mL/kg)	CL (mL/hr/kg)	半衰期 (hr)
抗PD-1 mAb:IL-21(R76E)[a,b]	10	53 ± 7	309 ± 50	210 ± 30	33 ± 5	26 ± 13
抗PD-1 mAb:IL-21(R76A)[a,b]	10	4.7 ± 1.4	28.2 ± 9.3	2900 ± 700	380 ± 110	21 ± 14
抗PD-1 mAb:IL-21(D15N)[a,b]	10	2.4 ± 1	8.0 ± 2.8	10000 ± 4000	1400 ± 600	15 ± 9
抗PD-1 mAb[a,c]	8.25	200 ± 9	23600 ± 1500	56 ± 5	0.20 ± 0.01	200 ± 18
抗PD-1 mAb:IL-21[c,d]	1.0	0.27 ± 0.02	0.32 ± .02	5600 ± 800	2900 ± 200	2.8 ± 0.2

[a] 非人類靈長類動物研究

[b] 利用人類Fc偵測之人類IL21捕捉

[c] 利用人類Fc偵測之人類Fc捕捉

[d] 非人類靈長類動物研究

實例5

【0354】 本實例說明IL-21雙重突變體小組之產生，及包含IL-21雙重突變體同源二聚體(除非另作說明)之融合蛋白的表現及表徵。

【0355】 基於細胞活性資料(例如在PD-1^{-ve} Hut78 T細胞上活性之減弱程度最高)及可製造性，選擇具有單一胺基酸取代之三種突變蛋白，包括(突變體第77號(R76A)及突變體第79號(R76E))，用於額外工程改造。結構引導之工程改造用於在IL-21單一突變體序列內產生額外突變(亦即產生雙重突變體)，以進一步減弱細胞介素與IL-21R之α鏈(IL-21Rα)的結合。使雙重突變體序列與抗PD-1 mAb之序列融合，且表現融合蛋白且在細胞分析中進行測試。所製造及測試之雙重突變體融合蛋白的清單提供

於表7中。

表7

雙重突變體編號	胺基酸取代	SEQ ID NO:
1	D15N、I71L	214
2	D15N、K72A	215
3	D15N、K73A	216
4	D15N、S70T	213
5	I71L、K73Q	217
6	I71L、R76A	227
7	I71L、R76D	228
8	I71L、R76E	229
9	K72A、K73Q	218
10	K72A、R76A	230
11	K72A、R76D	231
12	K72A、R76E	232
13	K73A、R76A	233
14	K73A、R76D	234
15	K73A、R76E	235
17	S70T、K73Q	255
18	S70T、R76A	246
19	S70T、R76D	247
20	S70T、R76E	248
21	R9E、R76E	245
22	R9A、R76E	243
23	R5E、R76E	239
24	R5A、R76E	237
25	R5Q、R76E	241
26	R9E、R76A	244
27	R9A、R76A	242
28	R5E、R76A	238
29	R5A、R76A	236
30	R5Q、R76A	240

【0356】因為需要具有高減弱特性之雙重突變體融合蛋白，所以選擇標準設定為相對於rhIL-21之效力，在IL-21R陽性、PD-1陰性(PD-1^{-ve}) Hut78 T細胞上效力(EC_{50})超過1000 nM。另外，如同含有單一胺基酸取代之突變蛋白一樣，針對IL-21R結合，對雙重突變體融合蛋白進行表徵(ForteBio Octet)。最終，使用Jurkat PD-1報導基因分析，針對PD-1活

性，對雙重突變體融合蛋白進行表徵。此等分析之結果展示於表8中。

表8

所測試之融合蛋白	Hut78 PD-1+ T細胞(n1)中pSTAT3 EC50 (nM)	Hut78 PD-1+ T細胞(n2)中pSTAT3 EC50 (nM)	Hut78 PD-1- T細胞(n1)中pSTAT3 EC50 (nM)	Hut78 PD-1- T細胞(n2)中pSTAT3 EC50 (nM)	KD (nM) Hu IL-21R	KD (nM) Cyno IL-21R	KD (nM) Hu PD-1	KD (nM) Cyno PD-1
rhIL-21	0.085	0.053	0.056	0.050	0.028-0.037	0.019-0.051	-	-
R76A	0.341	0.147	100.277	35.477	>10 (兩相)	>10 (兩相)	7.5	6.4
R76E	0.744	0.376	194.523	122.87	>10 (兩相)	>10 (兩相)	7.2	6.0
R76E單體	0.197	0.136	23.516	26.965	>10 (兩相)	>10 (兩相)	5.8	7.3
R5E:R76A	1.979	1.487	>1000	>1000	> 300	>300	7.0	5.9
R5Q:R76E	2.211	1.663	>1000	>1000	> 300	>300	6.3	6.3
R9E:R76A	16.6	-	>1000	>1000	> 300	>300	8.9	5.9
抗PD-1 mAb	-	-	-	-	-	-	13.4	6.3

所測試之融合蛋白	hPD1 報導體N1 (nM)	hPD1 報導體N2 (nM)
R76A	1.44	2.17
R76E	0.85	1.68
R76E單體	0.685	0.637
R5Q:R76E	0.954	0.942
抗PD-1 mAb	1.39	1.77

Hu =人類；Cyno =食蟹獼猴

pSTAT3 EC50 (2.5倍變化)

Octet：結合於固定之單價人類及食蟹獼猴IL-21R-his

【0357】 如表8所示，雙重突變體融合蛋白在表現低水準PD-1（例

如低於PD-1之可偵測水準)之T細胞上展現極低IL-21活性，但在表現PD-1之細胞上保留顯著IL-21活性。雙重突變體融合蛋白展現與IL-21R之弱結合(Kd > 300 nM)，但保留與PD-1結合及阻斷PD-1信號傳導之能力。

實例6

【0358】 本實例說明比較包含抗PD-1 mAb及IL-21雙重突變體同源二聚體或IL-21單一突變體同源二聚體之融合蛋白的活體外初級細胞分析。

【0359】 在活體外初級細胞分析(混合淋巴細胞反應(MLR))中測試包含抗PD-1 mAb及具有R5Q及R76E胺基酸取代之IL-21的融合蛋白。MLR包含包括表現IL-21R但不表現PD-1之樹突狀細胞(DC)的IL-21R^{+}細胞、表現PD-1之T細胞及不表現PD-1之T細胞的混合群體。MLR暴露於(i)包含R5Q及R76E胺基酸取代之融合蛋白；(ii)僅僅包含R76E胺基酸取代之融合蛋白；(iii)重組人類IL-21 (rHu IL-21)；(iv)抗PD-1 mAb；(v) rHu IL-21與抗PD-1 mAb之組合；或(vi)對照IgG。

【0360】 如圖11所示，rhIL-21抑制DC功能且當共同給與時主要控制PD-1反應。具有減弱活性之包含IL-21雙重突變蛋白的融合蛋白展現降低之脫靶活性。此外，rhIL-21及僅僅包含R76E胺基酸取代之融合蛋白在DC上各展現顯著脫靶活性且抑制細胞介素產生。相比之下，PD-1 mAb及包含R5Q及R76E胺基酸取代之融合蛋白僅僅遞送IL-21信號至標靶PD-1^{+ve} T細胞(而非PD-1^{-ve}樹突狀細胞)，且保留加強細胞介素產生之能力(經由PD-1臂)。因此，此等結果表明包含IL-21雙重突變體之融合蛋白具有降低之免疫抑制，且對DC激活具有不利影響，且可允許新的T細胞純系募集及更持久之抗癌免疫反應。

實例7

【0361】 本實例說明包含IL-21雙重突變蛋白(同源二聚體)及抗PD-1 mAb之不同融合蛋白在初級細胞毒性T淋巴細胞(CTL)上之活性。藉由FACs量測初級CTL (來自人類供體之CMV反應性CTL細胞株)中的內源性STAT3磷酸化，且用作IL-21信號傳導之量度。結果顯示於圖12A-12C三個圖中。在CTL靜息48小時(以減少PD-1表現)之後，將細胞暴露(10分鐘)於(i)包含IL-21 R5E/R76A雙重突變蛋白之融合蛋白(左圖中之紅線)；(ii)包含IL-21 R5Q/R76E雙重突變蛋白之融合蛋白(中間圖中之紅線)；(iii)包含IL-21 R9E/R76A雙重突變蛋白之融合蛋白(右圖中之紅線)；(iv) IgG1對照物(各圖中之灰線)；(v) rhIL-21 (各圖中之藍線)；(vi)抗PD-1 mAb (各圖中之綠色實線)；(vii) rhIL-21與抗PD-1 mAb之組合(各圖中之綠色點線)；或(viii)包含IL-21 R76E單一突變蛋白之融合蛋白(各圖中之紫線)。FACs結果顯示於圖12A-12C中。包含IL-21雙重突變蛋白之各融合蛋白的IL-21活性相對於用(iv) IgG1對照物、(v) rhIL-21、(vi)抗PD-1 mAb、(vii) rhIL-21與抗PD-1 mAb之組合及(viii)包含IL-21 R76E單一突變蛋白之融合蛋白實現的活性繪圖。此初級細胞分析證明雙重突變體融合物微弱地刺激靜息CTL (其表現低水準之PD-1)中IL-21誘導之STAT3信號傳導。雙重突變蛋白融合物之IL-21活性減弱最多(且類似於在抗PD-1 mAb及IgG1對照物下所見)，其中單一突變體融合物展現中度IL-21活性減弱，且rhIL-21與抗PD-1 mAb之組合具有類似於rhIL-21之活性。

【0362】 亦探索在長期刺激後包含抗PD-1 mAb及IL-21雙重突變蛋白同源二聚體之融合蛋白對CTL介導之細胞毒性功能上的作用。將CTL用CD3/CD28活化且暴露於(i)包含IL-21 R5E/R76A雙重突變蛋白之融合蛋白；(ii)包含IL-21 R5Q/R76E雙重突變蛋白之融合蛋白；(iii)包含IL-21

R9E/R76A雙重突變蛋白之融合蛋白；(iv) IgG4對照物；(v) rhIL-21、(vi)抗PD-1 mAb；或(vii) rhIL-21與抗PD-1 mAb之組合。在刺激七天之後，將細胞與經CMV肽脈衝之黑色素瘤癌細胞株共培養且量測細胞毒性。此分析之結果展示於圖13A-13C中。

【0363】 如圖13A-13C所示，融合蛋白能夠以優於抗PD-1 mAb單一療法之方式維持CTL功能。在長期刺激後IL-21突變蛋白融合蛋白可維持CTL介導之細胞毒性功能。此等結果支持如下觀念：在如在癌症中觀察到之長期活化的條件下IL-21可維持CTL功能。IL-21遞送至PD-1+抗原特異性T細胞可選擇性地維持T細胞群體之功能，此驅動治療功效。

實例8

【0364】 本實例說明雙重突變蛋白構築體之活體內藥物動力學。

【0365】 藉由靜脈內推注，向未處理食蟹獼猴投與包含抗PD-1 mAb及IL-21雙重突變蛋白或IL-21單一突變蛋白之融合蛋白，以表徵藥物暴露。表9顯示向動物投與之各構築體的劑量。單一突變蛋白變異體(IL-21 R76E)呈同源二聚體及單體在活體內進行測試，以更好地瞭解可如何進一步提高暴露。

【0366】 在向未處理食蟹獼猴靜脈內推注後PD-1 mAb及PD-1:IL-21融合物的血清濃度-時間概況展示於圖14中，其中在表9中列出之投與之後第一週觀察到藥物暴露。

表9

動物編號：	構築體：	劑量 (mg/kg)	AUC_{0-168}/劑量 (hr*kg*μg/mL/mg)
	PD-1 mAb [a,b]	8.25	2260 ± 150
	PD-1:IL-21(R76A)同源二聚體[a,c]	10	2.82 ± 0.93

803及804	PD-1:IL-21(R5E/R76A)同源二聚體[d,e]	5	39.1 ± 14.0
801及802	PD-1:IL-21(R76E)同源二聚體[d,e]	5	38.0 ± 19.6
807及808	PD-1:IL-21(R76E)單價[d,e]	5	195 ± 4.8
805及806	PD-1:IL-21(R5Q/R76E)同源二聚體[c,d]	5	114 ± 14

[a] 非人類靈長類動物研究

[b] 利用人類Fc偵測之人類Fc捕捉

[c] 利用人類Fc偵測之人類IL-21捕捉

[d] 非人類靈長類動物研究

[e] 利用人類IL21偵測之PD-1捕捉

【0367】 如表9所示，與同源二聚體R76E融合蛋白相比，單體R76E融合蛋白在靜脈內給與後展現優良暴露。觀察到包含IL-21雙重突變蛋白(R5Q/R76E及R5E/R76A)之融合蛋白的暴露比親本單一突變蛋白同源二聚體融合蛋白構築體(分別R76E及R76A)大(圖14；表9)。

【0368】 亦在食蟹獼猴中活體內測試藥效學(PD)參數。使用不競爭PD-1之抗體測定PD-1表現，且此PD-1取樣在第-5天、第7天及第21天發生。在第1天給與動物第一劑(i)包含抗PD-1 mAb及IL-21 R76E單一突變蛋白之同源二聚體的融合蛋白；(ii)包含抗PD-1 mAb及IL-21 R76E單一突變蛋白之單體的融合蛋白；或(iii)包含抗PD-1 mAb及IL-21 R5Q / R76E雙重突變蛋白之融合蛋白，且在第8天給與第二劑。參見圖15A。

【0369】 圖15B-15D顯示如在第7天量測之PD-1陽性/CD4陽性細胞之變化倍數(相對於第-5天) (圖15B)，如在第7天量測之PD-1陽性/CD8陽性細胞之變化倍數(相對於第-5天) (圖15C)，及如在第21天量測之PD-1陽性/CD8陽性細胞之變化倍數(相對於第-5天) (圖15D)。

【0370】 如圖15B-15D所示，即使單劑包含抗PD-1 mAb及IL-21雙重突變體之融合蛋白亦擴增周圍PD-1+/CD8+ T細胞。此研究證明雙重突變體融合蛋白能夠以優於單一突變蛋白親本變異體之方式顯著擴增PD-1+ CD8 T細胞。

【0371】 亦檢查PD生物標記物之差異，且資料表明在投與單劑後單體構築體具有較低標靶覆蓋及PD反應，但在投與多劑後PD及標靶覆蓋之變化相等。此等資料表明融合蛋白之PK特性可用單體格式進一步提高。

【0372】 如圖16所示，雙重突變體(動物803、805、806)在CD8+細胞上之受體佔用率(RO)一般與PD-1+ CD8 T細胞擴增相關。單一突變體同源二聚體構築體(動物801、802)無法擴增PD-1+ CD8 T細胞，可能係由於其相對不良之藥物動力學特性。值得注意地，具有更合乎需要之藥物動力學特性的雙重突變蛋白構築體擴增PD-1+ CD8 T細胞且PD反應與標靶覆蓋相關。資料表明雙重突變體融合蛋白可擴增已知與保護性抗腫瘤免疫有關之相關T細胞群體。

【0373】 圖17展示在重複給與後CD8+ T細胞中之PD-1標靶覆蓋類似於針對抗PD-1 mAb所觀察到的(抗PD-1 mAb資料未示)。總而言之，關於雙重突變體，圖16及17支持如下觀念：標靶群體(PD-1+ CD8 T細胞)之調節需要足夠標靶覆蓋且提高之標靶覆蓋與提高之藥效學反應有關。

實例9

【0374】 本實例說明一組包含不同抗PD-1 mAb與變化同二聚體IL-21雙重突變蛋白融合之融合蛋白的產生。

【0375】 如實例12中所述，產生一組抗PD-1 mAb且進行測試，且使主要mAb與某些IL-21雙重突變蛋白融合。在PD-1^{-ve}與PD-1^{+ve} Hut78 T

細胞中，使用STAT3磷酸化分析測試十二種包含同二聚體IL-21雙重突變蛋白及抗PD-1 mAb之融合蛋白的IL-21活性，使用ForteBio Octet分析測試IL-21R結合及PD-1結合，使用PD-1 Jurkat報導體分析測試PD-1活性，且使用MLR (混合淋巴細胞反應)分析測試活體外活性。此等實驗基本上如先前實例中所述進行。

【0376】十二種包含抗PD-1 mAb及IL-21雙重突變蛋白之融合蛋白及如此等分析中量測之其活性的清單提供於表10-12中。

表10

如藉由STAT3磷酸化分析量測之IL-21活性

PD-1 mAb	IL-21 雙重突變蛋白之胺基酸取代	Hut78 (n1) PD-1^{+ve} EC50 (nM)	Hut78 (n2) PD-1^{+ve} EC50 (nM)	Hut78 (n1) PD-1^{-ve} EC50 (nM)	Hut78 (n2) PD-1^{-ve} EC50 (nM)
A-1-003 (20A2.003)	(R5A、R76E)	7.55	14.74	>1000	>1000
A-1-003 (20A2.003)	(R5Q、R76E)	3.37	16.9	>1000	>1000
A-1-003 (20A2.003)	(R5E、R76A)	5.70	25.07	618.28	>1000
A-1-003 (20A2.003)	(R9E、R76A)	25.26	59.10	>1000	>1000
A-4-006 (20C1.006)	(R5A、R76E)	7.40	15.33	>1000	>1000
A-3-009 (20C1.009)	(R5Q、R76E)	3.75	16.39	>1000	>1000
A-3-009 (20C1.009)	(R5E、R76A)	5.27	10.71	471.56	>1000
A-3-009 (20C1.009)	(R9E、R76A)	19.44	56.43	>1000	>1000
A-2-006 (22D4.006)	(R5A、R76E)	6.90	8.04	>1000	>1000
A-2-006 (22D4.006)	(R5Q、R76E)	4.45	10.32	>1000	>1000
A-2-006 (22D4.006)	(R5E、R76A)	5.34	13.11	652.02	826.11
A-2-006 (22D4.006)	(R9E、R76A)	17.41	45.63	>1000	>1000
rhIL-21(av)	-	0.15	0.625	0.22	0.715

PD-1 mAb	IL-21 雙重突變蛋白之胺基酸取代	Hut78 (n1) PD-1^{+ve} EC50 (nM)	Hut78 (n2) PD-1^{+ve} EC50 (nM)	Hut78 (n1) PD-1^{-ve} EC50 (nM)	Hut78 (n2) PD-1^{-ve} EC50 (nM)
抗 PD-1 mAb (IgG4 同型)		-	-	-	-
抗 PD-1 mAb (IgG1 同型)		-	-	-	-
第二抗PD-1 mAb (IgG4 同型)		-	-	-	-

表11

IL-21R結合及PD-1結合

PD-1 mAb	IL-21雙重突變蛋白之胺基酸取代	IL-21R Hu Kd (nM)	IL-21R Cy Kd (nM)	hPD-1 Kd (nM)	CyPD-1 Kd (nM)
A-1-003 (20A2.003)	(R5A、R76E)	>300	>300	1.9	3.1
A-1-003 (20A2.003)	(R5Q、R76E)	>300	>300	2.4	2.6
A-1-003 (20A2.003)	(R5E、R76A)	>300	>300	4.4	4.7
A-1-003 (20A2.003)	(R9E、R76A)	>300	>300	1.5	3.3
A-4-006 (20C1.006)	(R5A、R76E)	>300	>300	0.8	1.6
A-3-009 (20C1.009)	(R5Q、R76E)	>300	>300	0.7	1.4
A-3-009 (20C1.009)	(R5E、R76A)	>300	>300	0.9	2.3
A-3-009 (20C1.009)	(R9E、R76A)	>300	>300	0.7	1.7
A-2-006 (22D4.006)	(R5A、R76E)	>300	>300	1.0	1.5
A-2-006 (22D4.006)	(R5Q、R76E)	>300	>300	1.2	1.4
A-2-006 (22D4.006)	(R5E、R76A)	>300	>300	1.2	1.0
A-2-006 (22D4.006)	(R9E、R76A)	>300	>300	1.3	1.3
rhIL-21(av)	-	0.038	<0.010	-	-
抗 PD-1 mAb (IgG4 同型)		-	-	約9	約9

PD-1 mAb	IL-21雙重突變蛋白之胺基酸取代	IL-21R Hu Kd (nM)	IL-21R Cy Kd (nM)	hPD-1 Kd (nM)	CyPD-1 Kd (nM)
抗 PD-1 mAb (IgG1同型)		-	-	約6	約4
第二抗PD-1 mAb (IgG4同型)		-	-	2.4	1.0

表12

PD-1活性及MLR

PD-1 mAb	IL-21雙重突變蛋白之胺基酸取代	hPD-1 報導體N1 (nM)	hPD-1 報導體N1 (nM)	MLR N1 IL-2 (nM)	MLR N2 IL-2 (nM)
A-1-003 (20A2.003)	(R5A、R76E)	0.748	0.622	3.438	2.198
A-1-003 (20A2.003)	(R5Q、R76E)	0.997	0.805	4.021	1.821
A-1-003 (20A2.003)	(R5E、R76A)	0.344	0.47	2.472	1.397
A-1-003 (20A2.003)	(R9E、R76A)	0.788	0.712	2.872	1.252
A-4-006 (20C1.006)	(R5A、R76E)	-	-	-	-
A-3-009 (20C1.009)	(R5Q、R76E)	0.472	0.738	1.04	1.186
A-3-009 (20C1.009)	(R5E、R76A)	0.445	0.46	0.345	0.77
A-3-009 (20C1.009)	(R9E、R76A)	0.669	0.409	1.191	0.68
A-2-006 (22D4.006)	(R5A、R76E)	0.331	0.269	0.469	0.88
A-2-006 (22D4.006)	(R5Q、R76E)	0.369	0.255	0.769	0.458
A-2-006 (22D4.006)	(R5E、R76A)	0.281	0.177	0.59	0.31
A-2-006 (22D4.006)	(R9E、R76A)	0.429	0.112	1.042	0.446
rhIL-21(av)	-	-	-	-	-
抗 PD-1 mAb (IgG4同型)		1.915	2.905	1.354	3.216
抗 PD-1 mAb (IgG1同型)		-	-	-	-

PD-1 mAb	IL-21雙重突變蛋白之胺基酸取代	hPD-1報導體N1 (nM)	hPD-1報導體N1 (nM)	MLR N1 IL-2 (nM)	MLR N2 IL-2 (nM)
第二抗PD-1 mAb (IgG4同型)		0.555	0.695	0.627	0.708

【0377】 若非全部，則大多數候選融合蛋白與兩種抗PD-1 mAb效能一樣佳(若非更佳)。若干在MLR分析中顯示針對PD-1活性之效力大於或等於抗PD-1 mAb之效力。

【0378】 在12種候選融合蛋白中，選擇兩種進行進一步研究。兩種中之一種具有包含R5Q/R76E突變之IL-21雙重突變蛋白，且第二種具有包含R9E/R76A突變之IL-21雙重突變蛋白。與PD-1 mAb小組不同的抗PD-1 mAb用於與兩種IL-21突變蛋白中之一種一起製造融合蛋白。十種抗PD-1 mAb用於R5Q/R76E融合蛋白，包括20A2.003 (橙色菱形)、20C1.006 (紅色正方形)、20C1.009 (綠色三角形)及22D4.006 (暗紫色圓形)抗PD-1 mAb。七種抗PD-1 mAb用於R9E/R76A融合蛋白，包括20A2.003 (紫色三角形)、20C1.006 (紅色正方形)、20C1.009 (綠色三角形)及22D4.006 (黑色圓形)抗PD-1 mAb。使用STAT3磷酸化分析測試融合蛋白之IL-21活性，基本上如本文所述。圖18A-18B及19A-19B顯示相對於rhIL-21信號(熱粉色線)，在PD-1^{-ve}及PD-1^{+ve} HUT78 T細胞中之活性。如此等圖所示，融合蛋白在PD-1^{-ve} HUT78 T細胞中展現>1000倍減弱，但在PD-1^{+ve} HUT78 T細胞中保留效力。

實例10

【0379】 本實例說明一組包含不同抗PD-1 mAb與變化單體及同二聚體IL-21雙重突變蛋白融合之融合蛋白的產生。

【0380】 產生一組包含抗PD-1 mAb及單體或同二聚體IL-21雙重突

變蛋白之融合蛋白。包含抗PD-1 mAb及IL-21雙重突變蛋白之一系列融合蛋白提供於表13中。

表13

PD-1 mAb	IL-21雙重突變蛋白之胺基酸取代	IL-21突變蛋白：同源二聚體或單體	融合蛋白之IL-21突變蛋白部分之SEQ ID NO:
A-2-006 V4 (22D4.006 V4)	R5E/R76A	單體	238
A-2-006 V4 (22D4.006 V4)	R9E/R76A	單體	244
A-2-006 V4 (22D4.006 V4)	R5A/R76E	單體	237
A-2-006 V4 (22D4.006 V4)	R5Q/R76E	單體	241
A-2-006 (22D4.006)	R5E/R76A	同源二聚體	238
A-2-006 (22D4.006)	R9E/R76A	同源二聚體	244
A-2-006 (22D4.006)	R5A/R76E	同源二聚體	237
A-2-006 (22D4.006)	R5Q/R76E	同源二聚體	241
A-2-006 V106 (22D4.006 V106)	R5Q/R76E	單體	241
A-2-006 V112	R5Q/R76E	單體	241
A-2-006 V106 (22D4.006 V106)	R9E/R76A	單體	244
A-2-006 V112 ((22D4.006 V112)	R9E/R76A	單體	244
A-1-003 V4 (20A2.003 V4)	R5E/R76A	單體	238
A-1-003 V4 (20A2.003 V4)	R9E/R76A	單體	244
A-1-003 V4 (20A2.003 V4)	R5A/R76E	單體	237
A-1-003 V4 (20A2.003 V4)	R5Q/R76E	單體	241
A-1-003 (20A2.003)	R5E/R76A	同源二聚體	238
A-1-003 (20A2.003)	R9E/R76A	同源二聚體	244
A-1-003 (20A2.003)	R5A/R76E	同源二聚體	237
A-1-003 (20A2.003)	R5Q/R76E	同源二聚體	241
A-1-003 V106 (20A2.003 V106)	R5Q/R76E	單體	241
A-1-003 V112 (20A2.003 V112)	R5Q/R76E	單體	241
A-1-003 V106 (20A2.003 V106)	R9E/R76A	單體	244
A-1-003 V112 (20A2.003 V112)	R9E/R76A	單體	244
rhIL-21(av)	-		
抗PD-1 mAb (IgG4同型)			
抗PD-1 mAb (IgG1同型)			
第2抗PD-1 mAb (IgG4同型)			

【0381】 在PD-1^{-ve}與PD-1^{+ve} Hut78 T細胞中，使用STAT3磷酸化分析測試融合蛋白之IL-21活性，使用ForteBio Octet分析測試IL-21R結合

及PD-1結合，使用PD-1 Jurkat報導體分析測試PD-1活性，且使用MLR分析測試活體外活性。此等實驗基本上如先前實例中所述進行。如此等活體外分析中量測之活性展示於圖20-23中。

【0382】 圖20A-20D表示在若干抗PD-1 mAb-IL-21單體或同二聚體雙重突變蛋白融合物下觀察到的pSTAT3信號傳導之量。用rhIL-21刺激之pSTAT3信號傳導以紅色展示於圖頂部，而用IgG1對照物刺激之pSTAT3信號傳導以灰色展示(圖底部)，且用IgG2對照物刺激之pSTAT3信號傳導以橙色顯示(圖底部)。經抗PD-1 mAb (呈mAb存在；亦即，並非呈融合物)刺激之pSTAT3信號傳導以綠色顯示(圖底部)。用對照抗PD-1 mAb刺激之pSTAT3信號傳導以橙色及黃色顯示(圖底部)，而其餘線代表在用抗PD-1 mAb-IL-21單體或二聚雙重突變蛋白融合物(具有多個電荷對突變)刺激後實現之pSTAT3信號傳導，其中雙重突變體為R5E/R76A；R9E/R76A；R5A/R76E或R5Q/R76E。如此組圖所示，rhIL-21顯示在PD-1^{-ve}與PD-1^{+ve}細胞中之活性。相比之下，單體及同二聚體雙重突變蛋白融合物僅僅在PD-1^{+ve}細胞中能夠顯示pSTAT3 (基於IL-21)活性，而在PD-1^{-ve}細胞中則不能。因此，具有IL-21雙重突變體之單體融合物展現與其對應二聚融合物類似水準的在PD-1^{-ve}細胞中之IL-21活性減弱及PD-1^{+ve}細胞中之IL-21活性拯救。

【0383】 在PD-1報導基因分析(RGA；圖21A及21B)及MLR分析(圖21C及21D)中測試在圖20A-20D中評估之融合蛋白。圖21A-21D中所示之結果證明抗PD-1 mAb-IL-21單體及二聚雙重突變蛋白融合物能夠誘導PD-1活性。

【0384】 測試除不同抗PD-1 mAb外，與圖20A-20D中之構築體相

同之抗PD-1 mAb-IL-21單體及二聚雙重突變蛋白融合物構築體的pSTAT3分析之結果展示於圖22A-22D中。圖22A-22D中之結果類似於圖20A-20D中所見之結果。

【0385】 測試除不同抗PD-1 mAb外，與圖21A-21D中之構築體相同之抗PD-1 mAb-IL-21單體及二聚雙重突變蛋白融合物構築體的PD-1報導基因分析及MLR分析之結果展示於圖23A-23D中。

【0386】 此等資料證明包含IL-21雙重突變蛋白之融合蛋白部分減弱可無需同源二聚體組態。選擇以下雙重突變蛋白(呈單體或同源二聚體融合)與抗PD-1 mAb融合(表14)，用於進一步評估。

表14

	IL-21突變蛋白	**格式**
A-2-017 (22D4.017)	R5Q:R76E	同源二聚體
A-2-017 (22D4.017)	R5Q:R76E	V1單體
A-2-017 (22D4.017)	R9E:R76A	同源二聚體
A-2-017 (22D4.017)	R9E:R76A	V1單體

【0387】 基於細胞之資料表明此等突變蛋白在與PD-1抗體融合時，可選擇性地靶向表現PD-1受體之T細胞(使用T細胞株證明)。此等雙官能PD-1×IL-21分子具有自融合分子之各臂(抗PD-1 mAb及IL-21突變蛋白)獲得之獨特性質。

實例11

【0388】 以下材料及方法用於實例中。

抗PD-1 Ab-IL-21突變蛋白融合物之產生

【0389】 將重組抗PD-1 Ab-IL-21突變蛋白序列選殖至pTT5中以在HEK293-6E中短暫表現，或選殖至含有抗生素選擇卡閘之載體中以在CHO-K1細胞中穩定表現。表現產生在36℃下進行5-7天，且收穫上清液進行純化。所有蛋白質批次藉由蛋白A親和層析法(Mab Select SuRe)來純化，接著陽離子交換

(SP Sepharose HP)，且緩衝液交換(UF/DF)成A5.2Su緩衝液。藉由尺寸排阻層析，所有批次均>95%主峰，其中內毒素< 0.2 EU/mg (Endosafe LAL, Charles River)。

Jurkat PD-1報導基因分析

【0390】將GloResponse Jurkat NFAT-luc2/PD-1穩定效應細胞(Promega，#CS187102)及CHO PD-L1穩定細胞株(Promega，#CS178103)以1.25:1之比率在連續稀釋之抗體存在下在37℃、5% CO_2下一式三份地共培養6小時。使用Bio-Glo螢光素酶分析系統(Promega，#G7940)量測發光。

STAT3磷酸化分析

【0391】pSTAT3 AlphaScreen. 接著將HuT 78親本及HuT 78 PD-1穩定細胞株在連續稀釋之抗體存在下在37℃、5% CO_2下以每孔40,000個細胞一式三份地接種至單獨盤上，歷時40分鐘。使用AlphaLisa Surefire Ultra Pstat3 (Tyr705)分析套組(Perkin Elmer，#ALSU-PST3-A10K)量測Pstat3 Tyr705水準。

【0392】HTRF磷酸化STAT3分析. 將細胞在補充有1% L-麩醯胺酸之RPMI 1860培養基(HyClone目錄號SH30034.01)中血清饑餓隔夜。接著使細胞以2.5×10^6細胞/毫升懸浮於不含鈣及鎂之漢克平衡鹽液(Hanks' Balanced Salt Solution)(HBSS；ThermoFisher目錄號14175095)中，且8微升/孔塗鋪在384孔小體積白色盤(Perkin Elmer目錄號6008289)。接著在37℃下用在HBSS中稀釋之4微升/孔IL-21突變蛋白分子刺激細胞40分鐘。根據製造商之建議(Cisbio目錄號64NT3PEH)使用HTRF®磷酸化-STAT3 (Tyr705)分析套組，偵測STAT3磷酸化。使用EnVision Multilable盤式讀數器(Perkin Elmer)偵測來自分析之FRET信號。藉由如Cisbio所建議，首先測定HTRF比率，接著使用來自未受刺激之細胞的資料計算相對於背景值之倍數來分析資料。對於每個實驗，繪製給與曲線，

且所給與分子之效力表示為觀察到界定之相對於背景值之倍數的濃度。

混合淋巴細胞反應(MLR)

【0393】自AllCells公司獲得錯配供體對leukopak。使用全T細胞分離套組(Milteny Biotec，# 130-096-535)分離供體T細胞，且使用全單核細胞分離套組(Miltenyi Biotec，#130-096-537)分離錯配供體之單核細胞。使用CellXVivo人類單核細胞衍生之樹突狀細胞分化套組(R&D Systems，#CDK004)使單核細胞進一步成熟10天。將全T細胞與成熟單核細胞在37℃、5% CO_2下在連續稀釋之抗體存在下以10:1之比率一式三份地培養72小時。藉由ELISA (Mesoscale Discoveries，#K151QQD-4)量測上清液IL-2水準。

IL-21R及PD-1結合分析

【0394】**人類及食蟹獼猴IL-21R結合親和力**：測試單價IL-21R-FLAG-His與二價IL-21R-Fc重組試劑，但產生非常類似之結果(約2-3倍內)。重組可溶性IL-21R試劑最低程度地生物素化，且捕捉在抗生蛋白鏈菌素SAX尖端上至2.0 nm負載水準。接著將尖端在其中PD-1抗體-IL-21樣品3倍連續稀釋之孔中培育。對於野生型IL-21融合物，最高樣品濃度為10 nM，而對於IL-21突變蛋白融合物，最高樣品濃度為300 nM。20分鐘之締合時間及1.5小時之解離時間用於最大化結合圖中之曲率以得到準確動力學擬合。

【0395】**人類及食蟹獼猴PD-1結合親和力**：人類及食蟹獼猴PD-1結合親和力藉由首先經由EDC-NHS胺與AR2G尖端偶合來捕捉PD-1抗體-IL-21樣品進行測試；樣品負載通常在pH 6下進行2000秒，接著用1 M乙醇胺淬滅，以固定至少2 nm水準。一旦樣品固定，將尖端在含有可溶性重組受體人類PD-1(1-170)-FLAG-His或食蟹獼猴PD-1(1-167)-FLAG-His之3倍連續稀釋液的孔中培育。在兩種情況下，最高PD-1濃度為30 nM。使用300秒之締合及500秒之解

離，因為其產生足夠曲率用於準確動力學擬合。

【0396】 用ForteBio Octet HTX及RED384儀器定量以上人類/食蟹獼猴IL-21R及人類/食蟹獼猴PD-1結合親和力。在所有情況下，標準Octet樣品緩衝液用於樣品稀釋及所有結合基線、締合及解離步驟(10 mM Tris pH 7.5、150 mM NaCl、1 mM CaCl2、0.10 mg.ml BSA、0.13% (v/v) Triton X-100)。

【0397】 所有ForteBio原始數據均以下列方式使用標準儀器數據分析軟體(v9及v10)進行處理：(a)將具有固定標靶但無相互作用(亦即僅僅緩衝液)之兩種參考尖端曲線求平均值且自相同管柱中之剩餘樣品尖端曲線中減去；(b)分離締合與解離曲線且對準Y軸；(c)對準締合及解離中間步驟；(d)執行薩維茨基-格雷過濾(Savitzky-Golay filtering)以減少信號雜訊；及(e)所得到之各樣品-標靶相互作用之締合及解離曲線組整體上擬合單一1:1結合模型，以確定締合速率常數k_a及解離速率常數k_d之量測值；平衡解離常數K_D計算為解離速率與締合速率常數之比率(= k_d/k_a)。

實例12

【0398】 本實例描述用於包含IL-21突變蛋白之融合蛋白中的抗PD-1 mAb之產生。

抗PD-1免疫反應之產生

小鼠品系

【0399】 藉由對XENOMOUSE®轉殖基因小鼠進行免疫接種來產生針對人類PD-1之完全人類抗體(美國專利第6,114,598號；第6,162,963號；第6,833,268號；第7,049,426號；第7,064,244號，其以引用的方式整體併入本文中；Green等人，1994, Nature Genetics 7:13-21；Mendez等人，1997, Nature Genetics 15:146-156；Green及Jakobovits, 1998, J. Ex. Med, 188:483-495；

Kellerman及Green, Current Opinion in Biotechnology 13, 593-597, 2002)。來自XMG4-K及XMG4-KL XENOMOUSE®品系之動物用於此等免疫接種。

免疫接種

【0400】 基於細胞之免疫接種途徑用於產生抗人類PD-1免疫反應。將CHO-S細胞用經由Gly-Ser-Ser連接子與E3K T細胞抗原決定基標籤融合之人類PD-1或者食蟹獼猴PD-1作為免疫原來源短暫轉染。將動物用此等經短暫轉染之CHO細胞中之任一者進行免疫接種，將Alum與CpG-ODN混合，使用TIP (尾根及腹膜內)注射在8週內進行13次。初始之增強免疫由四百萬表現人類PD-1之細胞構成，而隨後之增強免疫含有兩百萬表現人類或食蟹獼猴PD-1之細胞。用人類PD-1 (1-6、8、10及13)進行總共9次免疫接種，且剩餘4次免疫接種用食蟹獼猴PD-1進行。在第10次增強免疫之後將動物放血，以評定PD-1特異性力價。

【0401】 藉由Accuri流式細胞儀上活細胞FACS分析，監測PD-1特異性血清力價。簡言之，將HEK293細胞用人類或食蟹獼猴PD-1模擬轉染或短暫轉染。將來自經免疫接種之動物的血清稀釋100倍且在轉染細胞上冰上培育1小時。接著洗滌細胞，以移除未結合之抗體，且用Cy5標記之二級抗人類Fc特異性抗體在細胞上在4℃下額外培育15分鐘。將細胞洗滌一次，以移除未結合之二級抗體，且藉由FACS定量細胞上之螢光信號。針對人類及食蟹獼猴PD-1具有最高抗原特異性血清天然力價的動物用於產生雜交瘤(Kohler及Milstein, 1975)。

免疫原	佐劑	品系	收穫
人類PD-1或食蟹獼猴PD-1短暫轉染至CHO-S	Alum + CpG ODN	G4K	4隻小鼠
		G4KL	4隻小鼠

單株抗體之製備

雜交瘤產生

【0402】 鑑別展現合適血清力價之動物且自脾及/或引流淋巴結獲得淋巴

細胞。藉由在合適培養基(例如達爾伯克改良伊格爾培養基(Dulbecco's Modified Eagle Medium，DMEM)；Invitrogen, Carlsbad, CA)中研磨，自淋巴組織解離彙集之淋巴細胞(來自各次收穫)。使用標準方法選擇及/或擴增B細胞，且使用此項技術中已知之技術與合適融合搭配物融合。

膜製劑之產生：

【0403】使用293fectin™轉染試劑(Thermo Fisher，目錄號：12347019)將2000萬293T細胞用pTT5-mini4:huPD-1::GSS:E3K轉染。在轉染之後24小時，藉由將293T細胞在含有EZ-Link™ NHS-LC-LC-生物素(Thermo Fisher，目錄號：21343)之pH 8.6 PBS中以400 μg/mL培育30分鐘，將該等細胞生物素化。接著在中性pH PBS中洗滌細胞，接著再懸浮於含有無EDTA之蛋白酶抑制劑及10% triton X100之低滲緩衝液中。藉由經具有26規格針之注射器重複抽吸使細胞破碎。藉由在12000G下離心20分鐘，使細胞片段粒化。接著收集含有膜顆粒之上清液，且在Amicon Ultracel 100k離心管柱(Millipore，目錄號UFC810024)中用PBS洗滌3次，以移除清潔劑。接著在追蹤命中(對PD-1具有特異性之陽性對照雜交瘤細胞)上測試膜製劑以檢查IgG相關之膜製劑結合。接著將膜製劑等分試樣，且冷凍在-20℃下，直至使用。

雜交瘤細胞之抗原特異性染色：

【0404】將雜交瘤細胞自燒瓶移除，且在無菌FACS緩衝液(含2% FBS之PBS)中洗滌。接著將細胞與PD-1膜製劑(在FACS緩衝液中1:10稀釋，1 mL反應體積，例如900 μL FACS緩衝液中100 μL膜製劑)混合且在4℃下培育1小時。將細胞再次在FACS緩衝液中洗滌，且用1 mL含有5 μg/mL Alexa Fluor 488結合之F(ab')2片段山羊抗人類IgG Fc (Jackson，目錄號：109-546-098)及Alexa Fluor 647結合之抗生蛋白鏈菌素(Jackson，目錄號：016-600-084)的偵測混合物染

色，接著在4℃下在黑暗中培育30分鐘。將細胞再次在FACS緩衝液中洗滌，再懸浮於培養基中，接著穿過40微米細胞過濾器以移除聚集之細胞。使用BD FACSAria 3，藉由對展現Alexa Fluor 488與Alexa Fluor 647螢光之群體(IgG+及抗原結合細胞)進行閘控，將抗原特異性細胞分類。

【0405】 將經分類之細胞在雜交瘤培養基中培養幾天。取出富集細胞之小樣品，且使用與如上所提及相同的染色條件，測試與PD-1膜製劑之結合。在證實PD-1特異性細胞成功富集之後，接著使用BD FACSAria 3，將雜交瘤進行單細胞分類至384孔微量滴定盤。在培養2週之後，自微量滴定盤收集上清液，且針對PD-1結合進行篩選。

PD-1特異性結合抗體之初始選擇

【0406】 藉由Cell Insight，針對與在HEK293細胞上短暫表現之人類PD-1的結合，測試耗盡型雜交瘤上清液。簡言之，使用293Fectin將HEK293細胞用編碼PD-1之哺乳動物表現構築體短暫轉染。第二天，將15 μL耗盡型雜交瘤培養基添加至384孔FMAT盤之各孔中。接著將經轉染之HEK293細胞(270萬/mL)、核染劑Hoechst 33342 (7.5 μg/mL)及二級偵測抗體(0.75 μg/mL-山羊抗人類IgG (H+L) Alexa 488 (Jackson ImmunoResearch))混合，且將30 μL此混合物添加至384孔FMAT盤之各孔中。在約3小時之後，使用AquaMax盤式讀數器吸出上清液，且使用多點儀器將30 μL FACS緩衝液添加至各孔中。將盤置於Big Bear盤式震盪器上，以使細胞均勻分佈在孔中，接著在Cell Insight平台上使用Cell Health Bio-App讀取。此分析可鑑別出來自此次收穫之383種抗原特異性抗體。

Jurkat人類PD-1/NFAT-螢光素酶報導體分析

【0407】 將穩定表現人類PD-1及NFAT-螢光素酶報導體之Jurkat細胞

(Promega)在補充有10%胎牛血清(Sigma)、2 mM L-麩醯胺酸(Sigma)、10 mM HEPES (Hyclone, GE Healthcare Life Sciences)、500 μg/mL遺傳黴素(geneticin) (Gibco Life Technologies)、100 μg/mL潮黴素B (Invitrogen)之RPMI 1640培養基(Sigma)中在37℃/5% CO_2下培養。將穩定表現食蟹獼猴PD-1及NFAT-螢光素酶報導體之Jurkat細胞(Promega)在補充有10%胎牛血清(Sigma)、2 mM L-麩醯胺酸(Sigma)、10 mM HEPES (Hyclone, GE Healthcare Life Sciences)、200 μg/mL潮黴素B (Invitrogen)、300 μg/mL zeocin (Invitrogen)之RPMI 1640培養基(Sigma)中在37℃/5% CO_2下培養。將穩定表現人類PD-L1之中國倉鼠卵巢(CHO)純系細胞株99 (Promega)在Nutrient Mixture F12 HAM (Sigma)、10%胎牛血清、10 mM HEPES、250 μg/mL遺傳黴素、200 μg/mL潮黴素B中在37℃/5% CO_2下培養。在實驗當天，將Jurkat NFAT-螢光素酶/PD-1細胞及CHO純系99 PD-L1細胞(用胰蛋白酶分離)在200×g下離心5分鐘，且再懸浮於分析培養基(RPMI 1640培養基、2%胎牛血清、15 mM HEPES)中。在384孔黑色/透明底分析盤(Corning)中使用分析緩衝液稀釋及滴定測試分子。藉由首先以1:1比率混合所製備之細胞，接著添加細胞混合物至分析盤中，將所製備之細胞以40,000細胞/孔接種。將盤在37℃/5% CO_2下培育18至24小時。藉由Bio-Glo螢光素酶分析系統試劑(Promega)量測產生之螢光素酶之量，接著將盤在室溫下培育20分鐘，且用EnVision盤式讀數器(PerkinElmer)偵測發光。對於單點分析，首先定量ESN樣品，標準化且以0.5 μg/mL測試。為測定效力，將ESN樣品或純化抗體在分析培養基中連續滴定3倍且用於處理人類或食蟹獼猴PD-1報導細胞。在單一濃度篩選及效力分級期間顯示所需活性之抗體數目展示於表15中。

表15

單點	效力分級	獨特序列
86 / 383	12 / 86	4 / 12

【0408】 經純化之抗PD-1抗體(對於所示人類PD-1分析，n = 1)的活性展示於圖24中且在人類及食蟹獼猴PD-1報導體分析中純化之抗PD-1抗體之效力列於表16中。

表 16

Ab ID	效力(nM)			
	人類PD-1 n=1	人類PD-1 n=2	食蟹獼猴PD-1 n=1	食蟹獼猴PD-1 n=2
A-1 (20A2)	3.10	1.27	2.34	ND
A-3 (20C1)	5.51	1.88	5.17	4.16
A-2 (22D4)	2.43	0.71	2.72	2.89

PD-1 拮抗劑抗體之分子拯救及測序

【0409】 使用Qiagen RNeasy mini或Invitrogen mRNA catcher plus套組，自含有產生PD-1拮抗劑抗體之雜交瘤細胞的孔純化RNA (總RNA或mRNA)。經純化之RNA用於使用cDNA合成，經由逆轉錄、接著聚合酶鏈反應(RT-PCR)來擴增抗體重鏈及輕鏈可變區(V)基因。使用Qiagen單步逆轉錄酶PCR套組(Qiagen)獲得完全人類抗體γ重鏈。此方法用於自RNA模板產生第一鏈cDNA，接著使用多路PCR擴增γ重鏈之可變區。將5' γ鏈特異性引子與抗體重鏈之信號序列黏接，而3'引子與γ恆定域之區域黏接。使用Qiagen單步逆轉錄酶PCR套組(Qiagen)獲得完全人類κ輕鏈。此方法用於自RNA模板產生第一鏈cDNA，接著使用多路PCR擴增κ輕鏈之可變區。將5' κ輕鏈特異性引子與抗體輕鏈之信號序列黏接，而3'引子與κ恆定域之區域黏接。使用Qiagen單步逆轉錄酶PCR套組(Qiagen)獲得完全人類λ輕鏈。此方法用於自RNA模板產生第一鏈cDNA，接著使用多路PCR擴增λ輕鏈之可變區。將5' λ輕鏈特異性引子與輕鏈之信號序列黏接，而3'引子與λ恆定域之區域黏接。

【0410】 使用外切核酸酶I及鹼性磷酸酶將擴增之cDNA以酶法純化，且直接對經純化之PCR產物測序。藉由生物資訊學方法，自對應核酸序列推導出

胺基酸序列。各雜交瘤樣品完成兩次額外獨立之RT-PCR擴增及測序循環，以證實觀察到之任何突變並非PCR之結果。接著分析衍生之胺基酸序列，以確定抗體之生殖系序列起源，且鑑別與生殖系序列之偏差。指示重鏈及輕鏈序列各者與其原始生殖系序列之比較。將對應於測序抗體之互補決定區(CDR)之胺基酸序列比對，且此等比對用於藉由類似性將純系分組。

初級細胞結合分析

【0411】藉由流式細胞術測試雜交瘤上清液與由初級人類及食蟹獼猴細胞表現之PD-1的結合。對於人類初級細胞結合分析，將經純化之人類T細胞(Biological Specialty公司)解凍且以2.5×10^6細胞/毫升之濃度懸浮。在37℃/5% CO^2下將T細胞在預塗5 μg/mL抗小鼠IgG Fc (Pierce)之盤中用5 ug/mL抗人類CD3純系OKT3 (eBioscience)及1 μg/mL抗人類CD28 (BD Pharmingen)刺激72小時。在72小時之後，移出細胞，洗滌且以0.5×10^6細胞/毫升之濃度用10 ng/mL IL-2 (Pepro Tech)懸浮。接著將細胞在37℃/5% CO_2下再培育48小時。對於食蟹獼猴初級細胞結合分析，將食蟹獼猴PBMC (SNBL)解凍且以介於4×10^6與5×10^6細胞/毫升之間的濃度懸浮。在37℃/5% CO_2下將PBMC在預塗5 μg/mL抗小鼠IgG Fc (Pierce)之盤中用1 μg/mL抗人類CD3純系SP34 (BD Pharmingen)及1 μg/mL抗人類CD28 (BD Pharmingen)刺激72小時。在72小時之後，移出細胞，洗滌且以0.5×10^6細胞/毫升之濃度用20 ng/mL IL-2 (Pepro Tech)懸浮。接著將細胞在37℃/5% CO_2下再培育48小時。在最終培育之後，藉由以1 μg/ mL最終濃度與標準化之雜交瘤上清液、陽性對照抗體及同型對照抗體一起培育來製備細胞，以用於流式細胞術。5 μg/mL Alexa Fluor 647 AffiniPure F(ab')$_2$片段山羊抗人類IgG (H+L) (Jackson ImmunoReserach)用於二級偵測且8.25 nM YoPro1 (Invitrogen)用於活/死細胞染色。接著細胞在BD FACSCanto II流式細胞儀上跑動以偵測抗PD-

1抗體結合。結果表示為表現PD-1之細胞之FACS幾何平均值，且資料展示於表17中。

表 17

抗體ID	初級食蟹獼猴(FACS幾何平均值)	初級人類(FACS幾何平均值)
A-1 (20A2)	194	326
A-3 (20C1)	187	312
A-2 (22D4)	188	329

受體-配位體競爭分析

【0412】接著測試結合PD-1之雜交瘤上清液阻斷PD-1結合配位體之能力。在抗原特異性雜交瘤上清液樣品上，使用FACS，在短暫表現人類PD-1之HEK293細胞上如下進行競爭性結合分析。將表現人類PD-1之HEK293細胞與抗體樣品(對PD-1具有特異性之雜交瘤上清液)混合且在4℃下培育1小時，接著洗滌兩次。接著將具有結合樣品之細胞與huPD-L1-Fc-Alexa647或huPD-L2-Fc-Alexa 647 (R&D systems, Minneapolis, MN)在4℃下一起培育45分鐘。接著添加7-AAD細胞活力染劑，且將細胞在4℃下進一步培育15分鐘，洗滌兩次且再懸浮於FACS緩衝液中。使用BD Accuri™流式細胞儀及Intellicyt HyperCyt自動取樣器分析樣品。表18中之數據反映在1 ug/mL下人類PD-L1或PD-L2與人類PD-1之結合的抑制百分比。

表 18

PD-L1 或 PD-L2 與 PD-1 結合之抗 PD-1 抗體的競爭分析

抗體ID	R-L PD-L1 (抑制%)	R-L PD-L2 (抑制%)
A-1 (20A2)	72%	71%
A-3 (20C1)	64%	65%
A-2 (22D4)	71%	72%

親和力缺口分析

【0413】使用KinExA®方法評估若干抗體之動力學量測。此方法包括基於溶液，測定平衡狀態下之形式親和力量測。

【0414】藉由首先用生物素化BSA、Neutravidin吸附塗佈PMMA珠粒，接著用生物素化PD-1塗佈，將聚(甲基丙烯酸甲酯)或PMMA珠粒用生物素化人類PD-1塗佈。

【0415】使用自動化流動免疫分析系統KinExA 3200進行KinExA實驗，其中與PD-1偶合之珠粒用作固相。簡言之，將恆定量之抗hPD-1 mAb (3 nM或1 nM或100 pM)與在樣品緩衝液(具有0.1% BSA之PBS以減少非特異性結合)中以100 nM起始之滴定濃度之h-PD-1或cy-PD-1一起培育。將抗原/抗體複合物在室溫下培育48小時至72小時以達到平衡。使混合物穿過PD-1偶合之珠粒以累積未結合之抗體。變化混合物之體積及流速，視各實驗中獲得之特定信號而定。

【0416】使用含有二級Ab山羊抗Hu IgG (H+L)-Alexa647抗體於樣品緩衝液中之溶液偵測捕捉之mAb。結合信號轉變成相對值，呈缺少hu-PD-1或cy-PD-1下對照物之比例形式。針對所有平衡實驗，量測各樣品之兩個複製物。使用KinExA n-曲線分析軟體內含有之單點均一結合模型，自資料之非線性回歸分析獲得平衡解離常數(Kd)。軟體計算Kd且藉由將數據點與理論Kd曲線擬合，確定95%信賴區間。給與95%信賴區間為Kd低及Kd高。

表 19

經純化之抗 PD-1 抗體對重組人類及食蟹獼猴 PD-1 之親和力

	對人類PD-1之親和力			對食蟹獼猴PD-1之親和力			
mAb ID	KD (pM)	95% CI (pM)	% 活性 mAb	KD (pM)	95% CI (pM)	% 活性 mAb	Hu:Cy 差異倍數
A-1 (20A2)	17	13-23	25	15	12-19	21	0.9
A-3 (20C1)	16	13-21	17	60	52-68	18	3.8
A-2 (22D4)	4.5	3.6-5.5	27	3.7	2.7-4.8	23	0.8

Kd 藉由取 PD-1 濃度為已知濃度且用軟體計算 Kd 及 mAb 濃度來計算。

MLR 分析中證實經純化抗體之活性

【0417】將人類不成熟單核細胞衍生之樹突狀細胞(Astarte)解凍且使用CellXVivo人類單核細胞衍生之樹突狀細胞分化套組(R & D Systems #CDK004)，經由在IL-4、GM-CSF及TNF-a中培養72小時，分化成成熟樹突狀細胞。將未黏附及鬆散黏附之細胞移除，組合且離心以使細胞粒化。在移除培養基之後，使細胞以400×10^3細胞/毫升再懸浮於X-Vivo-15培養基中且將樹突狀細胞添加至96孔盤之各孔(50 μL中20k細胞)。使人類T細胞(Astarte)迅速解凍，且在X-Vivo-15培養基中洗滌。使細胞以2×10^6細胞/毫升再懸浮且添加100 μL至各孔(200k細胞/100 μL)。將抗體稀釋且以50 μL總體積添加至各孔中。將混合物在37℃下培育三天。此時，將細胞短暫離心，且175 μL用於根據製造商建議，使用IL-2 V-Plex套組(MSD)量測IL2產生，作為T細胞增殖之量度。

表 20

抗體 ID	MLR IC50 (nM)	MLR IC50 (nM)
A-1 (20A2)	0.73	0.80
A-3 (20C1)	0.97	1.65
A-2 (22D4)	0.65	0.58

實例 13

【0418】可能時，對A-1 (20A2)、A-3 (20C1)及A-2 (22D4)抗PD-1可變域序列進行工程改造以移除具有側鏈降解風險之基元。此類胺基酸基元包括：(1)有天冬醯胺脫醯胺傾向之CDR 『NG』及『NT』序列；(2)有天冬胺酸異構化傾向之CDR 『DG』、『DH』、『DS』及『DT』序列；及(3)有氧化傾向之CDR3色胺酸。通常，取代性質來源於生殖系序列或序列相關之PD-1結合mAb。對於生物資訊學或結構分析不提供明確取代性質之情況下，選擇化學上類似於親本殘基之殘基類型。

【0419】亦移除違反基於多重序列比對之成對殘基協方差趨勢的可變域序列基元。經由用生殖系或生殖系相關之殘基類型補救成對協方差違反者可使可製造性更佳，因為mAb表現水準及生物物理學穩定性增加。參見Kannan, G. Method of Correlated Mutational Analysis to Improve Therapeutic Antibodies. 美國專利申請案PCT/US2012/028596 2012年3月9日申請。如上所論述，使用類似於用於補救降解位點之方法，選擇協方差違反者之取代性質。

【0420】20A2工程改造產生20A2.003。20C1工程改造產生20C1.006及20C1.009。22D4工程改造產生22D4.006及22D4.017。

實例 14

【0421】在未處理之非人類食蟹獼猴中評估包含抗PD-1抗體22D4.017與包含R9E及R76A突變之IL-21雙重突變蛋白融合的融合蛋白(「[22D4.017]-[R9E:R76A] (單體)」)之活體內活性。第一組猴接受單獨抗PD-1抗體22D4.017(不與IL-21突變蛋白融合)，且第二組猴接受融合蛋白[22D4.017]-[R9E:R76A](單體)。使用FACS，在外周血中監測藥效學(PD)參數，且包括免疫細胞動力學及淋巴細胞中之STAT3轉錄因子磷酸化(pSTAT3)。亦藉由Millipore Milliplex® 多分析物概況分析(MAP)多路分析，檢查血清細胞介素及穿孔素。進行外周血參數之給與前分析以允許數據集相對於基線標準化。給與在第1天開始。在預定固定時間點提取血液及血清。

【0422】儘管T細胞中Ki67 **[圖25A及25B]**及STAT3 **[圖25C及25D]**活化，但在投與22D4.017抗體或者[22D4.017]-[R9E:R76A] (單體)融合蛋白之組中未觀察到整批T細胞群體顯著增加**[圖25A及25B]**，此表明此等處理自身均不足以誘導整批T細胞群體擴增**[圖25E及25F]**。此等資料支持以下概念：PD-1信號傳導之全身性阻斷可能對整批T細胞群體具有更整體之影響，包括活化STAT3信號

傳導及Ki67，但此等變化可能單獨不足以表明顯著功能輸出(亦如抗PD-1單一療法或融合蛋白治療無法誘導更廣泛之T細胞擴增所證明)。

【0423】 為更好地瞭解近端信號傳導之變化可如何具體地影響表現PD-1之T細胞，且因為PD-1 (+) T細胞僅僅反映外周血中整批T細胞群體之一小部分，所以藉由使用非競爭性PD-1偵測mAb對PD-1 (+) CD4及CD8 T細胞進行閘控，更直接地檢查此等細胞**[圖16及17]**。在循環PD-1 (+)細胞之絕對數初始輕度減少之後，在[22D4.017]抗體組中此群體保持穩定。相比之下，在外周血PD-1 (+) CD4及CD8 T細胞的數目初始減少之後，在[22D4.017]-[R9E:R76A] (單體)融合蛋白處理組群體中給與後336小時觀察到PD-1 (+)細胞的數目顯著回彈(超過基線) **[圖25G]**。因此，儘管缺乏整批群體之之顯著擴增，但此等資料表明在投與[22D4.017]-[R9E:R76A] (單體)融合蛋白後PD-1 (+) T細胞數目選擇性地增加**[圖]**。

【0424】 為確定PD-1(+) T細胞之擴增的可能功能影響，檢查PD-1(+) CD4/8 T細胞與血清穿孔素之間的關係。實際上，資料表明此兩個參數之間存在正向關係：血清穿孔素在投與[22D4.017]-[R9E:R76A] (單體)融合蛋白之動物中最高，其經歷外周血PD-1(+) T細胞之顯著增加**[圖25I]**。

【0425】 綜上所述，此等資料表明雖然[22D4.017]-[R9E:R76A] (單體)融合蛋白之全身性暴露無法顯現總的整批T細胞群體增加，但在相同細胞(表現PD-1)上PD-1之阻斷及IL-21信號之同時遞送足以誘導群體擴增。此亦與血清穿孔素之增加相關**[圖25I]**。

實例 15

【0426】 以下實例證明多種抗PD-1抗體之結合親和力。

【0427】 抗PD-1抗體::PD-1 Octet結合親和力如下表徵。為定量抗PD-1抗

體與重組可溶性人類及食蟹獼猴PD-1之間的K_D結合親和力(平衡解離常數)，使用16尖端之Pall® ForteBio® Octet® RED384儀器或者96尖端模式之Pall® Octet® HTX儀器量測締合及解離速率常數。在所有情況下，第二代胺反應性光纖生物感測器尖端(AR2G)用於共價捕捉抗體至介於2.5與4 nm之間的最終負載水準。結合分析法使用以下固定步驟：(1)在水中平衡，60秒；(2)用與10 mM N-羥基磺基丁二醯亞胺(磺基-NHS)混合之新鮮20 mM 1-乙基-3-[3-二甲基胺基丙基]碳化二亞胺鹽酸鹽(EDC)活化，600秒；(3)固定在10 mM乙酸鹽pH 6.0緩衝液中稀釋之20 nM抗體，2000秒；(4)用1M乙醇胺淬滅，300秒；及最終(5)在Octet操作緩衝液(10 mM TRIS pH 7.5、150 mM NaCl、1 mM $CaCl_2$、0.13% (v/v) Triton X-100及0.10 mg/ml牛血清白蛋白(BSA))中基線培育，60秒。所有實驗均用製造商提議之384孔黑色樣品盤(每孔100 μL體積)在27℃及1000 RPM下進行。

【0428】 對於各Ab::PD-1相互作用，如上所述用相同抗體同等固定一行八個尖端。三個尖端用於結合可溶性人類PD-1(1-170)-FLAG-His之三點稀釋系列，又三個尖端用於結合可溶性食蟹獼猴PD-1(1-167)-FLAG-His之三點稀釋系列，接著剩餘兩個尖端(如管柱中之其餘尖端，固定Ab)暴露於Octet緩衝液，因此其可為參考尖端。所有光纖尖端一旦使用即處理掉；亦即不再生。藉由在Octet操作緩衝液中產生可溶性PD-1受體之1:3倍連續稀釋系列而產生人類及食蟹獼猴PD-1結合曲線；最終PD-1濃度為30 nM、10 nM及3.3 nM (除了IgG4抗PD-1 mAb，其PD-1濃度為33 nM、11 nM、3.7 nM)。將具有固定抗體之光纖生物感測器在含有PD-1連續稀釋系列之孔中培育300秒(締合步驟)，接著用剛剛操作緩衝液移至孔中，歷時500秒(解離步驟)。

【0429】 原始數據用儀器數據分析軟體(v10)進行處理。對於感測器之各行，將兩個參考感測器之結合信號求平均值且自剩餘六個樣品感測器減去。接

著用預設軟體選擇處理減去參考之數據：Y軸對準基線，相對於解離進行中間步驟校正，且最終用薩維茨基-格雷過濾器處理。接著將結合於三種人類或三種食蟹獼猴PD-1濃度之每種抗體的最終處理之資料整體與1:1結合模型擬合且作圖。所有圖均顯示處理數據以及與1:1結合模型之擬合。1:1結合模型擬合用於確定締合速率常數(k_a；單位$M^{-1}sec^{-1}$)及解離速率常數(k_d；單位sec^{-1})。接著平衡解離常數(K_D；單位奈莫耳(nM) = 1×10^{-9} Mol/L)計算為k_d/k_a之比率。

【0430】 圖26顯示抗PD-1抗體22D4.017、20C1.009及20A2.003之結合概況，該等抗體與兩種PD-1 mAb (IgG1抗PD-1 mAb及IgG4抗PD-1 mAb)一起測試。使用FortéBio Octet®系統確定結合概況。顯示針對人類及食蟹獼猴PD-1受體之結合。

【0431】 如圖26A-26E所示，當針對人類PD-1蛋白測試時22D4.017、20C1.009及20A2.003 PD-1抗體展現比市售抗體大2至14倍之K_D值。另外，食蟹獼猴PD-1蛋白與22D4.017、20C1.009及20A2.003抗體之交叉反應性的分析顯示總體類似親和力，而市售抗體顯示約2倍之親和力差異(圖26F-26J)。

實例 16

【0432】 以下實例說明多種抗PD-1抗體之穩定性。

【0433】 抗PD-1抗體之熱構形穩定性如下表徵。藉由差示掃描量熱法(differential scanning calorimetry，DSC)評估抗體20C1.009及22D4.017之熱穩定性。DSC係一種量測隨溫度而變之熱容的技術。將來自樣品細胞之信號與缺乏蛋白質之參考細胞相比較。當細胞溫度升高時，量測各展開轉變之焓及熔融溫度、峰寬。此提供有關蛋白質之熱穩定性及高階結構，包括蛋白質結構域之熱穩定性的資訊。圖27表示在A52SuT中1 mg/mL之各抗PD-1抗體的DSC溫度記錄圖，且表21提供各測試抗體之Tm。

表 21

抗體	20C1.009	22D4.017
藉由DSC獲得之Tm	75.1℃	66.1℃

【0434】 黏度另外使用錐板式流變儀(TA Instruments, New Castle, DE)，藉由量測由分子之間的摩擦力引起之流動阻力來測定。使用20 mm 1.988°錐板及Peltier鋼板-990918，自100至1000 s-1，應用流動掃描程序。黏度以Pa▪s量測，其中1 m Pa▪s = 1000 s-1下1 cP。量測在0.01%界面活性劑添加至調配緩衝液(A52Su)下70 mg/mL及150 mg/mL之各抗體的黏度。在室溫下量測所有樣品。黏度資料(1000剪切速率)展示於圖28中且提供於表22。

表 22

抗體	cP 70 mg/mL	cP 150 mg/mL
22D4.017	3.4	44.7
20C1.009	2.5	7.1

【0435】 抗體之穩定性特性係在研發候選治療劑期間考慮之重要因素。舉例而言，抗體之聚集傾向(在溶液中形成大複合物，可引起沈澱)可影響存放期、投與模式(例如靜脈內對比皮下)及分子活性。通常，抗體之熱穩定性及黏度特性為抗體在高溫及高濃度下維持結構完整性之能力的優良指標。如以上資料所證明，20C1.009展現使其尤其適合作為能夠靜脈內與皮下(及高濃度)投與之治療劑的穩定性特性。

實例 17

【0436】 本實例說明由多種融合蛋白引起之IL-21活性。

【0437】 製造包含IL-21突變蛋白之多種融合蛋白，且使用pSTAT3 AlphaLISA®分析測試IL-21活性。一種包含抗TIGIT單株抗體(mAb)，而第二種包含抗LAG3 mAb。產生四種細胞株用於此等實驗中：(A) PD-1陽性之變異Hut78 T細胞株；(B) TIGIT陽性之變異Hut78 T細胞株；(C) LAG3陽性之變異

Hut78 T細胞株；及(D)不內源性表現PD-1、TIGIT或LAG3之親本Hut78 T細胞株。所有四種細胞株暴露於(i)單獨rhIL-21；(ii)單獨抗PD-1 mAb；(iii)單獨抗TIGIT mAb；(iv)單獨抗LAG3 mAb；(v)抗PD-1 mAb與IL-21 (R5Q:R76E)突變蛋白(單體)之融合物；(vi)抗TIGIT mAb與IL-21 (R5Q:R76E)突變蛋白(二聚體)之融合物；及(vii)抗LAG3 mAb與IL-21 (R5Q:R76E)突變蛋白(二聚體)之融合物。

【0438】 STAT3磷酸化分析之結果及各分子針對STAT信號傳導之EC50分別展示於圖29A-29D及表23中。

表 23

分子	Hut78 親本	Hut78/PD-1	Hut78/TIGIT	Hut78/Lag3
	EC50 (pM)	EC50 (pM)	EC50 (pM)	EC50 (pM)
rhIL-21	65	59	58	68
抗 PD-1 mAb	-	-	-	-
抗 TIGIT mAb	-	-	-	-
抗 LAG3 mAb	-	-	-	-
抗 PD-1 mAb + IL-21 突變蛋白之融合物	-	341	-	-
抗 TIGIT mAb + IL-21 突變蛋白之融合物	-	-	1390	-
抗 LAG3 mAb + IL-21 突變蛋白之融合物	-	-	-	-

【0439】 如圖29A-29D及表23所示，抗TIGIT及抗LAG3融合蛋白展現與rhIL-21相比顯著降低之效力(抗TIGIT)或效力不可量測(抗LAG3)。

【0440】 本文中引用之所有參考文獻，包括公開案、專利申請案及專利均在此以引用之方式併入本文中，其併入程度如同個別且特定地指示各參考文獻以引用之方式整體併入本文中及闡述一般。

【0441】 除非本文中另外指示或上下文明顯相矛盾，否則在描述本發明之上下文中(特別是在以下申請專利範圍之上下文中)使用術語「一(a/an)」及「該」以及類似指示物將視為涵蓋單數與複數。除非另作說明，否則術語「包含」、「具有」、「包括」及「含有」將視為開放性術語(亦即意謂「包括(但

不限於)」)。

【0442】除非本文中另外指示，否則本文中數值範圍之敍述僅僅意欲用作個別地提及在該範圍內之各獨立值及各終點的一種速記方法，且各獨立值及終點併入說明書中，如同本文中個別地敍述其一般。

【0443】除非本文中另外指示或與上下文另外明顯相矛盾，否則本文所述之所有方法均可按任何合適之順序進行。除非另外主張，否則關於本文提供之任何及所有實例或示例性語言(例如「諸如」)的使用僅係為了更好地說明本發明，而非對本發明之範疇施加限制。說明書中之語言不應視作指示任何未主張之要素為實施本發明所必要的。

【0444】本文描述本發明之較佳實施例，包括本發明人已知用於實施本發明之最佳方式。此項技術之一般技術人員在閱讀以上描述後，可顯而易見彼等較佳實施例之變化。本發明人預期熟練技術人員視情況採用此類變化，且本發明人意欲本發明以除本文特別描述外之方式實施。因此，本發明包括隨附申請專利範圍中敍述之標的物的為適用法律所允許的所有修改及同等物。此外，除非本文中另外指示或上下文另外明顯相矛盾，否則本發明涵蓋上述要素呈所有可能變體之任何組合。

【序列表】

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

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

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

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
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Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
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Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
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35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

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

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

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

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Xaa Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
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Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
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            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Xaa Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
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35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Xaa Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 20

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Xaa Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 21

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Xaa Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 23

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Xaa Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 24

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Xaa Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 25

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Xaa Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<223> Xaa 為任何胺基酸

<400> 26

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Xaa Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<223> Xaa 為任何胺基酸

<400> 27

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Xaa Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<223> Xaa 為任何胺基酸

<400> 28

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Xaa
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 29
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<222> (109)..(109)
<223> Xaa 為任何胺基酸

<400> 29

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                  10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Xaa Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
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<223> Xaa 為任何胺基酸

<400> 30

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Xaa Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 31
<211> 133
<212> PRT
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<222> (112)..(112)
<223> Xaa 為任何胺基酸

<400> 31

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Xaa
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<222> (113)..(113)
<223> Xaa 為任何胺基酸

<400> 32

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Xaa Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 33
<211> 133
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<222> (116)..(116)
<223> Xaa 為任何胺基酸

<400> 33

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Xaa Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 34
<211> 133
<212> PRT
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<222> (117)..(117)
<223> Xaa 為任何胺基酸

<400> 34

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Xaa Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 35
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<222> (119)..(119)
<223> Xaa 為任何胺基酸

<400> 35

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Xaa His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 36
<211> 133
<212> PRT

<213> 人工序列

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<222> (120)..(120)
<223> Xaa 為任何胺基酸

<400> 36

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                  10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile Xaa Gln His Leu Ser Ser Arg Thr His
        115                 120                 125
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Gly Ser Glu Asp Ser
130

<210> 37
<211> 133
<212> PRT
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<220>
<221> MISC_FEATURE
<222> (123)..(123)
<223> Xaa 為任何胺基酸

<400> 37

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Xaa Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 38
<211> 133
<212> PRT
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<220>
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<222> (5)..(5)
<223> Xaa 為 A、D、E、G、H、I、K、L、M、N、Q、S、T、V 或 Y

<400> 38

Gln Gly Gln Asp Xaa His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 39
<211> 133
<212> PRT
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<220>
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<222> (8)..(8)
<223> Xaa 為 A、D、E、G、N 或 S

<400> 39

Gln Gly Gln Asp Arg His Met Xaa Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 40
<211> 133
<212> PRT
<213> 人工序列

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<220>
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<222> (9)..(9)
<223> Xaa 為 A、D、E、G、H、I K、L、M、N、Q、S、T、V 或 Y

<400> 40

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Gln Gly Gln Asp Arg His Met Ile Xaa Met Arg Gln Leu Ile Asp Ile
1               5                  10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
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<210> 41
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<220>
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<222> (11)..(11)
<223> Xaa 為 D 或 S

<400> 41

Gln Gly Gln Asp Arg His Met Ile Arg Met Xaa Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 42
<211> 133
<212> PRT
<213> 人工序列

<220>
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<220>
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<222> (12)..(12)
<223> Xaa 為 A、D、E、N、S、T 或 V

<400> 42

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Xaa Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 43
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 43

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Asp Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys

100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 44
<211> 133
<212> PRT
<213> 人工序列

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<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa 為 A、D 或 S

<400> 44

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Xaa Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser

65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 45
<211> 133
<212> PRT
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<222> (15)..(15)
<223> Xaa 為 A、E、I、M、N、Q、S、T 或 V

<400> 45

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Xaa Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser

35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 46
<211> 133
<212> PRT
<213> 人工序列

<220>
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<220>
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<222> (16)..(16)
<223> Xaa 為 D 或 E

<400> 46

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Xaa

1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 47
<211> 133
<212> PRT
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<220>
<223> 合成多肽

<400> 47

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                  10                  15

Val Asp Asp Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
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<210> 48
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 48

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Asp Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 49
<211> 133
<212> PRT
<213> 人工序列

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<220>
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<222> (65)..(65)
<223> Xaa 為 D、G 或 P

<400> 49

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Xaa Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser

130

<210> 50
<211> 133
<212> PRT
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<220>
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<220>
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<222> (66)..(66)
<223> Xaa 為 D、G 或 P

<400> 50

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Xaa Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys

100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 51
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 51

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Gln Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 52
<211> 133
<212> PRT
<213> 人工序列

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<220>
<221> MISC_FEATURE
<222> (69)..(69)
<223> Xaa 為 D、G 或 P

<400> 52

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Xaa Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 53
<211> 133
<212> PRT
<213> 人工序列

<220>
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<220>
<221> MISC_FEATURE
<222> (70)..(70)
<223> Xaa 為 E、G、P、Y 或 T

<400> 53

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Xaa Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 54
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 54

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu

20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Leu Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 55
<211> 133
<212> PRT
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<220>
<221> MISC_FEATURE
<222> (72)..(72)
<223> Xaa 為 D、G、P 或 A

<400> 55

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Xaa Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 56
<211> 133
<212> PRT
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<220>
<221> MISC_FEATURE
<222> (73)..(73)
<223> Xaa 為 A、D、E、G、H、I、N、P、Q、S 或 V

<400> 56

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Xaa Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser

130

<210> 57

<400> 57
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<210> 58
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<220>
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<222> (75)..(75)
<223> Xaa 為 D、G 或 P

<400> 58

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Xaa Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 59
<211> 133
<212> PRT
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<220>
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<222> (76)..(76)
<223> Xaa 為 A、D、E、G、H、I、K、L、M、N、P、Q、S、T、V 或 Y

<400> 59

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Xaa Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 60
<211> 133
<212> PRT
<213> 人工序列

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<220>
<221> MISC_FEATURE
<222> (77)..(77)
<223> Xaa 為 D、G 或 P

<400> 60

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Xaa Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 61
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 61

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

```
Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Asp Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
```

<210> 62
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 62

```
Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                  10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Asp Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
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<210> 63
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<220>
<221> MISC_FEATURE
<222> (80)..(80)
<223> Xaa 為 G 或 P

<400> 63

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Xaa
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 64
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 64

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Lys Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 65
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 65

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                  10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Asp Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125
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Gly Ser Glu Asp Ser
130

<210> 66
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 66

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Asp
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 67
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 67

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Lys Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 68
<211> 133
<212> PRT
<213> 人工序列

<220>
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<220>
<221> MISC_FEATURE
<222> (116)..(116)
<223> Xaa 為 A、D、E、I、K、L、M、N、S、T 或 V

<400> 68

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Xaa Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 69
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 69

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Asp Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 70
<211> 133
<212> PRT
<213> 人工序列

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<220>
<221> MISC_FEATURE
<222> (119)..(119)
<223> Xaa 為 A、D、E、M、N、Q、S 或 T

<400> 70

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

```
Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Xaa His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
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<210> 71
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 71

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                   10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30
```

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile Asp Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 72
<211> 133
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<213> 人工序列

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<400> 72

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Asp Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 73
<211> 133
<212> PRT
<213> 人工序列

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<223> 合成多肽

<400> 73

Gln Gly Gln Asp Ala His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 74
<211> 133
<212> PRT
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<400> 74

Gln Gly Gln Asp Asp His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

```
Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
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<210> 75
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<400> 75

```
Gln Gly Gln Asp Glu His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                  10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
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<210> 76
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<212> PRT
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<400> 76

Gln Gly Gln Asp Gly His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 77
<211> 133
<212> PRT
<213> 人工序列

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<223> 合成多肽

<400> 77

Gln Gly Gln Asp His His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 78
<211> 133
<212> PRT
<213> 人工序列

<220>
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<400> 78

Gln Gly Gln Asp Ile His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 79
<211> 133

〈212〉 PRT
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〈220〉
〈223〉 合成多肽

〈400〉 79

```
Gln Gly Gln Asp Lys His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                  10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
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<210> 80
<211> 133
<212> PRT
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<400> 80

Gln Gly Gln Asp Leu His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 81
<211> 133
<212> PRT
<213> 人工序列

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<400> 81

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Gln Gly Gln Asp Met His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                  10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125
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Gly Ser Glu Asp Ser
130

<210> 82
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<220>
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<400> 82

Gln Gly Gln Asp Asn His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 83
<211> 133
<212> PRT
<213> 人工序列

<220>
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<400> 83

Gln Gly Gln Asp Gln His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 84
<211> 133
<212> PRT
<213> 人工序列

<220>
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<400> 84

Gln Gly Gln Asp Ser His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 85
<211> 133
<212> PRT
<213> 人工序列

<220>
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<400> 85

Gln Gly Gln Asp Thr His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 86
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 86

Gln Gly Gln Asp Val His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 87
<211> 133
<212> PRT
<213> 人工序列

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<223> 合成多肽

<400> 87

Gln Gly Gln Asp Tyr His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 88
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 88

Gln Gly Gln Asp Arg His Met Ala Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 89
<211> 133
<212> PRT
<213> 人工序列

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<223> 合成多肽

<400> 89

Gln Gly Gln Asp Arg His Met Asp Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 90
<211> 133
<212> PRT
<213> 人工序列

<220>
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<400> 90

Gln Gly Gln Asp Arg His Met Glu Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 91
<211> 133
<212> PRT
<213> 人工序列

<220>
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<400> 91

Gln Gly Gln Asp Arg His Met Gly Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 92
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<212> PRT
<213> 人工序列

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<400> 92

Gln Gly Gln Asp Arg His Met Asn Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 93
<211> 133
<212> PRT
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<400> 93

Gln Gly Gln Asp Arg His Met Ser Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 94
<211> 133
<212> PRT
<213> 人工序列

<220>
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<400> 94

Gln Gly Gln Asp Arg His Met Ile Ala Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 95
<211> 133
<212> PRT
<213> 人工序列

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<400> 95

Gln Gly Gln Asp Arg His Met Ile Asp Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 96
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 96

Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 97
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<212> PRT
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<400> 97

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Gln Gly Gln Asp Arg His Met Ile Gly Met Arg Gln Leu Ile Asp Ile
1               5                   10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
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<210> 98
<211> 133
<212> PRT
<213> 人工序列

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<223> 合成多肽

<400> 98

Gln Gly Gln Asp Arg His Met Ile His Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 99

Gln Gly Gln Asp Arg His Met Ile Ile Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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Gln Gly Gln Asp Arg His Met Ile Lys Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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〈212〉 PRT
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〈400〉 101

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Gln Gly Gln Asp Arg His Met Ile Leu Met Arg Gln Leu Ile Asp Ile
1               5                  10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
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<400> 102

Gln Gly Gln Asp Arg His Met Ile Met Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 103

Gln Gly Gln Asp Arg His Met Ile Asn Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 104

Gln Gly Gln Asp Arg His Met Ile Gln Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 105

Gln Gly Gln Asp Arg His Met Ile Ser Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 106

Gln Gly Gln Asp Arg His Met Ile Thr Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 107

Gln Gly Gln Asp Arg His Met Ile Val Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 108

Gln Gly Gln Asp Arg His Met Ile Tyr Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 109
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<400> 109

Gln Gly Gln Asp Arg His Met Ile Arg Met Asp Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 110

Gln Gly Gln Asp Arg His Met Ile Arg Met Ser Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 111

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Ala Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 112

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Asp Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 114

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ala Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 115

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Asp Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu

20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 116
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<400> 116

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ser Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 117
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<212> PRT
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<400> 117

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Ala Ile

1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 118
<211> 133
<212> PRT
<213> 人工序列

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<400> 118

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Glu Ile
1               5                  10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
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<210> 119
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<212> PRT
<213> 人工序列

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<400> 119

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Ile Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 120

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Met Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 121
<211> 133
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<400> 121

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asn Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 122

〈211〉 133
〈212〉 PRT
〈213〉 人工序列

〈220〉
〈223〉 合成多肽

〈400〉 122

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Gln Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 123
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<400> 123

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Ser Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser

130

<210> 124
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<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 124

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Val Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 125
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<212> PRT
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<400> 125

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Asp
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His

115 120 125

Gly Ser Glu Asp Ser
130

<210> 126
<211> 133
<212> PRT
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<223> 合成多肽

<400> 126

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Glu
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 127
<211> 133
<212> PRT
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<400> 127

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Asp Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys

100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Gly Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
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Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
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Gly Ser Glu Asp Ser
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20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Pro Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys

85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

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

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Asp Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

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

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Gly Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser

65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

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

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Pro Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

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

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu

50 55 60

Arg Ile Ile Asn Asp Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

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

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Gly Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
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Gly Ser Glu Asp Ser
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20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser

35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Pro Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Glu Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
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Gly Ser Glu Asp Ser
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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu

20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Gly Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Pro Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile

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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Tyr Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Thr Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Asp Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Gly Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Pro Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
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Gly Ser Glu Asp Ser
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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Ala Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Ala Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser

130

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Asp Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Glu Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His

115 120 125

Gly Ser Glu Asp Ser
130

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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Gly Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys His Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys

100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Ile Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Asn Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys

85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Pro Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Gln Leu Lys Arg Lys Pro Pro Ser

65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Ser Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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<400> 155

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
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Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu

50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Val Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
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Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Asp Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

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

35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
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Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Gly Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

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

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
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Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Pro Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

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

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
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Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
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20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Asp Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
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Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
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Gly Ser Glu Asp Ser
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20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Gly Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys His Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ile Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Lys Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Leu Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Met Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
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Gly Ser Glu Asp Ser

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20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Asn Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Pro Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
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Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His

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Gly Ser Glu Asp Ser
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Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Gln Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
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Gly Ser Glu Asp Ser
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20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ser Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys

100 105 110

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Thr Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

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

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Val Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys

85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
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Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Tyr Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Asp Pro Pro Ser

65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Gly Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu

50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Pro Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

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Gly Ser Glu Asp Ser
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20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Gly
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

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

35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Pro
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

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Gly Ser Glu Asp Ser
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20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Ala Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
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Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu

20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
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Ser Leu Leu Asp Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
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Ser Leu Leu Glu Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Ile Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Lys Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Leu Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Met Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Asn Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Ser Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Thr Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Val Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ala His Gln His Leu Ser Ser Arg Thr His

115 120 125

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
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Ser Leu Leu Gln Lys Met Asp His Gln His Leu Ser Ser Arg Thr His
115 120 125

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys

100 105 110

Ser Leu Leu Gln Lys Met Glu His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Met His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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<400> 195

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys

85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Asn His Gln His Leu Ser Ser Arg Thr His
115 120 125

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Gln His Gln His Leu Ser Ser Arg Thr His
115 120 125

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

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser

65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ser His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Thr His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Xaa Ile
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Xaa Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Xaa Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Xaa Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser

130

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Xaa Ile
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Xaa Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Xaa Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Xaa Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Xaa Lys Xaa Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Xaa Xaa Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 205

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Xaa Ile Lys Xaa Leu Lys Arg Lys Pro Pro Ser

65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
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Gly Ser Glu Asp Ser
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<400> 206

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Xaa Lys Lys Leu Lys Xaa Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
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Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Xaa Lys Leu Lys Xaa Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                   10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Xaa Leu Lys Xaa Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95
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Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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Gln Gly Gln Asp Xaa His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Xaa Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 211

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Gln Gly Gln Asp Arg His Met Ile Xaa Met Arg Gln Leu Ile Asp Ile
1               5                  10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Xaa Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
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<400> 212

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Xaa Ile Lys Lys Leu Lys Xaa Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 213

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asn Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Thr Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 214

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asn Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Leu Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asn Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Ala Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 216

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asn Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Ala Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<400> 217

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Leu Lys Gln Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 218
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<400> 218

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Ala Gln Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 219
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<400> 219

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Thr Ile Lys Gln Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                   10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Ser Leu Lys Lys Leu Lys Xaa Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
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<223> Xaa 為 A、D 或 E

<400> 221

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Ala Lys Leu Lys Xaa Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<223> Xaa 為 A、D 或 E

<400> 222

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Ala Leu Lys Xaa Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<223> Xaa 為 A、E 或 Q

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<223> Xaa 為 A 或 E

<400> 224

Gln Gly Gln Asp Xaa His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Xaa Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<223> Xaa 為 A 或 E

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<222> (76)..(76)
<223> Xaa 為 A 或 E

<400> 225

Gln Gly Gln Asp Arg His Met Ile Xaa Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Xaa Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<223> Xaa 為 A、D 或 E

<400> 226

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Thr Ile Lys Lys Leu Lys Xaa Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser

130

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<400> 227

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Leu Lys Lys Leu Lys Ala Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 228
<211> 133
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<220>
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<400> 228

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Leu Lys Lys Leu Lys Asp Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His

115 120 125

Gly Ser Glu Asp Ser
130

<210> 229
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<400> 229

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Leu Lys Lys Leu Lys Glu Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 230
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<400> 230

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Ala Lys Leu Lys Ala Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys

100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 231
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<400> 231

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Ala Lys Leu Lys Asp Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

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<212> PRT
<213> 人工序列

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<400> 232

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Ala Lys Leu Lys Glu Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys

85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 233
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<212> PRT
<213> 人工序列

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<223> 合成多肽

<400> 233

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Ala Leu Lys Ala Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 234
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<400> 234

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Ala Leu Lys Asp Lys Pro Pro Ser

65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 235
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<400> 235

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Ala Leu Lys Glu Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 236
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 236

Gln Gly Gln Asp Ala His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu

50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 237
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 237

Gln Gly Gln Asp Ala His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 238
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 238

Gln Gly Gln Asp Glu His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser

```
         35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
     50                  55                  60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
```

<210> 239
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 239

```
Gln Gly Gln Asp Glu His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                   10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30
```

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 240
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 240

Gln Gly Gln Asp Gln His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu

20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 241
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 241

Gln Gly Gln Asp Gln His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 242
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 242

Gln Gly Gln Asp Arg His Met Ile Ala Met Arg Gln Leu Ile Asp Ile

1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 243
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 243

Gln Gly Gln Asp Arg His Met Ile Ala Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 244
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 244

Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 245
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 245

Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 246
<211> 133
<212> PRT

〈213〉 人工序列

〈220〉
〈223〉 合成多肽

〈400〉 246

```
Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                  10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Thr Ile Lys Lys Leu Lys Ala Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
```

〈210〉 247

〈211〉 133
〈212〉 PRT
〈213〉 人工序列

〈220〉
〈223〉 合成多肽

〈400〉 247

```
Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1               5                  10                  15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
            20                  25                  30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
        35                  40                  45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
    50                  55                  60

Arg Ile Ile Asn Val Thr Ile Lys Lys Leu Lys Asp Lys Pro Pro Ser
65                  70                  75                  80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
                85                  90                  95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
            100                 105                 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
        115                 120                 125

Gly Ser Glu Asp Ser
    130
```

<210> 248
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 248

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Thr Ile Lys Lys Leu Lys Glu Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser

130

<210> 249
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 249

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Asp Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 250
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 250

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Glu Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His

115 120 125

Gly Ser Glu Asp Ser
130

<210> 251
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 251

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Asn Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 252
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 252

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Ser Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys

100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 253
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 253

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Thr Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 254
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 254

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Val Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys

85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 255
<211> 133
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 255

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Thr Ile Lys Gln Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 256
<211> 519
<212> PRT
<213> 智人

<400> 256

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp
20 25 30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
35 40 45

His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
65 70 75 80

```
Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
                85                  90                  95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
            100                 105                 110

Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe
        115                 120                 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
    130                 135                 140

Gly Asp Pro Trp Ala Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp
145                 150                 155                 160

Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
                165                 170                 175

Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
            180                 185                 190

Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
        195                 200                 205

Glu Glu Leu Lys Glu Gly Trp Asn Pro His Leu Leu Leu Leu Leu Leu
    210                 215                 220

Leu Val Ile Val Phe Ile Pro Ala Phe Trp Ser Leu Lys Thr His Pro
225                 230                 235                 240

Leu Trp Arg Leu Trp Lys Lys Ile Trp Ala Val Pro Ser Pro Glu Arg
                245                 250                 255
```

```
Phe Phe Met Pro Leu Tyr Lys Gly Cys Ser Gly Asp Phe Lys Lys Trp
            260                 265                 270

Val Gly Ala Pro Phe Thr Gly Ser Ser Leu Glu Leu Gly Pro Trp Ser
        275                 280                 285

Pro Glu Val Pro Ser Thr Leu Glu Val Tyr Ser Cys His Pro Pro Arg
    290                 295                 300

Ser Pro Ala Lys Arg Leu Gln Leu Thr Glu Leu Gln Glu Pro Ala Glu
305                 310                 315                 320

Leu Val Glu Ser Asp Gly Val Pro Lys Pro Ser Phe Trp Pro Thr Ala
                325                 330                 335

Gln Asn Ser Gly Gly Ser Ala Tyr Ser Glu Glu Arg Asp Arg Pro Tyr
            340                 345                 350

Gly Leu Val Ser Ile Asp Thr Val Thr Val Leu Asp Ala Glu Gly Pro
        355                 360                 365

Cys Thr Trp Pro Cys Ser Cys Glu Asp Asp Gly Tyr Pro Ala Leu Asp
    370                 375                 380

Leu Asp Ala Gly Leu Glu Pro Ser Pro Gly Leu Glu Asp Pro Leu Leu
385                 390                 395                 400

Asp Ala Gly Thr Thr Val Leu Ser Cys Gly Cys Val Ser Ala Gly Ser
                405                 410                 415

Pro Gly Leu Gly Gly Pro Leu Gly Ser Leu Leu Asp Arg Leu Lys Pro
            420                 425                 430
```

Pro Leu Ala Asp Gly Glu Asp Trp Ala Gly Gly Leu Pro Trp Gly Gly
435 440 445

Arg Ser Pro Gly Gly Val Ser Glu Ser Glu Ala Gly Ser Pro Leu Ala
450 455 460

Gly Leu Asp Met Asp Thr Phe Asp Ser Gly Phe Val Gly Ser Asp Cys
465 470 475 480

Ser Ser Pro Val Glu Cys Asp Phe Thr Ser Pro Gly Asp Glu Gly Pro
485 490 495

Pro Arg Ser Tyr Leu Arg Gln Trp Val Val Ile Pro Pro Pro Leu Ser
500 505 510

Ser Pro Gly Pro Gln Ala Ser
515

<210> 257
<211> 347
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 257

Leu Asn Thr Thr Ile Leu Thr Pro Asn Gly Asn Glu Asp Thr Thr Ala
1 5 10 15

Asp Phe Phe Leu Thr Thr Met Pro Thr Asp Ser Leu Ser Val Ser Thr
20 25 30

Leu Pro Leu Pro Glu Val Gln Cys Phe Val Phe Asn Val Glu Tyr Met
35 40 45

Asn Cys Thr Trp Asn Ser Ser Ser Glu Pro Gln Pro Thr Asn Leu Thr
50 55 60

Leu His Tyr Trp Tyr Lys Asn Ser Asp Asn Asp Lys Val Gln Lys Cys
65 70 75 80

Ser His Tyr Leu Phe Ser Glu Glu Ile Thr Ser Gly Cys Gln Leu Gln
85 90 95

Lys Lys Glu Ile His Leu Tyr Gln Thr Phe Val Val Gln Leu Gln Asp
100 105 110

Pro Arg Glu Pro Arg Arg Gln Ala Thr Gln Met Leu Lys Leu Gln Asn
115 120 125

Leu Val Ile Pro Trp Ala Pro Glu Asn Leu Thr Leu His Lys Leu Ser
130 135 140

Glu Ser Gln Leu Glu Leu Asn Trp Asn Asn Arg Phe Leu Asn His Cys
145 150 155 160

Leu Glu His Leu Val Gln Tyr Arg Thr Asp Trp Asp His Ser Trp Thr
165 170 175

Glu Gln Ser Val Asp Tyr Arg His Lys Phe Ser Leu Pro Ser Val Asp
180 185 190

Gly Gln Lys Arg Tyr Thr Phe Arg Val Arg Ser Arg Phe Asn Pro Leu
195 200 205

Cys Gly Ser Ala Gln His Trp Ser Glu Trp Ser His Pro Ile His Trp
210 215 220

```
Gly Ser Asn Thr Ser Lys Glu Asn Pro Phe Leu Phe Ala Leu Glu Ala
225                 230                 235                 240

Val Val Ile Ser Val Gly Ser Met Gly Leu Ile Ile Ser Leu Leu Cys
                245                 250                 255

Val Tyr Phe Trp Leu Glu Arg Thr Met Pro Arg Ile Pro Thr Leu Lys
            260                 265                 270

Asn Leu Glu Asp Leu Val Thr Glu Tyr His Gly Asn Phe Ser Ala Trp
        275                 280                 285

Ser Gly Val Ser Lys Gly Leu Ala Glu Ser Leu Gln Pro Asp Tyr Ser
    290                 295                 300

Glu Arg Leu Cys Leu Val Ser Glu Ile Pro Pro Lys Gly Gly Ala Leu
305                 310                 315                 320

Gly Glu Gly Pro Gly Ala Ser Pro Cys Asn Gln His Ser Pro Tyr Trp
                325                 330                 335

Ala Pro Pro Cys Tyr Thr Leu Lys Pro Glu Thr
            340                 345
```

<210> 258
<211> 160
<212> PRT
<213> 智人

<400> 258

```
Met Arg Ser Ser Pro Gly Asn Met Glu Arg Ile Val Ile Cys Leu Met
1               5                   10                  15
```

Val Ile Phe Leu Gly Thr Leu Val His Lys Ser Ser Ser Gln Gly Gln
20 25 30

Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp Gln
35 40 45

Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala Pro
50 55 60

Glu Asp Val Glu Thr Asn Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys
65 70 75 80

Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn
85 90 95

Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser Thr Asn Ala Gly
100 105 110

Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu
115 120 125

Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Ser Leu Leu Gln Lys
130 135 140

Met Ile His Gln His Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
145 150 155 160

<210> 259
<211> 152
<212> PRT
<213> 智人

<400> 259

```
Met Arg Ser Ser Pro Gly Asn Met Glu Arg Ile Val Ile Cys Leu Met
1               5                  10                  15

Val Ile Phe Leu Gly Thr Leu Val His Lys Ser Ser Ser Gln Gly Gln
            20                  25                  30

Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp Gln
        35                  40                  45

Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala Pro
    50                  55                  60

Glu Asp Val Glu Thr Asn Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys
65                  70                  75                  80

Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn
                85                  90                  95

Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser Thr Asn Ala Gly
            100                 105                 110

Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu
        115                 120                 125

Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln
    130                 135                 140

Lys Val Ser Thr Leu Ser Phe Ile
145                 150
```

<210> 260
<211> 29
<212> PRT
<213> 智人

<400> 260

Met Arg Ser Ser Pro Gly Asn Met Glu Arg Ile Val Ile Cys Leu Met
1 5 10 15

Val Ile Phe Leu Gly Thr Leu Val His Lys Ser Ser Ser
20 25

<210> 261
<211> 519
<212> PRT
<213> 智人

<400> 261

Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys
1 5 10 15

Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp
20 25 30

Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu
35 40 45

His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met
50 55 60

Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr
65 70 75 80

Asp Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala
85 90 95

Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val Thr Phe Ser
100 105 110

```
Gly Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala Phe
        115                 120                 125

Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn Arg
    130                 135                 140

Gly Asp Pro Trp Ala Val Ser Pro Arg Arg Lys Leu Ile Ser Val Asp
145                 150                 155                 160

Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser Ser
                165                 170                 175

Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr Gln
            180                 185                 190

Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln Ser
        195                 200                 205

Glu Glu Leu Lys Glu Gly Trp Asn Pro His Leu Leu Leu Leu Leu Leu
    210                 215                 220

Leu Val Ile Val Phe Ile Pro Ala Phe Trp Ser Leu Lys Thr His Pro
225                 230                 235                 240

Leu Trp Arg Leu Trp Lys Lys Ile Trp Ala Val Pro Ser Pro Glu Arg
                245                 250                 255

Phe Phe Met Pro Leu Tyr Lys Gly Cys Ser Gly Asp Phe Lys Lys Trp
            260                 265                 270

Val Gly Ala Pro Phe Thr Gly Ser Ser Leu Glu Leu Gly Pro Trp Ser
        275                 280                 285
```

Pro Glu Val Pro Ser Thr Leu Glu Val Tyr Ser Cys His Pro Pro Arg
290 295 300

Ser Pro Ala Lys Arg Leu Gln Leu Thr Glu Leu Gln Glu Pro Ala Glu
305 310 315 320

Leu Val Glu Ser Asp Gly Val Pro Lys Pro Ser Phe Trp Pro Thr Ala
325 330 335

Gln Asn Ser Gly Gly Ser Ala Tyr Ser Glu Glu Arg Asp Arg Pro Tyr
340 345 350

Gly Leu Val Ser Ile Asp Thr Val Thr Val Leu Asp Ala Glu Gly Pro
355 360 365

Cys Thr Trp Pro Cys Ser Cys Glu Asp Asp Gly Tyr Pro Ala Leu Asp
370 375 380

Leu Asp Ala Gly Leu Glu Pro Ser Pro Gly Leu Glu Asp Pro Leu Leu
385 390 395 400

Asp Ala Gly Thr Thr Val Leu Ser Cys Gly Cys Val Ser Ala Gly Ser
405 410 415

Pro Gly Leu Gly Gly Pro Leu Gly Ser Leu Leu Asp Arg Leu Lys Pro
420 425 430

Pro Leu Ala Asp Gly Glu Asp Trp Ala Gly Gly Leu Pro Trp Gly Gly
435 440 445

Arg Ser Pro Gly Gly Val Ser Glu Ser Glu Ala Gly Ser Pro Leu Ala
450 455 460

Gly Leu Asp Met Asp Thr Phe Asp Ser Gly Phe Val Gly Ser Asp Cys
465 470 475 480

Ser Ser Pro Val Glu Cys Asp Phe Thr Ser Pro Gly Asp Glu Gly Pro
485 490 495

Pro Arg Ser Tyr Leu Arg Gln Trp Val Val Ile Pro Pro Pro Leu Ser
500 505 510

Ser Pro Gly Pro Gln Ala Ser
515

<210> 262
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 262

Gly Gly Gly Gly Ser
1 5

<210> 263
<211> 268
<212> PRT
<213> 智人

<400> 263

Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr
1 5 10 15

Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe

20 25 30

Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr
35 40 45

Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu
50 55 60

Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu
65 70 75 80

Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn
85 90 95

Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala
100 105 110

Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg
115 120 125

Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly
130 135 140

Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly Leu Leu Gly Ser
145 150 155 160

Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys Ser Arg Ala Ala
165 170 175

Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro Leu Lys Glu Asp
180 185 190

Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly Glu Leu Asp Phe

195 200 205

Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro Cys Val Pro Glu
210 215 220

Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly Met Gly Thr Ser
225 230 235 240

Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg Ser Ala Gln Pro
245 250 255

Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
260 265

<210> 264
<211> 288
<212> PRT
<213> 食蟹獼猴

<400> 264

Met Gln Ile Pro Gln Ala Pro Trp Pro Val Val Trp Ala Val Leu Gln
1 5 10 15

Leu Gly Trp Arg Pro Gly Trp Phe Leu Glu Ser Pro Asp Arg Pro Trp
20 25 30

Asn Ala Pro Thr Phe Ser Pro Ala Leu Leu Leu Val Thr Glu Gly Asp
35 40 45

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

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65 70 75 80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
85 90 95

Val Thr Arg Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
100 105 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
115 120 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
130 135 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145 150 155 160

Arg Pro Ala Gly Gln Phe Gln Ala Leu Val Val Gly Val Val Gly Gly
165 170 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
180 185 190

Ser Arg Ala Ala Gln Gly Thr Ile Glu Ala Arg Arg Thr Gly Gln Pro
195 200 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
210 215 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Ala Pro
225 230 235 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
245 250 255

Leu Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
260 265 270

Ser Pro Arg Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
275 280 285

<210> 265
<211> 330
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 265

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

```
Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270
```

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 266
<211> 329
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 266

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 267
<211> 334
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 267

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

```
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220
```

```
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
                325                 330
```

〈210〉 268
〈211〉 595
〈212〉 PRT
〈213〉 人工序列

〈220〉
〈223〉 合成多肽

〈400〉 268

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
```

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Arg His Met
325 330 335

Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr
340 345 350

Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala Pro Glu Asp Val Glu
355 360 365

Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu
370 375 380

Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile
385 390 395 400

Lys Ala Leu Lys Glu Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln
405 410 415

Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro
420 425 430

Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile
435 440 445

His Gln His Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser Gln Gly
450 455 460

Gln Asp Ala His Met Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp
465 470 475 480

Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala
485 490 495

Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe
500 505 510

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

Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro Ser Thr Asn
530 535 540

Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser
545 550 555 560

Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu
565 570 575

Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His Gly Ser
580 585 590

Glu Asp Ser
595

<210> 269
<211> 329
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 269

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

```
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255
```

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 270
<211> 462
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 270

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

```
Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Glu His Met
                325                 330                 335

Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr
            340                 345                 350

Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala Pro Glu Asp Val Glu
        355                 360                 365

Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu
    370                 375                 380

Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile
385                 390                 395                 400

Lys Lys Leu Lys Ala Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln
                405                 410                 415
```

Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro
420 425 430

Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile
435 440 445

His Gln His Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
450 455 460

<210> 271
<211> 462
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 271

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

```
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255
```

```
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Gln His Met
                325                 330                 335

Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr
            340                 345                 350

Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala Pro Glu Asp Val Glu
        355                 360                 365

Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu
    370                 375                 380

Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile
385                 390                 395                 400

Lys Lys Leu Lys Glu Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln
                405                 410                 415

Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro
            420                 425                 430
```

Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile
435 440 445

His Gln His Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
450 455 460

<210> 272
<211> 462
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 272

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

```
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Arg His Met
                325                 330                 335

Ile Glu Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr
            340                 345                 350

Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala Pro Glu Asp Val Glu
        355                 360                 365

Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu
    370                 375                 380

Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile
385                 390                 395                 400

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

Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro
            420                 425                 430

Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile
        435                 440                 445

His Gln His Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
    450                 455                 460
```

<210> 273
<211> 462
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 273

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125
```

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

```
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Arg His Met
                325                 330                 335

Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr
            340                 345                 350

Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala Pro Glu Asp Val Glu
        355                 360                 365

Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu
    370                 375                 380

Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile
385                 390                 395                 400

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

Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro
            420                 425                 430

Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile
        435                 440                 445

His Gln His Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
    450                 455                 460
```

〈210〉 274
〈211〉 462
〈212〉 PRT
〈213〉 人工序列

<220>
<223> 合成多肽

<400> 274

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Arg His Met
325 330 335

Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr
340 345 350

Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala Pro Glu Asp Val Glu
355 360 365

Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu
370 375 380

Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile
385 390 395 400

Lys Lys Leu Lys Glu Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln
405 410 415

Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro
420 425 430

Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile
435 440 445

His Gln His Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
450 455 460

<210> 275
<211> 467
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 275

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175
```

```
Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gln Gly
                325                 330                 335

Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp
            340                 345                 350
```

Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala
355 360 365

Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe
370 375 380

Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile
385 390 395 400

Ile Asn Val Ser Ile Lys Ala Leu Lys Glu Lys Pro Pro Ser Thr Asn
405 410 415

Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser
420 425 430

Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu
435 440 445

Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His Gly Ser
450 455 460

Glu Asp Ser
465

<210> 276
<211> 467
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 276

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gln Gly
                325                 330                 335

Gln Asp Ala His Met Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp
            340                 345                 350

Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala
        355                 360                 365
```

```
Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe
    370                 375                 380

Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile
385                 390                 395                 400

Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro Ser Thr Asn
                405                 410                 415

Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser
            420                 425                 430

Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu
        435                 440                 445

Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His Gly Ser
    450                 455                 460

Glu Asp Ser
465
```

<210> 277
<211> 467
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 277

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15
```

```
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu
            180                 185                 190
```

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gln Gly
                325                 330                 335

Gln Asp Glu His Met Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp
            340                 345                 350

Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala
        355                 360                 365
```

Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe
370 375 380

Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile
385 390 395 400

Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro Ser Thr Asn
405 410 415

Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser
420 425 430

Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu
435 440 445

Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His Gly Ser
450 455 460

Glu Asp Ser
465

<210> 278
<211> 467
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 278

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gln Gly
325 330 335

Gln Asp Gln His Met Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp
340 345 350

Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala
355 360 365

Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe
370 375 380

Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile
385 390 395 400

Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro Ser Thr Asn
405 410 415

Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser
420 425 430

Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu
435 440 445

Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His Gly Ser
450 455 460

Glu Asp Ser
465

<210> 279
<211> 467
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 279

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

```
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205
```

```
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gln Gly
                325                 330                 335

Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile Asp Ile Val Asp
            340                 345                 350

Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala
        355                 360                 365

Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe
    370                 375                 380
```

Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile
385 390 395 400

Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro Ser Thr Asn
405 410 415

Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser
420 425 430

Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu
435 440 445

Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His Gly Ser
450 455 460

Glu Asp Ser
465

<210> 280
<211> 467
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 280

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gln Gly
325 330 335

Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp
340 345 350

Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala
355 360 365

Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe
370 375 380

Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile
385 390 395 400

Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro Ser Thr Asn
405 410 415

Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser
420 425 430

Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu
435 440 445

Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His Gly Ser
450 455 460

Glu Asp Ser
465

<210> 281
<211> 467
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 281

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

```
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220
```

```
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gln Gly
                325                 330                 335

Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Asp Ile Val Asp
            340                 345                 350

Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala
        355                 360                 365

Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe
    370                 375                 380

Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile
385                 390                 395                 400
```

Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro Ser Thr Asn
405 410 415

Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser
420 425 430

Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu
435 440 445

Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His Gly Ser
450 455 460

Glu Asp Ser
465

<210> 282
<211> 335
<212> PRT
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<400> 282

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser
325 330 335

<210> 283
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<400> 283

Gln Gly Gln Asp Arg His Met Ile Arg Met Arg Gln Leu Ile Thr Ile
1 5 10 15

Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu
20 25 30

Pro Ala Pro Glu Asp Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser
35 40 45

Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu
50 55 60

Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Arg Lys Pro Pro Ser
65 70 75 80

Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys
85 90 95

Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys
100 105 110

Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr His
115 120 125

Gly Ser Glu Asp Ser
130

<210> 284
<211> 330
<212> PRT
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<400> 284

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

```
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
```

<210> 285
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<212> PRT
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<400> 285

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175
```

```
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325
```

<210> 286
<211> 334
<212> PRT
<213> 人工序列

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<223> 合成多肽

<400> 286

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
325 330

<210> 287
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<400> 287

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125
```

```
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300
```

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser
325 330 335

<210> 288
<211> 330
<212> PRT
<213> 人工序列

<220>
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<400> 288

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

```
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Asp Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285
```

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 289
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<212> PRT
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<223> 合成多肽

<400> 289

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

```
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Lys
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255
```

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 290
<211> 329
<212> PRT
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<223> 合成多肽

<400> 290

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Asp Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 291
<211> 329
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 291

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

```
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205
```

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Lys
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 292
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<212> PRT
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<220>
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<400> 292

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Asp Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
                325                 330
```

<210> 293
<211> 334
<212> PRT
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<220>

〈223〉 合成多肽

〈400〉 293

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160
```

```
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Lys
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
                325                 330
```

<210> 294
<211> 330
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 294

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140
```

```
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320
```

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

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<223> 合成多肽

<400> 295

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

```
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
        275                 280                 285
```

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 296
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<212> PRT
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<400> 296

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 297
<211> 329
<212> PRT
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<400> 297

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 298
<211> 334
<212> PRT
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<400> 298

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
325 330

<210> 299
<211> 334
<212> PRT
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<220>
<223> 合成多肽

<400> 299

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

```
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190
```

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
                325                 330
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〈210〉 300
〈211〉 330
〈212〉 PRT
〈213〉 人工序列

〈220〉
〈223〉 合成多肽

<400> 300

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Asp Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 301
<211> 330

〈212〉 PRT
〈213〉 人工序列

〈220〉
〈223〉 合成多肽

〈400〉 301

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140
```

```
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Lys
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320
```

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

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<211> 329
<212> PRT
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<223> 合成多肽

<400> 302

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Asp Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 303
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<212> PRT
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<400> 303

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

```
Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Lys
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270
```

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 304
<211> 334
<212> PRT
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<220>
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<400> 304

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Asp Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
325 330

<210> 305
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<212> PRT
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<400> 305

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

```
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220
```

```
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Lys
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
                325                 330
```

〈210〉 306
〈211〉 330
〈212〉 PRT
〈213〉 人工序列

〈220〉
〈223〉 合成多肽

〈400〉 306

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
```

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

```
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
```

<210> 307
<211> 330
<212> PRT
<213> 人工序列

<220>
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<400> 307

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175
```

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 308
<211> 329
<212> PRT
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<220>
<223> 合成多肽

<400> 308

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160
```

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 309
<211> 329
<212> PRT
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<220>
<223> 合成多肽

<400> 309

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125
```

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 310
<211> 334
<212> PRT
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<400> 310

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
325 330

<210> 311
<211> 334
<212> PRT
<213> 人工序列

<220>
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<400> 311

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

```
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255
```

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
325 330

<210> 312
<211> 5
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<400> 312

Asn Tyr Gly Met His
1 5

<210> 313
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 313

Leu Ile Trp Tyr Asp Gly Ser Lys Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 314
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 314

Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 315
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 315

Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala Cys
1 5 10

<210> 316
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 316

Gln Asp Arg Lys Arg Pro Ser
1 5

<210> 317
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 317

Gln Ala Trp Asp Ser Ser Thr Glu Val
1 5

<210> 318
<211> 125
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 318

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Tyr Asp Gly Ser Lys Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 319
<211> 106
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 319

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Glu Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 320
<211> 477
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 320

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly
20 25 30

Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Phe Ser Asn Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ala Leu Ile Trp Tyr Asp Gly Ser Lys Lys
65 70 75 80

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85 90 95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100 105 110

Thr Ala Ala Tyr Tyr Cys Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser
115 120 125

Thr Gly Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
130 135 140

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
145 150 155 160

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
165 170 175

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
180 185 190

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
195 200 205

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
210 215 220

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
225 230 235 240

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
245 250 255

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
260 265 270

```
Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
        275                 280                 285

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
    290                 295                 300

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
305                 310                 315                 320

Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu
                325                 330                 335

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
            340                 345                 350

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
        355                 360                 365

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
    370                 375                 380

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
385                 390                 395                 400

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
                405                 410                 415

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
            420                 425                 430

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
        435                 440                 445
```

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
450 455 460

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470 475

<210> 321
<211> 231
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 321

Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Gly Thr Gly
1 5 10 15

Ser Trp Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
20 25 30

Pro Gly Gln Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp
35 40 45

Lys Tyr Ala Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu
50 55 60

Val Ile Tyr Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65 70 75 80

Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr
85 90 95

Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser
100 105 110

Thr Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
115 120 125

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
130 135 140

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
145 150 155 160

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
165 170 175

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
180 185 190

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
195 200 205

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
210 215 220

Val Ala Pro Thr Glu Cys Ser
225 230

<210> 322
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 322

Ser Tyr Asp Met Ser
1 5

<210> 323
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 323

Leu Ile Ser Gly Gly Gly Ser Asn Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 324
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 324

Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val
1 5 10

<210> 325
<211> 11
<212> PRT
<213> 人工序列

<220>

<223> 合成肽

<400> 325

Arg Ala Ser Gln Gly Ile Ser Asn Trp Leu Ala
1 5 10

<210> 326
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 326

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 327
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 327

Gln Gln Ala Asp Ser Phe Pro His Thr
1 5

<210> 328
<211> 120
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 328

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ala Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 329
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 329

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Phe Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Gly Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asp Ser Phe Pro His
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 330
<211> 472
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 330

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
20 25 30

```
Leu Val Gln Pro Gly Gly Ala Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Thr Phe Ser Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Val Ser Leu Ile Ser Gly Gly Gly Ser Asn Thr
65                  70                  75                  80

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
                85                  90                  95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            100                 105                 110

Thr Ala Val Tyr Phe Cys Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala
        115                 120                 125

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
    130                 135                 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
145                 150                 155                 160

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
        195                 200                 205
```

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
210 215 220

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
225 230 235 240

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln
305 310 315 320

Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 331
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 331

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

```
Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Gly Ile Ser Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Phe Ala Ala Ser Ser Leu Gln Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Gly Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

Ala Asp Ser Phe Pro His Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205
```

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 332
<211> 5
<212> PRT
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<220>
<223> 合成肽

<400> 332

Asp Tyr Ser Met Ser
1 5

<210> 333
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 333

Gly Ile Asn Trp Asn Gly Gly Arg Thr Arg Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 334
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 334

Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro
1 5 10

<210> 335
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 335

Ser Gly Asp Ala Leu Pro Lys Lys Tyr Ala Tyr
1 5 10

<210> 336
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 336

Glu Asp Ser Lys Arg Pro Ser
1 5

<210> 337
<211> 11
<212> PRT
<213> 人工序列

<220>

<223> 合成肽

<400> 337

Tyr Ser Thr Asp Ser Ser Gly Asn His Arg Val
1 5 10

<210> 338
<211> 121
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 338

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
20 25 30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 339
<211> 108
<212> PRT
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<220>
<223> 合成肽

<400> 339

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys Lys Tyr Ala
20 25 30

Tyr Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Ser
35 40 45

Glu Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Val Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Ser Ser Gly Asn His
85 90 95

Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

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<212> PRT
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<400> 340

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Val Glu Ser Gly Gly Ser
20 25 30

Val Val Arg Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Val Asp Asp Tyr Ser Met Ser Trp Val Arg Gln Val Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ser Gly Ile Asn Trp Asn Gly Gly Arg Thr
65 70 75 80

Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser
85 90 95

Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100 105 110

Thr Ala Leu Tyr Tyr Cys Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn
115 120 125

Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
130 135 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
145 150 155 160

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
165 170 175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
180 185 190

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
195 200 205

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
210 215 220

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
225 230 235 240

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
245 250 255

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
275 280 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290 295 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu
305 310 315 320

Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His
325 330 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355 360 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
370 375 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

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<211> 233

<212> PRT
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<223> 合成肽

<400> 341

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Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Gly Thr Gly
1               5                  10                  15

Ser Trp Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
            20                  25                  30

Pro Gly Gln Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys
        35                  40                  45

Lys Tyr Ala Tyr Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu
    50                  55                  60

Val Ile Ser Glu Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Ser Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala
                85                  90                  95

Gln Val Glu Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Ser Ser
            100                 105                 110

Gly Asn His Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
        115                 120                 125

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
    130                 135                 140
```

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
145 150 155 160

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
165 170 175

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
180 185 190

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
195 200 205

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
210 215 220

Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230

<210> 342
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 342

Ser Tyr Asp Met Ser
1 5

<210> 343
<211> 17
<212> PRT
<213> 人工序列

<220>

<223> 合成肽

<400> 343

Leu Ile Ser Gly Gly Gly Ser Asn Thr Tyr Tyr Ala Glu Ser Val Lys
1 5 10 15

Gly

<210> 344
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 344

Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val
1 5 10

<210> 345
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 345

Arg Ala Ser Gln Gly Ile Ser Asn Trp Leu Ala
1 5 10

<210> 346
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 346

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 347
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 347

Gln Gln Ala Glu Ser Phe Pro His Thr
1 5

<210> 348
<211> 120
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 348

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Leu Ile Ser Gly Gly Gly Ser Asn Thr Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 349
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 349

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Phe Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Glu Ser Phe Pro His
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 350
<211> 472
<212> PRT
<213> 人工序列

<220>
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<400> 350

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
20 25 30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Phe Ser Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ser Leu Ile Ser Gly Gly Gly Ser Asn Thr
65 70 75 80

Tyr Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85 90 95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100 105 110

Thr Ala Val Tyr Phe Cys Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala
115 120 125

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
130 135 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
145 150 155 160

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
165 170 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
180 185 190

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
195 200 205

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
210 215 220

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
225 230 235 240

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

```
Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            260                 265                 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        275                 280                 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    290                 295                 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln
305                 310                 315                 320

Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln
                325                 330                 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            340                 345                 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        355                 360                 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    370                 375                 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385                 390                 395                 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                405                 410                 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            420                 425                 430
```

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 351
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 351

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Gly Ile Ser Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Phe Ala Ala Ser Ser Leu Gln Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Ala Glu Ser Phe Pro His Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 352
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 352

Ser Tyr Asp Met Ser
1 5

<210> 353
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 353

Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val Lys
1 5 10 15

Gly

<210> 354
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 354

Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val
1 5 10

<210> 355
<211> 11

<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 355

Arg Ala Ser Gln Gly Ile Ser Asn Trp Leu Ala
1 5 10

<210> 356
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 356

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 357
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 357

Gln Gln Ala Glu Ser Phe Pro His Thr
1 5

<210> 358
<211> 120
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 358

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 359
<211> 107
<212> PRT
<213> 人工序列

<220>

<223> 合成肽

<400> 359

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Phe Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Glu Ser Phe Pro His
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 360
<211> 472
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 360

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

```
Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
            20                  25                  30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Thr Phe Ser Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Val Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr
65                  70                  75                  80

Tyr Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
                85                  90                  95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            100                 105                 110

Thr Ala Val Tyr Phe Cys Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala
        115                 120                 125

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
    130                 135                 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
145                 150                 155                 160

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190
```

```
His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
        195                 200                 205

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
    210                 215                 220

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
225                 230                 235                 240

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
                245                 250                 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            260                 265                 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        275                 280                 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    290                 295                 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln
305                 310                 315                 320

Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln
                325                 330                 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            340                 345                 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        355                 360                 365
```

```
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    370                 375                 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385                 390                 395                 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                405                 410                 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            420                 425                 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        435                 440                 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    450                 455                 460

Ser Leu Ser Leu Ser Pro Gly Lys
465                 470
```

<210> 361
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 361

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15
```

```
Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Gly Ile Ser Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Phe Ala Ala Ser Ser Leu Gln Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

Ala Glu Ser Phe Pro His Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190
```

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 362
<211> 5
<212> PRT
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<220>
<223> 合成肽

<400> 362

Asn Tyr Gly Met His
1 5

<210> 363
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 363

Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val Lys
1 5 10 15

Gly

<210> 364
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 364

Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 365
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 365

Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala Ser
1 5 10

<210> 366
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 366

Gln Asp Arg Lys Arg Pro Ser
1 5

<210> 367
<211> 9

<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 367

Gln Ala Phe Glu Ser Ser Thr Glu Val
1 5

<210> 368
<211> 125
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 368

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 369
<211> 106
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 369

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Phe Glu Ser Ser Thr Glu Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 370
<211> 477
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 370

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly
20 25 30

Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Phe Ser Asn Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys
65 70 75 80

Tyr Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85 90 95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100 105 110

Thr Ala Ala Tyr Tyr Cys Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser
115 120 125

Thr Gly Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
130 135 140

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
145 150 155 160

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
165 170 175

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
180 185 190

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
195 200 205

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
210 215 220

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
225 230 235 240

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
245 250 255

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
260 265 270

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
275 280 285

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
290 295 300

```
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
305                 310                 315                 320

Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu
                325                 330                 335

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
            340                 345                 350

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
        355                 360                 365

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
    370                 375                 380

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
385                 390                 395                 400

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
                405                 410                 415

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
            420                 425                 430

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
        435                 440                 445

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
    450                 455                 460

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475
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<210> 371
<211> 231
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 371

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Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Gly Thr Gly
1               5                  10                  15

Ser Trp Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
            20                  25                  30

Pro Gly Gln Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp
        35                  40                  45

Lys Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu
    50                  55                  60

Val Ile Tyr Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr
                85                  90                  95

Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Phe Glu Ser Ser
            100                 105                 110

Thr Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
        115                 120                 125
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Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
130 135 140

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
145 150 155 160

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
165 170 175

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
180 185 190

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
195 200 205

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
210 215 220

Val Ala Pro Thr Glu Cys Ser
225 230

<210> 372
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 372

Asp Tyr Ser Met Ser
1 5

<210> 373
<211> 17

<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 373

Gly Ile Asn Trp Asn Gly Gly Arg Thr Arg Tyr Ala Asp Ala Val Lys
1 5 10 15

Gly

<210> 374
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 374

Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro
1 5 10

<210> 375
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 375

Ser Gly Asp Ala Leu Pro Lys Lys Tyr Ala Tyr
1 5 10

<210> 376
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 376

Glu Asp Ala Lys Arg Pro Ser
1 5

<210> 377
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 377

Tyr Ser Thr Asp Ala Ser Gly Asn His Arg Val
1 5 10

<210> 378
<211> 121
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 378

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
20 25 30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 379
<211> 108
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 379

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys Lys Tyr Ala
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Ser
35 40 45

Glu Asp Ala Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Val Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Ala Ser Gly Asn His
85 90 95

Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 380
<211> 473
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 380

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Val Glu Ser Gly Gly Ser
20 25 30

Val Val Arg Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Val Asp Asp Tyr Ser Met Ser Trp Val Arg Gln Val Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ser Gly Ile Asn Trp Asn Gly Gly Arg Thr
65 70 75 80

Arg Tyr Ala Asp Ala Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser
85 90 95

Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100 105 110

Thr Ala Leu Tyr Tyr Cys Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn
115 120 125

Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
130 135 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
145 150 155 160

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
165 170 175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
180 185 190

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
195 200 205

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
210 215 220

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
225 230 235 240

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Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
                245                 250                 255

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            260                 265                 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        275                 280                 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    290                 295                 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu
305                 310                 315                 320

Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His
                325                 330                 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            340                 345                 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        355                 360                 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    370                 375                 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385                 390                 395                 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                405                 410                 415
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Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 381
<211> 233
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 381

Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Gly Thr Gly
1 5 10 15

Ser Trp Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
20 25 30

Pro Gly Gln Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys
35 40 45

Lys Tyr Ala Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu
50 55 60

```
Val Ile Ser Glu Asp Ala Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Ser Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala
                85                  90                  95

Gln Val Glu Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Ala Ser
            100                 105                 110

Gly Asn His Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
        115                 120                 125

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
    130                 135                 140

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
145                 150                 155                 160

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
                165                 170                 175

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
            180                 185                 190

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
        195                 200                 205

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
    210                 215                 220

Lys Thr Val Ala Pro Thr Glu Cys Ser
225                 230
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<210> 382
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 382

Asp Tyr Ser Met Ser
1 5

<210> 383
<211> 17
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 383

Gly Ile Asn Trp Asn Ala Gly Arg Thr Arg Tyr Ala Asp Ala Val Lys
1 5 10 15

Gly

<210> 384
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 384

Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro
1 5 10

<210> 385
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 385

Ser Gly Asp Ala Leu Pro Lys Lys Tyr Ala Tyr
1 5 10

<210> 386
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 386

Glu Asp Ala Lys Arg Pro Ser
1 5

<210> 387
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 387

Tyr Ser Thr Asp Ala Ser Gly Asn His Arg Val
1 5 10

〈210〉 388
〈211〉 121
〈212〉 PRT
〈213〉 人工序列

〈220〉
〈223〉 合成肽

〈400〉 388

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
20 25 30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

〈210〉 389
〈211〉 108

<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 389

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys Lys Tyr Ala
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Ser
35 40 45

Glu Asp Ala Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Val Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Ala Ser Gly Asn His
85 90 95

Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 390
<211> 473
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 390

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Val Glu Ser Gly Gly Ser
            20                  25                  30

Val Val Arg Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Thr Val Asp Asp Tyr Ser Met Ser Trp Val Arg Gln Val Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Val Ser Gly Ile Asn Trp Asn Ala Gly Arg Thr
65                  70                  75                  80

Arg Tyr Ala Asp Ala Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser
                85                  90                  95

Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            100                 105                 110

Thr Ala Leu Tyr Tyr Cys Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn
        115                 120                 125

Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
    130                 135                 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
145                 150                 155                 160

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
                165                 170                 175
```

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
180 185 190

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
195 200 205

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
210 215 220

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
225 230 235 240

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
245 250 255

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
275 280 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290 295 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu
305 310 315 320

Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His
325 330 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355 360 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
370 375 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 391
<211> 233
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 391

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Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Gly Thr Gly
1               5                  10                  15

Ser Trp Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
            20                  25                  30

Pro Gly Gln Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys
        35                  40                  45

Lys Tyr Ala Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu
    50                  55                  60

Val Ile Ser Glu Asp Ala Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Ser Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala
                85                  90                  95

Gln Val Glu Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Ala Ser
            100                 105                 110

Gly Asn His Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
        115                 120                 125

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
    130                 135                 140

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
145                 150                 155                 160

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
                165                 170                 175
```

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
180 185 190

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
195 200 205

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
210 215 220

Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230

<210> 392
<211> 15
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 392
aactatggca tgcat 15

<210> 393
<211> 51
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 393
cttatctggt atgatggaag taaaaaatac tatgcagact ccgtgaaggg c 51

<210> 394
<211> 48
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 394
gatccctcga gtctaactgg aagtacgggt tactacggta tggacgtc 48

<210> 395
<211> 33
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 395
tctggagata aattgggggga taaatatgct tgc 33

<210> 396
<211> 21
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 396
caagatagaa agcggccctc a 21

<210> 397
<211> 27
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 397
caggcgtggg acagtagcac tgaggta 27

<210> 398
<211> 375
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 398
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtccggctt caccttcagt aactatggca tgcattgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcactt atctggtatg atggaagtaa aaaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgcgt attactgtgc gagagatccc 300

tcgagtctaa ctggaagtac gggttactac ggtatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

<210> 399
<211> 318
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 399
tcctatgagc tgactcagcc accctcagtg tccgtgtccc caggacagac agccagcatc 60

acctgctctg gagataaatt gggggataaa tatgcttgct ggtatcagca gaagccaggc 120

cagtcccctg tgctggtcat ttatcaagat agaaagcggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacagcc actctgacca tcagcgggac ccaggctatg 240

gatgaggctg actattactg tcaggcgtgg gacagtagca ctgaggtatt cggcggaggg 300

accaagctga ccgtccta 318

<210> 400
<211> 1431
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 400
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg 60

cgctgtcagg tgcagctggt ggagtctggg ggaggcgtgg tccagcctgg gaggtccctg 120

agactctcct gtgcagcgtc cggcttcacc ttcagtaact atggcatgca ttgggtccgc 180

caggctccag gcaaggggct ggagtgggtg gcacttatct ggtatgatgg aagtaaaaaa 240

tactatgcag actccgtgaa gggccgattc accatctcca gagacaattc caagaacacg 300

ctgtatctgc aaatgaacag cctgagagcc gaggacacgg ctgcgtatta ctgtgcgaga 360

gatccctcga gtctaactgg aagtacgggt tactacggta tggacgtctg gggccaaggg 420

accacggtca ccgtctcctc agcctccacc aagggcccat cggtcttccc cctggcaccc 480

tcctccaaga gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc 540

cccgaaccgg tgacggtgtc gtggaactca ggcgccctga ccagcggcgt gcacaccttc 600

ccggctgtcc tacagtcctc aggactctac tccctcagca gcgtggtgac cgtgccctcc 660

agcagcttgg gcacccagac ctacatctgc aacgtgaatc acaagcccag caacaccaag 720

gtggacaaga aagttgagcc caaatcttgt gacaaaactc acacatgccc accgtgccca 780

gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 840

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 900

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 960

ccgtgcgagg agcagtacgg cagcacgtac cgttgcgtca gcgtcctcac cgtcctgcac 1020

caggactggc tgaatggcaa ggagtacaag tgcaaggtgt ccaacaaagc cctcccagcc 1080

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 1140

ctgccccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 1200

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 1260

tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcaagctc 1320

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1380

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa a 1431

<210> 401
<211> 693
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 401
atggcctggg ctctgctgct cctcaccctc ctcactcagg gcacagggtc ctgggcctcc 60

tatgagctga ctcagccacc ctcagtgtcc gtgtccccag gacagacagc cagcatcacc 120

tgctctggag ataaattggg ggataaatat gcttgctggt atcagcagaa gccaggccag 180

tcccctgtgc tggtcattta tcaagataga aagcggccct cagggatccc tgagcgattc 240

tctggctcca actctgggaa cacagccact ctgaccatca gcgggaccca ggctatggat 300

gaggctgact attactgtca ggcgtgggac agtagcactg aggtattcgg cggagggacc 360

aagctgaccg tcctaggtca gcccaaggct gcaccctcgg tcactctgtt cccgccctcc 420

tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc tcatcagtga cttctacccg 480

ggagccgtga cagtggcctg gaaggcagat agcagccccg tcaaggcggg agtggaaacc 540

accacaccct ccaaacaaag caacaacaag tacgcggcca gcagctatct gagcctgacg 600

cctgagcagt ggaagtccca cagaagctac agctgccagg tcacgcatga agggagcacc 660

gtggagaaga cagtggcccc tacagaatgt tca 693

<210> 402
<211> 15
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 402
agctatgaca tgagc 15

<210> 403
<211> 51
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 403
cttattagtg gtggtggtag taacacatac tacgcagact ccgtgaaggg c 51

<210> 404
<211> 33
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 404
cccagtggcc actacttcta cgctatggac gtc 33

<210> 405
<211> 33

〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 405
cgggcgagtc agggtattag caactggtta gcc 33

〈210〉 406
〈211〉 21
〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 406
gctgcatcca gtttgcaaag t 21

〈210〉 407
〈211〉 27
〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 407
caacaggctg acagtttccc tcacact 27

〈210〉 408
〈211〉 360
〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 408
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgaca tgagctgggt ccgccaggct 120

ccagggaagg ggctggaatg ggtctcactt attagtggtg gtggtagtaa cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat atttctgtgc gtcccccagt 300

ggccactact tctacgctat ggacgtctgg ggccaaggga ccacggtcac cgtctcctca 360

<210> 409
<211> 321
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 409
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgttggaga cagagtcacc 60

atcacttgtc gggcgagtca gggtattagc aactggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctttgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcggcg gcagtggatc tgggacagat ttcaccttca ccatcagcag cctgcagcct 240

gaagattttg caacttacta ttgtcaacag gctgacagtt tccctcacac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> 410
<211> 1416
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 410
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg 60

cgctgtgagg tgcagctgtt ggagtctggg ggaggcttgg tacagcctgg gggggccctg 120

agactctcct gtgcagcctc tggattcacc tttagcagct atgacatgag ctgggtccgc 180

caggctccag ggaaggggct ggaatgggtc tcacttatta gtggtggtgg tagtaacaca 240

tactacgcag actccgtgaa gggccggttc accatctcca gagacaattc caagaacacg 300

ctgtatctgc aaatgaacag cctgagagcc gaggacacgg ccgtatattt ctgtgcgtcc 360

cccagtggcc actacttcta cgctatggac gtctggggcc aagggaccac ggtcaccgtc 420

tcctcagcct ccaccaaggg cccatcggtc ttcccccctgg caccctcctc caagagcacc 480

tctgggggca cagcggccct gggctgcctg gtcaaggact acttccccga accggtgacg 540

gtgtcgtgga actcaggcgc cctgaccagc ggcgtgcaca ccttcccggc tgtcctacag 600

tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcag cttgggcacc 660

cagacctaca tctgcaacgt gaatcacaag cccagcaaca ccaaggtgga caagaaagtt 720

gagcccaaat cttgtgacaa aactcacaca tgcccaccgt gcccagcacc tgaactcctg 780

gggggaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg 840

acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 900

aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgtg cgaggagcag 960

tacggcagca cgtaccgttg cgtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1020

ggcaaggagt acaagtgcaa ggtgtccaac aaagccctcc cagcccccat cgagaaaacc 1080

atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1140

gaggagatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc 1200

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1260

cccgtgctgg actccgacgg ctccttcttc ctctatagca agctcaccgt ggacaagagc 1320

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tacacgcaga agagcctctc cctgtctccg ggtaaa 1416

<210> 411
<211> 708
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 411
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg 60

cgctgtgaca tccagatgac ccagtctcca tcttccgtgt ctgcatctgt tggagacaga 120

gtcaccatca cttgtcgggc gagtcagggt attagcaact ggttagcctg gtatcagcag 180

aaaccaggga aagcccctaa gctcctgatc tttgctgcat ccagtttgca aagtggggtc 240

ccatcaaggt tcggcggcag tggatctggg acagatttca ccttcaccat cagcagcctg 300

cagcctgaag attttgcaac ttactattgt caacaggctg acagtttccc tcacactttc 360

ggcggaggga ccaaggtgga gatcaaacga acggtggctg caccatctgt cttcatcttc 420

ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac 480

ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac 540

tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc 600

ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 660

cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgt 708

<210> 412
<211> 15
<212> DNA
<213> 人工序列

<220>

〈223〉 合成多核苷酸

〈400〉 412
gattatagca tgagc 15

〈210〉 413
〈211〉 51
〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 413
ggcattaatt ggaatggtgg taggacacgt tatgcagact ctgtgaaggg c 51

〈210〉 414
〈211〉 36
〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 414
gaattcaata acttcgagtc caactggttc gacccc 36

〈210〉 415
〈211〉 33
〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 415
tctggagatg cattgccaaa aaaatatgct tat 33

〈210〉 416
〈211〉 21

〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 416
gaggacagca aacgaccctc c 21

〈210〉 417
〈211〉 33
〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 417
tactcaacag acagcagtgg taatcatagg gtg 33

〈210〉 418
〈211〉 363
〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 418
gaggtgcagc tggtggagtc tgggggaagt gtggtacggc cgggggggtc cctgagactc 60

tcctgtgcag cctctggatt caccgttgat gattatagca tgagctgggt ccgccaagtt 120

ccagggaagg ggctggagtg ggtctctggc attaattgga atggtggtag gacacgttat 180

gcagactctg tgaagggccg attcaccatc tccagagaca gcgccaaaaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggat acggccttat attactgtgc gagagaattc 300

aataacttcg agtccaactg gttcgacccc tggggccagg gaaccctggt caccgtctcc 360

tca 363

<210> 419
<211> 324
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 419
tcctatgagc tgacacagcc accctcggtg tcagtgtccc caggacaaac ggccaggatc 60

acctgctctg gagatgcatt gccaaaaaaa tatgcttatt ggtaccagca gaagtcaggc 120

caggcccctg tgctggtcat ctctgaggac agcaaacgac cctccgggat ccctgagaga 180

ttctctggct ccagctcagg gacaatggcc accttgacta tcagtggggc ccaggtggag 240

gatgaagctg actactactg ttactcaaca gacagcagtg gtaatcatag ggtgttcggc 300

ggagggacca agctgaccgt ccta 324

<210> 420
<211> 1419
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 420
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg 60

cgctgtgagg tgcagctggt ggagtctggg ggaagtgtgg tacggccggg ggggtccctg 120

agactctcct gtgcagcctc tggattcacc gttgatgatt atagcatgag ctgggtccgc 180

caagttccag ggaaggggct ggagtgggtc tctggcatta attggaatgg tggtaggaca 240

cgttatgcag actctgtgaa gggccgattc accatctcca gagacagcgc caaaaactcc 300

ctgtatctgc aaatgaacag tctgagagcc gaggatacgg ccttatatta ctgtgcgaga 360

gaattcaata acttcgagtc caactggttc gacccctggg gccagggaac cctggtcacc 420

gtctcctcag cctccaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc 480

acctctgggg gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 540

acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta 600

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc 660

acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa 720

gttgagccca aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc 780

ctgggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 840

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 900

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gtgcgaggag 960

cagtacggca gcacgtaccg ttgcgtcagc gtcctcaccg tcctgcacca ggactggctg 1020

aatggcaagg agtacaagtg caaggtgtcc aacaaagccc tcccagcccc catcgagaaa 1080

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1140

cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 1200

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1260

cctcccgtgc tggactccga cggctccttc ttcctctata gcaagctcac cgtggacaag 1320

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1380

cactacacgc agaagagcct ctccctgtct ccgggtaaa 1419

<210> 421
<211> 699
<212> DNA
<213> 人工序列

<220>

〈223〉 合成多核苷酸

〈400〉 421
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tatgagctga cacagccacc ctcggtgtca gtgtccccag gacaaacggc caggatcacc 120

tgctctggag atgcattgcc aaaaaaatat gcttattggt accagcagaa gtcaggccag 180

gcccctgtgc tggtcatctc tgaggacagc aaacgaccct ccgggatccc tgagagattc 240

tctggctcca gctcagggac aatggccacc ttgactatca gtggggccca ggtggaggat 300

gaagctgact actactgtta ctcaacagac agcagtggta atcatagggt gttcggcgga 360

gggaccaagc tgaccgtcct aggtcagccc aaggctgcac cctcggtcac tctgttcccg 420

ccctcctctg aggagcttca agccaacaag gccacactgg tgtgtctcat cagtgacttc 480

tacccgggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg 540

gaaaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc 600

ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgaaggg 660

agcaccgtgg agaagacagt ggcccctaca gaatgttca 699

〈210〉 422
〈211〉 15
〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 422
agctatgaca tgagc 15

〈210〉 423
〈211〉 51
〈212〉 DNA
〈213〉 人工序列

<220>
<223> 合成多核苷酸

<400> 423
cttattagtg gtggtggtag taacacatac tacgcagaat ccgtgaaggg c 51

<210> 424
<211> 33
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 424
cccagtggcc actacttcta cgctatggac gtc 33

<210> 425
<211> 33
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 425
cgggcgagtc agggtattag caactggtta gcc 33

<210> 426
<211> 21
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 426
gctgcatcca gtttgcaaag t 21

<210> 427
<211> 27
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 427
caacaggctg aaagtttccc tcacact 27

<210> 428
<211> 360
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 428
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgaca tgagctgggt ccgccaggct 120

ccagggaagg ggctggaatg ggtctcactt attagtggtg gtggtagtaa cacatactac 180

gcagaatccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat atttctgtgc gtcccccagt 300

ggccactact tctacgctat ggacgtctgg ggccaaggga ccacggtcac cgtctcctca 360

<210> 429
<211> 321
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 429
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgttggaga cagagtcacc 60

atcacttgtc gggcgagtca gggtattagc aactggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctttgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcaccctca ccatcagcag cctgcagcct 240

gaagattttg caacttacta ttgtcaacag gctgaaagtt tccctcacac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> 430
<211> 1416
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 430
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg 60

cgctgtgagg tgcagctgtt ggagtctggg ggaggcttgg tacagcctgg ggggtccctg 120

agactctcct gtgcagcctc tggattcacc tttagcagct atgacatgag ctgggtccgc 180

caggctccag ggaaggggct ggaatgggtc tcacttatta gtggtggtgg tagtaacaca 240

tactacgcag aatccgtgaa gggccggttc accatctcca gagacaattc caagaacacg 300

ctgtatctgc aaatgaacag cctgagagcc gaggacacgg ccgtatattt ctgtgcgtcc 360

cccagtggcc actacttcta cgctatggac gtctggggcc aagggaccac ggtcaccgtc 420

tcctcagcct ccaccaaggg cccatcggtc ttcccccctgg caccctcctc caagagcacc 480

tctgggggca cagcggccct gggctgcctg gtcaaggact acttccccga accggtgacg 540

gtgtcgtgga actcaggcgc cctgaccagc ggcgtgcaca ccttcccggc tgtcctacag 600

tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcag cttgggcacc 660

cagacctaca tctgcaacgt gaatcacaag cccagcaaca ccaaggtgga caagaaagtt 720

gagcccaaat cttgtgacaa aactcacaca tgcccaccgt gcccagcacc tgaactcctg 780

gggggaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 840

acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 900

aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgtg cgaggagcag 960

tacggcagca cgtaccgttg cgtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1020

ggcaaggagt acaagtgcaa ggtgtccaac aaagccctcc cagccccat cgagaaaacc 1080

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cccgtgctgg actccgacgg ctccttcttc ctctatagca agctcaccgt ggacaagagc 1320

aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1380

tacacgcaga agagcctctc cctgtctccg ggtaaa 1416

<210> 431
<211> 708
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 431
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg 60

cgctgtgaca tccagatgac ccagtctcca tcttccgtgt ctgcatctgt tggagacaga 120

gtcaccatca cttgtcgggc gagtcagggt attagcaact ggttagcctg gtatcagcag 180

aaaccaggga aagcccctaa gctcctgatc tttgctgcat ccagtttgca aagtggggtc 240

ccatcaaggt tcagcggcag tggatctggg acagatttca ccctcaccat cagcagcctg 300

cagcctgaag attttgcaac ttactattgt caacaggctg aaagtttccc tcacactttc 360

ggcggaggga ccaaggtgga gatcaaacga acggtggctg caccatctgt cttcatcttc 420

ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac 480

ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac 540

tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc 600

ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 660

cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgt 708

<210> 432
<211> 15
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 432
agctatgaca tgagc 15

<210> 433
<211> 51
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 433
cttattagtg gtggtggtag tcaaacatac tacgcagaat ccgtgaaggg c 51

<210> 434
<211> 33
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 434
cccagtggcc actacttcta cgctatggac gtc 33

<210> 435
<211> 33
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 435
cgggcgagtc agggtattag caactggtta gcc 33

<210> 436
<211> 21
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 436
gctgcatcca gtttgcaaag t 21

<210> 437
<211> 27
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 437
caacaggctg aaagtttccc tcacact 27

<210> 438
<211> 360
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 438
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgaca tgagctgggt ccgccaggct 120

ccagggaagg ggctggaatg ggtctcactt attagtggtg gtggtagtca aacatactac 180

gcagaatccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat atttctgtgc gtcccccagt 300

ggccactact tctacgctat ggacgtctgg ggccaaggga ccacggtcac cgtctcctca 360

<210> 439
<211> 321
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 439
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgttggaga cagagtcacc 60

atcacttgtc gggcgagtca gggtattagc aactggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctttgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcaccctca ccatcagcag cctgcagcct 240

gaagattttg caacttacta ttgtcaacag gctgaaagtt tccctcacac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> 440
<211> 1416
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 440
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg 60

cgctgtgagg tgcagctgtt ggagtctggg ggaggcttgg tacagcctgg ggggtccctg 120

agactctcct gtgcagcctc tggattcacc tttagcagct atgacatgag ctgggtccgc 180

caggctccag ggaaggggct ggaatgggtc tcacttatta gtggtggtgg tagtcaaaca 240

tactacgcag aatccgtgaa gggccggttc accatctcca gagacaattc caagaacacg 300

ctgtatctgc aaatgaacag cctgagagcc gaggacacgg ccgtatattt ctgtgcgtcc 360

cccagtggcc actacttcta cgctatggac gtctggggcc aagggaccac ggtcaccgtc 420

tcctcagcct ccaccaaggg cccatcggtc ttcccccctgg caccctcctc caagagcacc 480

tctgggggca cagcggccct gggctgcctg gtcaaggact acttccccga accggtgacg 540

gtgtcgtgga actcaggcgc cctgaccagc ggcgtgcaca ccttcccggc tgtcctacag 600

tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcag cttgggcacc 660

cagacctaca tctgcaacgt gaatcacaag cccagcaaca ccaaggtgga caagaaagtt 720

gagcccaaat cttgtgacaa aactcacaca tgcccaccgt gcccagcacc tgaactcctg 780

gggggaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 840

acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 900

aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgtg cgaggagcag 960

tacggcagca cgtaccgttg cgtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 1020

ggcaaggagt acaagtgcaa ggtgtccaac aaagccctcc cagccccat cgagaaaacc 1080

atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1140

gaggagatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc 1200

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1260

cccgtgctgg actccgacgg ctccttcttc ctctatagca agctcaccgt ggacaagagc 1320

aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1380

tacacgcaga agagcctctc cctgtctccg ggtaaa 1416

<210> 441
<211> 708
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 441
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cgctgtgaca tccagatgac ccagtctcca tcttccgtgt ctgcatctgt tggagacaga 120

gtcaccatca cttgtcgggc gagtcagggt attagcaact ggttagcctg gtatcagcag 180

aaaccaggga aagcccctaa gctcctgatc tttgctgcat ccagtttgca aagtggggtc 240

ccatcaaggt tcagcggcag tggatctggg acagatttca ccctcaccat cagcagcctg 300

cagcctgaag attttgcaac ttactattgt caacaggctg aaagtttccc tcacactttc 360

ggcggaggga ccaaggtgga gatcaaacga acggtggctg caccatctgt cttcatcttc 420

ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac 480

ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac 540

tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc 600

ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 660

cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgt 708

<210> 442
<211> 15
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 442
aactatggca tgcat 15

<210> 443
<211> 51
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 443
cttatctggt atgatgcaag taaaaaatac tatgcagaat ccgtgaaggg c 51

<210> 444
<211> 48
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 444
gatccctcga gtctaactgg aagtacgggt tactacggta tggacgtc 48

<210> 445
<211> 33
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 445
tctggagata aattgggggga taaatatgct tcc 33

<210> 446
<211> 21
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 446
caagatagaa agcggccctc a 21

<210> 447
<211> 27
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 447
caggcgttcg aaagtagcac tgaggta 27

<210> 448
<211> 375
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 448
caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtccggctt caccttcagt aactatggca tgcattgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcactt atctggtatg atgcaagtaa aaaatactat 180

gcagaatccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgcgt attactgtgc gagagatccc 300

tcgagtctaa ctggaagtac gggttactac ggtatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

<210> 449
<211> 318
<212> DNA
<213> 人工序列

<220>
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<400> 449
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acctgctctg gagataaatt gggggataaa tatgcttcct ggtatcagca gaagccaggc 120

cagtcccctg tgctggtcat ttatcaagat agaaagcggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacagcc actctgacca tcagcgggac ccaggctatg 240

gatgaggctg actattactg tcaggcgttc gaaagtagca ctgaggtatt cggcggaggg 300

accaagctga ccgtccta 318

<210> 450
<211> 1431
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 450
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cgctgtcagg tgcagctggt ggagtctggg ggaggcgtgg tccagcctgg gaggtccctg 120

agactctcct gtgcagcgtc cggcttcacc ttcagtaact atggcatgca ttgggtccgc 180

caggctccag gcaaggggct ggagtgggtg gcacttatct ggtatgatgc aagtaaaaaa 240

tactatgcag aatccgtgaa gggccgattc accatctcca gagacaattc caagaacacg 300

ctgtatctgc aaatgaacag cctgagagcc gaggacacgg ctgcgtatta ctgtgcgaga 360

gatccctcga gtctaactgg aagtacgggt tactacggta tggacgtctg gggccaaggg 420

accacggtca ccgtctcctc agcctccacc aagggcccat cggtcttccc cctggcaccc 480

tcctccaaga gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc 540

cccgaaccgg tgacggtgtc gtggaactca ggcgccctga ccagcggcgt gcacaccttc 600

ccggctgtcc tacagtcctc aggactctac tccctcagca gcgtggtgac cgtgccctcc 660

agcagcttgg gcacccagac ctacatctgc aacgtgaatc acaagcccag caacaccaag 720

gtggacaaga aagttgagcc caaatcttgt gacaaaactc acacatgccc accgtgccca 780

gcacctgaac tcctgggggg accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 840

ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 900

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 960

ccgtgcgagg agcagtacgg cagcacgtac cgttgcgtca gcgtcctcac cgtcctgcac 1020

caggactggc tgaatggcaa ggagtacaag tgcaaggtgt ccaacaaagc cctcccagcc 1080

cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 1140

ctgcccccat cccgggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa 1200

ggcttctatc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 1260

tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta tagcaagctc 1320

accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1380

gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa a 1431

<210> 451
<211> 693
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 451
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tatgagctga ctcagccacc ctcagtgtcc gtgtccccag gacagacagc cagcatcacc 120

tgctctggag ataaattggg ggataaatat gcttcctggt atcagcagaa gccaggccag 180

tcccctgtgc tggtcattta tcaagataga aagcggccct cagggatccc tgagcgattc 240

tctggctcca actctgggaa cacagccact ctgaccatca gcgggaccca ggctatggat 300

gaggctgact attactgtca ggcgttcgaa agtagcactg aggtattcgg cggagggacc 360

aagctgaccg tcctaggtca gcccaaggct gcaccctcgg tcactctgtt cccgccctcc 420

tctgaggagc ttcaagccaa caaggccaca ctggtgtgtc tcatcagtga cttctacccg 480

ggagccgtga cagtggcctg gaaggcagat agcagccccg tcaaggcggg agtggaaacc 540

accacaccct ccaaacaaag caacaacaag tacgcggcca gcagctatct gagcctgacg 600

cctgagcagt ggaagtccca cagaagctac agctgccagg tcacgcatga agggagcacc 660

gtggagaaga cagtggcccc tacagaatgt tca 693

<210> 452
<211> 15
<212> DNA
<213> 人工序列

<220>

〈223〉 合成多核苷酸

〈400〉 452
gattatagca tgagc 15

〈210〉 453
〈211〉 51
〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 453
ggcattaatt ggaatggtgg taggacacgt tatgcagacg ctgtgaaggg c 51

〈210〉 454
〈211〉 36
〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 454
gaattcaata acttcgagtc caactggttc gacccc 36

〈210〉 455
〈211〉 33
〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 455
tctggagatg cattgccaaa aaaatatgct tat 33

〈210〉 456
〈211〉 21

<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 456
gaggacgcca aacgaccctc c 21

<210> 457
<211> 33
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 457
tactcaacag acgccagtgg taatcatagg gtg 33

<210> 458
<211> 363
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 458
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tcctgtgcag cctctggatt caccgttgat gattatagca tgagctgggt ccgccaagtt 120

ccagggaagg ggctggagtg ggtctctggc attaattgga atggtggtag gacacgttat 180

gcagacgctg tgaagggccg attcaccatc tccagagaca gcgccaaaaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggat acggccttat attactgtgc gagagaattc 300

aataacttcg agtccaactg gttcgacccc tggggccagg gaaccctggt caccgtctcc 360

tca 363

<210> 459
<211> 324
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 459
tcctatgagc tgacacagcc accctcggtg tcagtgtccc caggacaaac ggccaggatc 60

acctgctctg gagatgcatt gccaaaaaaa tatgcttatt ggtaccagca gaagccaggc 120

caggcccctg tgctggtcat ctctgaggac gccaaacgac cctccgggat ccctgagaga 180

ttctctggct ccagctcagg gacaatggcc accttgacta tcagtggggc ccaggtggag 240

gatgaagctg actactactg ttactcaaca gacgccagtg gtaatcatag ggtgttcggc 300

ggagggacca agctgaccgt ccta 324

<210> 460
<211> 1419
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 460
atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcg 60

cgctgtgagg tgcagctggt ggagtctggg ggaagtgtgg tacggccggg ggggtccctg 120

agactctcct gtgcagcctc tggattcacc gttgatgatt atagcatgag ctgggtccgc 180

caagttccag ggaaggggct ggagtgggtc tctggcatta attggaatgg tggtaggaca 240

cgttatgcag acgctgtgaa gggccgattc accatctcca gagacagcgc caaaaactcc 300

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gaattcaata acttcgagtc caactggttc gacccctggg gccagggaac cctggtcacc 420

gtctcctcag cctccaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc 480

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acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta 600

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc 660

acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa 720

gttgagccca aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc 780

ctgggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 840

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 900

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gtgcgaggag 960

cagtacggca gcacgtaccg ttgcgtcagc gtcctcaccg tcctgcacca ggactggctg 1020

aatggcaagg agtacaagtg caaggtgtcc aacaaagccc tcccagcccc catcgagaaa 1080

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1140

cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 1200

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1260

cctcccgtgc tggactccga cggctccttc ttcctctata gcaagctcac cgtggacaag 1320

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1380

cactacacgc agaagagcct ctccctgtct ccgggtaaa 1419

<210> 461
<211> 699
<212> DNA
<213> 人工序列

<220>

〈223〉 合成多核苷酸

〈400〉 461
atggcctggg ctctgctgct cctcaccctc ctcactcagg gcacagggtc ctgggcctcc 60

tatgagctga cacagccacc ctcggtgtca gtgtccccag gacaaacggc caggatcacc 120

tgctctggag atgcattgcc aaaaaaatat gcttattggt accagcagaa gccaggccag 180

gcccctgtgc tggtcatctc tgaggacgcc aaacgaccct ccgggatccc tgagagattc 240

tctggctcca gctcagggac aatggccacc ttgactatca gtggggccca ggtggaggat 300

gaagctgact actactgtta ctcaacagac gccagtggta atcatagggt gttcggcgga 360

gggaccaagc tgaccgtcct aggtcagccc aaggctgcac cctcggtcac tctgttcccg 420

ccctcctctg aggagcttca agccaacaag gccacactgg tgtgtctcat cagtgacttc 480

tacccgggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg 540

gaaaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc 600

ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgaaggg 660

agcaccgtgg agaagacagt ggcccctaca gaatgttca 699

〈210〉 462
〈211〉 15
〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 462
gattatagca tgagc 15

〈210〉 463
〈211〉 51
〈212〉 DNA
〈213〉 人工序列

<220>
<223> 合成多核苷酸

<400> 463
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<210> 464
<211> 36
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 464
gaattcaata acttcgagtc caactggttc gacccc 36

<210> 465
<211> 33
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 465
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<210> 466
<211> 21
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 466
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<210> 467
<211> 33
<212> DNA
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<220>
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<400> 467
tactcaacag acgccagtgg taatcatagg gtg 33

<210> 468
<211> 363
<212> DNA
<213> 人工序列

<220>
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tcctgtgcag cctctggatt caccgttgat gattatagca tgagctgggt ccgccaagtt 120

ccagggaagg ggctggagtg ggtctctggc attaattgga atgctggtag gacacgttat 180

gcagacgctg tgaagggccg attcaccatc tccagagaca gcgccaaaaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggat acggccttat attactgtgc gagagaattc 300

aataacttcg agtccaactg gttcgacccc tggggccagg gaaccctggt caccgtgtcc 360

tca 363

<210> 469
<211> 324
<212> DNA
<213> 人工序列

<220>
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<400> 469
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acctgctctg gagatgcatt gccaaaaaaa tatgcttatt ggtaccagca gaagccaggc 120

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gatgaagctg actactactg ttactcaaca gacgccagtg gtaatcatag ggtgttcggc 300

ggagggacca agctgaccgt ccta 324

<210> 470
<211> 1419
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

<400> 470
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cgctgtgagg tgcagctggt ggagtctggg ggaagtgtgg tacggccggg ggggtccctg 120

agactctcct gtgcagcctc tggattcacc gttgatgatt atagcatgag ctgggtccgc 180

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acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa 720

gttgagccca aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc 780

ctgggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 840

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 900

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aatggcaagg agtacaagtg caaggtgtcc aacaaagccc tcccagcccc catcgagaaa 1080

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1140

cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 1200

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1260

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cactacacgc agaagagcct ctccctgtct ccgggcaaa 1419

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<211> 699
<212> DNA
<213> 人工序列

<220>
<223> 合成多核苷酸

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tgctctggag atgcattgcc aaaaaaatat gcttattggt accagcagaa gccaggccag 180

gcccctgtgc tggtcatctc tgaggacgcc aaacgaccct ccgggatccc tgagagattc 240

tctggctcca gctcagggac aatggccacc ttgactatca gtggggccca ggtggaggat 300

gaagctgact actactgtta ctcaacagac gccagtggta atcatagggt gttcggcgga 360

gggaccaagc tgaccgtcct aggtcagccc aaggctgcac cctcggtcac tctgttcccg 420

ccctcctctg aggagcttca agccaacaag gccacactgg tgtgtctcat cagtgacttc 480

tacccgggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg 540

gaaaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc 600

ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgaaggg 660

agcaccgtgg agaagacagt ggcccctaca gaatgttca 699

<210> 472
<211> 330
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 472

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

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Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240
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Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Asp Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 473
<211> 330
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 473

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 474
<211> 329
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 474

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

```
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190
```

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Asp Ser Leu Ser Leu Ser Pro Gly
                325
```

<210> 475
<211> 329
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 475

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

〈210〉 476
〈211〉 334

〈212〉 PRT
〈213〉 人工序列

〈220〉
〈223〉 合成肽

〈400〉 476

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140
```

```
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320
```

Gln Asp Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
325 330

<210> 477
<211> 334
<212> PRT
<213> 人工序列

<220>
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<400> 477

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
325 330

<210> 478
<211> 330
<212> PRT
<213> 人工序列

<220>
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<400> 478

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

```
Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Glu Asn Gln Val Ser Leu Thr Cys Leu Val Glu Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270
```

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

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 479
<211> 330
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 479

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Lys
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

```
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
```

<210> 480
<211> 329
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 480

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45
```

```
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220
```

```
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Glu Asn Gln Val Ser Leu Thr Cys Leu Val Glu Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

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

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325
```

<210> 481
<211> 329
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 481

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
```

```
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205
```

```
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Lys
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325
```

<210> 482
<211> 334
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 482

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175
```

```
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Glu Asn Gln Val Ser Leu Thr Cys Leu Val Glu Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

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

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
                325                 330
```

<210> 483
<211> 334
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 483

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Lys
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
325 330

<210> 484
<211> 330
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 484

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125
```

```
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300
```

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Asp Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 485
<211> 330
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 485

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 486
<211> 329
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 486

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

```
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255
```

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Asp Ser Leu Ser Leu Ser Pro Gly
325

<210> 487
<211> 329
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 487

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 488
<211> 334
<212> PRT
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<220>
<223> 合成肽

<400> 488

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

```
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205
```

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Asp Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
325 330

<210> 489
<211> 334
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 489

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
                325                 330
```

<210> 490
<211> 330
<212> PRT
<213> 人工序列

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〈223〉 合成肽

〈400〉 490

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160
```

```
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Glu Asn Gln Val Ser Leu Thr Cys Leu Val Glu Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

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

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
```

<210> 491
<211> 330
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 491

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140
```

```
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Lys
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320
```

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 492
<211> 329
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 492

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

```
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Glu Asn Gln Val Ser Leu Thr Cys Leu Val Glu Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Glu Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285
```

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 493
<211> 329
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 493

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Lys
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 494
<211> 334
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 494

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240
```

Met Thr Glu Asn Gln Val Ser Leu Thr Cys Leu Val Glu Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

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

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
325 330

<210> 495
<211> 334
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 495

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Lys
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
325 330

<210> 496
<211> 584
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 496

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
            20                  25                  30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
            100                 105                 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190
```

```
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
    290                 295                 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365
```

```
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445

Pro Gly Lys Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu
    450                 455                 460

Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro
465                 470                 475                 480

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

Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly
            500                 505                 510

Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys
        515                 520                 525

Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys
    530                 535                 540
```

Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu
545 550 555 560

Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser
565 570 575

Arg Thr His Gly Ser Glu Asp Ser
580

<210> 497
<211> 584
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 497

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
20 25 30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
100 105 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

```
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
    290                 295                 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445
```

```
Pro Gly Lys Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu
    450                 455                 460

Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro
465                 470                 475                 480

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

Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly
            500                 505                 510

Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys
        515                 520                 525

Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys
    530                 535                 540

Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu
545                 550                 555                 560

Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser
                565                 570                 575

Arg Thr His Gly Ser Glu Asp Ser
            580
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<210> 498
<211> 583
<212> PRT
<213> 人工序列

<220>

〈223〉 合成肽

〈400〉 498

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Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
            20                  25                  30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
            100                 105                 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160
```

```
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
    290                 295                 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335
```

```
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445

Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile
    450                 455                 460

Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu
465                 470                 475                 480

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

Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn
            500                 505                 510
```

Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro
515 520 525

Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro
530 535 540

Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg
545 550 555 560

Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg
565 570 575

Thr His Gly Ser Glu Asp Ser
580

<210> 499
<211> 588
<212> PRT
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<220>
<223> 合成肽

<400> 499

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
20 25 30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
100 105 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
290 295 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

```
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445

Pro Gly Gly Gly Gly Gly Ser Gln Gly Gln Asp Arg His Met Ile Glu
    450                 455                 460

Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn
465                 470                 475                 480

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

Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser
            500                 505                 510

Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys
        515                 520                 525

Leu Lys Ala Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His
    530                 535                 540

Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys
545                 550                 555                 560

Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln
                565                 570                 575

His Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
            580                 585
```

<210> 500
<211> 588
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 500

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Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
            20                  25                  30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125
```

```
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
    290                 295                 300
```

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Gly Gly Gly Gly Ser Gln Gly Gln Asp Arg His Met Ile Glu
450 455 460

Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn
465 470 475 480

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

Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser
500 505 510

Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys
515 520 525

Leu Lys Glu Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His
530 535 540

Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys
545 550 555 560

Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln
565 570 575

His Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
580 585

<210> 501
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<212> PRT
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<400> 501

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
20 25 30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
100 105 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
290 295 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile
450 455 460

Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu
465 470 475 480

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

Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn
500 505 510

Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro
515 520 525

Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro
530 535 540

Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg
545 550 555 560

Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg
565 570 575

Thr His Gly Ser Glu Asp Ser
580

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<212> PRT
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<400> 502

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
20 25 30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

```
Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
            100                 105                 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270
```

```
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
    290                 295                 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445
```

```
Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile
    450                 455                 460

Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu
465                 470                 475                 480

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

Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn
            500                 505                 510

Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro
        515                 520                 525

Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro
    530                 535                 540

Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg
545                 550                 555                 560

Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg
                565                 570                 575

Thr His Gly Ser Glu Asp Ser
            580
```

<210> 503
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Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
            20                  25                  30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
            100                 105                 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175
```

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
290 295 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Glu Lys Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile
450 455 460

Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu
465 470 475 480

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

Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn
500 505 510

Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro
515 520 525

Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro
530 535 540

Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg
545 550 555 560

Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg
565 570 575

Thr His Gly Ser Glu Asp Ser
580

<210> 504
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<212> PRT
<213> 人工序列

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<223> 合成肽

<400> 504

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
20 25 30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
            100                 105                 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240
```

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
290 295 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

```
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445

Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile
    450                 455                 460

Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu
465                 470                 475                 480

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

Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn
            500                 505                 510

Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro
        515                 520                 525

Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro
    530                 535                 540

Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg
545                 550                 555                 560

Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg
                565                 570                 575

Thr His Gly Ser Glu Asp Ser
            580
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<210> 505
<211> 583
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 505

```
Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
            20                  25                  30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
            100                 105                 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140
```

```
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
    290                 295                 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320
```

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile
450 455 460

Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu
465 470 475 480

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

Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn
500 505 510

Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro
515 520 525

Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro
530 535 540

Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg
545 550 555 560

Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg
565 570 575

Thr His Gly Ser Glu Asp Ser
580

<210> 506
<211> 583
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 506

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
20 25 30

```
Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
            100                 105                 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205
```

```
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
    290                 295                 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Lys Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380
```

```
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445

Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile
    450                 455                 460

Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu
465                 470                 475                 480

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

Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn
            500                 505                 510

Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro
        515                 520                 525

Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro
    530                 535                 540

Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg
545                 550                 555                 560
```

Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg
565 570 575

Thr His Gly Ser Glu Asp Ser
580

<210> 507
<211> 588
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 507

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
115 120 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
290 295 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
355 360 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
405 410 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445

Leu Ser Leu Ser Pro Gly Lys Gln Gly Gln Asp Arg His Met Ile Glu
450 455 460

```
Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn
465                 470                 475                 480

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

Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser
            500                 505                 510

Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys
        515                 520                 525

Leu Lys Ala Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His
    530                 535                 540

Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys
545                 550                 555                 560

Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln
                565                 570                 575

His Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
            580                 585
```

<210> 508
<211> 587
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 508

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175
```

```
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                 215                 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
    290                 295                 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350
```

```
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445

Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met
    450                 455                 460

Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp
465                 470                 475                 480

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

Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala
            500                 505                 510

Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu
        515                 520                 525
```

Lys Ala Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg
530 535 540

Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu
545 550 555 560

Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His
565 570 575

Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
580 585

<210> 509
<211> 588
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 509

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

```
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                 215                 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255
```

```
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
    290                 295                 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430
```

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445

Leu Ser Leu Ser Pro Gly Lys Gln Gly Gln Asp Arg His Met Ile Glu
450 455 460

Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn
465 470 475 480

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

Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser
500 505 510

Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys
515 520 525

Leu Lys Glu Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His
530 535 540

Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys
545 550 555 560

Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln
565 570 575

His Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
580 585

<210> 510
<211> 587

<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 510

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140
```

```
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                 215                 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
    290                 295                 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320
```

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
355 360 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
405 410 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445

Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met
450 455 460

Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp
465 470 475 480

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

Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala
500 505 510

Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu
515 520 525

Lys Glu Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg
530 535 540

Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu
545 550 555 560

Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His
565 570 575

Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
580 585

<210> 511
<211> 592
<212> PRT
<213> 人工序列

<220>
<223> 合成肽

<400> 511

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
115 120 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
290 295 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
355 360 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
405 410 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445

Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gln Gly Gln Asp Arg
450 455 460

His Met Ile Glu Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys
465 470 475 480

Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala Pro Glu Asp
485 490 495

Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala
500 505 510

Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val
515 520 525

Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro Ser Thr Asn Ala Gly Arg
530 535 540

Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys
545 550 555 560

Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys
565 570 575

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

<210> 512
<211> 592
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<400> 512

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
100 105 110

```
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                 215                 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        275                 280                 285
```

```
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
    290                 295                 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445

Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser Gln Gly Gln Asp Arg
    450                 455                 460
```

```
His Met Ile Glu Met Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys
465                 470                 475                 480

Asn Tyr Val Asn Asp Leu Val Pro Glu Phe Leu Pro Ala Pro Glu Asp
                485                 490                 495

Val Glu Thr Asn Cys Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala
            500                 505                 510

Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val
        515                 520                 525

Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro Ser Thr Asn Ala Gly Arg
    530                 535                 540

Arg Gln Lys His Arg Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys
545                 550                 555                 560

Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys
                565                 570                 575

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

<210> 513
<211> 587
<212> PRT
<213> 人工序列

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<400> 513

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190
```

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
290 295 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys
355 360 365

```
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445

Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met
    450                 455                 460

Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp
465                 470                 475                 480

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

Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala
            500                 505                 510

Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu
        515                 520                 525

Lys Ala Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg
    530                 535                 540
```

Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu
545 550 555 560

Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His
565 570 575

Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
580 585

<210> 514
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<212> PRT
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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
115 120 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255

```
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
    290                 295                 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430
```

```
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445

Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met
    450                 455                 460

Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp
465                 470                 475                 480

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

Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala
            500                 505                 510

Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu
        515                 520                 525

Lys Ala Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg
    530                 535                 540

Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu
545                 550                 555                 560

Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His
                565                 570                 575

Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
            580                 585
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<210> 515
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<223> 合成肽

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```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160
```

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
290 295 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Lys Met Thr Lys
355 360 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400

Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser
405 410 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445

Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met
450 455 460

Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp
465 470 475 480

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

Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala
500 505 510

```
Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu
        515                 520                 525

Lys Ala Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg
    530                 535                 540

Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu
545                 550                 555                 560

Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His
                565                 570                 575

Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
            580                 585
```

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```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

```
Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                 215                 220
```

```
Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
    290                 295                 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400
```

Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser
405 410 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445

Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met
450 455 460

Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp
465 470 475 480

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

Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala
500 505 510

Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu
515 520 525

Lys Glu Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg
530 535 540

Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu
545 550 555 560

Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His
565 570 575

Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
580 585

<210> 517
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<400> 517

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
115 120 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
290 295 300

```
Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445

Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met
    450                 455                 460

Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp
465                 470                 475                 480
```

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

Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala
500 505 510

Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu
515 520 525

Lys Glu Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg
530 535 540

Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu
545 550 555 560

Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His
565 570 575

Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
580 585

<210> 518
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<400> 518

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190
```

```
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                 215                 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
    290                 295                 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Lys Met Thr Lys
        355                 360                 365
```

```
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445

Leu Ser Leu Ser Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met
    450                 455                 460

Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp
465                 470                 475                 480

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

Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala
            500                 505                 510

Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu
        515                 520                 525

Lys Glu Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg
    530                 535                 540
```

Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu
545 550 555 560

Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His
565 570 575

Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
580 585

<210> 519
<211> 583
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<400> 519

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
20 25 30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
100 105 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

```
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
    290                 295                 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445
```

```
Pro Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile
    450                 455                 460

Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu
465                 470                 475                 480

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

Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn
            500                 505                 510

Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro
        515                 520                 525

Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro
    530                 535                 540

Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg
545                 550                 555                 560

Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg
                565                 570                 575

Thr His Gly Ser Glu Asp Ser
            580
```

<210> 520
<211> 236
<212> PRT
<213> 人工序列

<220>

〈223〉 合成多肽

〈400〉 520

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Gly Ile Ser Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Phe Ala Ala Ser Ser Leu Gln Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

Ala Glu Ser Phe Pro His Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160
```

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 521
<211> 472
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 521

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
20 25 30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Phe Ser Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr
65 70 75 80

Tyr Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85 90 95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100 105 110

Thr Ala Val Tyr Phe Cys Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala
115 120 125

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
130 135 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
145 150 155 160

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
165 170 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
180 185 190

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
195 200 205

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
210 215 220

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
225 230 235 240

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln
305 310 315 320

Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 522
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 522

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Gly Ile Ser Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

```
Ala Pro Lys Leu Leu Ile Phe Ala Ala Ser Ser Leu Gln Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

Ala Glu Ser Phe Pro His Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235
```

<210> 523
<211> 472
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 523

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
            20                  25                  30

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Thr Phe Ser Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Val Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr
65                  70                  75                  80

Tyr Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
                85                  90                  95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            100                 105                 110

Thr Ala Val Tyr Phe Cys Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala
        115                 120                 125

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
    130                 135                 140
```

```
Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
145                 150                 155                 160

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
        195                 200                 205

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
    210                 215                 220

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
225                 230                 235                 240

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
                245                 250                 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            260                 265                 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        275                 280                 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    290                 295                 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln
305                 310                 315                 320
```

Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Asp His His
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Ser His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 524
<211> 231

<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 524

```
Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Gly Thr Gly
1               5                  10                  15

Ser Trp Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
            20                  25                  30

Pro Gly Gln Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp
        35                  40                  45

Lys Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu
    50                  55                  60

Val Ile Tyr Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr
                85                  90                  95

Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Phe Glu Ser Ser
            100                 105                 110

Thr Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
        115                 120                 125

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
    130                 135                 140
```

```
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
145                 150                 155                 160

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
                165                 170                 175

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
            180                 185                 190

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
        195                 200                 205

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
    210                 215                 220

Val Ala Pro Thr Glu Cys Ser
225                 230
```

<210> 525
<211> 477
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 525

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15

Leu Arg Gly Ala Arg Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly
            20                  25                  30

Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45
```

```
Phe Thr Phe Ser Asn Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Val Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys
65                  70                  75                  80

Tyr Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
                85                  90                  95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            100                 105                 110

Thr Ala Ala Tyr Tyr Cys Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser
        115                 120                 125

Thr Gly Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
    130                 135                 140

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
145                 150                 155                 160

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
                165                 170                 175

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
            180                 185                 190

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
        195                 200                 205

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
    210                 215                 220
```

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
225 230 235 240

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
245 250 255

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
260 265 270

Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu
275 280 285

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
290 295 300

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
305 310 315 320

Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu
325 330 335

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
340 345 350

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
355 360 365

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
370 375 380

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
385 390 395 400

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
405 410 415

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
420 425 430

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
435 440 445

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
450 455 460

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470 475

<210> 526
<211> 231
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 526

Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Gly Thr Gly
1 5 10 15

Ser Trp Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
20 25 30

Pro Gly Gln Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp
35 40 45

```
Lys Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu
    50                  55                  60

Val Ile Tyr Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr
                85                  90                  95

Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Phe Glu Ser Ser
            100                 105                 110

Thr Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
        115                 120                 125

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
    130                 135                 140

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
145                 150                 155                 160

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
                165                 170                 175

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
            180                 185                 190

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
        195                 200                 205

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
    210                 215                 220
```

Val Ala Pro Thr Glu Cys Ser
225 230

<210> 527
<211> 477
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 527

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly
20 25 30

Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Phe Ser Asn Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys
65 70 75 80

Tyr Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
85 90 95

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100 105 110

Thr Ala Ala Tyr Tyr Cys Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser
115 120 125

Thr Gly Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
130 135 140

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
145 150 155 160

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
165 170 175

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
180 185 190

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
195 200 205

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
210 215 220

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
225 230 235 240

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
245 250 255

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
260 265 270

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
275 280 285

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
290 295 300

```
Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
305                 310                 315                 320

Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu
                325                 330                 335

Thr Val Asp His His Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
            340                 345                 350

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
        355                 360                 365

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
    370                 375                 380

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
385                 390                 395                 400

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
                405                 410                 415

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
            420                 425                 430

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
        435                 440                 445

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ser
    450                 455                 460

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470                 475
```

<210> 528
<211> 232
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 528

Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Gly Thr Gly
1 5 10 15

Ser Trp Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
20 25 30

Pro Gly Gln Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys
35 40 45

Lys Tyr Ala Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu
50 55 60

Val Ile Ser Glu Asp Ala Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65 70 75 80

Ser Gly Ser Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala
85 90 95

Gln Val Glu Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Ala Ser
100 105 110

Gly Asn His Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
115 120 125

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
130 135 140

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
145 150 155 160

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
165 170 175

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
180 185 190

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
195 200 205

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
210 215 220

Lys Thr Val Ala Pro Thr Glu Cys
225 230

<210> 529
<211> 473
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 529

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Val Glu Ser Gly Gly Ser
20 25 30

```
Val Val Arg Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
        35                  40                  45

Phe Thr Val Asp Asp Tyr Ser Met Ser Trp Val Arg Gln Val Pro Gly
    50                  55                  60

Lys Gly Leu Glu Trp Val Ser Gly Ile Asn Trp Asn Ala Gly Arg Thr
65                  70                  75                  80

Arg Tyr Ala Asp Ala Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser
                85                  90                  95

Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            100                 105                 110

Thr Ala Leu Tyr Tyr Cys Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn
        115                 120                 125

Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
    130                 135                 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
145                 150                 155                 160

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
                165                 170                 175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
            180                 185                 190

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
        195                 200                 205
```

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
210 215 220

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
225 230 235 240

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
245 250 255

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270

Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys Val
275 280 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290 295 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu
305 310 315 320

Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His
325 330 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355 360 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
370 375 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 530
<211> 233
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 530

Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Gly Thr Gly
1 5 10 15

Ser Trp Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
20 25 30

```
Pro Gly Gln Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys
        35                  40                  45

Lys Tyr Ala Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu
    50                  55                  60

Val Ile Ser Glu Asp Ala Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Ser Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala
                85                  90                  95

Gln Val Glu Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Ala Ser
            100                 105                 110

Gly Asn His Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
        115                 120                 125

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
    130                 135                 140

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
145                 150                 155                 160

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
                165                 170                 175

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
            180                 185                 190

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
        195                 200                 205
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His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
210 215 220

Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230

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<400> 531

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Leu Arg Gly Ala Arg Cys Glu Val Gln Leu Val Glu Ser Gly Gly Ser
20 25 30

Val Val Arg Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
35 40 45

Phe Thr Val Asp Asp Tyr Ser Met Ser Trp Val Arg Gln Val Pro Gly
50 55 60

Lys Gly Leu Glu Trp Val Ser Gly Ile Asn Trp Asn Ala Gly Arg Thr
65 70 75 80

Arg Tyr Ala Asp Ala Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser
85 90 95

Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
100 105 110

Thr Ala Leu Tyr Tyr Cys Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn
115 120 125

Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
130 135 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
145 150 155 160

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
165 170 175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
180 185 190

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
195 200 205

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
210 215 220

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
225 230 235 240

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
245 250 255

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
275 280 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290 295 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu
305 310 315 320

Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Asp His
325 330 335

His Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
340 345 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
355 360 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
370 375 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385 390 395 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
405 410 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
420 425 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Ser His Tyr Thr Gln
450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470

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〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

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gtcaccatca cttgtcgggc gagtcagggt attagcaact ggttagcctg gtatcagcag 180

aaaccaggga aagcccctaa gctcctgatc tttgctgcat ccagtttgca aagtggggtc 240

ccatcaaggt tcagcggcag tggatctggg acagatttca ccctcaccat cagcagcctg 300

cagcctgaag attttgcaac ttactattgt caacaggctg aaagtttccc tcacactttc 360

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ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac 480

ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac 540

tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc 600

ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 660

cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgt 708

〈210〉 533
〈211〉 1416
〈212〉 DNA
〈213〉 人工序列

〈220〉

〈223〉 合成多核苷酸

〈400〉 533

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agactctcct gtgcagcctc tggattcacc tttagcagct atgacatgag ctgggtccgc 180

caggctccag ggaaggggct ggaatgggtg tcacttatta gtggtggtgg tagtcaaaca 240

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cccagtggcc actacttcta cgctatggac gtctggggcc aagggaccac ggtcaccgtg 420

tcctcagcct ccaccaaggg cccatcggtc ttcccccctgg caccctcctc caagagcacc 480

tctgggggca cagcggccct gggctgcctg gtcaaggact acttccccga accggtgacg 540

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ggcaaggagt acaagtgcaa ggtgtccaac aaagccctcc cagccccccat cgagaaaacc 1080

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gtcaccatca cttgtcgggc gagtcagggt attagcaact ggttagcctg gtatcagcag 180

aaaccaggga aagcccctaa gctcctgatc tttgctgcat ccagtttgca aagtggggtc 240

ccatcaaggt tcagcggcag tggatctggg acagatttca ccctcaccat cagcagcctg 300

cagcctgaag attttgcaac ttactattgt caacaggctg aaagtttccc tcacactttc 360

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ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 660

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cccagtggcc actacttcta cgctatggac gtctggggcc aagggaccac ggtcaccgtg 420

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tgctctggag ataaattggg ggataaatat gcttcctggt atcagcagaa gccaggccag 180

tcccctgtgc tggtcattta tcaagataga aagcggccct cagggatccc tgagcgattc 240

tctggctcca actctgggaa cacagccact ctgaccatca gcgggaccca ggctatggat 300

gaggctgact attactgtca ggcgttcgaa agtagcactg aggtattcgg cggagggacc 360

aagctgaccg tcctaggtca gcccaaggct gcaccctcgg tcactctgtt cccgccctcc 420

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〈400〉 538

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gtggagaaga cagtggcccc tacagaatgt tca 693

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〈212〉 DNA
〈213〉 人工序列

〈220〉
〈223〉 合成多核苷酸

〈400〉 539

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agactctcct gtgcagcgtc cggcttcacc ttcagtaact atggcatgca ttgggtccgc 180

caggctccag gcaaggggct ggagtgggtg gcacttatct ggtatgatgc aagtaaaaaa 240

tactatgcag aatccgtgaa gggccgattc accatctcca gagacaattc caagaacacg 300

ctgtatctgc aaatgaacag cctgagagcc gaggacacgg ctgcgtatta ctgtgcgaga 360

gatccctcga gtctaactgg aagtacgggt tactacggta tggacgtctg gggccaaggg 420

accacggtca ccgtgtcctc agcctccacc aagggcccat cggtcttccc cctggcaccc 480

tcctccaaga gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc 540

cccgaaccgg tgacggtgtc gtggaactca ggcgccctga ccagcggcgt gcacaccttc 600

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cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 1140

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gaagctgact actactgtta ctcaacagac gccagtggta atcatagggt gttcggcgga 360

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ccctcctctg aggagcttca agccaacaag gccacactgg tgtgtctcat cagtgacttc 480

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gaagctgact actactgtta ctcaacagac gccagtggta atcatagggt gttcggcgga 360

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gaattcaata acttcgagtc caactggttc gacccctggg gccagggaac cctggtcacc 420

gtgtcctcag cctccaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc 480

acctctgggg gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 540

acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta 600

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc 660

acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa 720

gttgagccca aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc 780

ctgggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 840

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 900

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gtgcgaggag 960

cagtacggca gcacgtaccg ttgcgtcagc gtcctcaccg tggaccacca cgactggctg 1020

aatggcaagg agtacaagtg caaggtgtcc aacaaagccc tcccagcccc catcgagaaa 1080

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1140

cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 1200

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1260

cctcccgtgc tggactccga cggctccttc ttcctctata gcaagctcac cgtggacaag 1320

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacagc 1380

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<400> 544

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

```
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Asp
            180                 185                 190

His His Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285
```

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ser His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Asp
180 185 190

His His Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ser His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

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<400> 547

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

```
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15
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```
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Asp
            180                 185                 190
```

```
His His Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ser His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
                325                 330
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<210> 549
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<400> 549

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175
```

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
325 330

<210> 550
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<400> 550

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                  10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140
```

```
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Asp
            180                 185                 190

His His Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ser His Tyr Thr
305                 310                 315                 320
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Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

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<212> PRT
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<400> 551

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

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<400> 552

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Asp
180 185 190

His His Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ser His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 553
<211> 329
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<220>
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<400> 553

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
325

<210> 554
<211> 334
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<400> 554

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

```
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                165                 170                 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220
```

```
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
                325                 330
```

<210> 555
<211> 334
<212> PRT
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<400> 555

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
```

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

```
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Gly Ser
                325                 330
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<210> 556
<211> 450
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 556

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Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
            20                  25                  30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
            100                 105                 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175
```

```
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
    290                 295                 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350
```

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

<210> 557
<211> 450
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 557

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
20 25 30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
100 105 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
290 295 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

```
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Asp Ser Leu Ser Leu Ser
        435                 440                 445

Pro Gly
    450
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<210> 558
<211> 450
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<223> 合成多肽

<400> 558

```
Glu Val Gln Leu Val Glu Ser Gly Gly Ser Val Val Arg Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Asp Asp Tyr
            20                  25                  30

Ser Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

```
Ser Gly Ile Asn Trp Asn Ala Gly Arg Thr Arg Tyr Ala Asp Ala Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Phe Asn Asn Phe Glu Ser Asn Trp Phe Asp Pro Trp Gly
            100                 105                 110

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

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220
```

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
    290                 295                 300

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Glu Asn Gln Val Ser
        355                 360                 365

Leu Thr Cys Leu Val Glu Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Glu Thr Thr Pro Pro
385                 390                 395                 400
```

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

<210> 559
<211> 454
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 559

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
115 120 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
290 295 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
355 360 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp
385 390 395 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
405 410 415

Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445

Leu Ser Leu Ser Pro Gly
450

<210> 560
<211> 454
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 560

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
85 90 95

```
Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
    130                 135                 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
        195                 200                 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
    210                 215                 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270
```

```
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
    290                 295                 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
                325                 330                 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp
385                 390                 395                 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415

Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
            420                 425                 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Asp Ser
        435                 440                 445
```

Leu Ser Leu Ser Pro Gly
450

<210> 561
<211> 454
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 561

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Tyr Asp Ala Ser Lys Lys Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Ser Ser Leu Thr Gly Ser Thr Gly Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
115 120 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135 140

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145 150 155 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
165 170 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
180 185 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
195 200 205

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
210 215 220

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
225 230 235 240

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
275 280 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr
290 295 300

Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Glu
355 360 365

Asn Gln Val Ser Leu Thr Cys Leu Val Glu Gly Phe Tyr Pro Ser Asp
370 375 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Glu
385 390 395 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
405 410 415

Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445

Leu Ser Leu Ser Pro Gly
450

〈210〉 562
〈211〉 583

〈212〉 PRT
〈213〉 人工序列

〈220〉
〈223〉 合成多肽

〈400〉 562

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
            100                 105                 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140
```

```
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    290                 295                 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320
```

```
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile
    450                 455                 460

Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu
465                 470                 475                 480

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

Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn
500 505 510

Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro
515 520 525

Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro
530 535 540

Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg
545 550 555 560

Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg
565 570 575

Thr His Gly Ser Glu Asp Ser
580

<210> 563
<211> 582
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 563

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
100 105 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
290 295 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile Asp
450 455 460

Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe
465 470 475 480

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

Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn
500 505 510

Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro
515 520 525

Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser
530 535 540

Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe
545 550 555 560

Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr
565 570 575

His Gly Ser Glu Asp Ser
580

<210> 564
<211> 583
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 564

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
100 105 110

```
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285
```

```
Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    290                 295                 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile
    450                 455                 460
```

```
Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu
465                 470                 475                 480

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

Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn
            500                 505                 510

Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro
        515                 520                 525

Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro
    530                 535                 540

Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg
545                 550                 555                 560

Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg
                565                 570                 575

Thr His Gly Ser Glu Asp Ser
            580
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<210> 565
<211> 582
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 565

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
            100                 105                 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
```

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
290 295 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile Asp
450 455 460

Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe
465 470 475 480

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

Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn
500 505 510

Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro
515 520 525

Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser
530 535 540

Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe
545 550 555 560

Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr
565 570 575

His Gly Ser Glu Asp Ser
580

<210> 566
<211> 587
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 566

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
100 105 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

```
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    290                 295                 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430
```

```
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Gly Gly Gly Gly Ser Gln Gly Gln Asp Arg His Met Ile Glu Met
    450                 455                 460

Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp
465                 470                 475                 480

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

Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala
            500                 505                 510

Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu
        515                 520                 525

Lys Ala Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg
    530                 535                 540

Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu
545                 550                 555                 560

Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His
                565                 570                 575

Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
            580                 585
```

<210> 567
<211> 587
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 567

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
            100                 105                 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
```

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
290 295 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

```
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Gly Gly Gly Gly Ser Gln Gly Gln Asp Arg His Met Ile Glu Met
    450                 455                 460

Arg Gln Leu Ile Asp Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp
465                 470                 475                 480

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

Glu Trp Ser Ala Phe Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala
            500                 505                 510
```

```
Asn Thr Gly Asn Asn Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu
        515                 520                 525

Lys Glu Lys Pro Pro Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg
    530                 535                 540

Leu Thr Cys Pro Ser Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu
545                 550                 555                 560

Phe Leu Glu Arg Phe Lys Ser Leu Leu Gln Lys Met Ile His Gln His
                565                 570                 575

Leu Ser Ser Arg Thr His Gly Ser Glu Asp Ser
            580                 585
```

<210> 568
<211> 582
<212> PRT
<213> 人工序列

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<223> 合成多肽

<400> 568

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

```
Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
            100                 105                 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220
```

```
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    290                 295                 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400
```

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile Asp
450 455 460

Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe
465 470 475 480

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

Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn
500 505 510

Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro
515 520 525

Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser
530 535 540

Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe
545 550 555 560

Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr
565 570 575

His Gly Ser Glu Asp Ser
580

<210> 569
<211> 582
<212> PRT
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<223> 合成多肽

<400> 569

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
100 105 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
290 295 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile Asp
450 455 460

Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe
465 470 475 480

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

Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn
500 505 510

Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro
515 520 525

Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser
530 535 540

Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe
545 550 555 560

Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr
565 570 575

His Gly Ser Glu Asp Ser
580

<210> 570
<211> 582
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 570

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
            100                 105                 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
```

```
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    290                 295                 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Lys Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365
```

```
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile Asp
    450                 455                 460

Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe
465                 470                 475                 480

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

Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn
            500                 505                 510

Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Ala Lys Pro Pro
        515                 520                 525

Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser
    530                 535                 540
```

Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe
545 550 555 560

Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr
565 570 575

His Gly Ser Glu Asp Ser
580

<210> 571
<211> 582
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 571

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
100 105 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
290 295 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile Asp
450 455 460

Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe
465 470 475 480

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

Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn
500 505 510

Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro
515 520 525

Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser
530 535 540

Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe
545 550 555 560

Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr
565 570 575

His Gly Ser Glu Asp Ser
580

<210> 572
<211> 582
<212> PRT
<213> 人工序列

<220>

〈223〉 合成多肽

〈400〉 572

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
            100                 105                 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160
```

```
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    290                 295                 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335
```

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile Asp
450 455 460

Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe
465 470 475 480

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

Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn
500 505 510

Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro
515 520 525

Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser
530 535 540

Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe
545 550 555 560

Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr
565 570 575

His Gly Ser Glu Asp Ser
580

<210> 573
<211> 582
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 573

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
50 55 60

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
            100                 105                 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240
```

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    290                 295                 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Lys Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415
```

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Gln Gly Gln Asp Arg His Met Ile Glu Met Arg Gln Leu Ile Asp
450 455 460

Ile Val Asp Gln Leu Lys Asn Tyr Val Asn Asp Leu Val Pro Glu Phe
465 470 475 480

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

Ser Cys Phe Gln Lys Ala Gln Leu Lys Ser Ala Asn Thr Gly Asn Asn
500 505 510

Glu Arg Ile Ile Asn Val Ser Ile Lys Lys Leu Lys Glu Lys Pro Pro
515 520 525

Ser Thr Asn Ala Gly Arg Arg Gln Lys His Arg Leu Thr Cys Pro Ser
530 535 540

Cys Asp Ser Tyr Glu Lys Lys Pro Pro Lys Glu Phe Leu Glu Arg Phe
545 550 555 560

Lys Ser Leu Leu Gln Lys Met Ile His Gln His Leu Ser Ser Arg Thr
565 570 575

His Gly Ser Glu Asp Ser
580

<210> 574
<211> 449
<212> PRT
<213> 人工序列

<220>
<223> 合成多肽

<400> 574

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
```

```
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    290                 295                 300
```

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 575
<211> 449
<212> PRT
<213> 人工序列

<220>
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<400> 575

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
100 105 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
290 295 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

```
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Asp Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly
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<210> 576
<211> 449
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<213> 人工序列

<220>
<223> 合成多肽

<400> 576

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Leu Ile Ser Gly Gly Gly Ser Gln Thr Tyr Tyr Ala Glu Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Ser Pro Ser Gly His Tyr Phe Tyr Ala Met Asp Val Trp Gly Gln
            100                 105                 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
```

```
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
    290                 295                 300

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350
```

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Glu Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Glu Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Glu Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

【發明申請專利範圍】

【請求項1】

一種結合物，其包含IL-21突變蛋白及抗PD-1抗體，其中該IL-21突變蛋白包含SEQ ID NO: 2之胺基酸序列，

QGQDX HMXXM XXXXX XVDXL KNXVN DLVPE FLPAP EDVET NCEWS AFSCF QKAQL KSANT GNNEX XIXXX XXXLX XXXXX TNAGR RQKHR LTCPS CDSYE KKPPK EFLXX FXXLL XXMXX QHXSS RTHGS EDS (SEQ ID NO: 2)，

其中「X」表示任何胺基酸，

其中該IL-21突變蛋白胺基酸序列與人類IL-21之胺基酸序列(SEQ ID NO: 1)的差異為1或2個胺基酸，

其中該IL-21突變蛋白包含：

a. 在SEQ ID NO: 1之位置5、8、9、12、14、15、65、66、69、70、72、73、75、76、77、80、116或119處之脂族胺基酸；

b. 在SEQ ID NO: 1之位置5、8、9、11、12、13、14、15、16、19、23、65、66、69、70、72、73、75、76、77、78、79、110、112、116、117、119、120或123處之酸性胺基酸；

c. 在SEQ ID NO: 1之位置5、9、73、76、109、113或116處之鹼性胺基酸；

d. 在SEQ ID NO: 1之位置5、8、9、70或76處之芳族胺基酸；

e. 在SEQ ID NO: 1之位置5、8、9、12、15、73、76、116或119處之包含側鏈醯胺之胺基酸；

f. 在SEQ ID NO: 1之位置5、8、9、11、12、14、15、73、76、

116或119處之包含側鏈羥基之非芳族胺基酸；

g. 在SEQ ID NO: 1之位置65、66、69、70、72、73、75、76、77或80處之亞胺基酸；

h. 在SEQ ID NO: 1之位置5、9、15、76、116或119處之包含含硫側鏈之胺基酸；或

i. 其組合。

【請求項2】

一種結合物，其包含IL-21突變蛋白及抗PD-1抗體，其中該IL-21突變蛋白包含SEQ ID NO: 2之胺基酸序列，

QGQDX HMXXM XXXXX XVDXL KNXVN DLVPE FLPAP EDVET NCEWS AFSCF QKAQL KSANT GNNEX XIXXX XXXLX XXXXX TNAGR RQKHR LTCPS CDSYE KKPPK EFLXX FXXLL XXMXX QHXSS RTHGS EDS (SEQ ID NO: 2)，

其中「X」表示任何胺基酸，

其中該IL-21突變蛋白胺基酸序列與人類IL-21之胺基酸序列(SEQ ID NO: 1)的差異為1或2個胺基酸，

其中該IL-21突變蛋白包含1或2個選自表A之胺基酸取代：

表A

SEQ ID NO: 1之胺基酸位置	胺基酸(按單字母代碼)		SEQ ID NO: 1之胺基酸位置	胺基酸(按單字母代碼)
5	A、D、E、G、H、I、K、L、M、N、Q、S、T、V或Y		72	D、G或P
8	A、D、E、N、		73	A、D、E、G、H、I、N、P、

	S、T、V或Y			Q、S或V
9	A、D、E、G、H、I、K、L、M、N、Q、S、T、V或Y		75	D、G或P
11	D或S		76	A、D、E、G、H、I、K、L、M、N、P、Q、S、T、V或Y
12	A、D、E、N、S、T或V		77	D、G或P
13	D		78	D
14	A、D或S		79	D
15	A、E、I、M、N、Q、S、T或V		80	G或P
16	D或E		109	K
19	D		110	D
23	D		112	D
65	D、G或P		113	K
66	D、G或P		116	A、D、E、I、K、L、M、N、S、T或V
68	Q		117	D
69	D、G或P		119	A、D、E、M、N、Q、S或T
70	E、G、P或Y		120	D
71	L		123	D

。

【請求項3】

一種結合物，其包含IL-21突變蛋白及抗PD-1抗體，其中該IL-21突變蛋白包含：

(a) SEQ ID NO: 3-21、23-56、58-112、114-198、249-254及283

中任一者之胺基酸序列；或

(b) SEQ ID NO: 199至208、210至222、224至248及255中任一者之胺基酸序列。

【請求項4】

如請求項1至3中任一項之結合物，其中該IL-21突變蛋白包含相對於人類IL-21之胺基酸序列(SEQ ID NO: 1)具有一個胺基酸取代的胺基酸序列。

【請求項5】

如請求項1至3中任一項之結合物，其中該IL-21突變蛋白包含相對於人類IL-21之胺基酸序列(SEQ ID NO: 1)具有兩個胺基酸取代的胺基酸序列。

【請求項6】

如請求項5之結合物，其中該胺基酸取代出現在SEQ ID NO: 1之位置5、8、9、11、12、13、14、15、16、19、23、65、66、68、69、70、71、72、73、75、76、77、78、79、80、109、110、112、113、116、117、119、120或123中之兩者處。

【請求項7】

如請求項6之結合物，其中該等胺基酸取代出現在SEQ ID NO: 1之位置5、9、73及76中之兩者處。

【請求項8】

如請求項7之結合物，其中該IL-21突變蛋白包含以下任兩者：

(i) SEQ ID NO: 1之位置5處之胺基酸，其中該胺基酸係選自以下所組成之群：A、D、E、G、H、I、K、L、M、N、Q、S、T、V

或Y；

(ii) SEQ ID NO: 1之位置9處之胺基酸，其中該胺基酸係選自以下所組成之群：A、D、E、G、H、I、K、L、M、N、Q、S、T、V或Y；

(iii) SEQ ID NO: 1之位置73處之胺基酸，其中該胺基酸係選自以下所組成之群：A、D、E、G、H、I、N、P、Q、S或V；及

(iv) SEQ ID NO: 1之位置76處之胺基酸，其中該胺基酸係選自以下所組成之群：A、D、E、G、H、I、K、L、M、N、Q、S、T、V或Y。

【請求項9】

如請求項1至3中任一項之結合物，其中該IL-21突變蛋白包含SEQ ID NO: 1之位置5、9或73處之胺基酸取代，其中該取代之胺基酸選自：

SEQ ID NO: 1之胺基酸位置	胺基酸 (單字母代碼)
5	A、D、E、G、H、I、K、L、M、N、Q、S、T、V或Y
9	A、D、E、G、H、I、K、L、M、N、Q、S、T、V或 Y
73	A、D、E、G、H、I、N、P、Q、S或 V

。

【請求項10】

如請求項1至3中任一項之結合物，其中該IL-21突變蛋白包含SEQ ID NO: 1之位置76之胺基酸取代，且該位置76處之取代胺基酸為脂族胺基酸或酸性胺基酸。

【請求項11】

如請求項10之結合物，其中該脂族胺基酸為丙胺酸且其中該酸性胺基酸為麩胺酸。

【請求項12】

如請求項1至3中任一項之結合物，其中該IL-21突變蛋白直接附接於該抗體之Fc。

【請求項13】

如請求項1至3中任一項之結合物，其中該IL-21突變蛋白經由連接子附接於該抗體之Fc。

【請求項14】

如請求項1至3中任一項之結合物，其中該結合物包含單一IL-21突變蛋白，其中該單一IL-21突變蛋白連接於兩個抗體重鏈中之一者的C端。

【請求項15】

如請求項1至3中任一項之結合物，其中該結合物包含兩個IL-21突變蛋白，其中第一IL-21突變蛋白連接於第一抗體重鏈之C端，且第二IL-21突變蛋白連接於第二抗體重鏈之C端。

【請求項16】

如請求項15之結合物，其中該第一IL-21突變蛋白具有與該第二IL-21突變蛋白相同之胺基酸序列。

【請求項17】

如請求項15之結合物，其中該第一IL-21突變蛋白與該第二IL-21突變蛋白具有不同之胺基酸序列。

【請求項18】

如請求項1至3中任一項之結合物，其中該結合物為包含IL-21突變蛋白及抗PD-1抗體之融合蛋白。

【請求項19】

如請求項18之結合物，其中該融合蛋白包含：

(i) 兩條輕鏈，各包含SEQ ID NO: 391之輕鏈，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO: 498至500或519中任一者之融合至IL-21突變蛋白的重鏈；或

(ii) 兩條輕鏈，各包含SEQ ID NO: 391之輕鏈，

一條融合至IL-21突變蛋白之重鏈，其包含SEQ ID NO: 501至506中任一者之融合至IL-21突變蛋白的重鏈；及

一條重鏈，其包含SEQ ID NO: 556至558中任一者之重鏈；或

(iii) 兩條輕鏈，各包含SEQ ID NO: 371之輕鏈，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO: 508至512中任一者之融合至IL-21突變蛋白的重鏈；或

(iv) 兩條輕鏈，各包含SEQ ID NO: 371之輕鏈，

一條融合至IL-21突變蛋白之重鏈，其包SEQ ID NO: 513至518中任一者之胺基酸序列；及

一條重鏈，其包SEQ ID NO: 559至561中任一者之胺基酸序列；或

(v) 兩條輕鏈，各包含SEQ ID NO: 389之輕鏈可變區，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO: 498至500或519中任一者之融合至IL-21突變蛋白的重鏈；或

(vi) 兩條輕鏈，各包含SEQ ID NO: 389之輕鏈可變區，

一條融合至IL-21突變蛋白之重鏈，其包含SEQ ID NO: 501至506中任一者之融合至IL-21突變蛋白的重鏈；及

一條重鏈，其包含SEQ ID NO: 556至558中任一者之重鏈；或

(vii) 兩條輕鏈，各包含SEQ ID NO: 369之輕鏈可變區，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO: 508至512中任一者之融合至IL-21突變蛋白的重鏈；或

(viii)兩條輕鏈，各包含SEQ ID NO: 369之輕鏈可變區，

一條融合至IL-21突變蛋白之重鏈，其包SEQ ID NO: 513至518中任一者之融合至IL-21突變蛋白的重鏈；及

一條重鏈，其包SEQ ID NO: 559至561中任一者之重鏈；或

(ix) 兩條輕鏈，各包含SEQ ID NO: 389之輕鏈可變區及SEQ ID NO: 391之輕鏈恆定區，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO: 498至500或519中任一者之融合至IL-21突變蛋白的重鏈；或

(x) 兩條輕鏈，各包含SEQ ID NO: 389之輕鏈可變區及SEQ ID NO: 391之輕鏈恆定區，

一條融合至IL-21突變蛋白之重鏈，其包含SEQ ID NO: 501至506中任一者之融合至IL-21突變蛋白的重鏈；及

一條重鏈，其包含SEQ ID NO: 556至558中任一者之重鏈；或

(xi) 兩條輕鏈，各包含SEQ ID NO: 369之輕鏈可變區及SEQ ID NO: 371之輕鏈恆定區，

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO: 508至512中任一者之融合至IL-21突變蛋白的重鏈；或

(xii) 兩條輕鏈，各包含SEQ ID NO: 369之輕鏈可變區及SEQ ID NO: 371之輕鏈恆定區，

一條融合至IL-21突變蛋白之重鏈，其包SEQ ID NO: 513至518中任一者之胺基酸序列；及

一條重鏈，其包SEQ ID NO: 559至561中任一者之重鏈。

【請求項20】

如請求項1至3中任一項之結合物，其中該結合物為融合蛋白，該融合蛋包含IL-21突變蛋白及抗PD-1抗體，其中該融合蛋白包含：

(i) 兩條輕鏈，各包含LC CDR1、LC CDR2及LC CDR3，其分別包含SEQ ID NO:385、386及387之胺基酸序列；

(ii) 兩條重鏈，各包含HC CDR1、HC CDR2及HC CDR3，其分別包含SEQ ID NO:382、383及384之胺基酸序列；及

(iii) IL-21突變蛋白，其包含SEQ ID NO:244之胺基酸序列，其中該IL-21突變蛋白融合至抗體重鏈之一。

【請求項21】

如請求項20之結合物，其中各輕鏈包含SEQ ID NO:389之輕鏈可變區，且其中各重鏈包含SEQ ID NO:388之重鏈可變區。

【請求項22】

如請求項1至3中任一項之結合物，其中該結合物為融合蛋白，該融合蛋白包含IL-21突變蛋白及抗PD-1抗體，其中該融合蛋白包含：

(i) 兩條輕鏈，各包含SEQ ID NO:391之輕鏈；

(ii) 一條重鏈，其包含SEQ ID NO:556之重鏈；及

(iii) 一條融合至IL-21突變蛋白之重鏈，其包含SEQ ID NO:501之融

合至IL-21突變蛋白的重鏈。

【請求項23】

如請求項1至3中任一項之結合物，其中該結合物為融合蛋白，該融合蛋白包含IL-21突變蛋白及抗PD-1抗體，其中：

(a) 該融合蛋白包含：

(i) 兩條輕鏈，各包含SEQ ID NO:389之輕鏈可變區；

(ii) 一條重鏈，其包含SEQ ID NO:556之重鏈可變區；及

(iii) 一條融合至IL-21突變蛋白之重鏈，其包含SEQ ID NO:501之融合至IL-21突變蛋白的重鏈；或

(b) 該融合蛋白包含：

(i) 兩條輕鏈，各包含SEQ ID NO:389之輕鏈可變區及SEQ ID NO:391之輕鏈恆定區；

(ii) 一條重鏈，其包含SEQ ID NO:556之重鏈；及

(iii) 一條融合至IL-21突變蛋白之重鏈，其包含SEQ ID NO:501之融合至IL-21突變蛋白的重鏈。

【請求項24】

如請求項1至3中任一項之結合物，其中該結合物為融合蛋白，該融合蛋白包含IL-21突變蛋白及抗PD-1抗體，其中該融合蛋白包含：

(i) 兩條輕鏈，各包含SEQ ID NO:391之輕鏈可變區，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO:499之融合至IL-21突變蛋白的重鏈；或

(ii) 兩條輕鏈，各包含SEQ ID NO:389之輕鏈可變區，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO:499之融

合至IL-21突變蛋白的重鏈；或

(iii) 兩條輕鏈，各包含SEQ ID NO:389之輕鏈可變區及SEQ ID NO:391之輕鏈恆定區，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO:499之融合至IL-21突變蛋白的重鏈；或

(iv) 兩條輕鏈，各包含SEQ ID NO:391之輕鏈，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO:519之融合至IL-21突變蛋白的重鏈；或

(v) 兩條輕鏈，各包含SEQ ID NO:389之輕鏈可變區，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO:519之融合至IL-21突變蛋白的重鏈；或

(vi) 兩條輕鏈，各包含SEQ ID NO:389之輕鏈可變區及SEQ ID NO:391之輕鏈恆定區，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO:519之融合至IL-21突變蛋白的重鏈。

【請求項25】

如請求項1至3中任一項之結合物，其中該結合物為融合蛋白，該融合蛋白包含IL-21突變蛋白及抗PD-1抗體，其中該融合蛋白包含：

(i) 兩條輕鏈，各包含LC CDR1、LC CDR2及LC CDR3，其分別包含SEQ ID NO:365、366及367之胺基酸序列；

(ii) 兩條重鏈，各包含HC CDR1、HC CDR2及HC CDR3，其分別包含SEQ ID NO:362、363及364之胺基酸序列；及

(iii) IL-21突變蛋白，其包含SEQ ID NO:244之胺基酸序列，其中該

IL-21突變蛋白融合至抗體重鏈之一。

【請求項26】

如請求項25之結合物，其中各輕鏈包含SEQ ID NO:369之輕鏈可變區，且各重鏈包含SEQ ID NO:368之重鏈可變區。

【請求項27】

如請求項1至3中任一項之結合物，其中該結合物為融合蛋白，該融合蛋白包含IL-21突變蛋白及抗PD-1抗體，其中：

(a) 該融合蛋白包含：

(i) 兩條輕鏈，各包含SEQ ID NO:371之輕鏈；

(ii) 一條重鏈，其包含SEQ ID NO:559之重鏈；及

(iii) 一條融合至IL-21突變蛋白之重鏈，其包含SEQ ID NO:513之融合至IL-21突變蛋白的重鏈；或

(b) 該融合蛋白包含：

(i) 兩條輕鏈，各包含SEQ ID NO:369之輕鏈可變區；

(ii) 一條重鏈，其包含SEQ ID NO:559之重鏈；及

(iii) 一條融合至IL-21突變蛋白之重鏈，其包含SEQ ID NO:513之融合至IL-21突變蛋白的重鏈；或

(c) 該融合蛋白包含：

(i) 兩條輕鏈，各包含SEQ ID NO:369之輕鏈可變區及SEQ ID NO:371之輕鏈恆定區；

(ii) 一條重鏈，其包含SEQ ID NO:559之重鏈；及

(iii) 一條融合至IL-21突變蛋白之重鏈，其包含SEQ ID NO:513之融合至IL-21突變蛋白的重鏈。

【請求項28】

如請求項1至3中任一項之結合物，其中該結合物為融合蛋白，該融合蛋白包含IL-21突變蛋白及抗PD-1抗體，其中該融合蛋白包含：

(i) 兩條輕鏈，各包含SEQ ID NO:371之輕鏈，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO:508之融合至IL-21突變蛋白的重鏈；或

(ii) 兩條輕鏈，各包含SEQ ID NO:369之輕鏈可變區，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO:508之融合至IL-21突變蛋白的重鏈；或

(iii) 兩條輕鏈，各包含SEQ ID NO:369之輕鏈可變區及SEQ ID NO:371之輕鏈恆定區，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO:508之融合至IL-21突變蛋白的重鏈；或

(iv) 兩條輕鏈，各包含SEQ ID NO:371之輕鏈，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO:511之融合至IL-21突變蛋白的重鏈；或

(v) 兩條輕鏈，各包含SEQ ID NO:369之輕鏈可變區，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO:511之融合至IL-21突變蛋白的重鏈；或

(vi) 兩條輕鏈，各包含SEQ ID NO:369之輕鏈可變區及SEQ ID NO:371之輕鏈恆定區，及

兩條重鏈-IL-21突變蛋白融合物，各包含SEQ ID NO:511之融合至IL-21突變蛋白的重鏈。

【請求項29】

一種套組，其包含如請求項1至28中任一項之結合物及容器。

【請求項30】

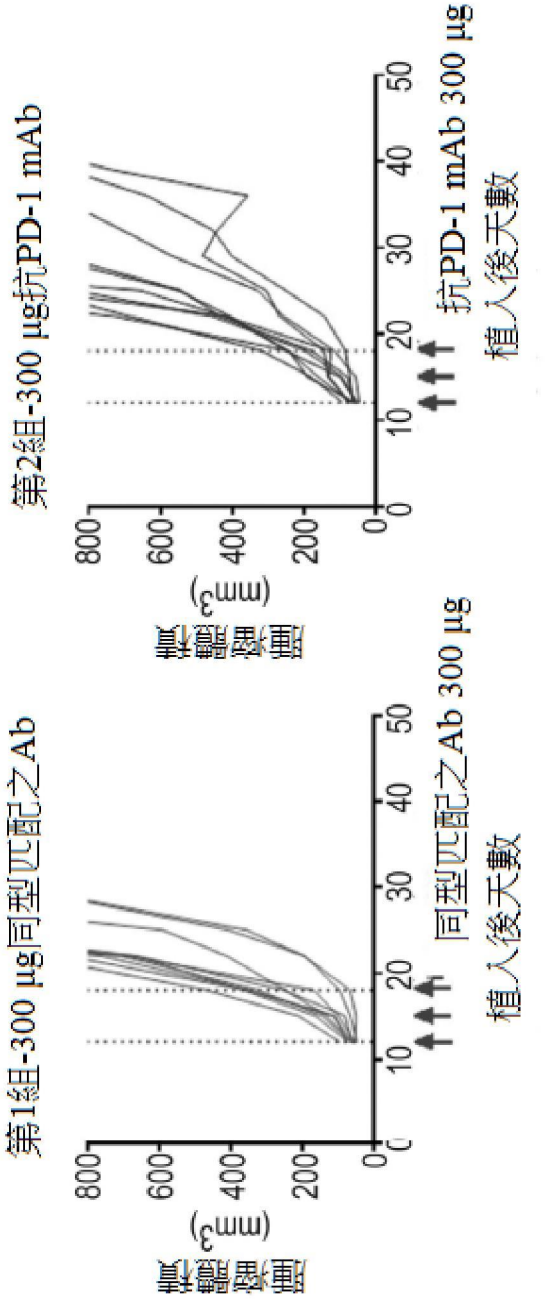
一種醫藥組合物，其包含如請求項1至28中任一項之結合物及醫藥上可接受之載劑、賦形劑或稀釋劑。

【請求項31】

一種如請求項30之醫藥組合物之用途，其係用於製備治療具有實體腫瘤個體之藥物。

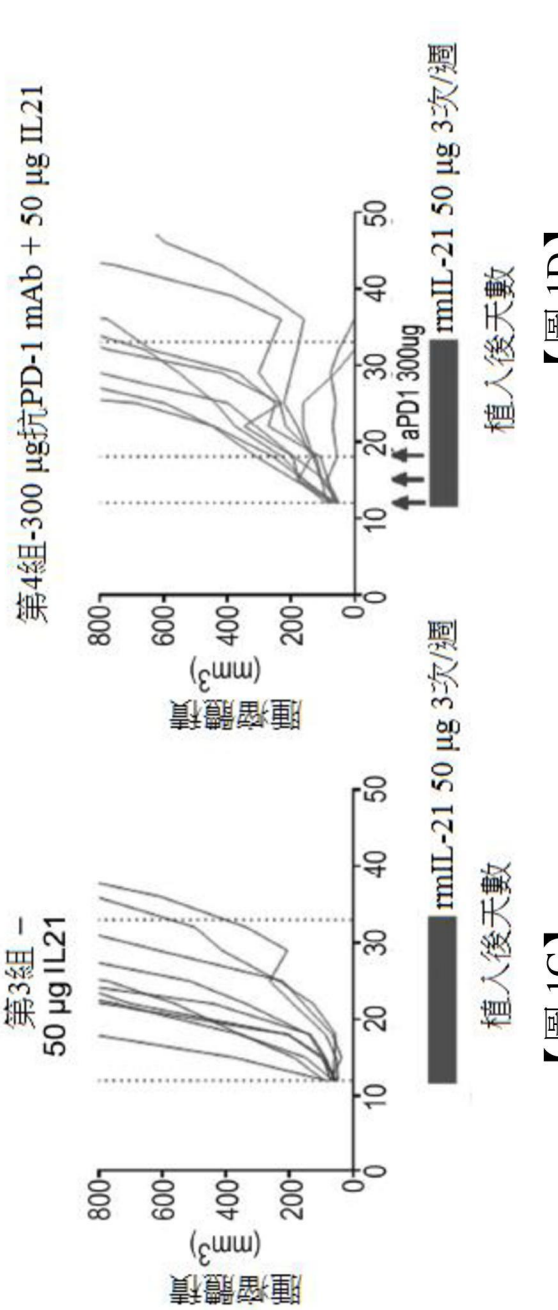
【發明圖式】

112年11月13日 所提修正



【圖 1A】

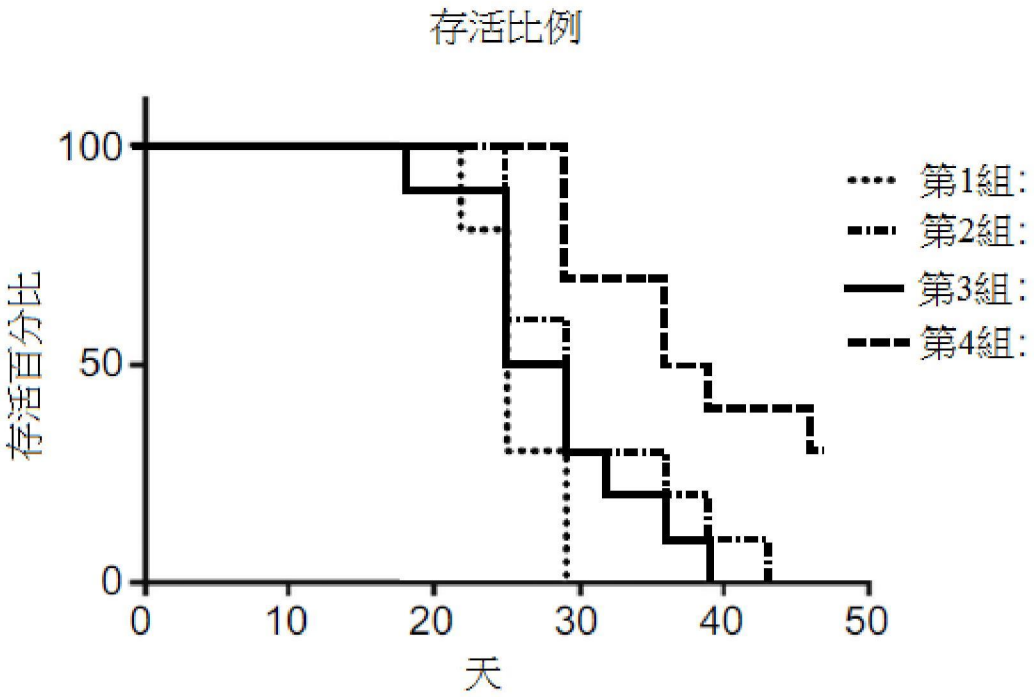
【圖 1B】



【圖 1C】

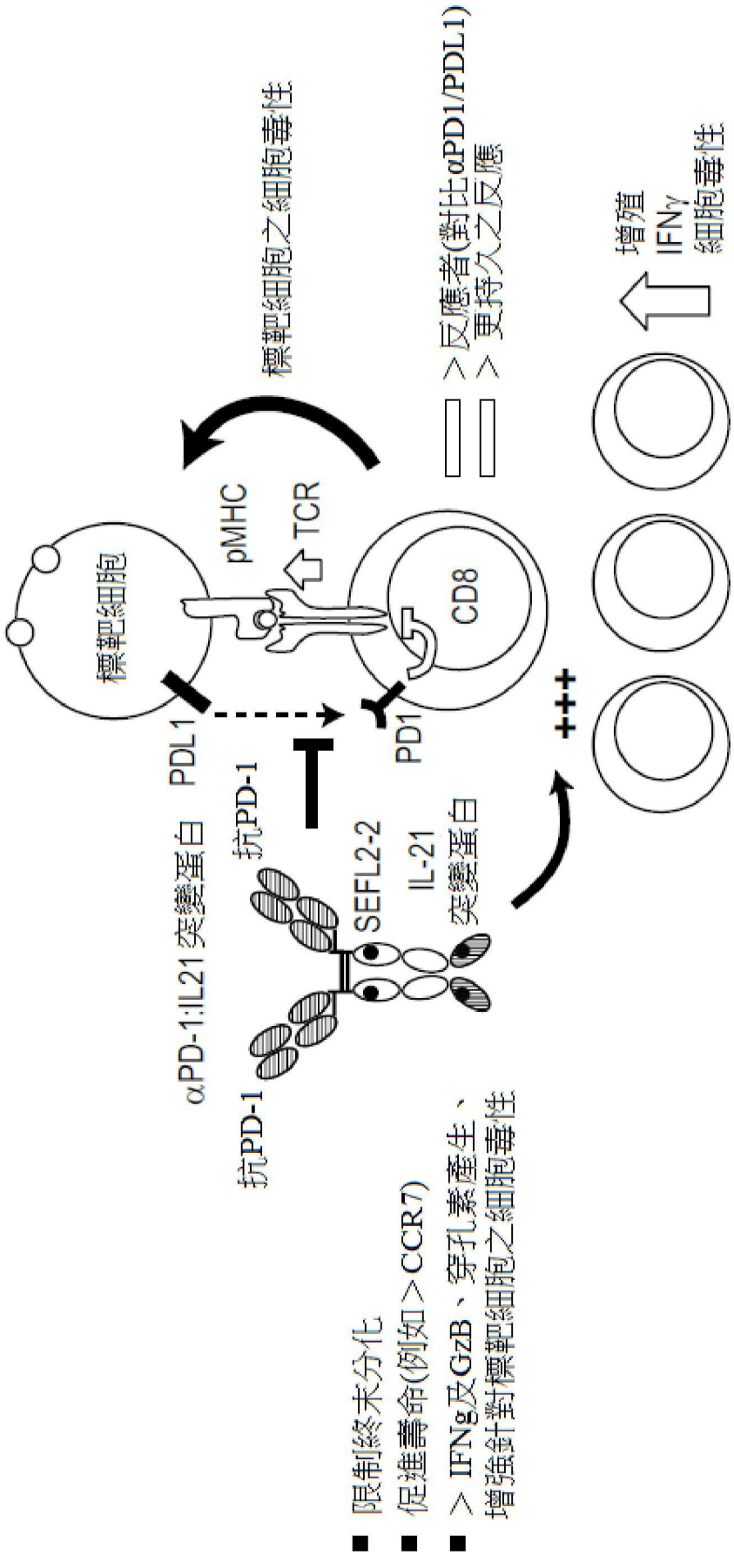
【圖 1D】

【圖 1】

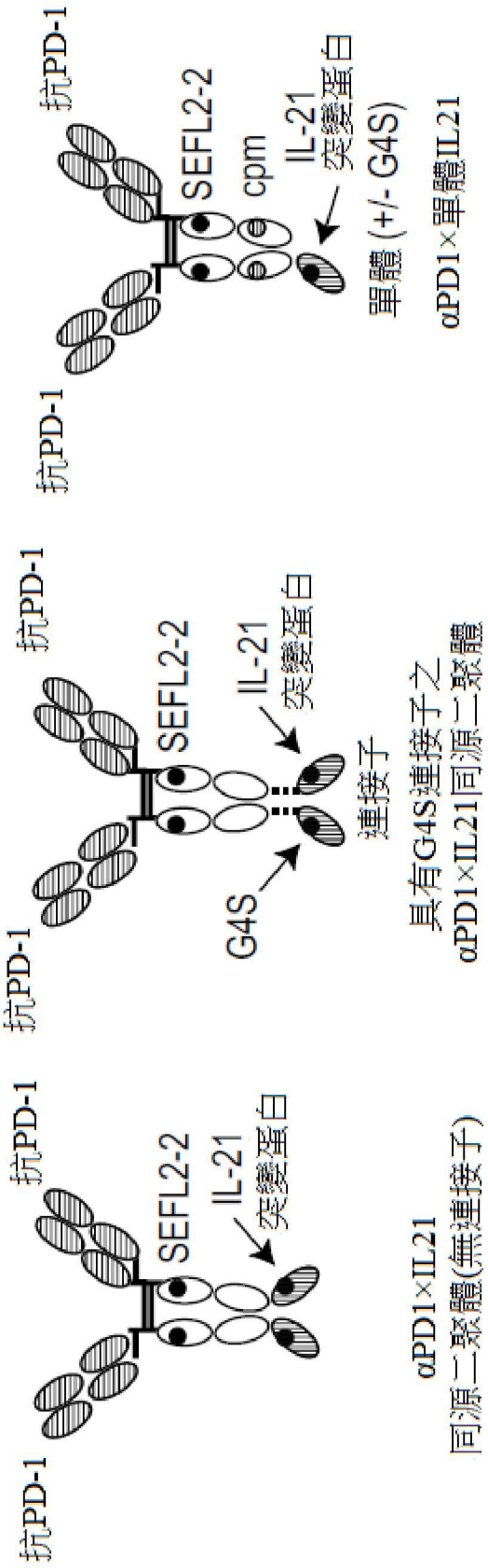


同型對比IL-21, p=ns, 0.1269
同型對比αPD-1 mAb, p=0.0408
同型組合, p=0.0002
αPD-1 mAb 對比組合, p=0.0143
IL-21對比組合, p=0.0047

【圖 2】


αPD-1:IL21突變蛋白
PDL1
抗PD-1
SEFL2-2
IL-21
突變蛋白
PD1
CD8
TCR
pMHC
標靶細胞
標靶細胞之細胞毒性
> 反應者(對比αPD1/PDL1)
> > 更持久之反應
+++
增殖
IFNγ
細胞毒性
抗PD-1
■ 限制終末分化
■ 促進壽命(例如>CCR7)
■ > IFNg及GzB、穿孔素產生、
增強針對標靶細胞之細胞毒性

【圖 3】



【圖 4A】 【圖 4B】 【圖 4C】

【圖 4】

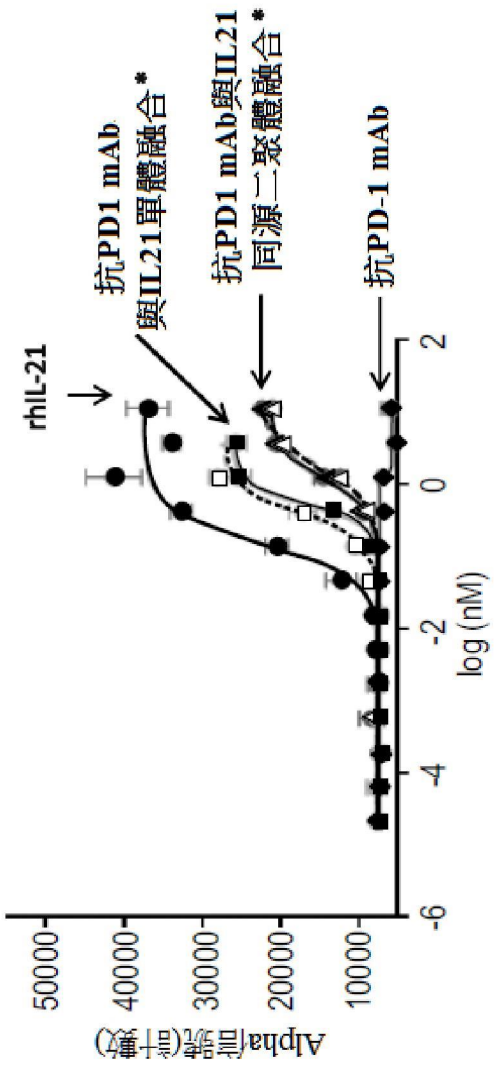


圖5A：
pSTAT3 AlphaLISA Hut78 T細胞：
PD-1^{+ve}

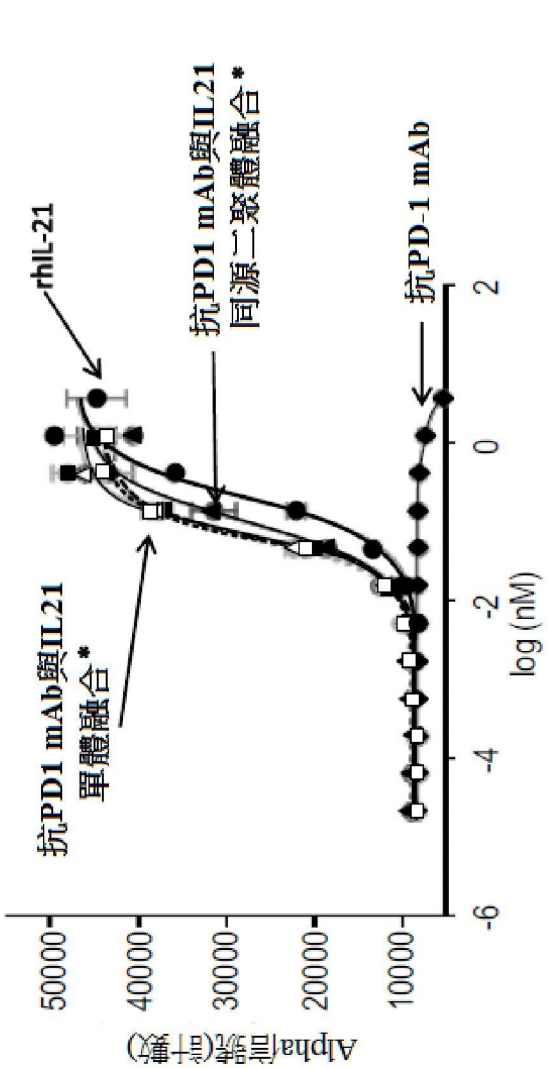
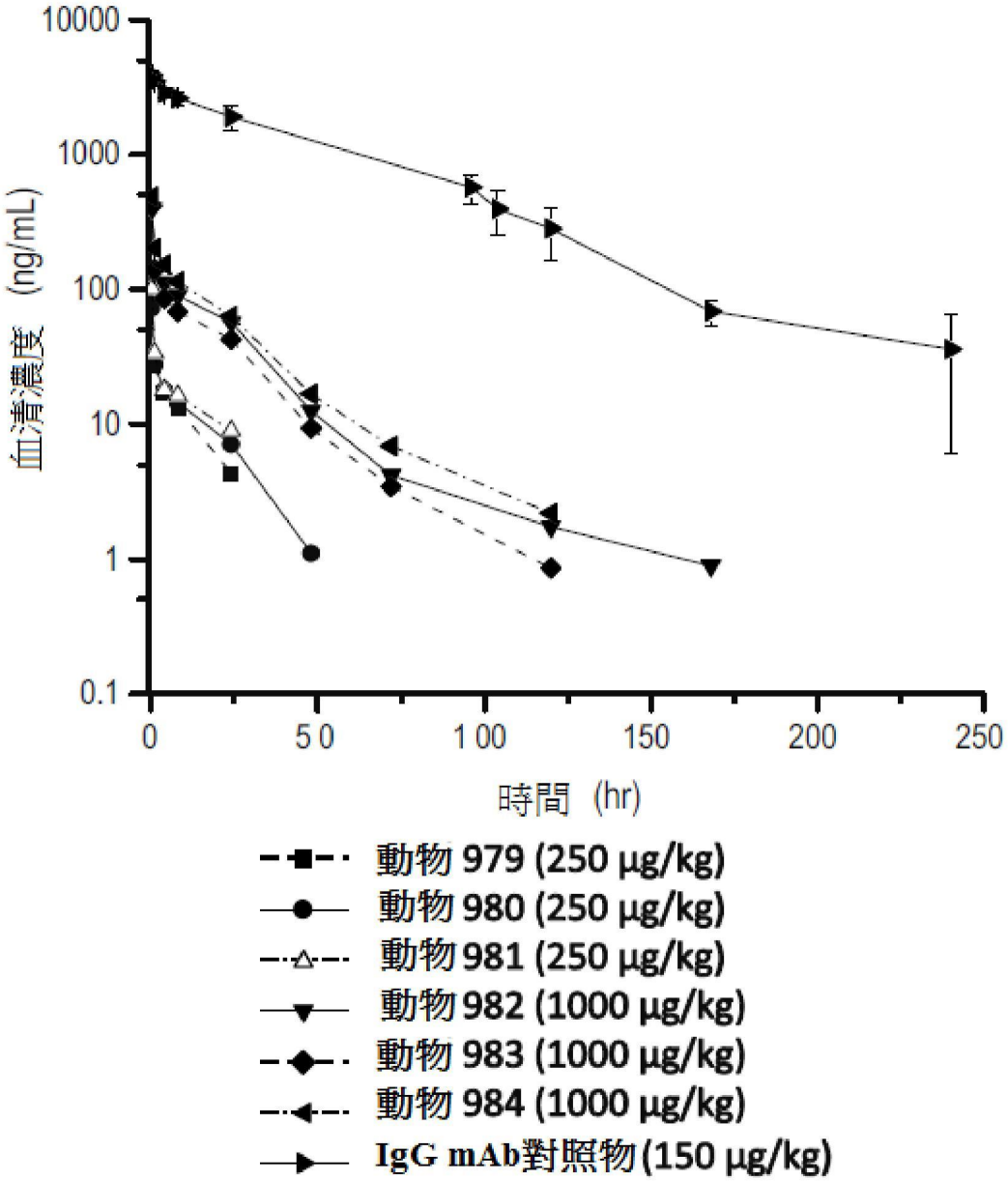


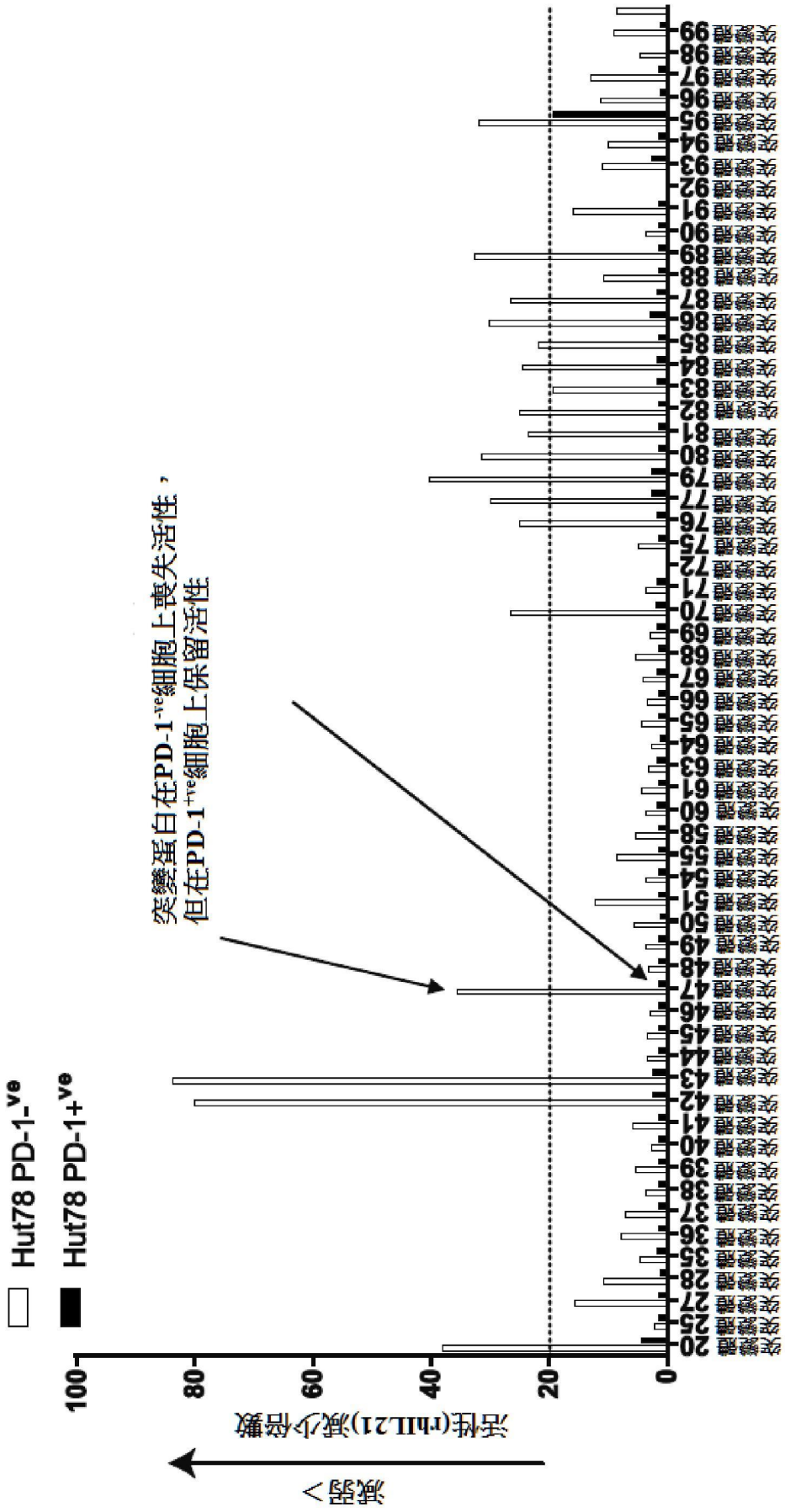
圖5B：
pSTAT3 AlphaLISA Hut78 T細胞：
PD-1^{+ve}

【圖 5】

*實線表示無連接子之融合物，
且點線表示有連接子之融合物

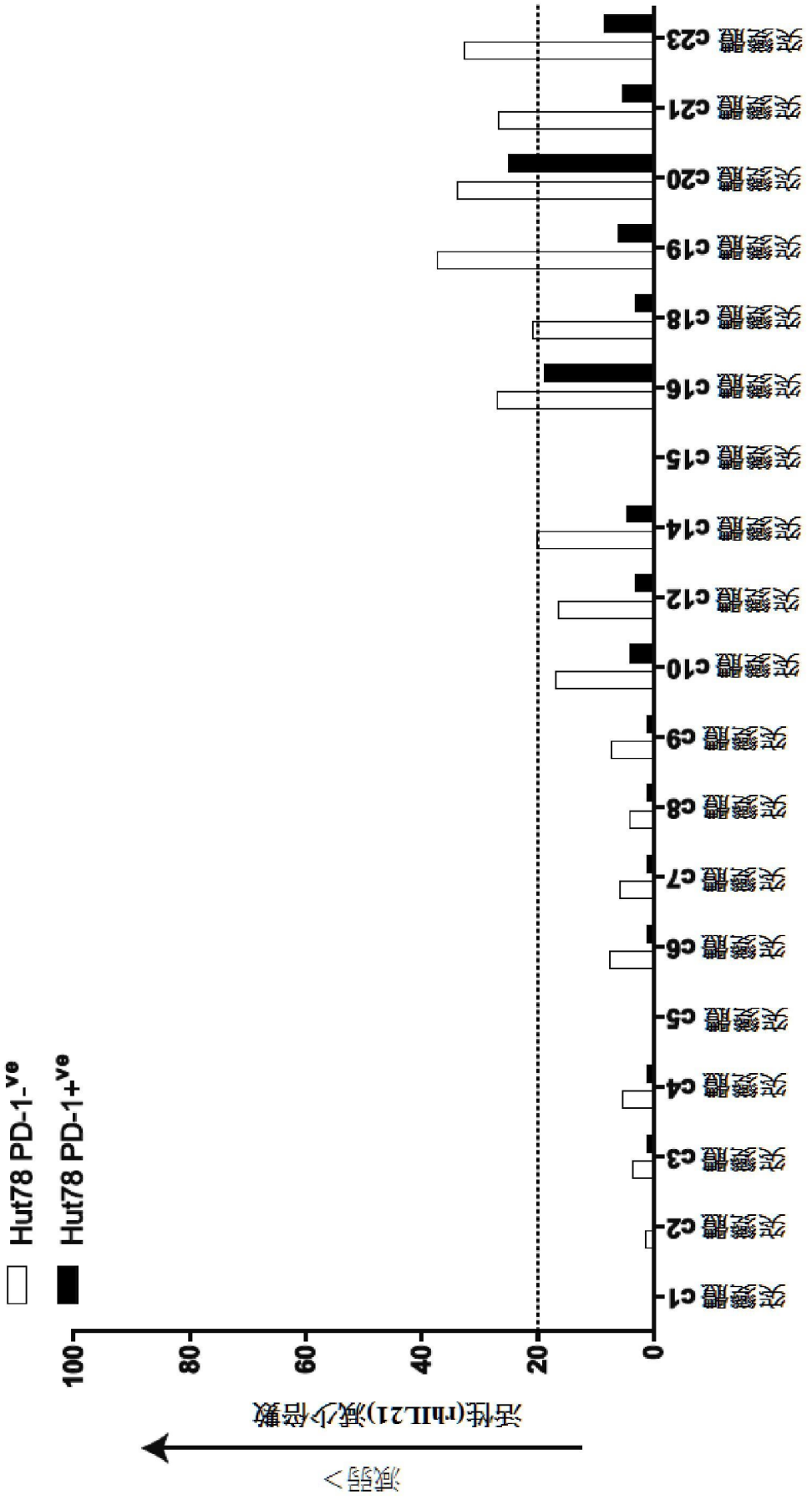

10000
1000
100
10
1
0.1
血清濃度 (ng/mL)
0
50
100
150
200
250
時間 (hr)
動物 979 (250 μg/kg)
動物 980 (250 μg/kg)
動物 981 (250 μg/kg)
動物 982 (1000 μg/kg)
動物 983 (1000 μg/kg)
動物 984 (1000 μg/kg)
IgG mAb對照物 (150 μg/kg)

【圖 6】



【圖 7】

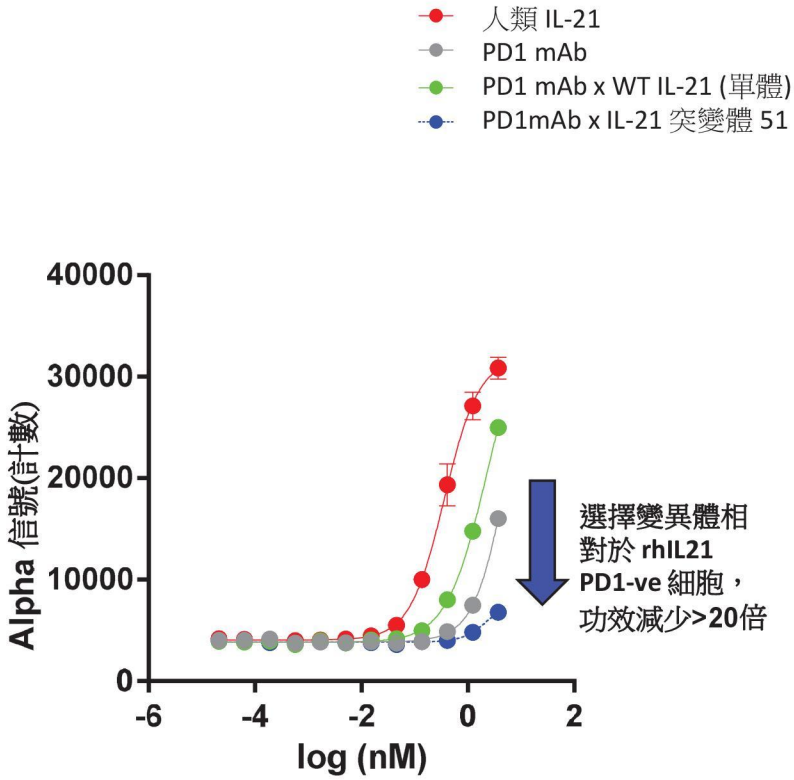
設計成對IL-21Rα之結合減少的突變蛋白
相對於rhIL21 PD1-ve細胞，標靶突變蛋白功效減少 > 20倍



設計成對IL-21Rα之結合減少的突變蛋白
3.7 nM融合蛋白/rhIL-21

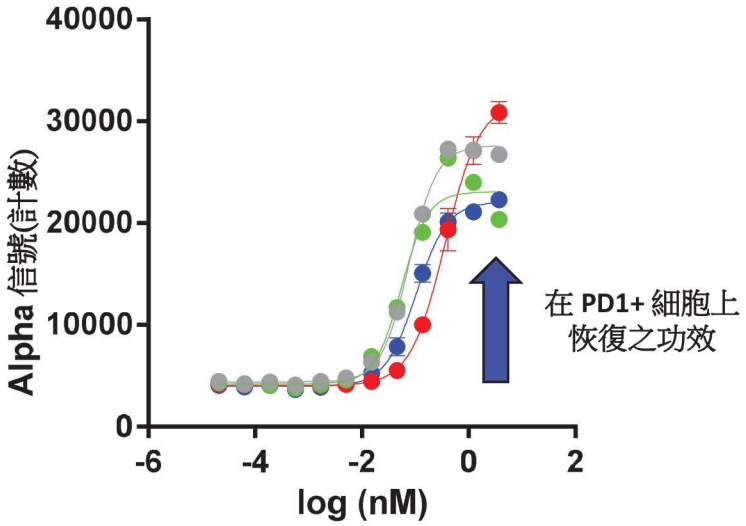
【圖 8】

鑑別符合標準(在PD-1^{-ve}細胞上減弱>20 倍) 且視 PD-1 而定進行靶向之突變蛋白



PD1^{-ve}

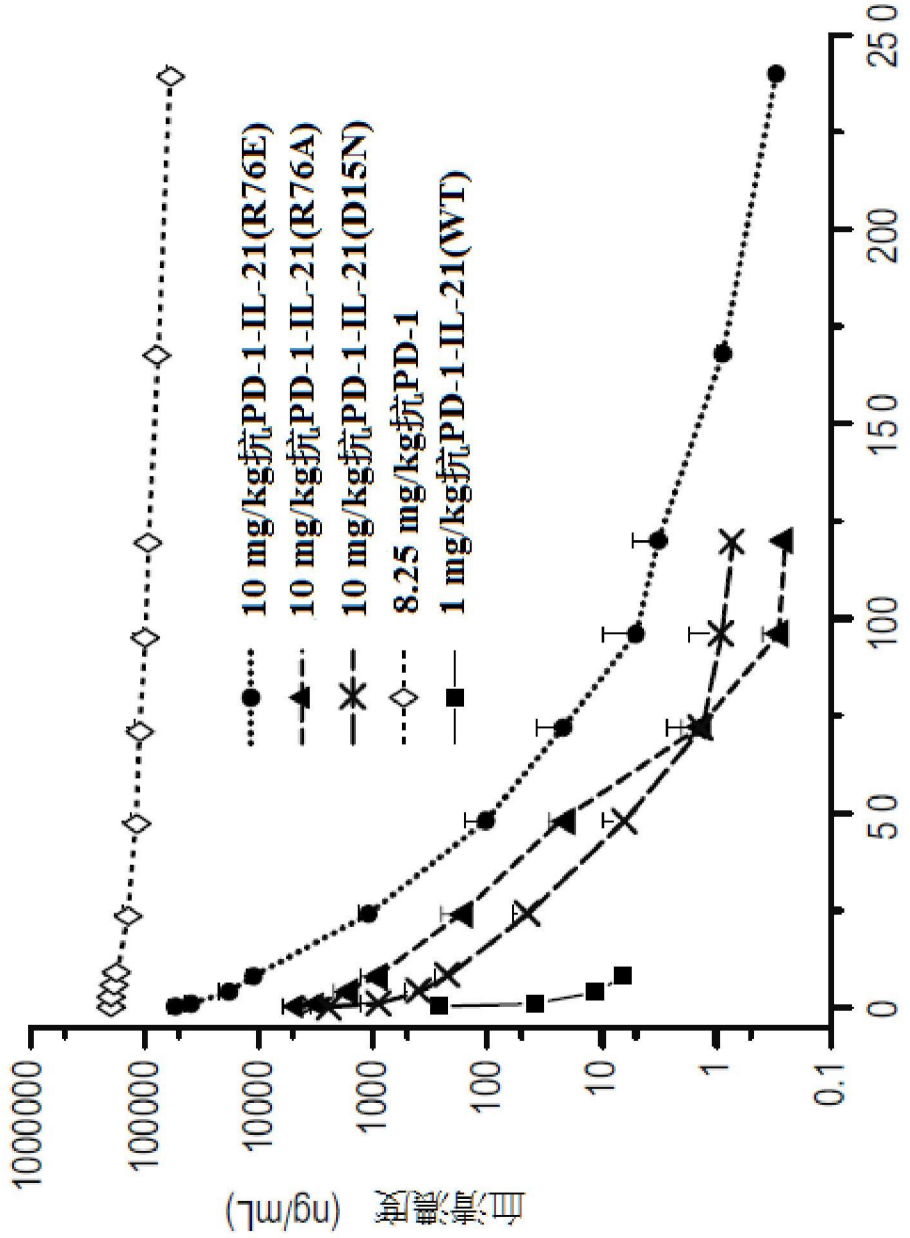
【圖 9A】



PD1^{+ve}

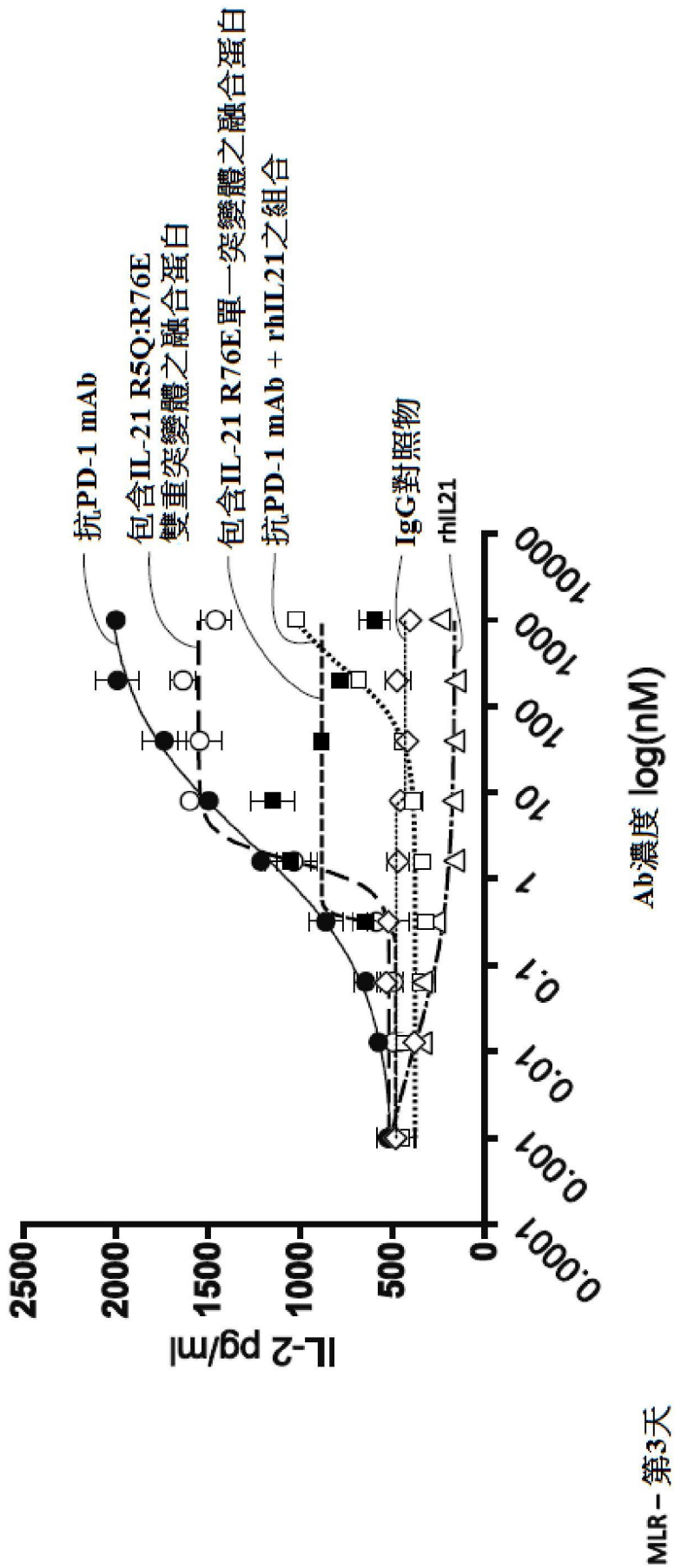
【圖 9B】

【圖9】



抗PD-1 mAb-IL21突變蛋白融合蛋白
展示與親本抗PD-1 mAb相比改變之分佈

【圖 10】


抗PD-1 mAb
包含IL-21 R5Q:R76E
雙重突變體之融合蛋白
包含IL-21 R76E單一突變體之融合蛋白
抗PD-1 mAb + rhIL21之組合
IgG對照物
rhIL21
IL-2 pg/ml
2500
2000
1500
1000
500
0
Ab濃度 log(nM)
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
MLR – 第3天

【圖 11】

aPD1 x 雙重突變體
aPD1 x 單一突變翻
rhIL21

圖 12A:
實線 = 包含抗PD-1 mAb
與 IL-21 R5E:R76A 雙重
突變蛋白融合之融合蛋白

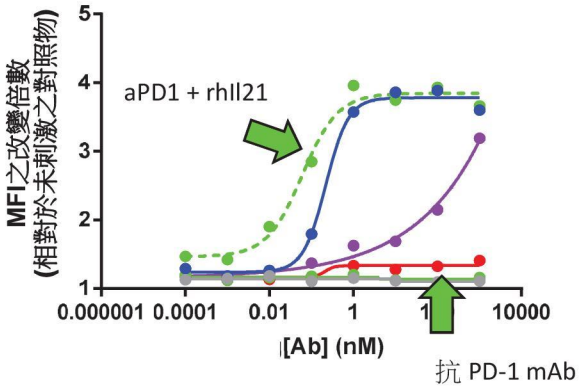


圖 12B:
實線 = 包含抗P-PD-1 mAb
與 IL-21 R5Q:R76E 雙重
突變蛋白融合之融合蛋白

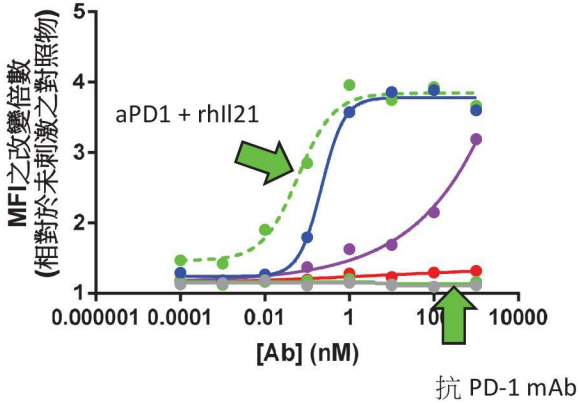
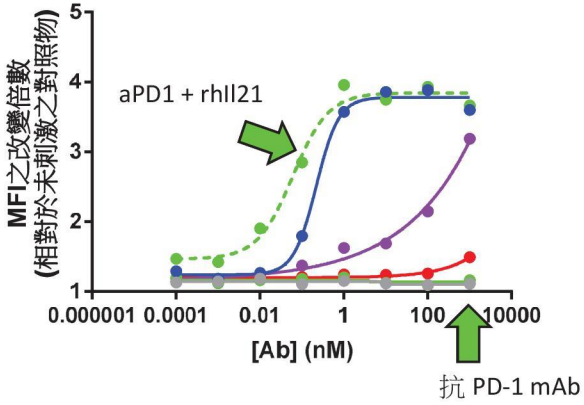


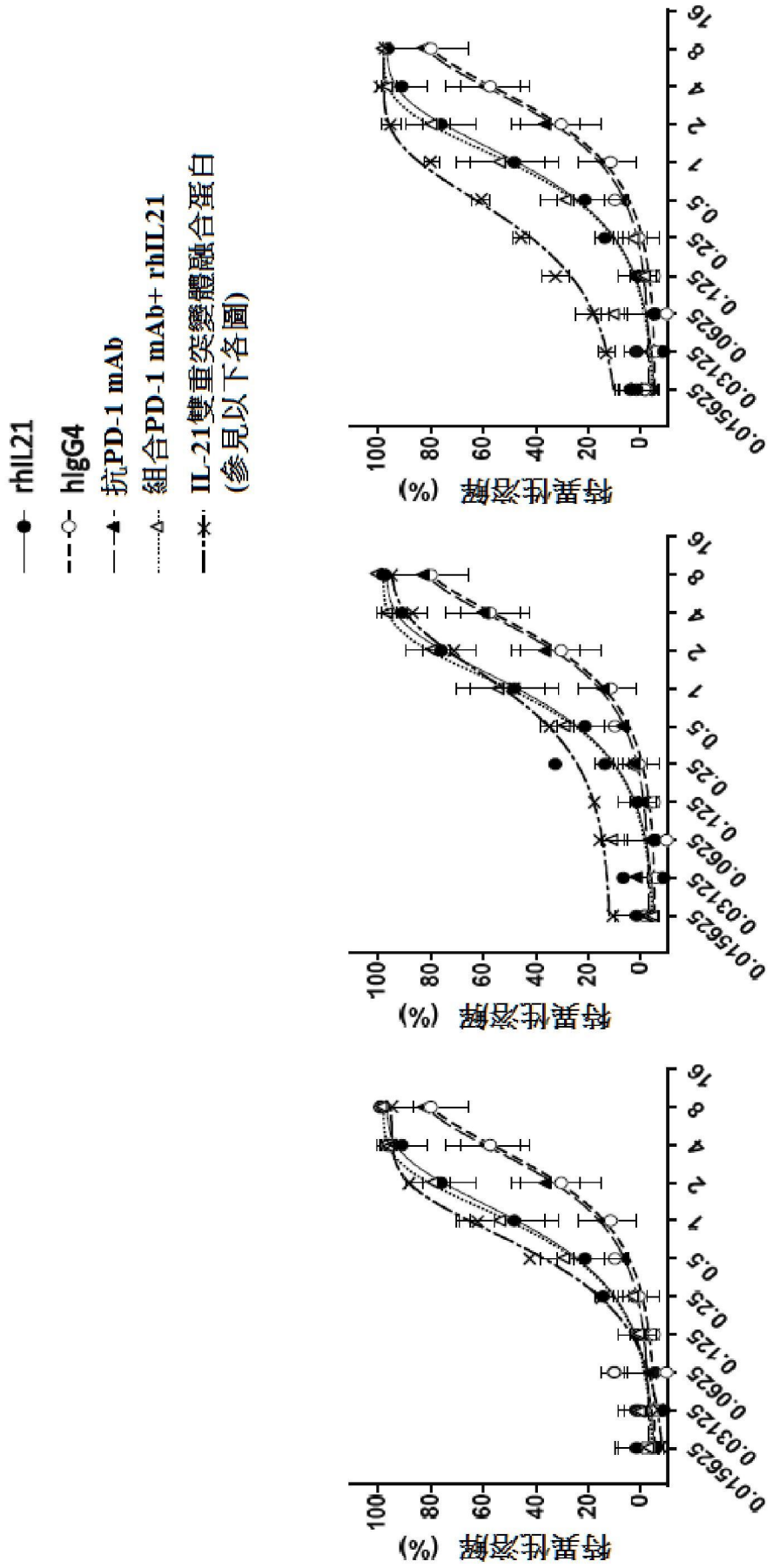
圖 12C:
實線 = 包含抗PD-1 mAb
與 IL-21 R9E:R76A 雙重
突變蛋白融合之融合蛋白



pSTAT3

在刺激10分鐘前使CTL靜怠48小時
靜怠24小時後基礎PD1為低的

【圖 12】

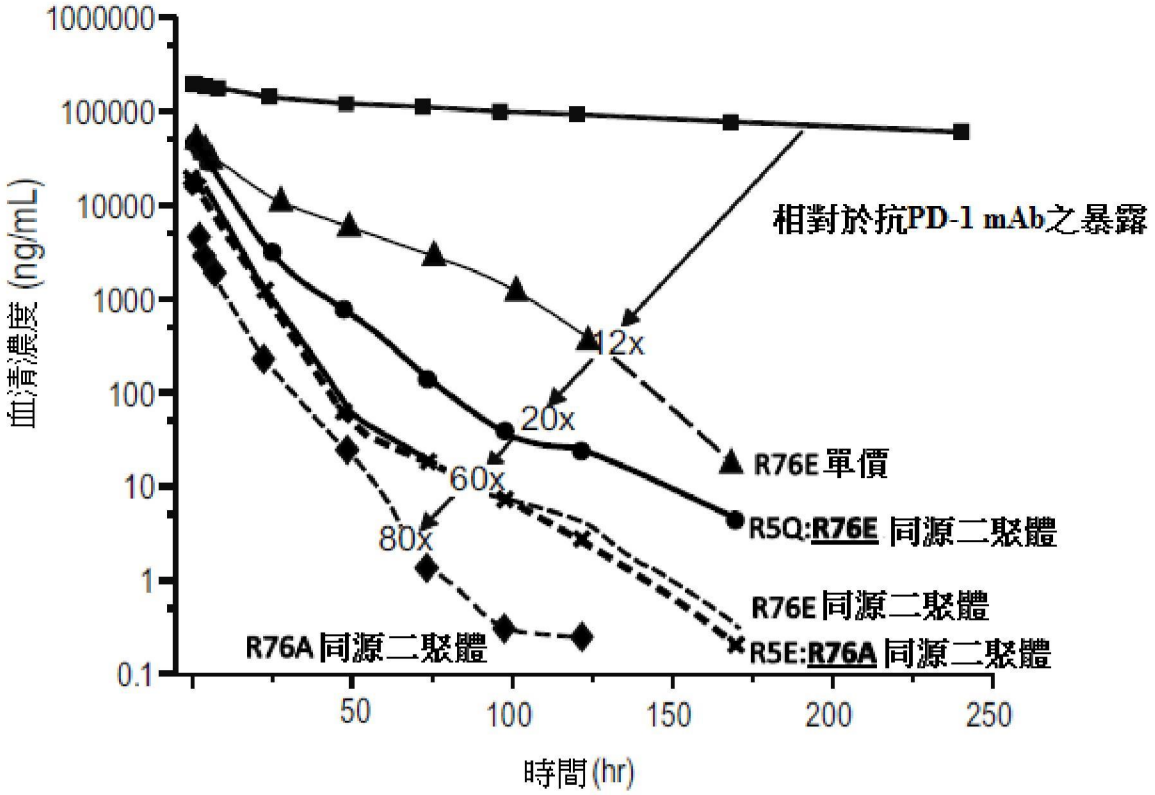


【圖 13A】

【圖 13B】

【圖 13C】

【圖 13】


1000000
100000
10000
1000
100
10
1
0.1
血清濃度 (ng/mL)
50
100
150
200
250
時間 (hr)
相對於抗PD-1 mAb之暴露
12x
20x
60x
80x
R76E單價
R5Q:R76E 同源二聚體
R76E同源二聚體
R5E:R76A 同源二聚體
R76A同源二聚體

【圖 14】

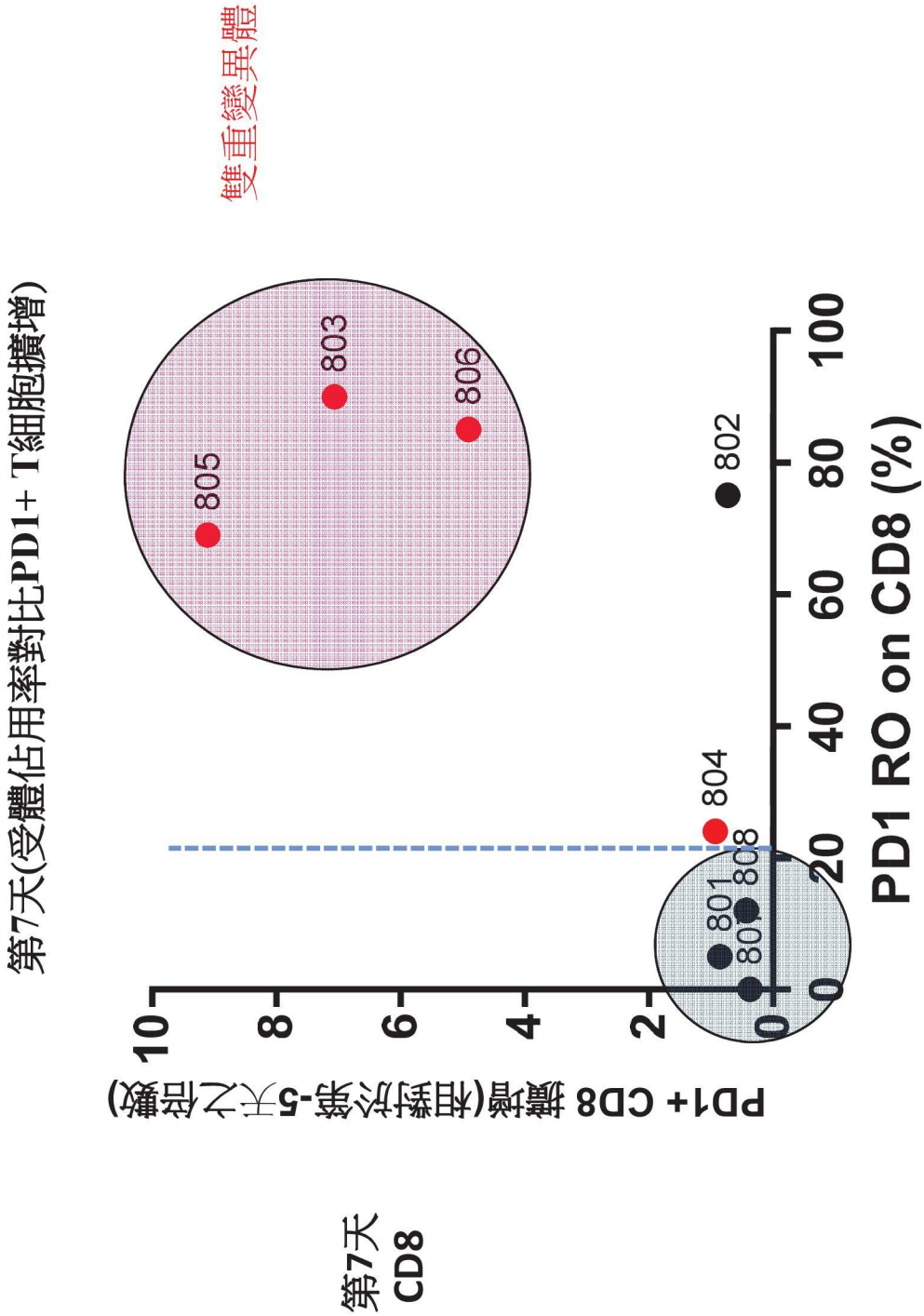
【圖 15A】

【圖 15B】

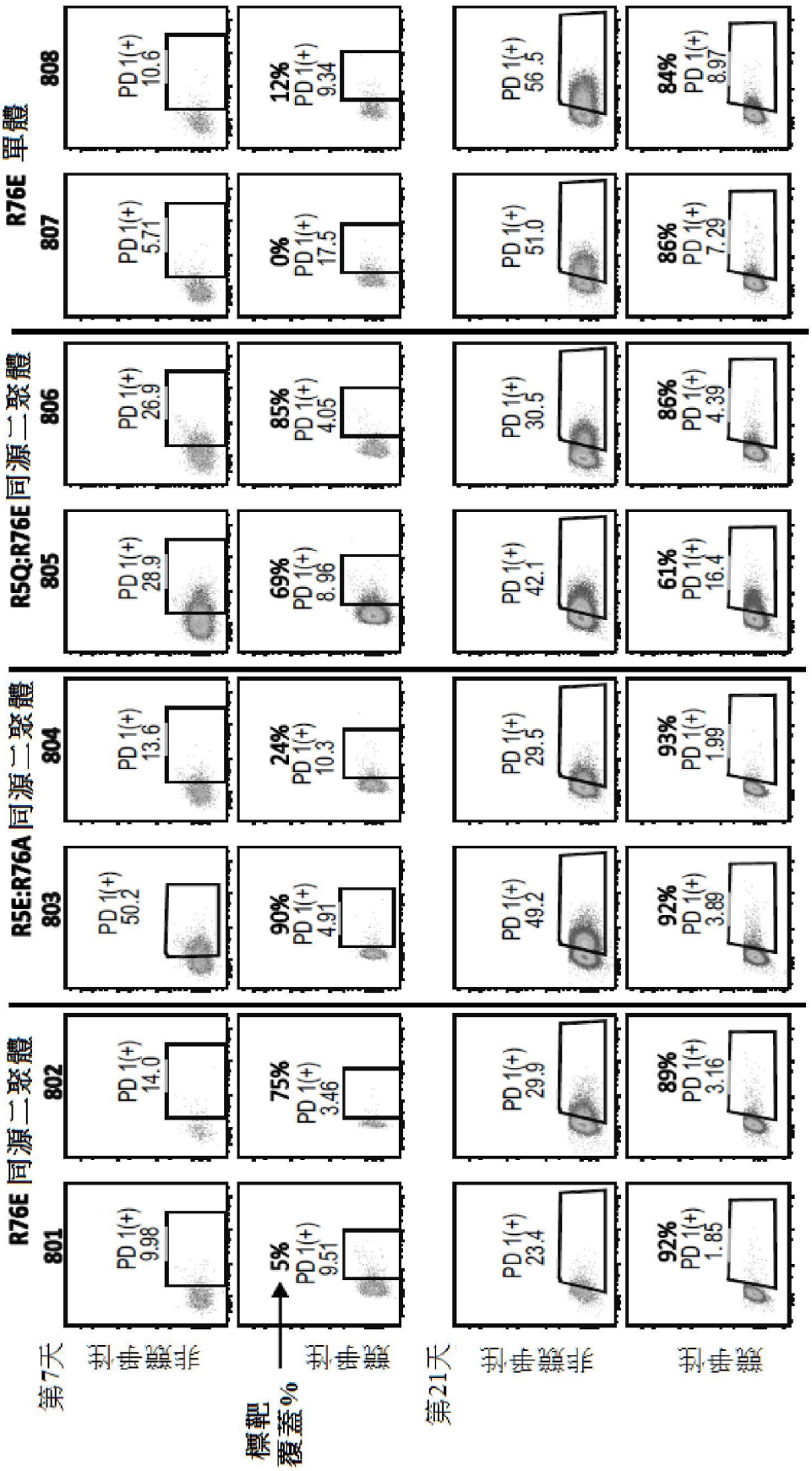
【圖 15C】

【圖 15D】

【圖 15】


雙重變異體
第7天(受體佔用率對比PD1+ T細胞擴增)
805
803
806
802
804
801
808
807
PD1+ CD8 擴增(相對於第-5天之倍數)
10
8
6
4
2
0
0
20
40
60
80
100
PD1 RO on CD8 (%)
第7天
CD8
單一突變體

【圖 16】

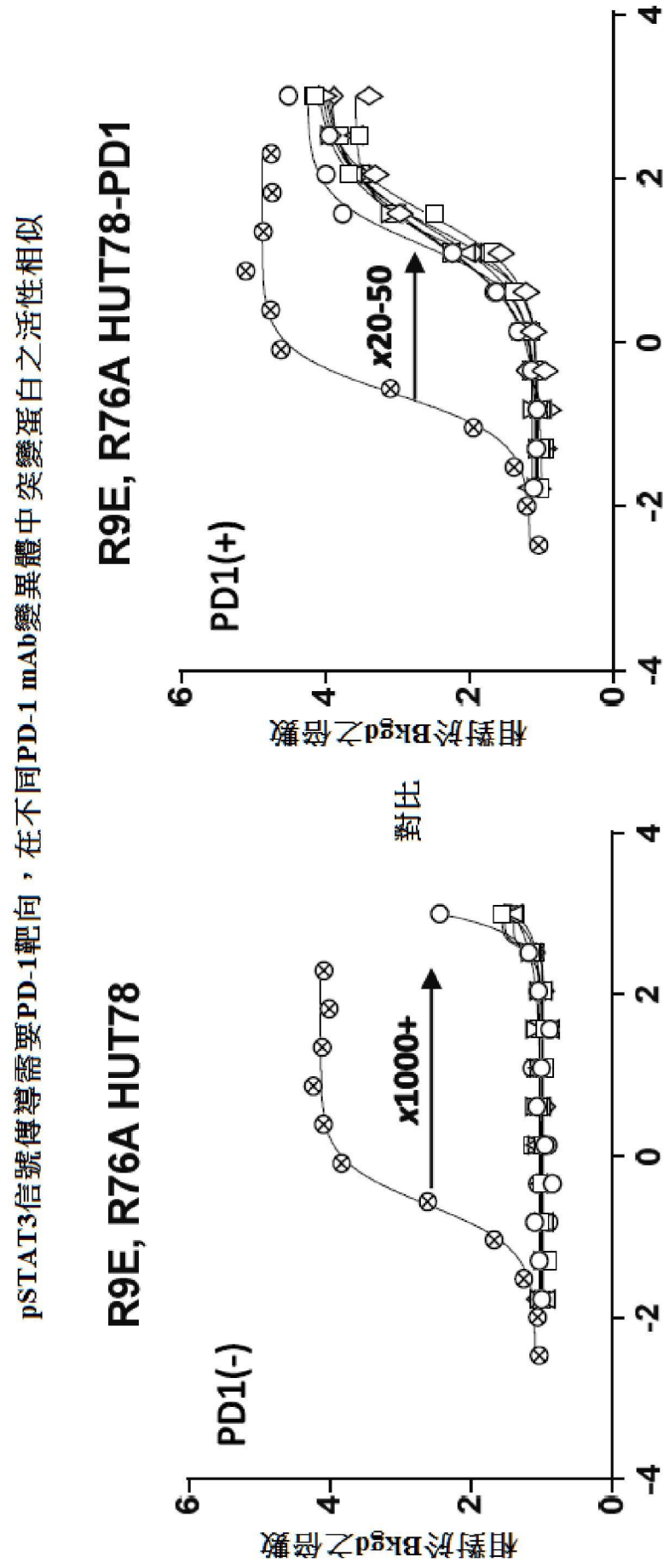

R76E 同源二聚體
R5E:R76A 同源二聚體
R5Q:R76E 同源二聚體
R76E 單體
801
802
803
804
805
806
807
808
第7天
第21天
非競爭性
競爭性
標靶覆蓋%
PD1表現
標靶覆蓋%
(表示為競爭性/非競爭性
抗PD-1 ab之間的比率%)
靜脈內給與5 mg/kg
第1天與第8天

【圖 17】

【圖 18】

【圖 18A】

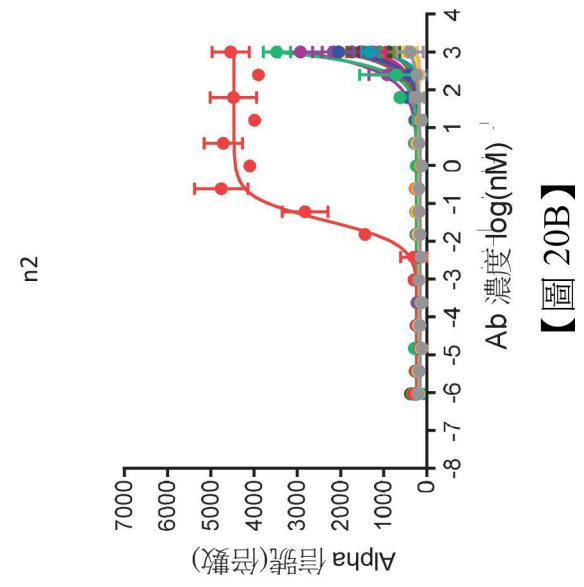
【圖 18B】



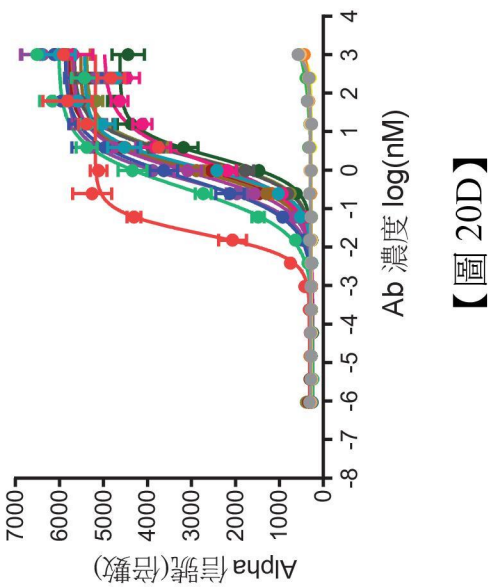
【圖 19A】

【圖 19B】

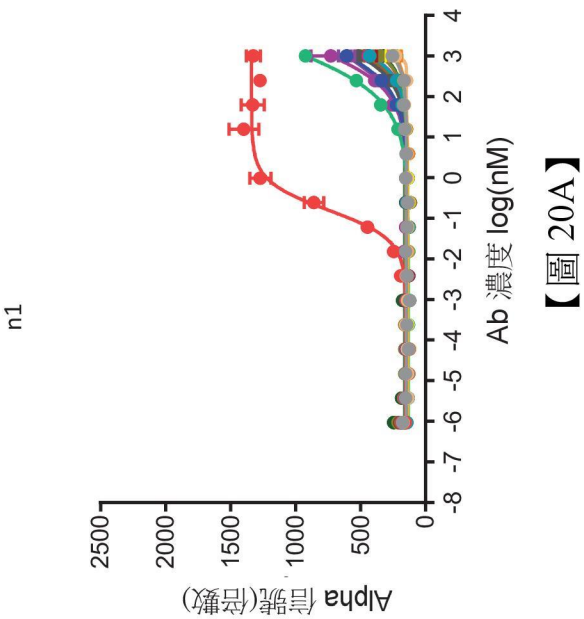
【圖 19】



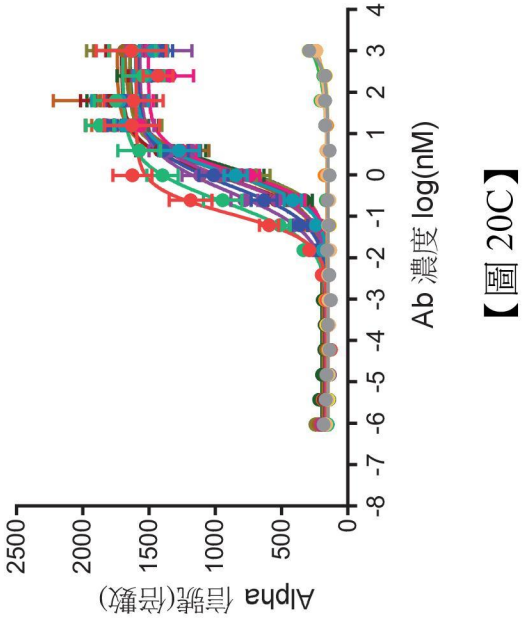
【圖 20B】



【圖 20D】



【圖 20A】

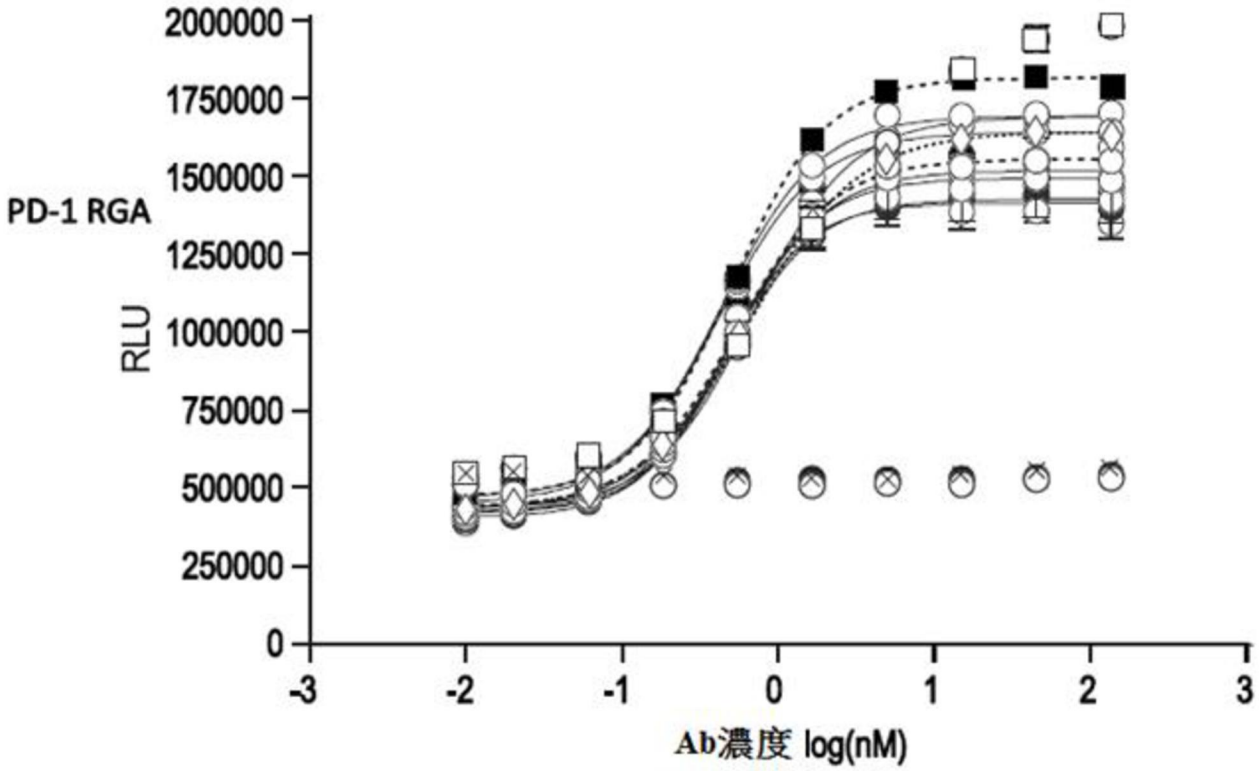


【圖 20C】

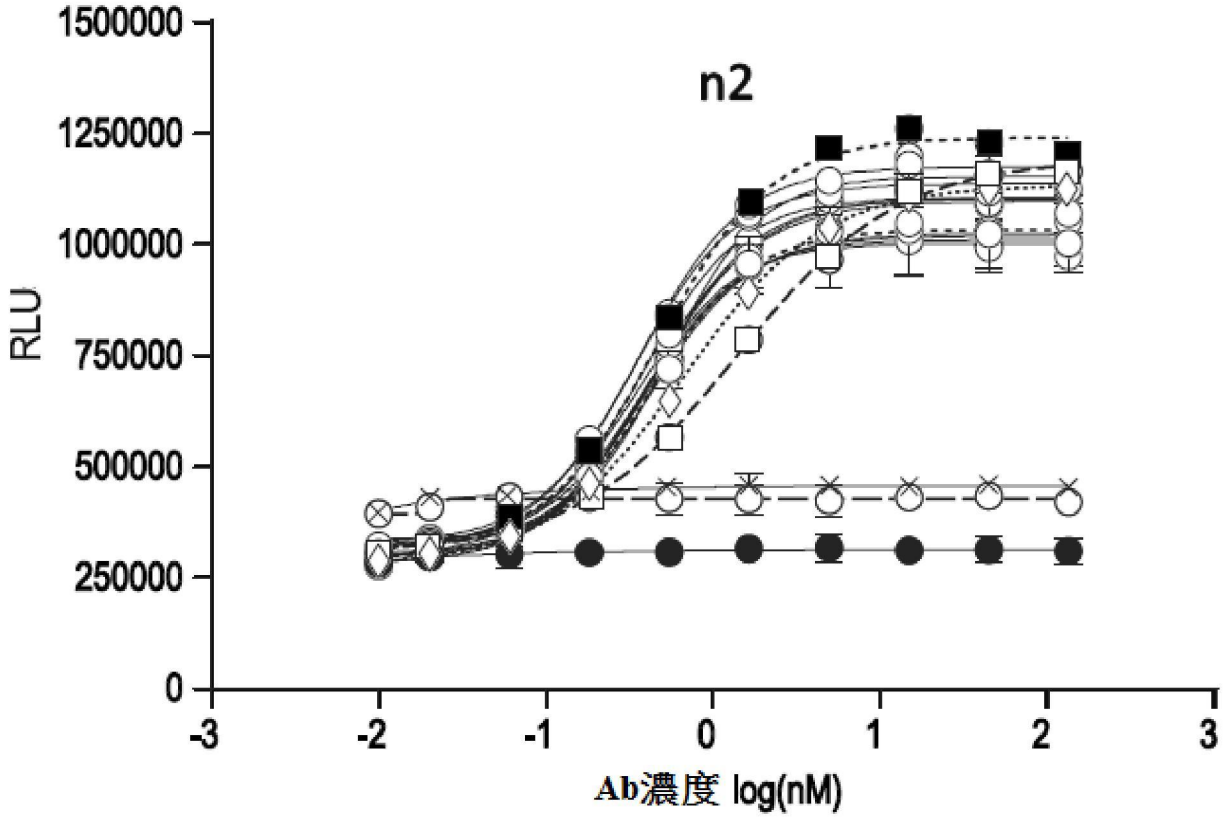
pSTAT3 PD-1(-)

pSTAT3 PD-1(+)

【圖 20】

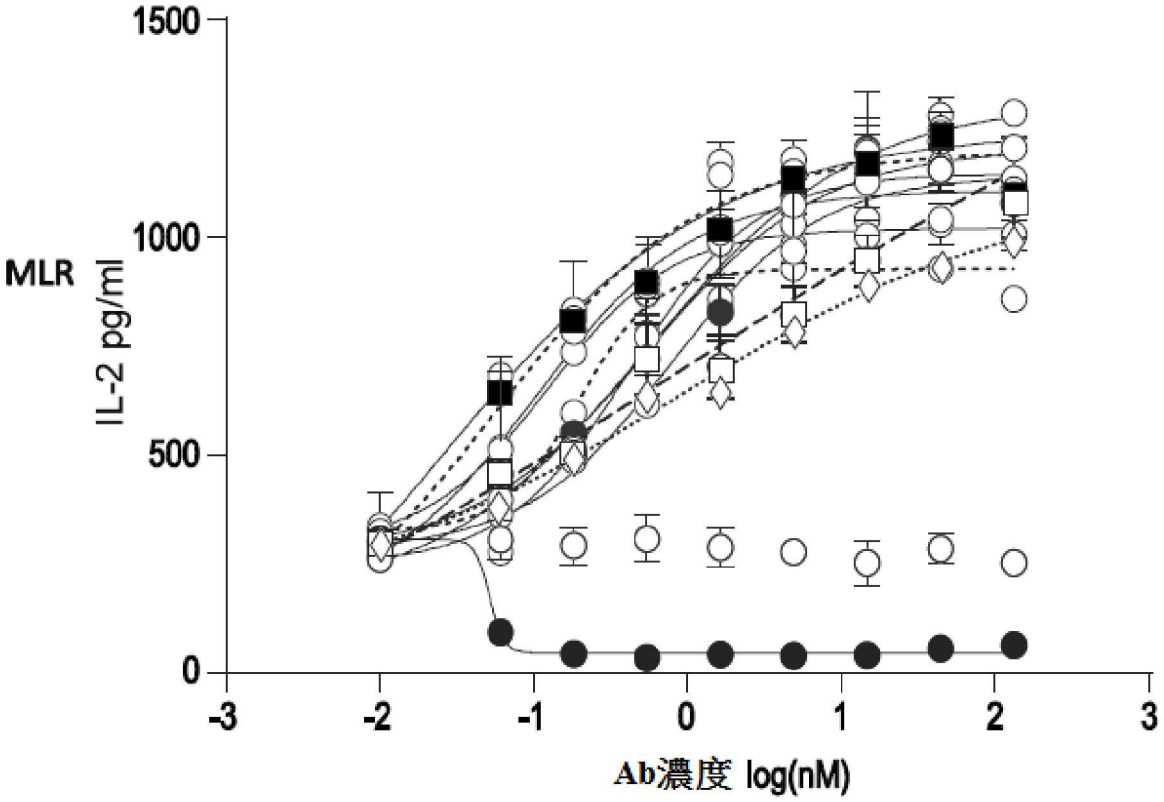


【圖 21A】

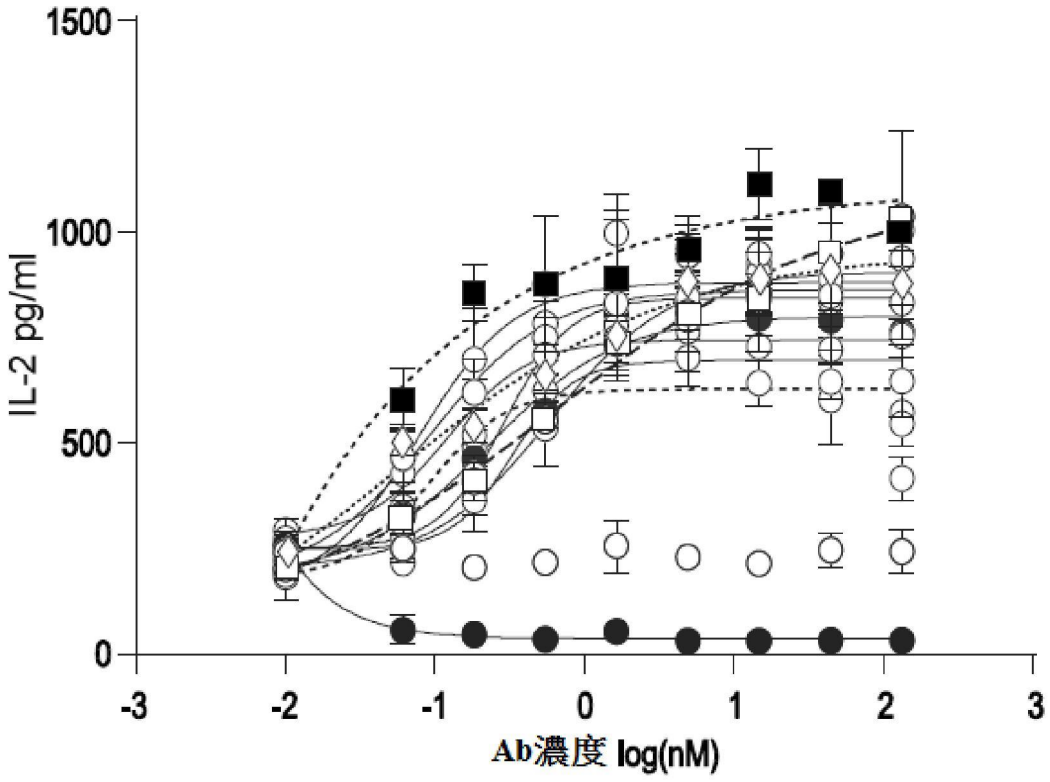


【圖 21B】

【圖 21】

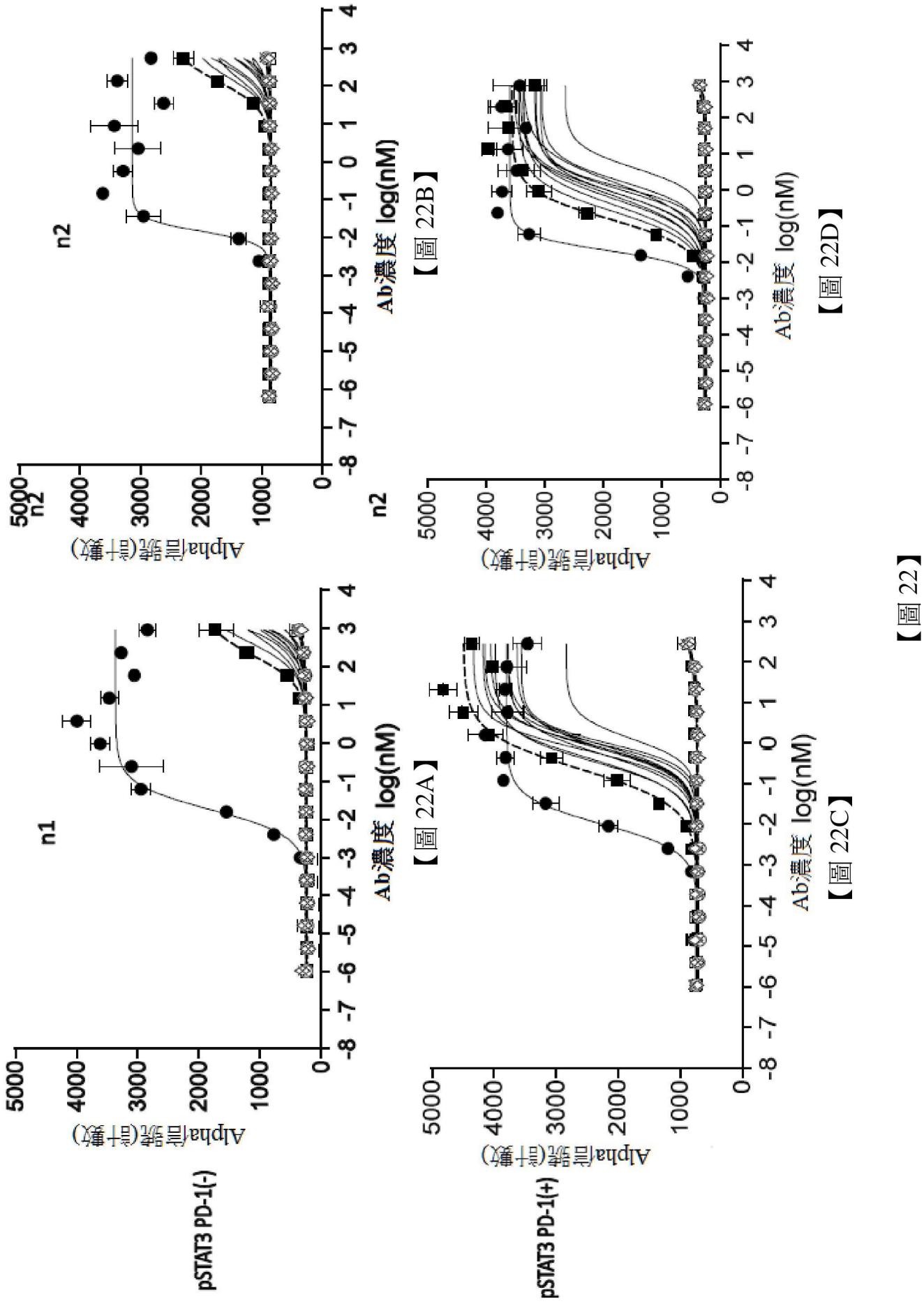


【圖 21C】



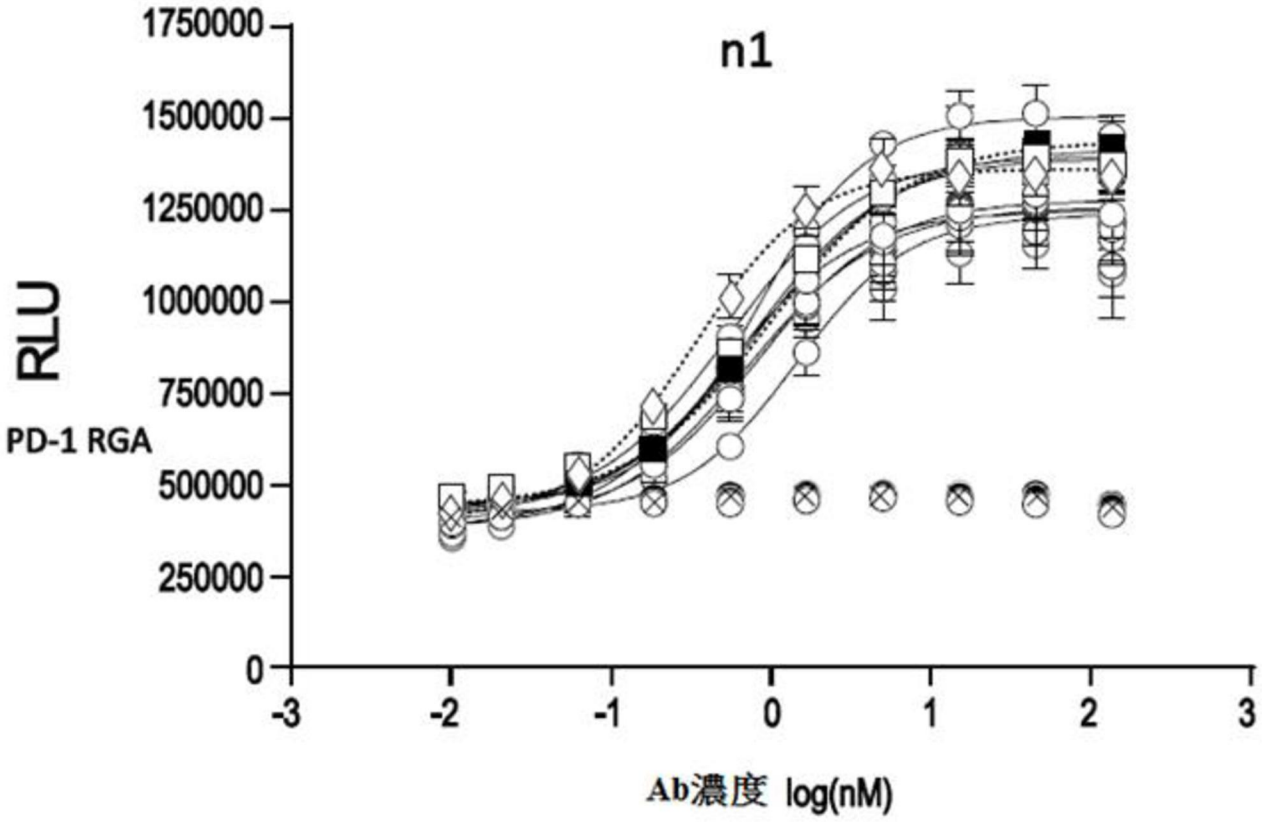
【圖 21D】

【圖 21】(續)

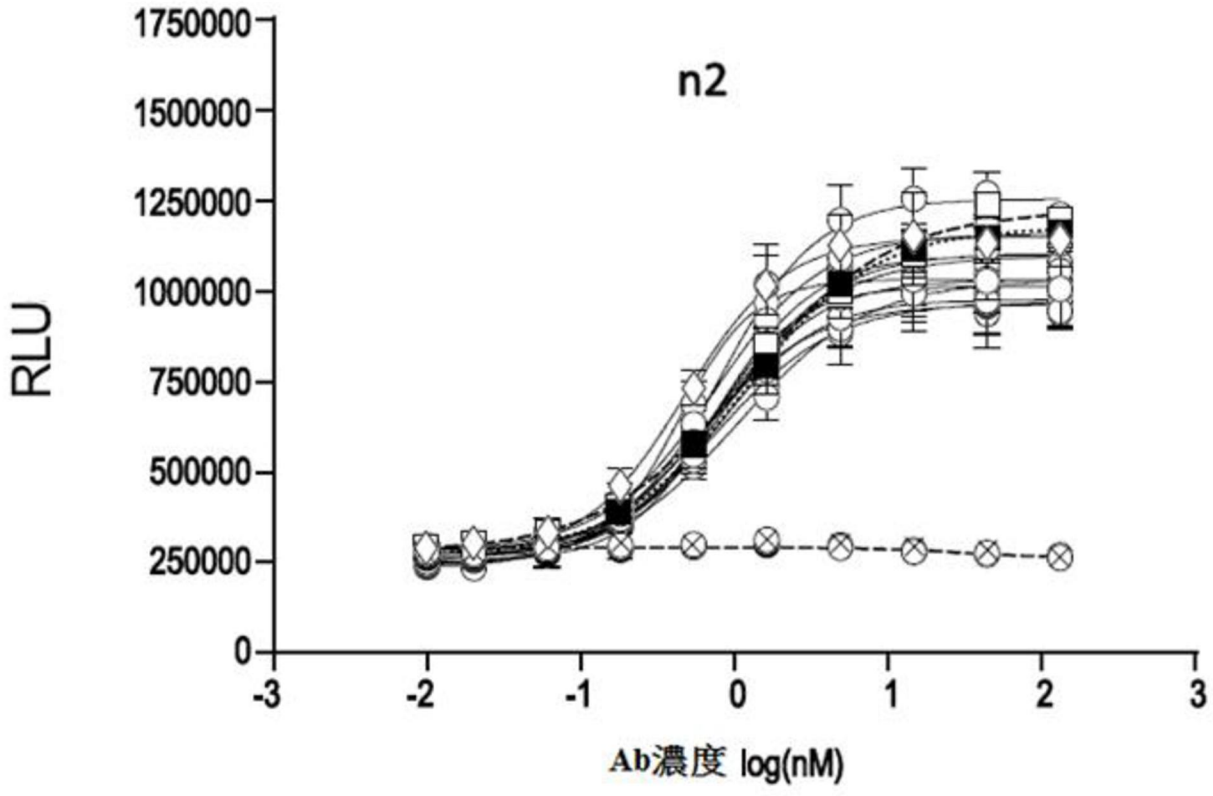


【圖 22A】 【圖 22B】 【圖 22C】 【圖 22D】

【圖 22】

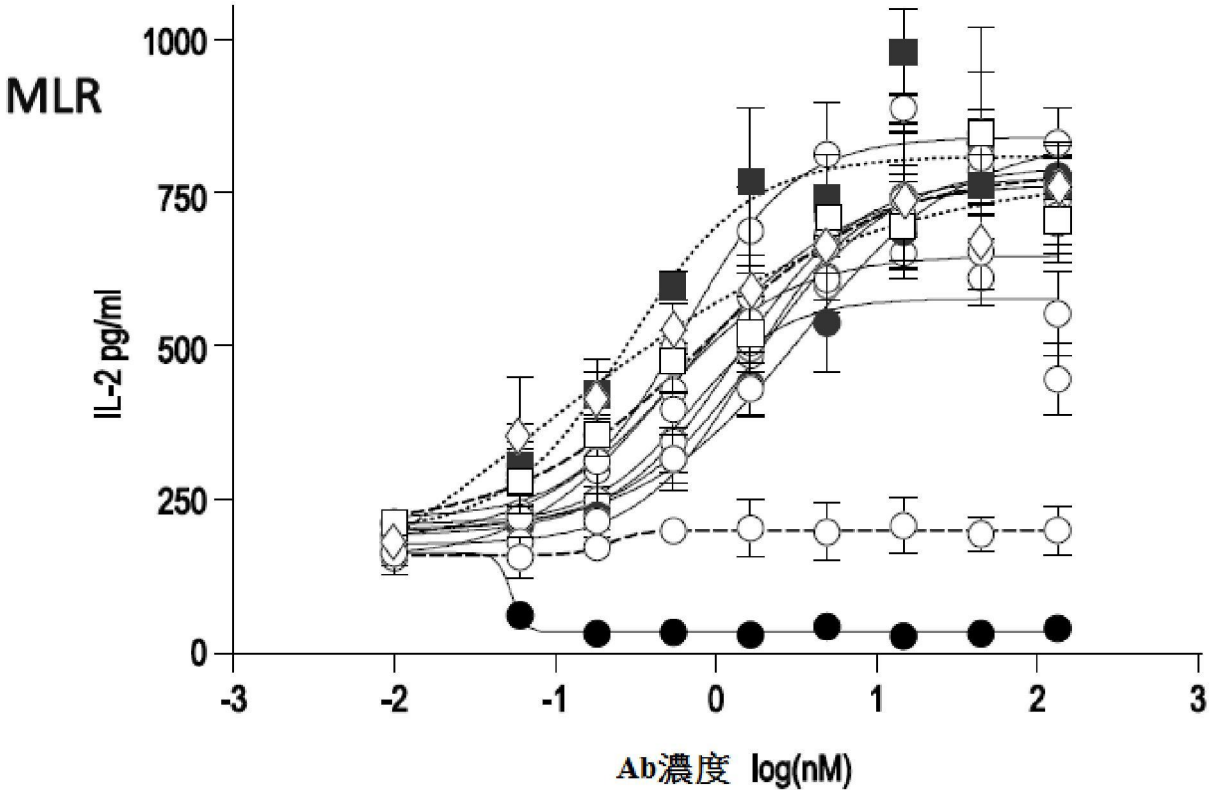


【圖 23A】

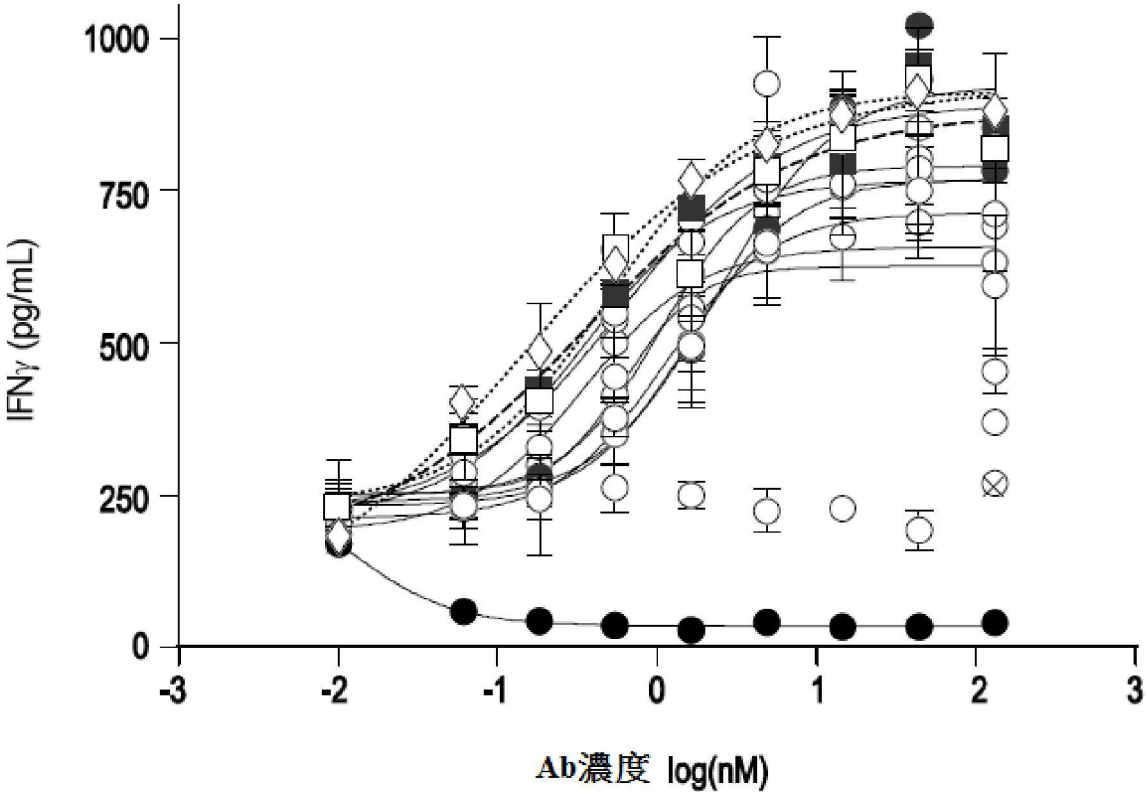


【圖 23B】

【圖 23】

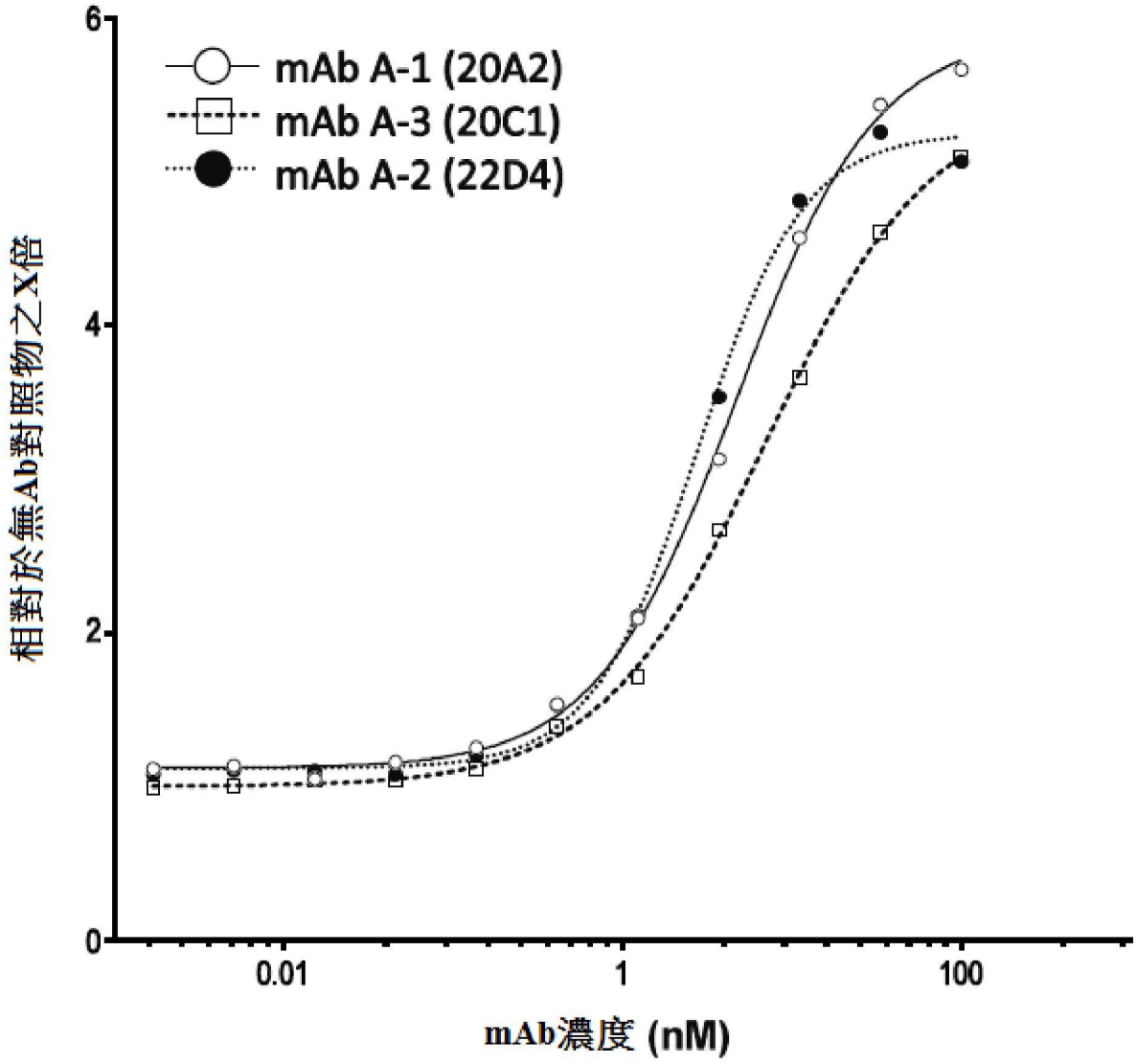


【圖 23C】

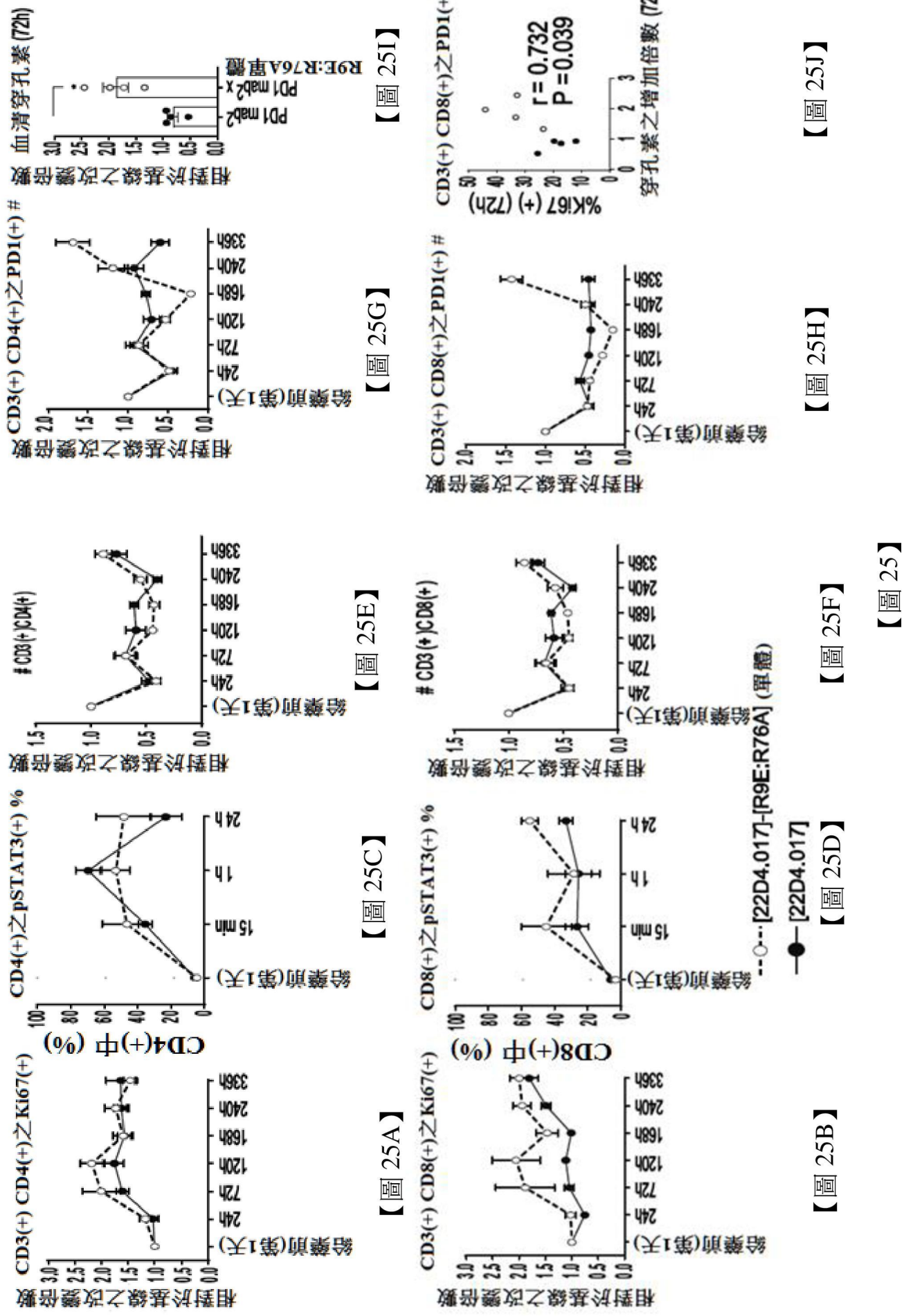


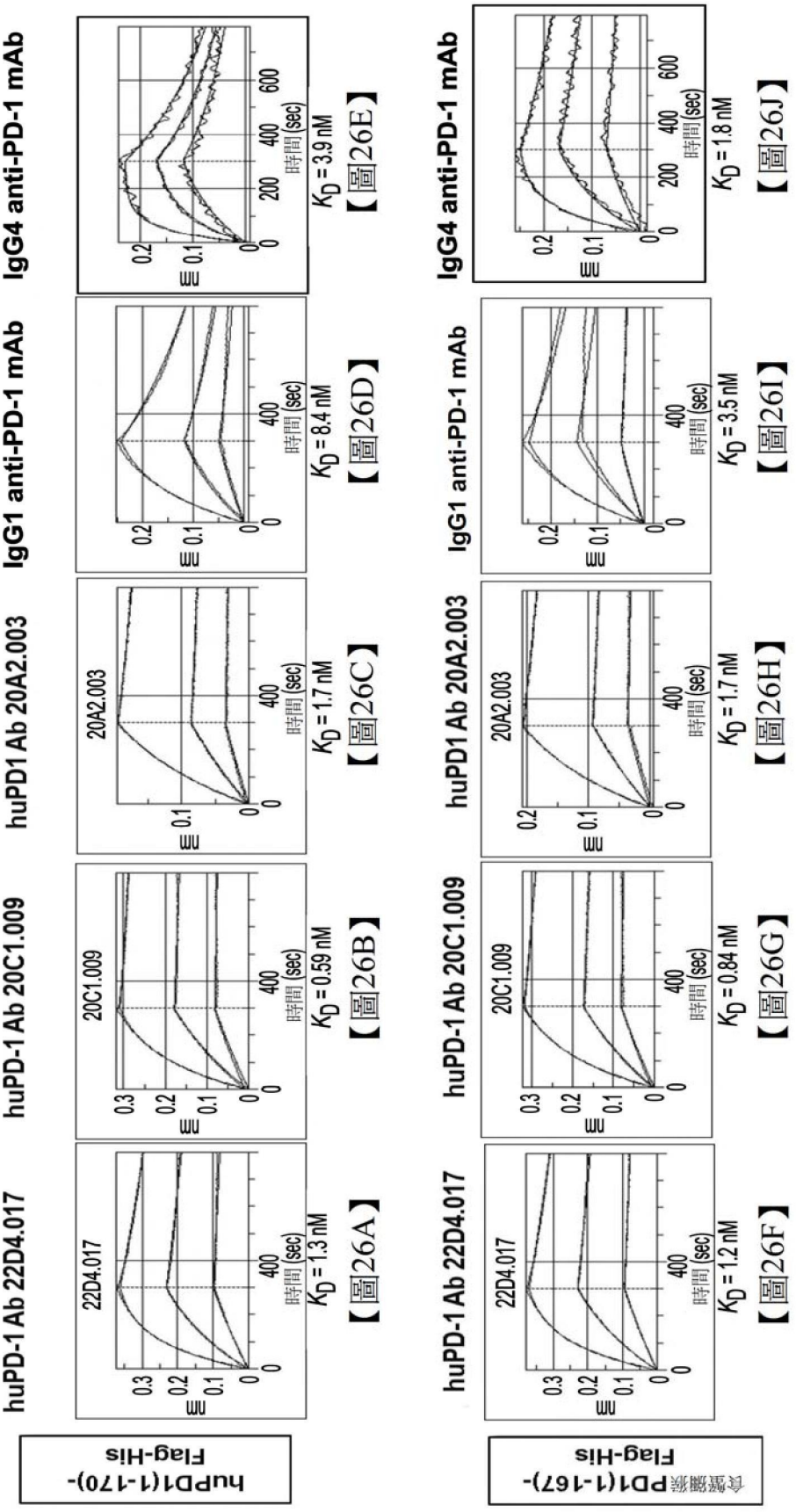
【圖 23D】

【圖 23】(續)

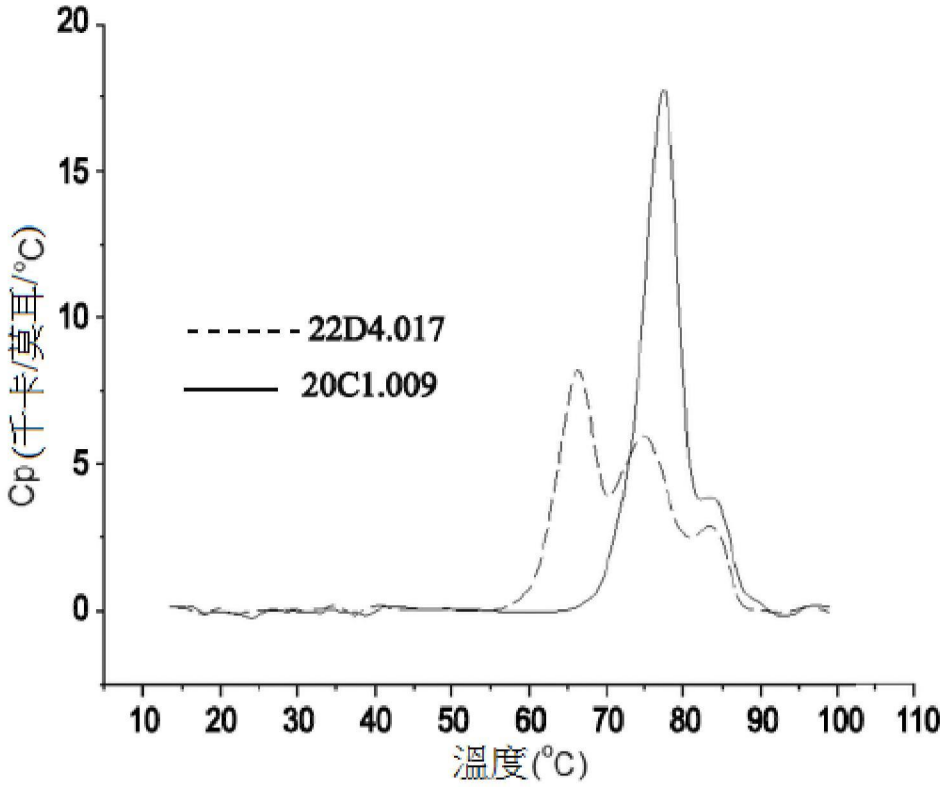

mAb A-1 (20A2)
mAb A-3 (20C1)
mAb A-2 (22D4)
相對於無Ab對照物之X倍
6
4
2
0
0.01
1
100
mAb濃度 (nM)

【圖 24】

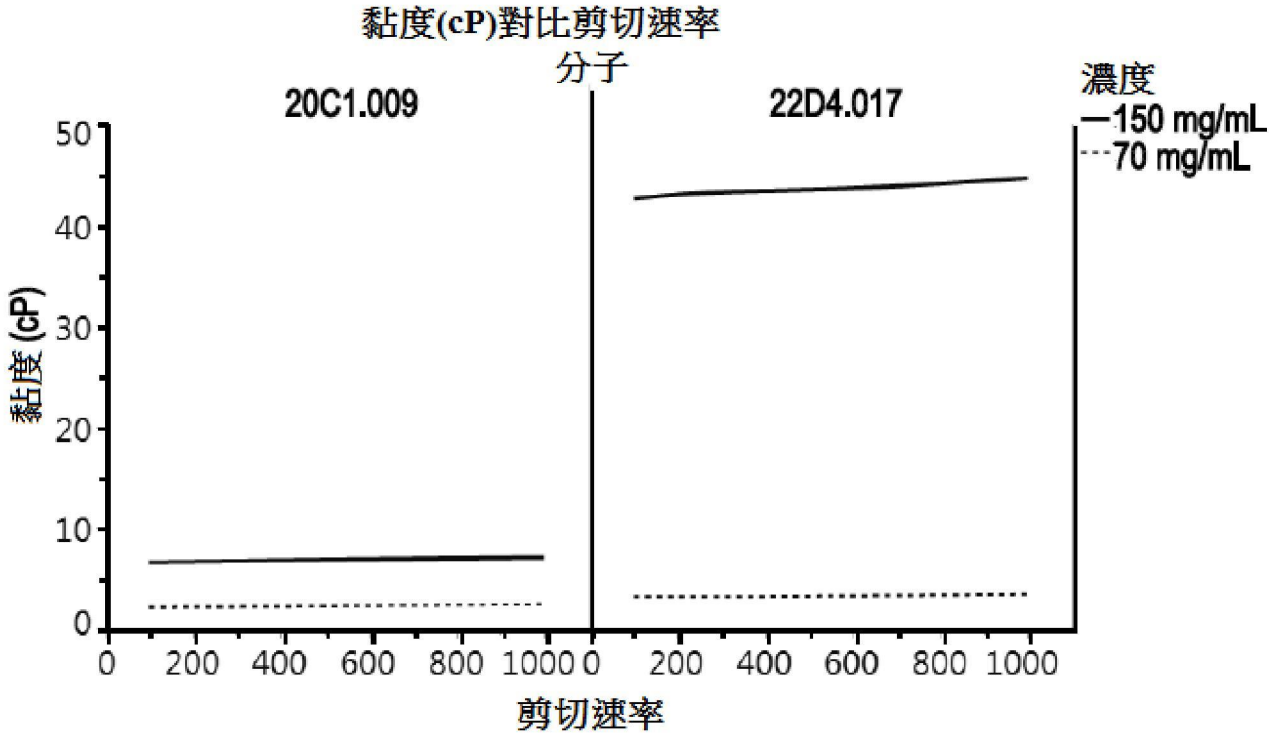

CD3(+) CD4(+)之Ki67(+)
CD4(+)中 (%)
CD4(+)之pSTAT3(+) %
CD3(+)CD4(+)
CD3(+) CD4(+)之PD1(+) #
血清穿孔素 (72h)
PD1 mab2
PD1 mab2 x R9E:R76A單體
CD3(+) CD8(+)之Ki67(+)
CD8(+)中 (%)
CD8(+)之pSTAT3(+) %
CD3(+)CD8(+)
CD3(+) CD8(+)之PD1(+) #
%KI67 (+) (72h)
穿孔素之增加倍數 (72h)
r = 0.732
P = 0.039
相對於基線之改變倍數
給藥前(第1天)
15 min
1h
24h
72h
120h
168h
240h
336h
[22D4.017]
[22D4.017]-[R9E:R76A] (單體)
【圖 25A】
【圖 25B】
【圖 25C】
【圖 25D】
【圖 25E】
【圖 25F】
【圖 25G】
【圖 25H】
【圖 25I】
【圖 25J】
【圖 25】


huPD1(1-170)-Flag-His
huPD-1 Ab 22D4.017
22D4.017
KD = 1.3 nM
【圖26A】
huPD-1 Ab 20C1.009
20C1.009
KD = 0.59 nM
【圖26B】
huPD1 Ab 20A2.003
20A2.003
KD = 1.7 nM
【圖26C】
IgG1 anti-PD-1 mAb
KD = 8.4 nM
【圖26D】
IgG4 anti-PD-1 mAb
KD = 3.9 nM
【圖26E】
食蟹猴PD1(1-167)-Flag-His
huPD-1 Ab 22D4.017
22D4.017
KD = 1.2 nM
【圖26F】
huPD-1 Ab 20C1.009
20C1.009
KD = 0.84 nM
【圖26G】
huPD1 Ab 20A2.003
20A2.003
KD = 1.7 nM
【圖26H】
IgG1 anti-PD-1 mAb
KD = 3.5 nM
【圖26I】
IgG4 anti-PD-1 mAb
KD = 1.8 nM
【圖26J】
nm
時間(sec)

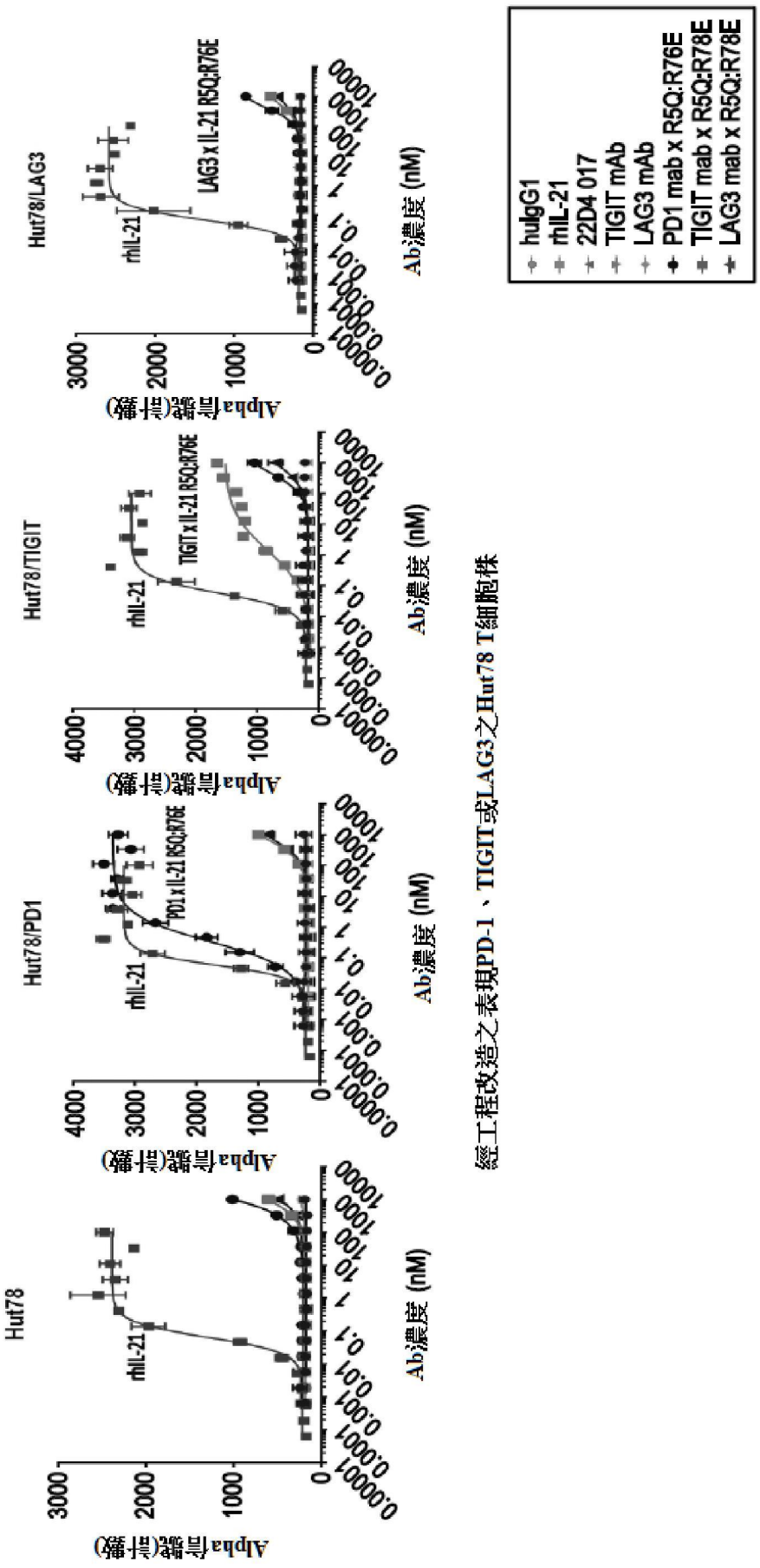
【圖 26】


20
15
10
5
0
Cp(千卡/莫耳/°C)
22D4.017
20C1.009
10
20
30
40
50
60
70
80
90
100
110
溫度(°C)

【圖 27】


黏度(cP)對比剪切速率
分子
20C1.009
22D4.017
濃度
150 mg/mL
70 mg/mL
黏度 (cP)
50
40
30
20
10
0
0
200
400
600
800
1000
剪切速率

【圖 28】



經工程改造之表現PD-1、TIGIT或LAG3之Hut78 T細胞株

【圖 29A】 【圖 29B】 【圖 29C】 【圖 29D】

【圖 29】