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61/288,930

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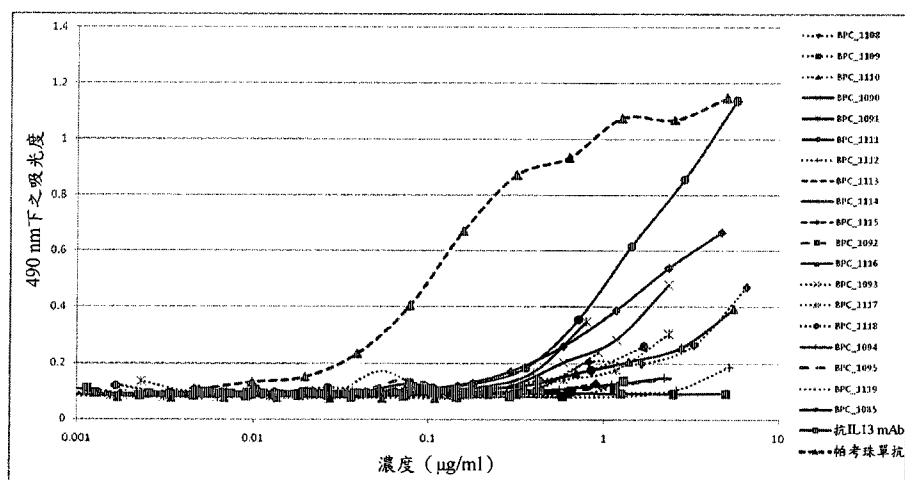
(54)名稱

免疫球蛋白

IMMUNOGLOBULINS

(57)摘要

本發明係關於一種人類 IL-13 之抗原結合蛋白(包括抗 IL-13 抗體及抗 IL-3/抗 IL-4 mAbdAb)、一種含有該等抗原結合蛋白之醫藥調配物，及此等抗原結合蛋白用於治療及/或預防發炎疾病(諸如哮喘或 IPF)的用途。



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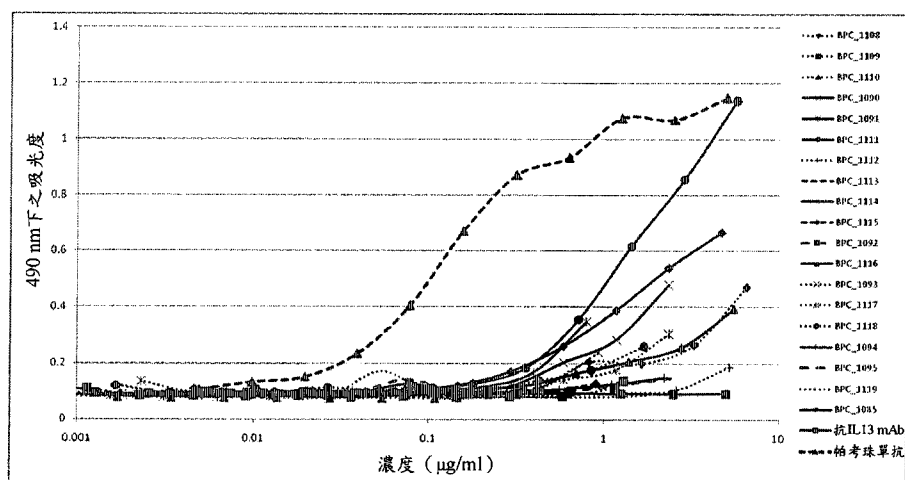
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六、發明說明：

【發明所屬之技術領域】

本發明係關於抗原結合蛋白(特定言之，結合至介白素13(IL-13)且中和其活性的抗體)、編碼此等抗原結合蛋白之聚核苷酸、含有該等抗原結合蛋白之醫藥調配物，及此等抗原結合蛋白用於治療及/或預防發炎相關疾病(諸如哮喘)的用途。從以下描述中可顯而易見本發明之其他態樣、目的及優點。

【先前技術】

介白素-13(IL-13)

IL-13為一種抑制炎性細胞激素產生之12 kDa分泌型細胞激素，其最初被描述為T細胞源細胞激素。結構研究指示其具有由兩個二硫鍵固定之四螺旋束排列。儘管IL-13具有四個潛在糖基化位點，但是對來自大鼠肺之天然IL-13的分析已指示其作為未糖基化分子而產生。NSO及COS-7細胞表現人類IL-13證實了此觀測結果(Eisenmesser等人，J. Mol. Biol. 2001 310(1):231-241；Moy等人，J. Mol. Biol. 2001 310(1):219-230；Cannon-Carlson等人，Protein Expression and Purification 1998 12(2):239-248)。

IL-13已牽涉哮喘、慢性阻塞性肺病(COPD)、過敏性疾病(包括異位性皮膚炎及過敏性鼻炎)、食道嗜伊紅血球增多症、腫瘤學適應症(例如B細胞慢性淋巴球性白血病(B-CLL)及霍奇金氏病(Hodgkin's disease))、發炎性腸病(例如潰瘍性結腸炎、克隆氏病(Crohn's disease)及不定型結腸

炎)、牛皮癬及牛皮癬關節炎、急性移植物抗宿主疾病、糖尿病性腎病變、纖維變性病狀(諸如肺纖維化,例如特發性肺纖維化(IPF))。

【發明內容】

本發明提供結合至IL-13之抗原結合蛋白,例如IL-13抗體,及此等IL-13抗體與IL-4拮抗劑及/或IL-5拮抗劑之組合。本發明之IL-13抗體與鼠類mAb 6A1相關或來源於鼠類mAb 6A1,其中CDRH3已突變。6A1鼠類重鏈可變區胺基酸序列提供為SEQ ID NO: 58。6A1鼠類輕鏈可變區胺基酸序列提供為SEQ ID NO: 59。

本發明之重鏈可變區(V_H)包含下列CDR(如Kabat(*Kabat*等人; *Sequences of proteins of Immunological Interest* NIH, 1987)所定義):

本發明之重鏈可變區之CDR可包含下列CDR:

CDR	根據Kabat
H1	DTYMH (SEQ ID NO: 1)
H2	TIDPANGNTKYVPKFQG (SEQ ID NO: 2)
H3	WIYDDYHYDDYYAMDY(SEQ ID NO: 4); 或 SVYDDYHYDDYYAMDY(SEQ ID NO: 5); 或 SIFDDYHYDDYYAMDY(SEQ ID NO: 6); 或 SIYEDYHYDDYYAMDY(SEQ ID NO: 7); 或 SIYDDYAYDDYYAMDY(SEQ ID NO: 8); 或 SIYDDYFYDDYYAMDY(SEQ ID NO: 9); 或 SIYDDYQYDDYYAMDY(SEQ ID NO: 10); 或 SIYDDYRYDDYYAMDY(SEQ ID NO: 11); 或 SIYDDYSYDDYYAMDY(SEQ ID NO: 12); 或

	SIYDDYTYDDYYAMDY(SEQ ID NO: 13)；或 SIYDDYVYDDYYAMDY(SEQ ID NO: 14)；或 SIYDDYHADDYYAMDY(SEQ ID NO: 15)；或 SIYDDYHIDDYYAMDY(SEQ ID NO: 16)；或 SIYDDYHWDDYYAMDY(SEQ ID NO: 17)；或 SIYDDYHVDDYYAMDY(SEQ ID NO: 18)
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本發明之輕鏈可變區包含下列CDR(如Kabat所定義)：

CDR	根據Kabat
L1	RSSQNIVHINGNTYLE(SEQ ID NO: 19)
L2	KISDRFS(SEQ ID NO: 20)
L3	FQGSHPWT(SEQ ID NO: 21)

如上表中所示，可依據Kabat編號系統(Kabat等人；Sequences of proteins of Immunological Interest NIH, 1987)確定抗體之CDR序列，或者其可藉由使用Chothia編號系統(Al-Lazikani等人，(1997) JMB 273, 927-948)、接觸定義法(contact definition method)(MacCallum R.M.及Martin A.C.R.及Thornton J.M, (1996), Journal of Molecular Biology, 262 (5), 732-745)或為熟習此項技術者已知用於編號抗體中之殘基且確定CDR的任何其他已確立方法來確定。

本文所述之本發明之CDR可經由任一此等方法或藉由將Chothia與Kabat編號組合使用來定義，舉例而言，CDRH1可定義為包含FYIKDTYMH(SEQ ID NO: 60)或GFYIKDTYMH(SEQ ID NO: 61)。

本發明亦提供一種包含連至一或多個抗原決定基結合域之本發明IL-13抗體的抗原結合蛋白，例如包含連至能夠

結合至IL-4之抗原決定基結合域之本發明IL-13抗體的抗原結合蛋白；或包含連至能夠結合至IL-5之抗原決定基結合域之本發明IL-13抗體的抗原結合蛋白；或包含連至能夠結合至IL-4之第一抗原決定基結合域及能夠結合至IL-5之第二抗原決定基結合域之本發明IL-13抗體的抗原結合蛋白。

本發明亦提供一種藉由殘基89(kabat編號)突變成「Q」(麩醯胺酸)來減少免疫球蛋白單可變域(例如人類VK結構域抗體)之聚集傾向的方法。在一實施例中，可對SEQ ID NO: 80之抗IL-4結構域抗體使用此方法，產生突變dAb序列，例如SEQ ID NO: 94。

此等突變dAb可單獨存在或作為較大序列之一部分(例如mAbdAb序列之一部分)存在，從而產生例如包含選自SEQ ID NO: 117-134之序列的dAb。

本發明亦提供具有改良之聚集概況的人類VK dAb，例如來源於選自以下之生殖系架構(germline framework)的人類VK dAb：IGKV1-17、IGKV1D-17、IGKV1/OR2-108、IGKV1-6、IGKV5-2、IGKV1D-42、IGKV2-24、IGKV2-28、IGKV2-30、IGKV2-40、IGKV2D-29、IGKV2D-30、IGKV2D-24及IGKV6-21，其中該VK dAb之殘基89(kabat編號)為「Q」(麩醯胺酸)。在一此實施例中，VK dAb包含的生殖系架構區選自IGKV1-17、IGKV1D-17、IGKV1/OR2-108、IGKV1-6、IGKV5-2、IGKV1D-42、IGKV2-24、IGKV2-28、IGKV2-30、IGKV2-40、IGKV2D-29、IGKV2D-

30、IGKV2D-24及IGKV6-21之生殖系架構，其中該VK dAb之殘基89(kabat編號)為「Q」(麩醯胺酸)。

在一實施例中，本發明提供一種包含SEQ ID NO: 94之序列的人類dAb。

本發明亦提供一種編碼本文所述之任一種抗原結合蛋白之重鏈的聚核苷酸序列，及一種編碼本文所述之任一種抗原結合蛋白之輕鏈的聚核苷酸。此等聚核苷酸代表對應於等效多肽序列之編碼序列，然而應瞭解此等聚核苷酸序列可隨起始密碼子、適當信號序列及終止密碼子一起選殖入表現載體中。

本發明亦提供一種重組轉型或轉染之宿主細胞，其包含一或多種編碼本文所述之任一種抗原結合蛋白之重鏈及輕鏈的聚核苷酸。

本發明進一步提供一種產生本文所述之任一種抗原結合蛋白之方法，該方法包含在適合培養基(例如無血清培養基)中培養包含第一及第二載體之宿主細胞的步驟，該第一載體包含編碼本文所述之任一種抗原結合蛋白之重鏈的聚核苷酸且該第二載體包含本文所述之任一種抗原結合蛋白之輕鏈的聚核苷酸。

本發明進一步提供一種包含如本文所述之抗原結合蛋白及醫藥學上可接受之載劑的醫藥組合物。

在另一態樣中，本發明提供一種藉由投與本發明之抗原結合蛋白來治療或預防與特異反應性疾病/病症及慢性發炎性疾病/病症相關之疾病或病症的方法。尤其關注其治

療哮喘之用途，諸如過敏性哮喘，特定言之，嚴重哮喘（亦即對當前治療（包括全身投與皮質類固醇）無反應之哮喘；參見Busse WW等人，J Allergy Clin. Immunol 2000, 106: 1033-1042）、「難治性」哮喘（定義為特徵為儘管投與最大推薦劑量之處方吸入類固醇但仍無法得到控制之哮喘表型，參見Barnes PJ, (1998), Eur Respir J 12:1208-1218）、「脆性」哮喘（定義患有嚴重不穩定哮喘的患者亞群，其儘管投與高劑量之吸入類固醇，但仍維持寬尖峰呼氣流量（peak expiratory flow, PEF）變化性，參見Ayres JG等人，(1998) Thorax 58:315-321）、夜間哮喘、經前哮喘、抗類固醇哮喘（參見Woodcock AJ, (1993) Eur Respir J 6:743-747）、類固醇依賴型哮喘（定義為僅可用高劑量口服類固醇控制之哮喘）、阿斯匹靈誘發性哮喘（aspirin induced asthma）、成年發作型哮喘、小兒哮喘。本發明之抗體可用於預防、降低急性哮喘發作（持續性哮喘（*status asthmaticus*））之頻率或緩和其效應。本發明之抗體亦可用於降低在治療哮喘中所用之其他藥劑的所需給藥（在投藥量或給藥頻率方面）。舉例而言，本發明之抗體可用於降低類固醇治療（諸如皮質類固醇治療）哮喘所需之給藥（「類固醇節省」）。其他可用本發明之抗體治療之疾病或病症包括異位性皮膚炎、過敏性鼻炎、克隆氏病、慢性阻塞性肺病（COPD）、嗜伊紅血球食道炎、纖維變性疾病或病症（諸如特發性肺纖維化、進行性全身性硬化（硬皮病）、肝纖維化）、肝肉芽瘤、血吸蟲病、利什曼體病（leishmaniasis）

及細胞週期調節疾病(例如霍奇金氏病、B細胞慢性淋巴細胞白血病)。

在另一態樣中，本發明提供本發明抗原結合蛋白用於製備藥劑之用途，該藥劑用於治療或預防特異反應性疾病/病症及慢性發炎性疾病/病症。尤其關注其治療哮喘之用途，諸如過敏性哮喘，特定言之，嚴重哮喘(亦即對當前治療(包括全身投與皮質類固醇)無反應之哮喘；參見Busse WW等人，J Allergy Clin. Immunol 2000, 106: 1033-1042)、「難治性」哮喘(定義為特徵為儘管投與最大推薦劑量之處方吸入類固醇但仍無法得到控制之哮喘表型，參見Barnes PJ, (1998), Eur Respir J 12:1208-1218)、「脆性(brittle)」哮喘(定義患有嚴重不穩定哮喘的患者亞群，其儘管投與高劑量之吸入類固醇，但仍維持寬尖峰呼氣流量(PEF)變化性，參見Ayres JG等人，(1998) Thorax 58:315-321)、夜間哮喘、經前哮喘、抗類固醇哮喘(參見Woodcock AJ, (1993) Eur Respir J 6:743-747)、類固醇依賴型哮喘(定義為僅可用高劑量口服類固醇控制之哮喘)、阿斯匹靈誘發性哮喘、成年發作型哮喘、小兒哮喘。本發明之抗體可用於預防、降低急性哮喘發作(持續性哮喘)之頻率或緩和其效應。本發明之抗體亦可用於降低在治療哮喘中所用之其他藥劑的所需給藥(在投藥量或給藥頻率方面)。舉例而言，本發明之抗體可用於降低類固醇治療(諸如皮質類固醇治療)哮喘所需之給藥(「類固醇節省」)。其他可用本發明之抗體治療之疾病或病症包括異位性皮膚

炎、過敏性鼻炎、克隆氏病、慢性阻塞性肺病(COPD)、嗜伊紅血球食道炎、纖維變性疾病或病症(諸如特發性肺纖維化、進行性全身性硬化(硬皮病)、肝纖維化)、肝肉芽瘤、血吸蟲病、利什曼體病及細胞週期調節疾病(例如霍奇金氏病、B細胞慢性淋巴細胞白血病)。

本發明之其他態樣及優點進一步描述於實施方式及其實施例中。

定義

如通篇本說明書關於本發明之人類IL-13抗原結合蛋白所用之術語「結合至人類IL-13」意謂該抗原結合蛋白結合人類IL-13(下文稱為hIL-13)而不結合至或不顯著結合至其他人類蛋白質(諸如IL-4)。特定言之，本發明之抗原結合蛋白結合至人類IL-13，因為在Biacore分析法(例如描述於實例3中之Biacore分析法)中可見其結合至人類IL-13。然而該術語並不排除本發明之某些抗原結合蛋白亦可與其他物種之IL-13(例如石蟹獼猴IL-13)交叉反應的事實。

如本文所用之術語「抗原結合蛋白」係指能夠結合且中和人類IL-13之抗體、抗體片段及其他蛋白質構築體。

術語Fv、Fc、Fd、Fab、或F(ab)₂依據其標準含義使用(參見，例如Harlow等人，Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory, (1988))。

「嵌合抗體」係指一類型之工程改造抗體，其含有來源於供者抗體之天然存在可變區(輕鏈及重鏈)以及來源於受者抗體之輕鏈及重鏈恆定區。

「人類化抗體」係指一類型之工程改造抗體，其CDR來源於非人類供者免疫球蛋白，該分子之其餘免疫球蛋白源部分係來源於一(或多)種人類免疫球蛋白。此外，可改變架構支撐殘基以保留結合親和力(參見，例如 Queen等人，Proc. Natl Acad Sci USA, 86:10029-10032 (1989)；Hodgson等人，Bio/Technology, 9:421 (1991))。適合的人類受者抗體可為根據與供者抗體之核苷酸及胺基酸序列的同源性選自以下習知資料庫者：例如KABAT[®]資料庫、Los Alamos 資料庫及瑞士蛋白質資料庫(Swiss Protein database)。特徵為與供者抗體之架構區同源(在胺基酸基礎上)之人類抗體可適於為插入供者CDR提供重鏈恆定區及/或重鏈可變架構區。可以類似方式選擇能夠提供輕鏈恆定區或可變架構區之適合受者抗體。應注意受者抗體重鏈及輕鏈不必來源於相同受者抗體。先前技術描述產生此等人類化抗體之若干方式-參見例如EP-A-0239400及EP-A-054951。

術語「供者抗體」係指一種抗體(單株及/或重組)，其向第一免疫球蛋白搭配物貢獻其可變區、CDR、或其他功能片段或其類似物之胺基酸序列，從而提供變異的免疫球蛋白編碼區及由此經表現之變異抗體，該變異抗體具有供者抗體所特有之抗原特異性及中和活性。

術語「受者抗體」係指與供者抗體異源之抗體(單株及/或重組)，其向第一免疫球蛋白搭配物貢獻編碼其重鏈及/或輕鏈架構區及/或其重鏈及/或輕鏈恆定區之所有(或任一

部分，但在一些實施例中為所有)胺基酸序列。在某些實施例中，人類抗體為受者抗體。

「CDR」定義為抗體之互補決定區胺基酸序列，其為免疫球蛋白重鏈及輕鏈之高變區。參見，例如Kabat等人，*Sequences of Proteins of Immunological Interest*，第4版，美國衛生福利部(U.S. Department of Health and Human Services)，國家衛生研究院(National Institutes of Health)(1987)。免疫球蛋白之可變部分中存在三個重鏈及三個輕鏈CDR(或CDR區)。因此，如本文所用之「CDR」係指所有三個重鏈CDR或所有三個輕鏈CDR(或所有重鏈CDR與所有輕鏈CDR(若適當))。抗體之結構及蛋白質摺疊可意謂其他殘基被視為抗原結合區之一部分且熟習此項技術者應理解為如此。參見例如Chothia等人，(1989) *Conformations of immunoglobulin hypervariable regions*; *Nature* 342，第877-883頁。

如本文所用之術語「結構域」係指摺疊的蛋白質結構，其具有不依賴於蛋白質之其餘部分的三級結構。一般而言，結構域負責蛋白質之個別功能性質且在許多情況下可添加、移除或轉移至其他蛋白質中而不損失蛋白質及/或結構域之其餘部分的功能。「抗體單可變域」為包含抗體可變域所特有之序列的摺疊多肽結構域。其因此包括完全抗體可變域及經修飾可變域(例如其中一或多個環已經不為抗體可變域所特有之序列置換)、或已截斷或包含N或C末端延伸之抗體可變域、以及至少保留全長結構域之結合

活性及特異性之可變域摺疊片段。

片語「免疫球蛋白單可變域」係指獨立於不同V區或域而特異性結合抗原或抗原決定基之抗體可變域(V_H 、 V_{HH} 、 V_L)。免疫球蛋白單可變域可呈具有其他不同可變區或可變域之形式(例如，同源或異源多聚體)存在，其中該等其他可變區或可變域不為免疫球蛋白單可變域結合抗原所需(亦即，其中免疫球蛋白單可變域獨立於其他可變域而結合抗原)。當用於本文時，術語「結構域抗體」或「dAb」與能夠結合抗原之「免疫球蛋白單可變域」相同。免疫球蛋白單可變域可為人類抗體可變域，但亦包括其他物種之抗體單可變域，諸如齧齒動物(例如，如WO 00/29004中所揭示)、護士鯊(nurse shark)及駱駝科(*Camelid*) V_{HH} dAb(奈米抗體(nanobody))。駱駝科 V_{HH} 為來源於包括駱駝、美洲駝、羊駝、單峰駝及原駝之物種之免疫球蛋白單可變域多肽，該等物種產生天然缺乏輕鏈之重鏈抗體。可根據此項技術中可用之標準技術使此等 V_{HH} 域人類化，且此等結構域仍然視為本發明之「結構域抗體」。如本文所用，「 V_H 」包括駱駝科 V_{HH} 域。於軟骨魚(包括護士鯊)中鑑別之NARV為另一類型之免疫球蛋白單可變域。此等結構域亦稱為新穎抗原受體可變區(通常縮寫成V(NAR)或NARV)。對於其他詳情，參見Mol. Immunol. **44**, 656-665 (2006)及US 20050043519A。

術語「抗原決定基結合域」係指獨立於不同V區或域而特異性結合抗原或抗原決定基的結構域，其可為結構域抗

體(dAb)，例如人類、駱駝科或鯊免疫球蛋白單可變域，或其可為來源於非免疫球蛋白骨架之結構域，例如選自由以下組成之群的非免疫球蛋白骨架：CTLA-4(伊維體(Evibody))；脂質運載蛋白；蛋白質A衍生分子，諸如蛋白質A之Z結構域(親和抗體(Affibody)，SpA)、A結構域(高親和性多聚體/最大抗體(Avimer/Maxibody))；熱休克蛋白，諸如GroEl及GroES；轉鐵蛋白(運載體(trans-body))；錨蛋白重複蛋白質(DARPin)；肽適體(peptide aptamer)；C型凝集素結構域(四連接素(Tetranectin))；人類 γ -晶狀體球蛋白及人類泛素(親和素(affilins))；PDZ結構域；蠍毒素；人類蛋白酶抑制劑之庫尼茲型結構域(kunitz type domain)；及纖維結合蛋白(黏結素(adnectin))；已對其進行蛋白質工程改造，以達成結合至除天然配位體之外的配位體。

CTLA-4(細胞毒性T淋巴細胞相關抗原4)為主要在CD4⁺T細胞上表現之CD28家族受體。其細胞外域具有類似可變域的Ig摺疊。對應於抗體CDR之環可經異源序列取代，以賦予不同結合特性。經工程改造而具有不同結合特異性之CTLA-4分子亦稱為伊維體(Evibody)。對於其他詳情，參見 *Journal of Immunological Methods* **248** (1-2), 31-45 (2001)。

脂質運載蛋白為轉運疏水性小分子(諸如類固醇、後膽色素(bilin)、類視黃素及脂質)之細胞外蛋白質家族。其具有剛性 β 摺疊二級結構(在錐形結構之開口端具有多個環)，該等環可經工程改造以結合不同靶抗原。抗運載蛋白

(Anticalin)之尺寸介於160-180個胺基酸之間，且來源於脂質運載蛋白。對於其他詳情，參見Biochim Biophys Acta 1482: 337-350 (2000)、US 7250297B1及US 20070224633。

親和抗體為來源於金黃色葡萄球菌 (*Staphylococcus aureus*)之蛋白質A的骨架，其可經工程改造以結合至抗原。該結構域由約58個胺基酸之三螺旋束組成。文庫已經由表面殘基之隨機化產生。對於其他詳情，參見Protein Eng. Des. Sel. 17, 455-462 (2004)及EP 1641818A1。

高親和性多聚體為來源於A結構域骨架家族之多結構域蛋白質。約35個胺基酸之天然結構域採用確定之二硫鍵鍵結結構。藉由改組(shuffling)A結構域家族所展現之天然變化來產生多樣性。對於其他詳情，參見Nature Biotechnology 23(12), 1556-1561 (2005)及Expert Opinion on Investigational Drugs 16(6), 909-917(2007年6月)。

轉鐵蛋白為單體血清轉運醣蛋白。轉鐵蛋白可藉由在容許之表面環中插入肽序列而加以工程改造以結合不同靶抗原。經工程改造之轉鐵蛋白骨架的實例包括運載體(Trans-body)。對於其他詳情，參見J. Biol. Chem 274, 24066-24073 (1999)。

所設計之錨蛋白重複蛋白(DARPin)來源於錨蛋白，錨蛋白為介導整合膜蛋白(integral membrane protein)與細胞骨架(cytoskeleton)連接之蛋白質家族。單個錨蛋白重複為由兩個 α 螺旋及一個 β 轉角(turn)組成之33個殘基基元。其可藉由隨機化各重複之第一 α 螺旋及 β 轉角中之殘基而加以工

程改造以結合不同靶抗原。其結合界面可藉由增加模組數而增加(一種親和力成熟法)。對於其他詳情，參見J. Mol. Biol. 332, 489-503 (2003)；PNAS 100(4), 1700-1705 (2003)及J. Mol. Biol. 369, 1015-1028 (2007)及US 20040132028A1。

纖維結合蛋白為可經工程改造以結合至抗原之骨架。黏結素(Adnectin)由第III型人類纖維結合蛋白(FN3)之15個重複單元之第10結構域之天然胺基酸序列主鏈組成。位於 β 夾層之一端之三個環可經工程改造以使黏結素(Adnectin)能夠特異性識別相關治療標靶。對於其他詳情，參見Protein Eng. Des. Sel. 18, 435-444 (2005)、US 20080139791、WO 2005056764及US 6818418B1。

肽適體為由恆定骨架蛋白質組成之組合識別分子，該恆定骨架蛋白通常為含有在活性位點處插入之限制性可變肽環的硫氧還蛋白(thioredoxin, TrxA)。對於其他詳情，參見Expert Opin. Biol. Ther. 5, 783-797 (2005)。

微體(Microbody)來源於長度為25-50個胺基酸之含有3-4個半胱胺酸橋(cysteine bridge)之天然存在微蛋白，微蛋白之實例包括KalataB1及芋螺毒素(conotoxin)及打結素(knottin)。微蛋白的環可經工程改造以包括多達25個胺基酸而不影響微蛋白之整體摺疊。對於工程改造之打結素結構域之其他詳情，參見WO 2008098796。

其他抗原決定基結合域包括已作為骨架用於工程改造不同靶抗原結合性質的蛋白質，包括人類 γ -晶狀體球蛋白及

人類泛素(親和素(affilins))、人類蛋白酶抑制劑之庫尼茲(kunitz)型結構域、Ras結合蛋白AF-6之PDZ結構域、蠍毒素(卡律蠍毒素(charybdotoxin))、C型凝集素結構域(四連接素)，該等其他抗原決定基結合域評述於Handbook of Therapeutic Antibodies之第7章 Non-Antibody Scaffolds (2007, Stefan Dubel編)及Protein Science 15:14-27 (2006)中。本發明之抗原決定基結合域可來源於任一此等替代蛋白質結構域。

如本文所用，術語「抗原結合位點」係指蛋白質上能夠特異性結合至抗原之位點，其可為單域，例如抗原決定基結合域，或其可為如標準抗體上可見之成對 V_H/V_L 域。在本發明之一些態樣中，單鏈Fv(ScFv)域可提供抗原結合位點。

本文中使用的術語「mAbdAb」及「dAbmAb」係指本發明之抗原結合蛋白。兩個術語可互換使用且當用於本文中時意欲具有相同含義。

如本文所用之術語「抗原結合蛋白」係指抗體、抗體片段(例如結構域抗體(dAb)、ScFv、FAb、FAb₂)及其他能夠結合至IL-13之蛋白質構築體。抗原結合分子可包含至少一個Ig可變域，例如抗體、結構域抗體、Fab、Fab'、F(ab')₂、Fv、ScFv、雙功能抗體、mAbdAb、親和抗體、異源結合抗體或雙特異性抗體。在一實施例中，抗原結合分子為抗體。在另一實施例中，抗原結合分子為dAb，亦即免疫球蛋白單可變域，諸如 V_H 、 V_{HH} 或 V_L ，其獨立於不

同V區或域而特異性結合抗原或抗原決定基。抗原結合分子能夠結合至兩個標靶，亦即其可為雙靶向蛋白質(dual targeting protein)。抗原結合分子可為抗體與抗原結合片段之組合，諸如一或多種結構域抗體及/或一或多種連至單株抗體之ScFv。抗原結合分子亦可包含非Ig結構域，例如來源於選自由以下組成之群之骨架的結構域：CTLA-4(伊維體(Evibody)))；脂質運載蛋白；蛋白質A衍生分子，諸如蛋白質A之Z結構域(親和抗體，SpA)、A結構域(高親和性多聚體/最大抗體)；熱休克蛋白，諸如GroEl及GroES；轉鐵蛋白(運載體)；錨蛋白重複蛋白(DARPin)；肽適體；C型凝集素結構域(四連接素)；人類 γ -晶狀體球蛋白及人類泛素(親和素)；PDZ結構域；蠍毒素；人類蛋白酶抑制劑之庫尼茲型結構域；及纖維結合蛋白(黏結素)；已對其進行蛋白質工程改造以達成結合至IL-13。如本文中所用，「抗原結合蛋白」能夠拮抗及/或中和人類IL-13。另外，抗原結合蛋白可藉由結合至IL-13及防止天然配位體結合及/或活化受體來阻斷IL-13活性。

如本文所用，「IL-13拮抗劑」包括任何能夠降低及或消除IL-13之至少一種活性的化合物。舉例而言，IL-13拮抗劑可結合至IL-13且彼結合可直接降低或消除IL-13活性，或該IL-13拮抗劑可藉由阻斷至少一種配位體結合受體而間接發揮作用。

如本文所用，「IL-4拮抗劑」包括任何能夠降低及或消除IL-4之至少一種活性的化合物。舉例而言，IL-4拮抗劑

可結合至IL-4且彼結合可直接降低或消除IL-4活性，或該IL-4拮抗劑可藉由阻斷至少一種配位體結合受體而間接發揮作用。

如本文所用，「IL-5拮抗劑」包括任何能夠降低及或消除IL-5之至少一種活性的化合物。在一實例中，IL-5拮抗劑可結合至IL-5且彼結合可直接降低或消除IL-5活性，或該IL-5拮抗劑可藉由阻斷至少一種配位體結合受體而間接發揮作用。

【實施方式】

在一實施例中，本發明之抗原結合蛋白包含重鏈可變區，該重鏈可變區含有選自由以下組成之清單的CDRH3：SEQ ID NO: 4、SEQ ID NO: 5、SEQ ID NO: 6、SEQ ID NO: 7、SEQ ID NO: 8及SEQ ID NO: 9、SEQ ID NO: 10、SEQ ID NO: 11、SEQ ID NO: 12、SEQ ID NO: 13、SEQ ID NO: 14及SEQ ID NO: 15、SEQ ID NO: 16、SEQ ID NO: 17及SEQ ID NO: 18，及適合CDRH1及CDRH2；以及與之成對的輕鏈可變區，該輕鏈可變區含有適合CDRL1、CDRL2及CDRL3，以形成結合至人類IL-13之抗原結合Fv單元。在一實施例中，本發明之抗原結合蛋白中和人類IL-13之活性。

在此實施例之一態樣中，如SEQ ID NO: 1或SEQ ID NO: 60或SEQ ID NO: 61中所示之CDRH1及如SEQ ID NO: 2中所示之CDRH2亦存在於重鏈可變區中。在此實施例之另一態樣中，如SEQ ID NO: 19中所示之CDRH1及如SEQ ID

NO: 20 中所示之 CDRL2 及如 SEQ ID NO: 21 中所示之 CDRL3 亦存在於輕鏈可變區中。

在另一態樣中，如經由 Biacore 所量測，抗原結合蛋白結合至人類 IL-13 的高親和力為 10 nM 或 10 nM 以下，且更特定而言，2 nM 或 2 nM 以下(例如介於約 0.8 nM 與 2 nM 之間)、1 nM 或 1 nM 以下、或 100 pM 或 100 pM 以下(例如介於約 20 pM 與約 100 pM 之間，或介於約 20 pM 與約 80 pM 之間，或介於約 20 pM 與約 60 pM 之間)。在一此實施例中，此係利用捕捉於生物感測器晶片上之抗原結合蛋白、經由 Biacore 來量測，例如實例 3 中所述。

本發明之重鏈可變區可連同允許結合至人類 IL-13 的輕鏈可變區一起形成習知免疫球蛋白樣式(例如人類 IgG、IgA、IgM 等)或形成結合至人類 IL-13 之任何其他「抗體樣」形式(例如單鏈 Fv、雙功能抗體、TandabsTM 等(對於替代「抗體」形式之概述，參見 Holliger 及 Hudson, Nature Biotechnology, 2005, 第 23 卷, 第 9 期, 1126-1136))。

本發明之抗原結合蛋白來源於具有如 SEQ ID NO: 58 及 SEQ ID NO: 59 中所述之可變區的鼠類抗體或其非鼠類等效物，諸如其大鼠、人類、嵌合或人類化變體，舉例而言，其來源於具有如 SEQ ID NO: 22 及 SEQ ID NO: 24 中所述之重鏈及輕鏈的人類化抗體。

在本發明之一態樣中，提供抗原結合蛋白，例如結合人類 IL-13 且包含 CDRH3 SIYDDYHYDDYYAMDY(SEQ ID NO: 3)之變體的抗體，其中 CDRH3 在一或多個下列位置

(使用 Kabat 編號)處經下文所示之替代胺基酸取代：

- a) 位置 1 中之 S95 取代為色胺酸 (W)
- b) 位置 2 中之 I96 取代為纈胺酸 (V)
- c) 位置 3 中之 Y97 取代為苯丙胺酸 (F)
- d) 位置 4 中之 D98 取代為麩醯胺酸 (E)
- e) 位置 7 中之 H100A 取代為丙胺酸 (A)，麩胺酸 (E)、麩醯胺酸 (Q)、精胺酸 (R)、絲胺酸 (S)、蘇胺酸 (T) 或纈胺酸 (V)，及
- f) 位置 8 中之 Y100B 取代為丙胺酸 (A)、異白胺酸 (I)、色胺酸 (W) 或纈胺酸 (V)。

在本發明之另一態樣中，提供抗原結合蛋白，例如結合人類 IL-13 且包含 SEQ ID NO: 3 中所示之 CDRH3 的抗體，其中 CDRH3 包含一或多個下列取代：S95W、I96V、Y97F、D98E、H100A_A、H100A_E、H100A_Q、H100A_R、H100A_S、H100A_T、H100A_V、Y100B_A、Y100B_I、Y100B_W 及 Y100B_V。

在一態樣中，本發明之抗原結合蛋白(例如本發明之抗體)包含的 CDRH3 序列選自以下所示的 CDRH3 序列：SEQ ID NO: 4、SEQ ID NO: 5、SEQ ID NO: 6、SEQ ID NO: 7、SEQ ID NO: 8 及 SEQ ID NO: 9、SEQ ID NO: 10、SEQ ID NO: 11、SEQ ID NO: 12、SEQ ID NO: 13、SEQ ID NO: 14 及 SEQ ID NO: 15、SEQ ID NO: 16、SEQ ID NO: 17 及 SEQ ID NO: 18。此等抗原結合蛋白可進一步包含下列 CDR 序列：

CDRH1：選自 SEQ ID NO: 1、60及61；

CDRH2：SEQ ID NO: 2；

CDRL1：SEQ ID NO: 19；

CDRL2：SEQ ID NO: 20；及

CDRL3：SEQ ID NO: 21。

在一實施例中，抗原結合蛋白包含下列CDR：

CDRH1：SEQ ID NO: 1；

CDRH2：SEQ ID NO: 2；

CDRH3：SEQ ID NO: 18；

CDRL1：SEQ ID NO: 19；

CDRL2：SEQ ID NO: 20；及

CDRL3：SEQ ID NO: 21。

在另一實施例中，抗原結合蛋白包含下列CDR：

CDRH1：SEQ ID NO: 1；

CDRH2：SEQ ID NO: 2；

CDRH3：SEQ ID NO: 17；

CDRL1：SEQ ID NO: 19；

CDRL2：SEQ ID NO: 20；及

CDRL3：SEQ ID NO: 21。

在另一實施例中，抗原結合蛋白包含下列CDR：

CDRH1：SEQ ID NO: 1；

CDRH2：SEQ ID NO: 2；

CDRH3：SEQ ID NO: 16；

CDRL1：SEQ ID NO: 19；

CDRL2 : SEQ ID NO: 20 ; 及

CDRL3 : SEQ ID NO: 21 。

在另一實施例中，抗原結合蛋白包含下列CDR：

CDRH1 : SEQ ID NO: 1 ;

CDRH2 : SEQ ID NO: 2 ;

CDRH3 : SEQ ID NO: 15 ;

CDRL1 : SEQ ID NO: 19 ;

CDRL2 : SEQ ID NO: 20 ; 及

CDRL3 : SEQ ID NO: 21 。

在整篇本說明書中，抗體序列中之胺基酸殘基皆根據Kabat方案編號。類似地，除非另有指示(例如如SEQ ID NO: 60及61中所示之CDRH3)，否則術語「CDR」、「CDRL1」、「CDRL2」、「CDRL3」、「CDRH1」、「CDRH2」、「CDRH3」皆遵循如Kabat等人；「*Sequences of proteins of Immunological Interest*」NIH, 1987中所述之Kabat編號系統。

在本發明之另一態樣中，提供抗原結合蛋白，諸如人類化抗體或其抗原結合片段，其包含具有選自以下之序列之重鏈：SEQ ID NO: 26、SEQ ID NO: 28、SEQ ID NO: 30、SEQ ID NO: 32、SEQ ID NO: 34、SEQ ID NO: 36、SEQ ID NO: 38、SEQ ID NO: 40、SEQ ID NO: 42、SEQ ID NO: 44、SEQ ID NO: 46、SEQ ID NO: 48、SEQ ID NO: 50、SEQ ID NO: 52、SEQ ID NO: 54、SEQ ID NO: 88、SEQ ID NO: 89、SEQ ID NO: 90及SEQ ID NO: 91；

及 SEQ ID NO: 24 之輕鏈。

本發明提供一種抗原結合蛋白，諸如人類化抗體或其抗原結合片段，其包含選自以下之重鏈：SEQ ID NO: 26、SEQ ID NO: 28、SEQ ID NO: 30、SEQ ID NO: 32、SEQ ID NO: 34、SEQ ID NO: 36、SEQ ID NO: 38、SEQ ID NO: 40、SEQ ID NO: 42、SEQ ID NO: 44、SEQ ID NO: 46、SEQ ID NO: 48、SEQ ID NO: 50、SEQ ID NO: 52、SEQ ID NO: 54、SEQ ID NO: 88、SEQ ID NO: 89、SEQ ID NO: 90。

本發明亦提供一種抗原結合蛋白，諸如人類化抗體或其抗原結合片段，其包含選自以下之輕鏈：SEQ ID NO: 108、SEQ ID NO: 110、SEQ ID NO: 112 及 SEQ ID NO: 114。

本發明進一步提供一種抗原結合蛋白，諸如人類化抗體或其抗原結合片段，其包含具有選自以下之序列之重鏈：SEQ ID NO: 26、SEQ ID NO: 28、SEQ ID NO: 30、SEQ ID NO: 32、SEQ ID NO: 34、SEQ ID NO: 36、SEQ ID NO: 38、SEQ ID NO: 40、SEQ ID NO: 42、SEQ ID NO: 44、SEQ ID NO: 46、SEQ ID NO: 48、SEQ ID NO: 50、SEQ ID NO: 52、SEQ ID NO: 54、SEQ ID NO: 88、SEQ ID NO: 89、SEQ ID NO: 90 及 SEQ ID NO: 91；及 SEQ ID NO: 108、SEQ ID NO: 110、SEQ ID NO: 112 及 SEQ ID NO: 114 之輕鏈。

在一實施例中，本發明之抗原結合蛋白包含一種抗體，

該抗體包含選自以下之重鏈：SEQ ID NO: 26、SEQ ID NO: 28、SEQ ID NO: 30、SEQ ID NO: 32、SEQ ID NO: 34、SEQ ID NO: 36、SEQ ID NO: 38、SEQ ID NO: 40、SEQ ID NO: 42、SEQ ID NO: 44、SEQ ID NO: 46、SEQ ID NO: 48、SEQ ID NO: 50、SEQ ID NO: 52、SEQ ID NO: 54、SEQ ID NO: 88、SEQ ID NO: 89、SEQ ID NO: 90及SEQ ID NO: 91；及選自SEQ ID NO: 24、SEQ ID NO: 108、SEQ ID NO: 110、SEQ ID NO: 112及SEQ ID NO: 114之輕鏈。

在一實施例中，本發明之抗原結合蛋白包含重鏈及輕鏈，該重鏈選自SEQ ID NO: 48、SEQ ID NO: 50、SEQ ID NO: 52及SEQ ID NO: 54且該輕鏈選自SEQ ID NO: 24、SEQ ID NO: 108、SEQ ID NO: 110、SEQ ID NO: 112及SEQ ID NO: 114，舉例而言，該抗原結合蛋白包含：SEQ ID NO: 48之重鏈及SEQ ID NO: 24之輕鏈，或SEQ ID NO: 50之重鏈及SEQ ID NO: 24之輕鏈，或SEQ ID NO: 52之重鏈及SEQ ID NO: 24之輕鏈，或SEQ ID NO: 54之重鏈及SEQ ID NO: 24之輕鏈，或SEQ ID NO: 88之重鏈及SEQ ID NO: 24之輕鏈，或SEQ ID NO: 89之重鏈及SEQ ID NO: 24之輕鏈，或SEQ ID NO: 90之重鏈及SEQ ID NO: 24之輕鏈，或SEQ ID NO: 91之重鏈及SEQ ID NO: 24之輕鏈，或SEQ ID NO: 48之重鏈及SEQ ID NO: 108之輕鏈，或SEQ ID NO: 50之重鏈及SEQ ID NO: 108之輕鏈，或SEQ ID NO: 52之重鏈及SEQ ID NO: 108之輕鏈，或SEQ ID NO: 54之

重鏈及SEQ ID NO: 108之輕鏈，或SEQ ID NO: 88之重鏈及SEQ ID NO: 108之輕鏈，或SEQ ID NO: 89之重鏈及SEQ ID NO: 108之輕鏈，或SEQ ID NO: 90之重鏈及SEQ ID NO: 108之輕鏈，或SEQ ID NO: 91之重鏈及SEQ ID NO: 108之輕鏈，或SEQ ID NO: 48之重鏈及SEQ ID NO: 110之輕鏈，或SEQ ID NO: 50之重鏈及SEQ ID NO: 110之輕鏈，或SEQ ID NO: 52之重鏈及SEQ ID NO: 110之輕鏈，或SEQ ID NO: 54之重鏈及SEQ ID NO: 110之輕鏈，或SEQ ID NO: 88之重鏈及SEQ ID NO: 110之輕鏈，或SEQ ID NO: 89之重鏈及SEQ ID NO: 110之輕鏈，或SEQ ID NO: 90之重鏈及SEQ ID NO: 110之輕鏈，或SEQ ID NO: 91之重鏈及SEQ ID NO: 110之輕鏈。

在一此實施例中，本發明之抗原結合蛋白包含選自SEQ ID NO: 48、SEQ ID NO: 50、SEQ ID NO: 52及SEQ ID NO: 54之重鏈及選自SEQ ID NO: 108及SEQ ID NO: 110之輕鏈，舉例而言，該抗原結合蛋白包含SEQ ID NO: 48之重鏈及SEQ ID NO: 108之輕鏈，或該抗原結合蛋白包含SEQ ID NO: 48之重鏈及SEQ ID NO: 110之輕鏈，或該抗原結合蛋白包含SEQ ID NO: 50之重鏈及SEQ ID NO: 108之輕鏈，或該抗原結合蛋白包含SEQ ID NO: 50之重鏈及SEQ ID NO: 110之輕鏈，或該抗原結合蛋白包含SEQ ID NO: 52之重鏈及SEQ ID NO: 108之輕鏈，或該抗原結合蛋白包含SEQ ID NO: 52之重鏈及SEQ ID NO: 110之輕鏈，或該抗原結合蛋白包含SEQ ID NO: 54之重鏈及SEQ ID

NO: 108之輕鏈，或該抗原結合蛋白包含SEQ ID NO: 50之重鏈及SEQ ID NO: 110之輕鏈。

本發明之IL-13抗體可與IL-4及/或IL-5拮抗劑(例如IL-4抗體或抗原決定基結合域及/或IL-5抗體或抗原決定基結合域)組合。此等分子可作為同時投與之各別分子的混合物而投與，亦即共投與，或彼此在24小時內投與，例如彼此在20小時內，或在15小時內或在12小時內，或在10小時內，或在8小時內，或在6小時內，或在4小時內，或在2小時內，或在1小時內，或在30分鐘內投與。

在另一實施例中，拮抗劑作為一種能夠結合至兩種或兩種以上抗原之分子而存在，舉例而言，本發明提供一種包含本發明之IL-13抗體的抗原結合蛋白，該IL-13抗體能夠結合至IL-13且其亦能夠結合至IL-4或其亦能夠結合至IL-5，或其亦能夠結合至IL-4及IL-5。

在一實施例中，本發明之抗原結合蛋白可為多特異性抗體，其至少包含CDRH3，且視情況包含本發明之CDRH1、CDRH2、CDRL1、CDRL2及CDRL3中之一或多者，其能夠結合至IL-13且其亦能夠結合至一或多種IL-4或IL-5。在一此實施例中，提供包含CDRH3的多特異性抗體，或包含能夠結合至IL-4或IL-5之另一抗原結合位點的如本文定義之抗原結合蛋白。

本發明抗原結合蛋白之一實例為連至一或多個抗原決定基結合域的抗體，該抗體對IL-13具有特異性且包含如本文定義之CDRH1、CDRH2、CDRH3、CDRL1、CDRL2及

CDRL3，該等抗原決定基結合域對IL-4或IL-5具有特異性，例如能夠結合至IL-13及IL-4、或IL-13及IL-5之雙特異性抗原結合蛋白，或能夠結合至IL-13、IL-4及IL-5之三特異性抗原結合蛋白。

應瞭解，本文所述之任一種抗原結合蛋白能夠同時結合兩種或兩種以上抗原，例如使用適合分析法(諸如描述於實例8中者)、經由化學計量分析所測定。

本發明提供一種包含連至一或多個抗原決定基結合域之本發明IL-13抗體的抗原結合蛋白，例如包含連至能夠結合至IL-4之抗原決定基結合域之本發明IL-13抗體的抗原結合蛋白；或包含連至能夠結合至IL-5之抗原決定基結合域之本發明IL-13抗體的抗原結合蛋白；或包含連至能夠結合至IL-4之第一抗原決定基結合域及能夠結合至IL-5之第二抗原決定基結合域之本發明IL-13抗體的抗原結合蛋白。

抗原決定基結合域可連接至IL-13抗體重鏈之c末端或n末端或IL-13抗體輕鏈之c末端或n末端。

適合連接子之實例包括長度可為以下的胺基酸序列：1個胺基酸至150個胺基酸，或1個胺基酸至140個胺基酸，例如1個胺基酸至130個胺基酸，或1至120個胺基酸，或1至80個胺基酸，或1至50個胺基酸，或1至20個胺基酸，或1至10個胺基酸，或5至18個胺基酸。此等序列可具有其自身三級結構，例如本發明之連接子可包含單可變域。一實施例中之連接子尺寸相當於單可變域。適合連接子尺寸可

為1至20埃(angstrom)，例如小於15埃，或小於10埃，或小於5埃。

在本發明之一實施例中，至少一個抗原決定基結合域經連接子直接連接至IL-13抗體，該連接子包含1至150個胺基酸，例如1至20個胺基酸，例如1至10個胺基酸。

此等連接子或此等連接子中之多者可選自SEQ ID NO: 82-87、92至93中所示任一者。

適用於本發明之抗原結合蛋白中之連接子可僅包含或除其他連接子外亦包含一或多組GS殘基，例如「GSTVAAPS」(SEQ ID NO: 92)或「TVAAPSGS」(SEQ ID NO: 87)或「GSTVAAPSGS」(SEQ ID NO: 93)。在一實施例中，連接子包含SEQ ID NO: 83。

在一實施例中，抗原決定基結合域經由連接子「(PAS)_n(GS)_m」連接至IL-13抗體。在另一實施例中，抗原決定基結合域經由連接子「(GGGGS)_n(GS)_m」連接至IL-13抗體。在另一實施例中，抗原決定基結合域經由連接子「(TVAAPS)_n(GS)_m」連接至IL-13抗體。在另一實施例中，抗原決定基結合域經由連接子「(GS)_m(TVAAPSGS)_n」連接至IL-13抗體。在另一實施例中，抗原決定基結合域經由連接子「(PAVPPP)_n(GS)_m」連接至IL-13抗體。在另一實施例中，抗原決定基結合域經由連接子「(TVSDVP)_n(GS)_m」連接至IL-13抗體。在另一實施例中，抗原決定基結合域經由連接子「(TGLDSP)_n(GS)_m」連接至IL-13抗體。在所有此等實施

例中， $n=1-10$ ，且 $m=0-4$ 。

此等連接子之實例包括 $(PAS)_n(GS)_m$ ，其中 $n=1$ 且 $m=1$ ； $(PAS)_n(GS)_m$ ，其中 $n=2$ 且 $m=1$ ； $(PAS)_n(GS)_m$ ，其中 $n=3$ 且 $m=1$ ； $(PAS)_n(GS)_m$ ，其中 $n=4$ 且 $m=1$ ； $(PAS)_n(GS)_m$ ，其中 $n=2$ 且 $m=0$ ； $(PAS)_n(GS)_m$ ，其中 $n=3$ 且 $m=0$ ； $(PAS)_n(GS)_m$ ，其中 $n=4$ 且 $m=0$ 。

此等連接子之實例包括 $(GGGGS)_n(GS)_m$ ，其中 $n=1$ 且 $m=1$ ； $(GGGGS)_n(GS)_m$ ，其中 $n=2$ 且 $m=1$ ； $(GGGGS)_n(GS)_m$ ，其中 $n=3$ 且 $m=1$ ； $(GGGGS)_n(GS)_m$ ，其中 $n=4$ 且 $m=1$ ； $(GGGGS)_n(GS)_m$ ，其中 $n=2$ 且 $m=0$ ； $(GGGGS)_n(GS)_m$ ，其中 $n=3$ 且 $m=0$ ； $(GGGGS)_n(GS)_m$ ，其中 $n=4$ 且 $m=0$ 。

此等連接子之實例包括 $(TVAAPS)_n(GS)_m$ ，其中 $n=1$ 且 $m=1$ (SEQ ID NO: 87)； $(TVAAPS)_n(GS)_m$ ，其中 $n=2$ 且 $m=1$ (SEQ ID NO: 145)； $(TVAAPS)_n(GS)_m$ ，其中 $n=3$ 且 $m=1$ (SEQ ID NO: 146)； $(TVAAPS)_n(GS)_m$ ，其中 $n=4$ 且 $m=1$ ； $(TVAAPS)_n(GS)_m$ ，其中 $n=2$ 且 $m=0$ ； $(TVAAPS)_n(GS)_m$ ，其中 $n=3$ 且 $m=0$ ； $(TVAAPS)_n(GS)_m$ ，其中 $n=4$ 且 $m=0$ 。

此等連接子之實例包括 $(GS)_m(TVAAPSGS)_n$ ，其中 $n=1$ 且 $m=1$ (SEQ ID NO:139)； $(GS)_m(TVAAPSGS)_n$ ，其中 $n=2$ 且 $m=1$ (SEQ ID NO:140)； $(GS)_m(TVAAPSGS)_n$ ，其中 $n=3$ 且 $m=1$ (SEQ ID NO:141)；或 $(GS)_m(TVAAPSGS)_n$ ，其中 $n=4$ 且 $m=1$ (SEQ ID NO:142)； $(GS)_m(TVAAPSGS)_n$ ，其中 $n=5$ 且 $m=1$ (SEQ ID NO:143)； $(GS)_m(TVAAPSGS)_n$ ，其中 $n=6$ 且 $m=1$ (SEQ ID NO:144)； $(GS)_m(TVAAPSGS)_n$ ，其中 $n=1$ 且

$m=0$ (SEQ ID NO:87) ; $(GS)_m(TVAAPSGS)_n$, 其中 $n=2$ 且 $m=10$; $(GS)_m(TVAAPSGS)_n$, 其中 $n=3$ 且 $m=0$; 或 $(GS)_m(TVAAPSGS)_n$, 其中 $n=0$ 。

此等連接子之實例包括 $(PAVPPP)_n(GS)_m$, 其中 $n=1$ 且 $m=1$; $(PAVPPP)_n(GS)_m$, 其中 $n=2$ 且 $m=1$ (SEQ ID NO: 65) ; $(PAVPPP)_n(GS)_m$, 其中 $n=3$ 且 $m=1$; $(PAVPPP)_n(GS)_m$, 其中 $n=4$ 且 $m=1$; $(PAVPPP)_n(GS)_m$, 其中 $n=2$ 且 $m=0$; $(PAVPPP)_n(GS)_m$, 其中 $n=3$ 且 $m=0$; $(PAVPPP)_n(GS)_m$, 其中 $n=4$ 且 $m=0$ 。

此等連接子之實例包括 $(TVSDVP)_n(GS)_m$, 其中 $n=1$ 且 $m=1$ (SEQ ID NO: 67) ; $(TVSDVP)_n(GS)_m$, 其中 $n=2$ 且 $m=1$; $(TVSDVP)_n(GS)_m$, 其中 $n=3$ 且 $m=1$; $(TVSDVP)_n(GS)_m$, 其中 $n=4$ 且 $m=1$; $(TVSDVP)_n(GS)_m$, 其中 $n=2$ 且 $m=0$; $(TVSDVP)_n(GS)_m$, 其中 $n=3$ 且 $m=0$; $(TVSDVP)_n(GS)_m$, 其中 $n=4$ 且 $m=0$ 。

此等連接子之實例包括 $(TGLDSP)_n(GS)_m$, 其中 $n=1$ 且 $m=1$; $(TGLDSP)_n(GS)_m$, 其中 $n=2$ 且 $m=1$; $(TGLDSP)_n(GS)_m$, 其中 $n=3$ 且 $m=1$; $(TGLDSP)_n(GS)_m$, 其中 $n=4$ 且 $m=1$; $(TGLDSP)_n(GS)_m$, 其中 $n=2$ 且 $m=0$; $(TGLDSP)_n(GS)_m$, 其中 $n=3$ 且 $m=0$; $(TGLDSP)_n(GS)_m$, 其中 $n=4$ 且 $m=0$ 。

在另一實施例中，抗原決定基結合域與IL-13抗體之間無連接子。在另一實施例中，抗原決定基結合域經由連接子「TVAAPS」(SEQ ID NO: 83)連接至IL-13抗體。在另一實施例中，抗原決定基結合域經由連接子「TVAAPSGS」

(SEQ ID NO: 87)連接至IL-13抗體。在另一實施例中，抗原決定基結合域經由連接子「GS」連接至IL-13抗體。在另一實施例中，抗原決定基結合域經由連接子「ASTKGPT」(SEQ ID NO: 84)連接至IL-13抗體。

適用於本發明中之抗原決定基結合域為獨立於不同V區或域而特異性結合抗原或抗原決定基的結構域，其可為結構域抗體或可為非免疫球蛋白結構域，例如來源於選自由以下組成之群之骨架的結構域：CTLA-4(伊維體(Evibody))；脂質運載蛋白；蛋白質A衍生分子，諸如蛋白質A之Z結構域(親和抗體，SpA)、A結構域(高親和性多聚體/最大抗體)；熱休克蛋白，諸如GroEl及GroES；轉鐵蛋白(運載體)；錨蛋白重複蛋白(DARPin)；肽適體；C型凝集素結構域(四連接素)；人類 γ -晶狀體球蛋白及人類泛素(親和素)；PDZ結構域；蠍毒素；人類蛋白酶抑制劑之庫尼茲型結構域；及纖維結合蛋白(黏結素)；已對其進行蛋白質工程改造以達成結合至除天然配位體之外的配位體。在一實施例中，其可為結構域抗體或其他適合結構域，諸如選自由以下組成之群的結構域：CTLA-4、脂質運載蛋白、SpA、親和抗體、高親和性多聚體、GroEl、轉鐵蛋白、GroES及纖維結合蛋白。在一實施例中，其可選自免疫球蛋白單可變域、親和抗體、錨蛋白重複蛋白(DARPin)及黏結素。在另一實施例中，其可選自親和抗體、錨蛋白重複蛋白(DARPin)及黏結素。在另一實施例中，其可為結構域抗體，例如選自人類、駱駝科(奈米抗體)、或鯊

(NARV)結構域抗體之結構域抗體。

此等抗原結合蛋白之實例包括具有作為IL-4拮抗劑之抗原決定基結合域的本發明IL-13抗體，該抗原決定基結合域連接至重鏈之c末端或n末端，或c末端。實例包括一種抗原結合蛋白，其包含以下所示之重鏈序列：SEQ ID NO: 26、SEQ ID NO: 28、SEQ ID NO: 30、SEQ ID NO: 32、SEQ ID NO: 34、SEQ ID NO: 36、SEQ ID NO: 38、SEQ ID NO: 40、SEQ ID NO: 42、SEQ ID NO: 44、SEQ ID NO: 46、SEQ ID NO: 48、SEQ ID NO: 50、SEQ ID NO: 52、SEQ ID NO: 54、SEQ ID NO: 98、SEQ ID NO: 100、SEQ ID NO: 102、SEQ ID NO: 104、SEQ ID NO: 106或SEQ ID NO: 117-138；及SEQ ID NO: 24、SEQ ID NO: 108、SEQ ID NO: 110、SEQ ID NO: 112或SEQ ID NO: 114中所示之輕鏈序列，其中重鏈及輕鏈之一或兩者進一步包含一或多個能夠拮抗IL-4之抗原決定基結合域，例如能夠結合至IL-4之單可變域。此等抗原決定基結合域可選自SEQ ID NO: 78-81及94中所示者。

在一實施例中，本發明之抗原結合構築體包含：SEQ ID NO: 62之重鏈序列及SEQ ID NO: 24之輕鏈序列，或SEQ ID NO: 64之重鏈序列及SEQ ID NO: 24之輕鏈序列，或SEQ ID NO: 66之重鏈序列及SEQ ID NO: 24之輕鏈序列，或SEQ ID NO: 68之重鏈序列及SEQ ID NO: 24之輕鏈序列，或SEQ ID NO: 70之重鏈序列及SEQ ID NO: 24之輕鏈序列，或SEQ ID NO: 72之重鏈序列及SEQ ID NO: 24之輕

鏈序列，或SEQ ID NO: 74之重鏈序列及SEQ ID NO: 24之輕鏈序列，或SEQ ID NO: 76之重鏈序列及SEQ ID NO: 24之輕鏈序列。

在一實施例中，本發明之抗原結合構築體包含：SEQ ID NO: 94之重鏈序列及SEQ ID NO: 24之輕鏈序列，或SEQ ID NO: 96之重鏈序列及SEQ ID NO: 24之輕鏈序列，或SEQ ID NO: 98之重鏈序列及SEQ ID NO: 24之輕鏈序列，或SEQ ID NO: 100之重鏈序列及SEQ ID NO: 24之輕鏈序列，或SEQ ID NO: 102之重鏈序列及SEQ ID NO: 24之輕鏈序列，或SEQ ID NO: 104之重鏈序列及SEQ ID NO: 24之輕鏈序列，或SEQ ID NO: 106之重鏈序列及SEQ ID NO: 24之輕鏈序列。

在一實施例中，本發明之抗原結合構築體包含：SEQ ID NO: 62之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 64之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 66之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 68之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 70之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 72之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 74之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 76之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 62之重鏈序列及SEQ ID NO: 110之輕鏈序列，或SEQ ID NO: 64之重鏈序列及SEQ ID NO: 110之輕鏈序列，或SEQ ID NO: 66之重

鏈序列及SEQ ID NO: 110之輕鏈序列，或SEQ ID NO: 68之重鏈序列及SEQ ID NO: 110之輕鏈序列，或SEQ ID NO: 70之重鏈序列及SEQ ID NO: 110之輕鏈序列，或SEQ ID NO: 72之重鏈序列及SEQ ID NO: 110之輕鏈序列，或SEQ ID NO: 74之重鏈序列及SEQ ID NO: 110之輕鏈序列，或SEQ ID NO: 76之重鏈序列及SEQ ID NO: 110之輕鏈序列。

在一實施例中，本發明之抗原結合構築體包含：SEQ ID NO: 96之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 98之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 100之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 102之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 104之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 106之重鏈序列及SEQ ID NO: 108之輕鏈序列，或SEQ ID NO: 96之重鏈序列及SEQ ID NO: 110之輕鏈序列，或SEQ ID NO: 98之重鏈序列及SEQ ID NO: 110之輕鏈序列，或SEQ ID NO: 100之重鏈序列及SEQ ID NO: 110之輕鏈序列，或SEQ ID NO: 102之重鏈序列及SEQ ID NO: 110之輕鏈序列，或SEQ ID NO: 104之重鏈序列及SEQ ID NO: 110之輕鏈序列，或SEQ ID NO: 106之重鏈序列及SEQ ID NO: 110之輕鏈序列。

在一實施例中，IL-13抗體重鏈係選自SEQ ID NO: 48、SEQ ID NO: 50、SEQ ID NO: 52及SEQ ID NO: 54中所示者。在另一實施例中，重鏈係選自SEQ ID NO: 88-91、

SEQ ID NO: 96-106及SEQ ID NO: 117-138中所示者。在此實施例中，重鏈係選自SEQ ID NO: 96、SEQ ID NO: 98、SEQ ID NO: 100、SEQ ID NO: 102、SEQ ID NO: 104及SEQ ID NO: 106。

在一實施例中，抗原結合蛋白將包含連至作為IL-5拮抗劑之抗原決定基結合域的抗IL-13抗體，其中該抗IL-13抗體包含選自SEQ ID NO: 3-18(例如SEQ ID NO: 15-18)中所示者之CDRH3及SEQ ID NO: 24之輕鏈序列。

實例包括一種抗原結合蛋白，其包含SEQ ID NO: 26、28、30、32、34、36、38、40、42、44、46、48、50、52或54中所示之重鏈序列及SEQ ID NO: 24中所示之輕鏈序列，其中重鏈及輕鏈之一或兩者進一步包含一或多個能夠拮抗IL-5之抗原決定基結合域，例如能夠結合至IL-5之免疫球蛋白單可變域。

在另一實施例中，抗原結合蛋白將包含SEQ ID NO: 26、28、30、32、34、36、38、40、42、44、46、48、50、52或54中所示之重鏈序列及SEQ ID NO: 24中所示之輕鏈序列，其中重鏈及輕鏈之一或兩者進一步包含一或多個能夠拮抗IL-4之抗原決定基結合域(例如能夠結合至IL-4之免疫球蛋白單可變域)及一或多個能夠拮抗IL-5之抗原決定基結合域(例如能夠結合至IL-5之免疫球蛋白單可變域)。

在一實施例中，本發明之抗原結合蛋白包含至少一個抗原決定基結合域，其能夠結合人血清白蛋白。

在一實施例中，存在至少3個抗原結合位點，例如存在4或5或6或8或10個抗原結合位點且抗原結合蛋白能夠結合至少3或4或5或6或8或10種抗原，例如其能夠同時結合3或4或5或6或8或10種抗原。

在一實施例中，第一抗原決定基結合域連接至蛋白骨架且第二抗原決定基結合域連接至該第一抗原決定基結合域，舉例而言，當蛋白骨架為IgG骨架時，第一抗原決定基結合域可連接至IgG骨架之重鏈的c末端，且彼抗原決定基結合域可在其c末端連接第二抗原決定基結合域，或舉例而言，第一抗原決定基結合域可連接至IgG骨架之輕鏈的c末端，且彼第一抗原決定基結合域可進一步在其c末端連接至第二抗原決定基結合域，或舉例而言，第一抗原決定基結合域可連接至IgG骨架之輕鏈的n末端，且彼第一抗原決定基結合域可進一步在其n末端連接至第二抗原決定基結合域，或舉例而言，第一抗原決定基結合域可連接至IgG骨架之重鏈的n末端，且彼第一抗原決定基結合域可進一步在其n末端連接至第二抗原決定基結合域。

當抗原決定基結合域為結構域抗體時，一些結構域抗體可匹配於骨架內之特定位置。

適用於本發明中之免疫球蛋白單可變域可連接於IL-13 mAb之重鏈及/或輕鏈的C末端。此外，一些免疫球蛋白單可變域可連接至習知抗體之重鏈與輕鏈的C末端。

在其中免疫球蛋白單可變域之N末端融合至抗體恆定域(C_{H3} 或CL)的構築體中，肽連接子可有助於免疫球蛋白單

可變域結合至抗原。實際上，dAb之N末端位於緊靠涉及抗原結合活性之CDR處。因此，短肽連接子在抗原決定基結合域與抗體之恆定域之間充當間隔子(spacer)，其可允許dAb CDR更容易地到達抗原，因此可以高親和力結合。

免疫球蛋白單可變域連接至IgG之環境將視其融合至哪條抗體鏈而變：

當在抗體輕鏈之C末端融合時，預期各免疫球蛋白單可變域位於抗體鉸鏈及Fc部分附近。此等免疫球蛋白單可變域彼此可能相隔較遠。在習知抗體中，Fab片段之間的角度及各Fab片段與Fc部分之間的角度可顯著不同。就mAbdAb而言，Fab片段之間的角度可能將不會迥然不同，而對各Fab片段與Fc部分之間之角度可能會觀測到一些角度限制。

當在抗體重鏈之C末端融合時，預期各免疫球蛋白單可變域位於Fc部分之 C_H3 域附近。預期此不會影響Fc對Fc受體(例如Fc γ RI、Fc γ RII、Fc γ RIII及FcRn)之結合性質，因為此等受體與 C_H2 域啣合(對於Fc γ RI、Fc γ RII及Fc γ RIII類受體而言)或與介於 C_H2 與 C_H3 域之間的鉸鏈啣合(例如FcRn受體)。此等抗原結合蛋白之另一特徵為預期兩個免疫球蛋白單可變域在空間上彼此接近且若藉由供給適當連接子來提供柔順性，則此等免疫球蛋白單可變域可甚至形成同源二聚種類，因此擴展了Fc部分的「拉鏈」(zipped)四級結構，從而可增強構築體穩定性。

此等結構考慮可有助於選擇最適合位置以將抗原決定基

結合域(例如免疫球蛋白單可變域)連接至抗體上。

抗原之尺寸、其定位(於血液中或細胞表面上)、其四級結構(單體或多聚體)可變化。習知抗體由於存在鉸鏈區而容易設計成充當接附構築體(adaptor construct)，其中Fab片段頂端之兩個抗原結合位點的定向可廣泛變化且因此適應抗原之分子特徵及其環境。相反，連接至無鉸鏈區之抗體的免疫球蛋白單可變域可能直接或間接地具有較小之結構柔順性。

瞭解免疫球蛋白單可變域之溶解狀態及結合模式亦為有益的。已積累的證據表明，活體外人類dAb可主要呈溶解之單體、同源二聚體或多聚體形式存在(Reiter等人，(1999) J Mol Biol 290第685-698頁；Ewert等人，(2003) J Mol Biol 325，第531-553頁；Jespers等人，(2004) J Mol Biol 337第893-903頁；Jespers等人，(2004) Nat Biotechnol 22第1161-1165頁；Martin等人，(1997) Protein Eng. 10第607-614頁；Sepulveda等人，(2003) J Mol Biol 333第355-365頁)。可清楚地回顧活體內所觀測之Ig結構域之多聚化事件，諸如本瓊氏蛋白質(Bence-Jones protein)(其為免疫球蛋白輕鏈之二聚體(Epp等人，(1975) Biochemistry 14第4943-4952頁；Huan等人，(1994) Biochemistry 33第14848-14857頁；Huang等人，(1997) Mol immunol 34第1291-1301頁))及澱粉狀蛋白纖維(James等人，(2007) J Mol Biol. 367:603-8)。

舉例而言，可能需要將溶解時傾向於二聚合之dAb優先

連接至Fc部分的C末端而非輕鏈C末端，因為連接至Fc之C末端將允許彼等dAb在本發明之抗原結合蛋白情形下二聚合。

本發明之抗原結合蛋白可包含對單一抗原具有特異性之抗原結合位點，或可具有對兩種或兩種以上抗原，或對單一抗原上之兩個或兩個以上抗原決定基具有特異性之抗原結合位點，或可存在的抗原結合位點各對相同或不同抗原上之不同抗原決定基具有特異性。

本發明之抗原結合蛋白可包含本發明之重鏈可變區及輕鏈可變區，其可形成天然抗體或其功能片段或其等效物之結構。本發明之抗原結合蛋白因此可包含本發明之VH區，其與適當輕鏈成對時形成全長抗體、(Fab')₂片段、Fab片段、或其等效物(諸如scFV、雙功能抗體、三功能抗體或四功能抗體、四價雙特異性抗體(Tandab)等)。該抗體可為IgG1、IgG2、IgG3、或IgG4；或IgM；IgA、IgE或IgD或其經修飾變體。可相應選擇抗體重鏈之恆定域。輕鏈恆定域可為κ或λ恆定域。此外，抗原結合蛋白可包含所有種類之修飾，例如IgG二聚體、不再結合Fc受體或介導C1q結合之Fc突變體。抗原結合蛋白亦可為WO 86/01533中所述類型之嵌合抗體，其包含抗原結合區及非免疫球蛋白區。

根據任何所需功能性選擇恆定區。IgG1可藉由結合至補體而顯示溶解能力及/或介導ADCC(抗體依賴型細胞介導之細胞毒性)。若需要非細胞毒性阻斷抗體，則可使用

IgG4。然而，IgG4抗體在產生中可顯示不穩定性且因此一種可選方案為修飾一般而言更穩定之IgG1。EP 0307434中描述建議之修飾，例如位置235及237處之突變。本發明因此提供一種溶解或非溶解形式之抗原結合蛋白，例如本發明之抗體。

在某些形式中，本發明之抗體為全長(例如H2L2四聚體)溶解或非溶解IgG1抗體，其具有本文所述之任一重鏈可變區。

在另一態樣中，本發明提供編碼如本文所述之輕鏈及重鏈可變區的聚核苷酸。

在本發明之一實施例中，抗原結合位點結合至抗原的 K_d 為至少約1 mM，例如結合至各種抗原的 K_d 為至少約10 nM，至少約1 nM，至少約500 pM，至少約200 pM，至少約100 pM，或至少約50 pM，如經由BiacoreTM所量測。

在本發明之一實施例中，抗原結合位點結合至抗原的 K_d 為至少約1 mM，例如結合至各種抗原的 K_d 為至少約10 nM，至少約1 nM，至少約500 pM，至少約200 pM，至少約100 pM，或至少約50 pM，如經由BiacoreTM所量測。

在一實施例中，本發明提供抗原結合蛋白，其對人類IL-13的親和力為包含SEQ ID NO: 22中所示之重鏈序列及SEQ ID NO: 24中所示之輕鏈序列之抗IL-13抗體的至少2倍，或至少4倍，或至少6倍，或至少8倍，或至少10倍，如經由Biacore所量測。

如通篇本說明書關於本發明抗原結合蛋白所用之術語

「中和」及其文法變化形式意謂，相較於不存在此等抗原結合蛋白時之IL-13活性，存在本發明之抗原結合蛋白時之IL-13生物活性完全或部分降低。中和可歸因於(但不限於)以下一或多者：阻斷配位體結合、阻止配位體活化受體、下調IL-13受體或影響效應物功能性。中和程度可依若干方式量測，例如使用如下文實例中所述之分析法，例如TF1分析法，其可如例如實例4中所述進行。此分析法中對IL-13、IL-4或此等兩種細胞激素的中和程度係藉由評估中和抗原結合蛋白之存在對TF1細胞增殖的抑制作用來量測。

評估中和程度之其他方法(例如評估在中和抗原結合蛋白存在下之IL-13與其受體之間結合度的減少)在此項技術中為已知且包括例如Biacore分析法。

在本發明之替代態樣中，提供具有與本文所例示抗體至少實質上相當之中和活性的抗原結合蛋白，例如在TF1細胞增殖分析法中保持A1Y100BAIaL1、A1Y100BIleL1、A1Y100BTrpL1或A1Y100BValL1之中和活性的抗原結合蛋白，該TF1細胞增殖分析法可如實例4中所述進行。

抗原結合蛋白(例如本發明之抗體)可藉由用包含本發明之抗原結合蛋白之編碼序列的表現載體轉染宿主細胞產生。表現載體或重組質體係藉由將抗原結合蛋白之此等編碼序列定位在與能夠控制宿主細胞中之複製及表現及/或宿主細胞之分泌的習知調節控制序列操作性連接來產生。調節序列包括啟動子序列(例如CMV啟動子)及可來源於其

他已知抗體之信號序列。類似地，可產生具有編碼互補抗原結合蛋白輕鏈或重鏈之DNA序列的第二表現載體。在某些實施例中，除編碼序列及可選擇標記以外，此第二表現載體與第一表現載體相同，以儘可能確保各多肽鏈具有功能上表現。或者，抗原結合蛋白之重鏈及輕鏈編碼序列可存在於單個載體上。

經由習知技術，用第一載體與第二載體共轉染(或僅用單個載體轉染)所選宿主細胞以產生本發明之經轉染宿主細胞，其包含重組或合成輕鏈與重鏈。接著經由習知技術培養經轉染細胞，以產生本發明之經工程改造抗原結合蛋白。藉由適當分析法(諸如ELISA或RIA)自培養物中篩檢包括相聯結之重組重鏈與/或輕鏈的抗原結合蛋白。類似習知技術可用於構築其他抗原結合蛋白。

熟習此項技術者可選擇用於本發明之方法及組合物建構中之選殖及次選殖步驟的適合載體。舉例而言，可使用習知pUC系列之選殖載體。一種載體，pUC19，可自供應機構(諸如Amersham(Buckinghamshire, United Kingdom)或Pharmacia(Uppsala, Sweden))購得。另外，能夠輕易複製、具有豐裕選殖位點及可選擇基因(例如抗生素抗性基因)且易於操作之任何載體可用於選殖。因此，選殖載體之選擇不為本發明中之限制因素。

表現載體亦可由適於擴增異源DNA序列之表現的基因(例如哺乳動物二氫葉酸還原酶基因(DHFR))表徵。其他載體序列包括poly A信號序列(諸如牛生長激素(BGH)之poly

A信號序列)及 β 球蛋白啟動子序列(betaglopro)。適用於本文中之表現載體可經由熟習此項技術者熟知之技術來合成。

此等載體之組分(例如複製子、選擇基因、增強子、啟動子、信號序列及其類似組分)可自商業或天然來源獲得或經由用於指導在所選宿主中表現及/或分泌重組DNA之產物的已知程序來合成。為此目的亦可選擇在此項技術中已知用於哺乳動物、細菌、昆蟲、酵母、及真菌表現的許多類型的其他適當表現載體。

本發明亦涵蓋經含有本發明抗原結合蛋白之編碼序列之重組質體轉染的細胞株。適用於此等選殖載體之選殖及其他操作的宿主細胞亦為習知的。然而，來自大腸桿菌之各種菌株的細胞可用於選殖載體之複製及建構本發明抗原結合蛋白的其他步驟。

適合表現本發明之抗原結合蛋白的宿主細胞或細胞株包括哺乳動物細胞(諸如NS0、Sp2/0、CHO(例如DG44)、COS、HEK)、纖維母細胞(例如3T3)及骨髓瘤細胞，舉例而言，本發明之抗原結合蛋白可在CHO或骨髓瘤細胞中表現。可使用人類細胞，從而使分子能夠經由人類糖基化模式修飾。或者，可使用其他真核細胞株。適合哺乳動物宿主細胞之選擇及用於轉型、培養、擴增、篩檢及產物產生及純化之方法在此項技術中為已知的。參見，例如上文引用之Sambrook等人。

細菌細胞經證實可適用作適於表現重組Fab或本發明之

其他實施例的宿主細胞(參見, 例如 Plückthun, A., Immunol. Rev., 130: 151-188 (1992))。然而, 由於細菌細胞中所表現的蛋白質易呈未摺疊或不適當摺疊形式或非糖基化形式, 因此需篩檢細菌細胞中所產生之任何重組 Fab 以保留抗原結合能力。若細菌細胞所表現之分子呈適當摺疊形式產生, 則彼細菌細胞為所需宿主, 或在替代實施例中, 分子可在細菌宿主中表現且隨後再摺疊。舉例而言, 用於表現之大腸桿菌之各種菌株在生物技術領域中作為宿主細胞已熟知。在此方法中亦可使用枯草芽孢桿菌 (*B. subtilis*)、鏈黴菌 (*Streptomyces*)、其他桿菌之各種菌株及類似物。

需要時, 亦可利用熟習此項技術者已知之酵母細胞菌株以及昆蟲細胞(例如果蠅 (*Drosophila*) 及鱗翅目昆蟲 (*Lepidoptera*)) 及病毒表現系統作為宿主細胞。參見, 例如 Miller 等人, Genetic Engineering, 8: 277-298, Plenum Press (1986) 及其中所引用之參考文獻。

可藉以建構載體之一般方法、產生本發明之宿主細胞所需之轉染方法、及自此宿主細胞中產生本發明抗原結合蛋白所需之培養方法皆可為習知技術。本發明之培養方法通常為無血清培養方法, 其一般藉由在無血清懸浮液中培養細胞。同樣, 本發明之抗原結合蛋白產生後即可根據此項技術之標準程序(其包括硫酸銨沈澱、親和管柱、管柱層析法、凝膠電泳法及類似方法)自細胞培養內含物中純化。此等技術在此項技術之技能範圍內且不限制本發明。

舉例而言，WO 99/58679及WO 96/16990中描述變異抗體之製備。

然而表現抗原結合蛋白之另一方法可利用轉殖基因動物中之表現，諸如美國專利第4,873,316號中所述。此係關於一種使用動物酪蛋白啟動子之表現系統，當以轉殖基因方式併入哺乳動物中時，其允許雌性動物於其乳中產生所需重組蛋白質。

在本發明之另一態樣中，提供一種產生本發明之抗體的方法，該方法包含培養經編碼本發明抗體之輕鏈及/或重鏈之載體轉型或轉染的宿主細胞及回收藉此產生之抗體的步驟。

根據本發明，提供一種產生本發明之抗IL-13抗體的方法，該IL-13抗體結合至人類IL-13且中和人類IL-13之活性，該方法包含以下步驟：

- a) 提供編碼該抗體重鏈之第一載體；
- b) 提供編碼該抗體輕鏈之第二載體；
- c) 用該第一及第二載體轉型哺乳動物宿主細胞(例如CHO)；
- d) 在可增進該抗體自該宿主細胞分泌進入該培養基中之條件下培養步驟(c)之宿主細胞；
- e) 回收步驟(d)之分泌抗體。

抗體經由所需方法表現後，接著藉由使用適當分析法檢驗其活體外活性。目前使用習知ELISA分析法形式來定性及定量評估抗體與IL-13之結合。另外，亦可使用其他活

體外分析法驗證中和功效，隨後執行人類臨床研究以評估抗體於體內的續存(不論常見清除機制)。

治療劑量及持續時間係關於本發明分子在人體循環中的相對持續時間，且可視所治療病狀及患者之一般健康狀況由熟習此項技術者調整。預計可能需要長期(例如四至六個月)重複給藥(例如一週一次或每兩週一次)以達成最大治療功效。

本發明治療劑之投藥模式可為將藥劑傳遞至宿主的任何適當途徑。本發明之抗原結合蛋白及醫藥組合物尤其適用於非經腸(亦即皮下(s.c.)、鞘內、腹膜內、肌肉內(i.m.)、靜脈內(i.v.)或鼻內)投與。

本發明之治療劑可製備成於醫藥學上可接受之載劑中含有有效量之本發明抗原結合蛋白作為活性成份的醫藥組合物。在一實施例中，本發明之預防劑為呈備妥注射形式之含有抗原結合蛋白的水性懸浮液或溶液。在一實施例中，懸浮液或溶液在生理pH值下經緩衝。在一實施例中，非經腸投藥之組合物將包含溶於醫藥學上可接受之載劑中之本發明抗原結合蛋白或其混合物(cocktail)的溶液。在一實施例中，載劑為水性載劑。可使用多種水性載劑，例如0.9%鹽水、0.3%甘胺酸及其類似物。此等溶液可製備為無菌且一般不含顆粒物質。此等溶液可經由習用、熟知滅菌技術(例如過濾)進行滅菌。組合物可含有接近生理條件所需之醫藥學上可接受之助劑，諸如pH值調節劑及緩衝劑等。本發明抗原結合蛋白在此等醫藥調配物中之濃度可廣泛變

化，亦即，小於約0.5重量%(通常為或至少約1重量%)至多達約15重量%或20重量%，且主要基於流體體積、黏度等、根據所選特定投藥模式選擇。

因此，用於肌肉內注射之本發明醫藥組合物可製備成含有約1 mL無菌緩衝水，及介於約1 ng至約100 mg，例如約50 ng至約30 mg或約5 mg至約25 mg之間的抗原結合蛋白，例如本發明之抗體。類似地，用於靜脈內輸注之本發明醫藥組合物可製備成含有約250 ml無菌林格氏液(Ringer's solution)、及每毫升林格氏液約1 mg至約30 mg或5 mg至約25 mg之本發明抗原結合蛋白。製備可非經腸投與之組合物之實際方法為熟知的或對於熟習此項技術者顯而易知，且更詳細描述於例如 Remington's Pharmaceutical Science，第15版，Mack Publishing Company, Easton, Pennsylvania中。對於製備本發明之可靜脈內投與之抗原結合蛋白調配物，參見Lasmar U及Parkins D「The formulation of Biopharmaceutical products」，Pharma. Sci.Tech.today，第129-137頁，第3卷(2000年4月3日)；Wang, W「Instability, stabilisation and formulation of liquid protein pharmaceuticals」，Int. J. Pharm 185 (1999) 129-188；Stability of Protein Pharmaceuticals Part A and B Ahern T.J.編，Manning M.C., New York, NY: Plenum Press (1992)；Akers, M.J.「Excipient-Drug interactions in Parenteral Formulations」，J. Pharm Sci 91 (2002) 2283-2300；Imamura, K等人，「Effects of types of sugar on

stabilization of Protein in the dried state」, J Pharm Sci 92 (2003) 266-274 ; Izutsu, Kkojima, S. 「Excipient crystallinity and its protein-structure-stabilizing effect during freeze-drying」, J Pharm. Pharmacol, 54 (2002) 1033-1039 ; Johnson, R, 「Mannitol-sucrose mixtures-versatile formulations for protein lyophilization」, J. Pharm. Sci, 91 (2002) 914-922 及 Ha,E Wang W, Wang Y.j. 「Peroxide formation in polysorbate 80 and protein stability」, J. Pharm Sci, 91, 2252-2264,(2002), 其全部內容以引用的方式併入本文中且讀者特定參考該等文獻。

在一實施例中，本發明之治療劑當含於醫藥製劑中時，係呈單位劑量形式存在。熟習此項技術者將輕易地確定適當治療有效劑量。適用於患者之劑量可根據患者體重計算，舉例而言，適合劑量的範圍可為約0.1至約20 mg/kg，例如約1至約20 mg/kg，例如約10至約20 mg/kg或例如約1至約15 mg/kg，例如約10至約15 mg/kg。為了有效治療人類病狀(諸如哮喘或IPF)，本發明之抗原結合蛋白的適合劑量可在以下範圍內：約0.1至約1000 mg，例如約0.1至約500 mg，例如約500 mg，例如約0.1至約100 mg，或約0.1至約80 mg，或約0.1至約60 mg，或約0.1至約40 mg，或例如約1至約100 mg，或約1至約50 mg，其可非經腸(例如皮下、靜脈內或肌肉內)投與。需要時，可在由醫師酌情所選之適當時間間隔下重複此劑量。

本文所述的抗原結合蛋白可凍乾以便儲存且在使用之前

於適合載劑中復原。此技術已顯示對習知免疫球蛋白有效且可使用此項技術已知之凍乾及復原技術。

在另一態樣中，本發明提供一種包含本發明抗原結合蛋白或其功能片段及醫藥學上可接受之載劑的醫藥組合物以治療或預防特異反應性疾病/病症及慢性發炎性疾病/病症，例如哮喘，諸如過敏性哮喘，特定言之，嚴重哮喘（亦即對當前治療（包括全身投與皮質類固醇）無反應之哮喘；參見Busse WW等人，J Allergy Clin. Immunol 2000, 106: 1033-1042）、「難治性」哮喘（定義為特徵為儘管投與最大推薦劑量之處方吸入類固醇但仍無法得到控制之哮喘表型，參見Barnes PJ (1998), Eur Respir J 12:1208-1218）、「脆性」哮喘（定義患有嚴重不穩定哮喘的患者亞群，其儘管投與高劑量之吸入類固醇，但仍維持寬尖峰呼氣流量（PEF）變化性，參見Ayres JG等人，(1998) Thorax 58:315-321）、夜間哮喘、經前哮喘、抗類固醇哮喘（參見Woodcock AJ, (1993) Eur Respir J 6:743-747）、類固醇依賴型哮喘（定義為僅可用高劑量口服類固醇控制之哮喘）、阿斯匹靈誘發型哮喘、成年發作型哮喘、小兒哮喘。本發明之抗體可用於預防、降低急性哮喘發作（持續性哮喘）之頻率或緩和其效應。本發明之抗體亦可用於降低在治療哮喘中所用之其他藥劑的所需給藥（在投藥量或給藥頻率方面）。舉例而言，本發明之抗體可用於降低類固醇治療（諸如皮質類固醇治療）哮喘所需之給藥（「類固醇節省」）。其他可用本發明之抗體治療之疾病或病症包括異位性皮膚

炎、過敏性鼻炎、克隆氏病、慢性阻塞性肺病(COPD)、嗜伊紅血球食道炎、纖維變性疾病或病症(諸如特發性肺纖維化、進行性全身性硬化(硬皮病)、肝纖維化)、肝肉芽瘤、血吸蟲病、利什曼體病及細胞週期調節疾病(例如霍奇金氏病、B細胞慢性淋巴細胞白血病)。在一實施例中，病症為嚴重哮喘。在另一實施例中，病症為纖維變性病症，諸如IPF。

在另一態樣中，本發明提供一種包含本發明抗原結合蛋白或其功能片段及醫藥學上可接受之載劑的醫藥組合物以治療特異反應性疾病/病症及慢性炎性疾病/病症，例如哮喘，諸如過敏性哮喘，特定言之，嚴重哮喘(亦即對當前治療(包括全身投與皮質類固醇)無反應之哮喘；參見Busse WW等人，J Allergy Clin. Immunol 2000, 106: 1033-1042)、「難治性」哮喘(定義為特徵為儘管投與最大推薦劑量之處方吸入類固醇但仍無法得到控制之哮喘表型，參見Barnes PJ (1998), Eur Respir J 12:1208-1218)、「脆性」哮喘(定義患有嚴重不穩定哮喘的患者亞群，其儘管投與高劑量之吸入類固醇，但仍維持寬尖峰呼氣流量(PEF)變化性，參見Ayres JG等人，(1998) Thorax 58:315-321)、夜間哮喘、經前哮喘、抗類固醇哮喘(參見Woodcock AJ, (1993) Eur Respir J 6:743-747)、類固醇依賴型哮喘(定義為僅可用高劑量口服類固醇控制之哮喘)、阿斯匹靈誘發型哮喘、成年發作型哮喘、小兒哮喘。本發明之抗體可用於預防、降低急性哮喘發作(持續性哮喘)之頻率或緩和其效

應。本發明之抗體亦可用於降低在治療哮喘中所用之其他藥劑的所需給藥(在投藥量或給藥頻率方面)。舉例而言，本發明之抗體可用於降低類固醇治療(諸如皮質類固醇治療)哮喘所需之給藥(「類固醇節省」)。其他可用本發明之抗體治療之疾病或病症包括異位性皮膚炎、過敏性鼻炎、克隆氏病、慢性阻塞性肺病(COPD)、嗜伊紅血球食道炎、纖維變性疾病或病症(諸如特發性肺纖維化、進行性全身性硬化(硬皮病)、肝纖維化)、肝肉芽瘤、血吸蟲病、利什曼體病及細胞週期調節疾病(例如霍奇金氏病、B細胞慢性淋巴細胞白血病)。在一實施例中，病症為嚴重哮喘。在另一實施例中，病症為纖維變性病，諸如IPF。

應瞭解本文所述序列(SEQ ID NO: 26至SEQ ID NO: 55及SEQ NO: 62至SEQ ID NO: 146)包括與本文所述序列實質上一致之序列，例如至少90%一致之序列，例如至少91%，或至少92%，或至少93%，或至少94%，或至少95%，或至少96%，或至少97%或至少98%，或至少99%一致之序列。

對於核酸而言，術語「實質一致性」指示當利用適當核苷酸插入或缺失進行最佳比對及比較時，兩個核酸或其指定序列在至少約80%核苷酸，至少約90%至約95%，或至少約98%至約99.5%核苷酸上一致。或者，當區段在選擇性雜交條件下與互補股雜交時，存在實質一致性。

對於核苷酸及胺基酸序列而言，術語「一致」指示當利用適當插入或缺失進行最佳比對及比較時，兩個核酸或胺

基酸序列之間的一致性程度。或者，當DNA區段在選擇性雜交條件下與互補股雜交時，存在實質一致性。

在考慮兩個序列最佳比對所需引入之間隙數及各間隙之長度的情況下，兩個序列之間的一致性百分比為該等序列所共有之相同位置數的函數(亦即一致性% = 相同位置數 / 總位置數 × 100)。如下文非限制性實例中所述，可使用數學演算法比較序列及確定兩個序列之間的一致性百分比。

可使用 GCG 套裝軟體中之 GAP 程式、使用 NWSgapdna.CMP 矩陣及間隙權重 40、50、60、70 或 80 及長度權重 1、2、3、4、5 或 6 確定兩個核苷酸序列之間的一致性百分比。亦可使用已併入 ALIGN 程式 (2.0 版) 中之 E. Meyers 及 W. Miller 之演算法 (Comput. Appl. Biosci., 4:11-17 (1988))、使用 PAM120 權重殘基表 (weight residue table)、間隙長度罰分 12 及間隙罰分 4 確定兩個核苷酸或胺基酸序列之間的一致性百分比。此外，可使用已併入 GCG 套裝軟體之 GAP 程式中的 Needleman 及 Wunsch (J. Mol. Biol. 48:444-453 (1970)) 演算法、使用 Blossum 62 矩陣或 PAM250 矩陣及間隙權重 16、14、12、10、8、6 或 4 及長度權重 1、2、3、4、5 或 6 確定兩個胺基酸序列之間的一致性百分比。

舉例而言，本發明之聚核苷酸序列可與 SEQ ID NO: 25 之參考序列一致，亦即 100% 一致，或其相較於該參考序列可包括多達某整數個核苷酸變異。此等變異係選自由以下組成之群：至少一個核苷酸缺失、取代(包括轉移及易

位)或插入，且其中該等變異可發生於參考核苷酸序列之5'或3'末端位置處或彼等末端位置之間的任何位置處(個別地散置於參考序列之核苷酸中或以一或多個鄰接群散置於參考序列內)。如下確定核苷酸變異數：以各別一致性百分比之百分比數值(除以100)乘SEQ ID NO: 25中之核苷酸總數且自SEQ ID NO: 25中之核苷酸之該總數中減去彼乘積，或：

$$nn \leq xn - (xn \cdot y),$$

其中nn為核苷酸變異數，xn為SEQ ID NO: 25中之核苷酸總數，且y對於50%為0.50，對於60%為0.60，對於70%為0.70，對於80%為0.80，對於85%為0.85，對於90%為0.90，對於95%為0.95，對於97%為0.97或對於100%為1.00，且其中xn與y之任何非整數乘積在自xn中將其減去之前向下捨入至最接近之整數。SEQ ID NO: 25之聚核苷酸序列的變異可在此編碼序列中產生無意義(nonsense)、誤義(missense)或讀框轉移(frameshift)突變且藉此使發生此等變異後之聚核苷酸所編碼的多肽變異。

類似地，在另一實例中，本發明之多肽序列可與由SEQ ID NO: 24編碼之參考序列一致，亦即100%一致，或其相較於該參考序列可包括多達某整數個胺基酸變異，從而一致性%小於100%。此等變異係選自由以下組成之群：至少一個胺基酸缺失、取代(包括保守及非保守取代)或插入，且其中該等變異可發生於參考多肽序列之胺基或羧基末端位置處或彼等末端位置之間的任何位置處(個別地散置於

參考序列之胺基酸中或以一或多個鄰接群散置於參考序列內)。既定一致性%之胺基酸變異數係藉由以各別一致性百分比之百分比數值(除以100)乘SEQ ID NO: 24所編碼之多肽序列中之胺基酸總數且接著自SEQ ID NO: 24所編碼之多肽序列之該胺基酸總數中減去彼乘積來確定，或：

$$na \leq xa - (xa \cdot y),$$

其中na為胺基酸變異數，xa為SEQ ID NO: 24所編碼之多肽序列之胺基酸總數，且y例如對於70%為0.70，對於80%為0.80，對於85%為0.85等，且其中xa與y之任何非整數乘積在自xa中將其減去之前向下捨入至最接近之整數。

下列實例說明但不限制本發明。

實例

實例1-建構重組抗IL-13抗體

藉由重組人類IL-13免疫小鼠來產生初始鼠類mAb。收集有反應動物之脾且與骨髓瘤細胞融合中以產生融合瘤。針對結合來篩檢融合瘤上清液物質。使用標準技術單選殖相關融合瘤。所得鼠類抗體(6A1)包含SEQ ID NO: 58及SEQ ID NO: 59中所示之可變區。此鼠類抗體及此抗體A1L1(SEQ ID NO: 22及24)之人類化形式的其他詳情描述於WO 2006/003407中，該文獻以引用的方式併入本文中。抗IL-13 mAb抗體A1L1在若干下列實例中作為比較抗體使用。

產生包含SEQ ID NO: 22中所示之重鏈之人類化抗體的許多變體。此等變體在抗體之CDRH3區(SEQ ID NO: 3)皆

不相同。

藉由建立重疊寡核苷酸來重新製備本發明抗體之基本DNA表現構築體SEQ ID NO: 23(重鏈)及SEQ ID NO: 25(輕鏈)，該等重疊寡核苷酸包括用於選殖入Rld及Rln哺乳動物表現載體中之限制性位點以及人類信號序列。引入Hind III及Spe I限制性位點以框住含有用於選殖入Rld中之信號序列(SEQ ID NO: 56)的V_H域，該Rld含有人類 γ 1恆定區。引入Hind III及BsiW I限制性位點以框住含有用於選殖入Rln中之信號序列(SEQ ID NO: 56)的V_L域，該Rln含有人類 κ 恆定區。使用亦包括人類恆定區之pTT載體產生替代構築體。適當時，使用定點突變誘發(SDM)產生不同人類化構築體。

實例2-抗體表現於HEK 293 6E細胞中

將分別編碼重鏈及輕鏈之pTT質體短暫共轉染於HEK 293 6E細胞中且小規模表現以產生抗體。評估直接來自組織培養液上清液中的抗體。使用固定蛋白質A管柱純化其他抗體且藉由讀取280 nm下之吸光度進行定量且需要時，在下述實例所述中之分析法中評估該純化的抗體物質。

當用代碼(亦即A1Y100BTrpL1)提及抗體時，係指藉由所述第一及第二質體之共轉染及表現所產生之mAb，例如「A1Y100BTrpL1」係關於藉由將含有A1Y100BTrp序列之質體與含有L1序列之質體共轉染於適合細胞株中所產生的mAb。

實例3-抗IL-13人類化mAb之Biacore分析

動力學分析

在ProteOn XPR36(Biorad)上進行CDRH3突變體之初始篩檢。方法如下：藉由一級胺偶聯使抗人類IgG(Biacore BR-1008-39)固定在GLM晶片上，接著CDRH3突變體抗體捕捉於此表面上且IL13在256、64、16、4、1 nM下通過(0 nM進樣(亦即僅用緩衝液)用作雙重參照)。使用3 M MgCl₂再生捕捉表面，移除所結合CDRH3突變體抗體為另一輪捕捉及分析物進樣作準備。使用機器固有軟體針對1:1模型擬合數據。所有研究皆使用直接來自組織培養液上清液中之抗體，作為純化物質之親本抗體除外。

篩檢鑑別似乎比親本分子具有更佳動力學概況之多種抗體，接著使用類似方法在Biacore T100上分析此等相同樣品以證實結果，其中藉由一級胺偶聯使抗人類IgG捕捉抗體固定在CM5晶片上，IL13在256、64、16、4、1及0.25 nM下通過表面(0 nM用作雙重參照)，用3 M MgCl₂再生且針對T100固有之1:1模型擬合數據。表1詳述來自ProteOn篩檢及T100操作之所選構築體的總親和力(平衡解離常數K_D)。

表 1

分子	ProteOn K _D (pM)	Biacore K _D (pM)
A1S95TrpL1	不可分析	216
A1I96ValL1	395	696
A1Y97PheL1	683	618
A1D98GluL1	873	779
A1H100AAlaL1	不可分析	172

A1H100A GluL1	110	195
A1H100A GlnL1	195	278
A1H100A ArgL1	256	307
A1H100A SerL1	131	174
A1H100A ThrL1	158	211
A1H100A ValL1	112	152
A1Y100B AlaL1	75	83
A1Y100B IleL1	75	73
A1Y100B TrpL1	68	95
A1L1	~450-600*	366

*A1L1在ProteOn篩檢期間操作了若干次因此為所得數值之範圍。

數據強調了Y100B殘基處之若干突變似乎會改良總親和力。據此，使用ProteOn、使用如前所述之相同方法且再次使用直接來自組織培養液上清液中之抗體來測試不存在於初始篩檢中之此殘基處的突變。在所測試之突變中，A1Y100B ValL1似乎改良總親和力(平衡解離常數 K_D)，相較於0.390-0.460 nM之親本值，所得值為0.166 nM。當使用如前所述之相同方法在Biacore T100上測試Y100B Val時，相較於0.346 nM之親本值，所量測之平衡解離常數 K_D 為0.025 nM。

根據迄今使用直接來自組織培養液上清液中之抗體突變體所進行之研究，產生A1Y100BL1突變體Ala、Ile及Trp的純化抗體。此等純化抗體(包括在此階段未純化之A1Y100B ValL1突變體)皆使用如前所述之相同方法在Biacore T100上操作。表2展示得自此實驗之數據。

表 2

分子	$k_a(M^{-1}s^{-1})$	$k_d(s^{-1})$	$K_D(nM)$
A1Y100B ValL1(上清液)	1.018E+6	3.455E-5	0.034
A1Y100B AlaL1	9.599E+5	3.004E-5	0.031
A1Y100B IleL1	1.149E+6	5.584E-5	0.049
A1Y100B TrpL1	2.572E+6	1.627E-4	0.063
A1L1	1.267E+6	4.560E-4	0.360

實驗證實突變體相較於親本分子確實會改良對IL13之結合親和力。

若純化A1Y100BL1突變體產生的結合親和力優於獲自組織培養液上清液中之彼等者，則純化A1Y100B ValL1且與親和力亦改良之其他純化A1Y100BL1突變體一起使用前述方法、使用Biacore T100機器操作。表3展示得自此實驗之數據。此實驗與表2中數據良好吻合且證實Y100B突變使親和力改良。

表 3

分子	$k_a(M^{-1}s^{-1})$	$k_d(s^{-1})$	$K_D(nM)$
A1Y100B IleL1(純化)	9.886E+5	4.214E-5	0.043
A1Y100B ValL1(純化)	7.757E+5	2.123E-5	0.027
A1Y100B AlaL1(純化)	8.096E+5	2.583E-5	0.032
A1Y100B TrpL1(純化)	2.385E+6	1.253E-4	0.053
A1L1(純化)	1.128E+6	3.677E-4	0.326

實例 4-在細胞增殖生物分析法中對大腸桿菌所表現之重組人類IL-13之中和

TF-1細胞回應於許多不同細胞激素(包括人類IL-13)而增殖。此等細胞對於IL-13之增殖反應因此可用於量測IL-13之生物活性且隨後已開發一種分析法以測定mAb中和IL-13

之效能(抑制IL-13生物活性)。

該分析法在無菌條件下於無菌96孔組織培養盤中進行且所有測試孔皆一式三份進行。將14 ng/ml經重組大腸桿菌表現之人類IL-13與各種稀釋度之mAb(通常自93.4 nM以3倍稀釋度滴定至0.014 nM)在37°C下一起預培育1小時。無關特異性之抗體作為陰性對照以類似方式滴定。接著將此等樣品添加至無菌96孔組織培養盤中之50 μ l TF-1細胞(每毫升 2×10^5 個細胞之濃度)中。因此最終100 μ l分析體積含有各種稀釋度之mAb(46.7 nM以3倍稀釋度滴定至0.007 nM之最終濃度)、重組大腸桿菌表現之人類IL-13(7 ng/ml之最終濃度)及TF-1細胞(每毫升 1×10^5 個細胞之最終濃度)。分析盤在含濕氣CO₂培育箱中在37°C下培育約3天。接著使用購自Promega之「CellTitre 96®非放射性細胞增殖分析法」(產品目錄第G4100號)如製造商說明書中所述來測定細胞增殖量。96孔盤中之樣品的吸光度於讀盤器中在570 nm下讀取。

mAb中和重組大腸桿菌所表現之人類IL-13生物活性的能力表述為將一定量之人類IL-13(7 ng/ml)之生物活性中和50%所需之mAb的濃度(=ND₅₀)。所需mAb之濃度越低，則中和能力越強。使用Microsoft Excel中之Robosage來計算本文提供之ND₅₀數據(表4)。數據之圖形表示可見於圖1中。

表 4

分子	ND ₅₀ (nM)	標準誤差(nM)
A1L1	9.77	34.82
A1Y100BAla L1	0.92	0.08
A1Y100BIle L1	1.10	0.21
A1Y100BTrpL1	1.25	0.34

實例 5- 建構及表現包含 CDRH3 變體抗 IL-13 mAb 之 mAb-dAb

使用標準分子生物學技術，將編碼 A1 抗體之 CDRH3 變體重鏈可變區之各序列的基因自現有構築體轉移至含有 hIgG1 恆定區的表現載體中，該 hIgG1 恆定區在其 c 末端經由 TVAAPS 或 ASTKGPS 連接子融合至抗人類 IL-4 結構域抗體 (DOM9-112-210)。所建構重鏈之詳情列於表 5 中。

表 5

分子編號	名稱	描述	蛋白質 Seq ID	DNA Seq ID
BPC1624	A1Y100BAla H-TVAAPS-210 L1	H鏈=A1Y100B Ala H鏈-TVAAPS連接子-DOM9-112-210 dAb	62	63
		L鏈=L1	24	25
BPC1625	A1Y100BIle H-TVAAPS-210 L1	H鏈=A1Y100BIle H鏈-TVAAPS連接子-DOM9-112-210 dAb	64	65
		L鏈=L1	24	25
BPC1626	A1Y100BTrp H-TVAAPS-210 L1	H鏈=A1Y100BTrp H鏈-TVAAPS連接子-DOM9-112-210 dAb	66	67
		L鏈=L1	24	25

BPC1627	A1Y100BVal H-TVAAPS-210 L1	H鏈=A1Y100BVal H鏈-TVAAPS連接子-DOM9-112-210 dAb	68	69
		L鏈=L1	24	25
BPC1628	A1Y100BAla H-ASTKGPS-210 L1	H鏈=A1Y100B Ala H鏈-ASTKGPS連接子-DOM9-112-210 dAb	70	71
		L鏈=L1	24	25
BPC1629	A1 Y100BIle H-ASTKGPS-210 L1	H鏈=A1Y100BIle H鏈-ASTKGPS連接子-DOM9-112-210 dAb	72	73
		L鏈=L1	24	25
BPC1630	A1Y100BTrp H-ASTKGPS-210 L1	H鏈=A1Y100BTrp H鏈-ASTKGPS連接子-DOM9-112-210 dAb	74	75
		L鏈=L1	24	25
BPC1631	A1Y100BVal H-ASTKGPS-210 L1	H鏈=A1Y100BVal H鏈-ASTKGPS連接子-DOM9-112-210 dAb	76	77
		L鏈=L1	24	25

在 HEK293 細胞中表現 BPC1624、BPC1625、BPC1626 及 BPC1627。簡而言之，用預先經 293fectin 試劑 (Invitrogen # 51-0031) 培育之重鏈及輕鏈表現質體共轉染 250 ml (1.5×10^6 個細胞/毫升) HEK293 細胞。此等細胞於振盪培育箱中、在 37°C、5% CO₂ 及 95% 相對濕度下置放。24 小時後添加胰化蛋白飼料培養基且細胞再生長 5 天。離心收集上清液且無菌過濾。使用固定蛋白質 A 管柱、經由親和層析法來純化所表現之分子且藉由量測 280 nm 下之吸光度來測定濃度。經由尺寸排阻層析法 (size exclusion chromatography) 測定純化樣品中之聚集蛋白質的含量。純化蛋白質之產量及聚

集程度展示於表 5b 中。

表 5b

BPC	名稱	產量	聚集物%
BPC1624	586Y100BA H-TVAAPS-210	0.81 mg	3.6%
BPC1625	586Y100BI H-TVAAPS-210	0.944 mg	6.7%
BPC1626	586Y100BW H-TVAAPS-210	1.14 mg	5.5%
BPC1627	586Y100BV H-TVAAPS-210	1.26 mg	8.4%

實例 6- 包含 CDRH3 變體抗 IL-13 mAb 之 mAb-dAb 之中和活性數據

在 TF-1 細胞增殖生物分析法中測試包含 CDRH3 變體抗 IL-13 mAb 的 mAb-dAb 對大腸桿菌所表現之重組人類 IL-13 的中和程度。

該分析法在無菌條件下於無菌 96 孔組織培養盤中進行且所有測試孔皆一式三份進行。將約 20 ng/ml 經重組大腸桿菌表現之人類 IL-13 與各種稀釋度之 mAbdAb (通常自 50 nM 以 3 倍稀釋度滴定至 0.02 nM) (彼等 mAbdAb 於 HEK 細胞中製備且如實例 5 中所述純化) 以 50 μ l 總體積在 37°C 下預培育 1 小時。無關特異性之抗體作為陰性對照以類似方式滴定 (數據未示)。接著將此等樣品添加至無菌 96 孔組織培養盤中之 50 μ l TF-1 細胞 (每毫升 2×10^5 個細胞之濃度) 中。因此最終 100 μ l 分析體積含有各種稀釋度之 mAbdAb (25 nM 以 3 倍稀釋度滴定至 0.01 nM 之最終濃度)、重組大腸桿菌表現之人類 IL-13 (10 ng/ml 之最終濃度) 及 TF-1 細胞 (每毫升 1×10^5 個細胞之最終濃度)。分析盤在含濕氣 CO₂ 培育箱中在 37°C 下培育約 3 天。接著使用 Promega 之「CellTitre 96®

非放射性細胞增殖分析法」(產品目錄第G4100號)如製造商說明書中所述來測定細胞增殖量。96孔盤中之樣品的吸光度於讀盤器中在570 nm下讀取。

mAbdAb中和重組大腸桿菌表現之人類IL-13生物活性的能力表述為將一定量之人類IL-13(10 ng/ml)的生物活性中和50%所需之mAb-dAb的濃度(=ND₅₀)。所需mAbdAb之濃度越低，則中和能力越強。使用GraphPad Prism來計算本文提供之ND₅₀數據(表6)。此等數據圖示於圖2中。

表 6

抗體ID	描述	ND ₅₀ (人類IL-13)
BPC1624	A1Y100BAIa H-TVAAPS-210L1	0.553 nM
BPC1625	A1Y100BIle H-TVAAPS-210L1	0.542 nM
BPC1626	A1Y100BTrp H-TVAAPS-210L1	0.681 nM
BPC1627	A1Y100BVal H-TVAAPS-210L1	0.615 nM
A1L1	抗IL-13抗體	2.524 nM

實例 7-在CHOE1a表現系統中表現包含CDRH3變體抗IL-13 mAb之mAb-dAb

亦於CHOE1a細胞中表現如表5中所示之分子BPC 1624至1631。將編碼重鏈及輕鏈之DNA載體共電穿孔進入懸浮CHO細胞中。細胞在37°C、5% CO₂、130 rpm下在MR1基本選擇性培養基中於搖瓶中傳代直至細胞活力且細胞數提高。接著將CHO細胞接種於MR1基本x2選擇性培養基中且在34°C、5% CO₂、130 rpm下培育8至12天。離心集結細胞且無菌過濾上清液。

使用固定蛋白質A管柱、經由親和層析法來純化所表現

之物質且藉由量測280 nm下之吸光度來測定產量。經由尺寸排阻層析法測定聚集物含量。經由製備型尺寸排阻層析法移除聚集物且再評估產量。表7列出自此表現系統獲得之聚集物之產量及含量。

表 7

分子	表現體積 (ml)	產量(mg) (蛋白質A預清 洗後)	聚集物(%) (蛋白質A預清 洗後)	最終產量 (mg)	最終聚集物 (%)
BPC1628	850	80.70	17.1%	39.50	2.6%
BPC1629	850	77.90	20.3%	35.25	2.8%
BPC1630	850	69.30	15.7%	38.00	3.3%
BPC1631	850	61.47	20.3%	30.00	2.3%
BPC1624	850	88.65	15.2%	45.00	2.6%
BPC1625	850	77.49	16.2%	37.49	2.3%
BPC1626	850	65.16	12.6%	30.80	3.1%
BPC1627	850	73.26	15.2%	34.44	1.9%

實例8-抗原結合蛋白之化學計量評估(使用 Biacore™)

此實例為預示性的。其為進行可測試本發明之抗原結合蛋白的另一分析法提供指導。

藉由一級胺偶聯將抗人類IgG固定在CM5生物感測器晶片上。抗原結合蛋白捕捉於此表面上，隨後，單一濃度之IL-13或IL-4或IL-5通過，此濃度足以飽和結合表面且所觀測之結合信號達到完全R-max。接著使用既定公式計算化學計量：

化學計量 = $R_{\max} \times Mw(\text{配位體}) / Mw(\text{分析物}) \times R(\text{所固定或捕捉之配位體})$

當計算一種以上分析物同時結合之化學計量時，使不同

抗原以飽和抗原濃度依序通過且如上計算化學計量。該研究可在25℃下使用HBS-EP操作緩衝液在Biacore 3000上進行。

實例9-對經改良之人類化變體mAb的劑量預測

開發抗體-配位體結合PK-PD模型，以基於結合親和力及預測之人類潛在治療劑量對不同單株抗體(mAb)候選劑評級。

出於此目的，將預測之人類潛在治療劑量定義為在每月靜脈內投與mAb後對肺(作用部位)中之靶IL-13提供穩定狀態之90%抑制持續1 h的劑量。假定各分子之分子量相同且等於mAb之標準分子量，亦即150 kDa。此外，在缺乏不同候選劑之動物或人類藥物動力學數據的情況下，A1L1抗體之人類藥物動力學推定至所有候選劑。

對各種mAb使用相同的抗體-配位體結合PK-PD模型以及關於靶濃度、靶轉換(target turnover)、靶組織:血漿比率及mAb組織穿透之相同假定。經由該模型所提供之評級因此僅基於分子之結合親和力(此為唯一不同之參數)。在此等條件下，預測4種候選劑(A1Y100B1leL1、A1Y100BValL1、A1Y100BA1aL1及A1Y100BTrpL1)之人類潛在治療劑量以得到勝過對A1L1預測之人類潛在治療劑量的實質改良。

實例10-含有變體IL-4 dAb之抗IL13/IL4 mAbdAb

10.1 建構及表現

使用聚集預測算法研究抗IL-4 dAb(DOM9-155-154，

SEQ ID NO: 80)之有聚集傾向的殘基。Kabat位置89處之白胺酸殘基被鑑別為促進聚集之關鍵殘基。

為了降低含有此dAb之mAbdAb的聚集潛力，此胺基酸殘基被取代為其他胺基酸以產生許多mAb-dAb變體。使用編碼現有mAbdAb構築體之重鏈的DNA表現載體、經由定點突變誘發來產生表現構築體。包含突變dAb序列之所得新mAbdAb重鏈的蛋白質序列於SEQ ID NO: 117-134中給出。

在位置89處合併另一突變之其他重鏈序列為SEQ ID NO: 96-106。此等分子詳述於實例11中。

表8提供所表現之分子清單。

表 8

標識符	替代名稱	連接子	分子描述	蛋白質 SEQ ID NO:
BPC1090	829H- (TVAAPS) ₂ GS- 154 (89G)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89G)	117
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1091	829H- (TVAAPS) ₂ GS- 154 (89S)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89S)	118
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1092	829H- (TVAAPS) ₂ GS- 154 (89H)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89H)	119
			L鏈：抗人類IL-13 mAb輕鏈	24

標識符	替代名稱	連接子	分子描述	蛋白質 SEQ ID NO:
BPC1093	829H- (TVAAPS) ₂ GS- 154 (89M)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89M)	120
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1094	829H- (TVAAPS) ₂ GS- 154 (89A)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89A)	121
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1095	829H- (TVAAPS) ₂ GS- 154 (89T)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89T)	122
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1108	829H- (TVAAPS) ₂ GS- 154 (89C)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89C)	123
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1109	829H- (TVAAPS) ₂ GS- 154 (89R)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89R)	124
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1110	829H- (TVAAPS) ₂ GS- 154 (89W)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89W)	125
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1111	829H- (TVAAPS) ₂ GS- 154 (89E)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89E)	126
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1112	829H- (TVAAPS) ₂ GS- 154 (89K)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89K)	127

標識符	替代名稱	連接子	分子描述	蛋白質 SEQ ID NO:
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1113	829H- (TVAAPS) ₂ GS- 154 (89D)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89D)	128
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1114	829H- (TVAAPS) ₂ GS- 154 (89N)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89N)	129
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1115	829H- (TVAAPS) ₂ GS- 154 (89Y)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89Y)	130
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1116	829H- (TVAAPS) ₂ GS- 154 (89V)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89V)	131
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1117	829H- (TVAAPS) ₂ GS- 154 (89I)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89I)	132
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1118	829H- (TVAAPS) ₂ GS- 154 (89F)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89F)	133
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1119	829H- (TVAAPS) ₂ GS- 154 (89P)	(TVAAPS) ₂ GS	H鏈：抗人類IL-13 mAb重鏈 Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154 (89P)	134
			L鏈：抗人類IL-13 mAb輕鏈	24

10.2 分子表現於HEK 293 6E細胞中

將分別編碼重鏈及輕鏈之pTT質體短暫共轉染入HEK

293 6E細胞中且小規模表現以產生抗體分子。轉染長達24小時後將胰化蛋白飼料添加至各細胞培養液中且3天後收集細胞。評估直接來自組織培養液上清液中之抗體分子且使用Gyrolab工作站進行定量。

定量細胞上清液中之抗體分子的Gyrolab工作站方法

使用Gyrolab Bioaffy工作站(Gyros)、經由定量免疫分析法來定量來自組織培養液上清液中之由HEK 2936E小規模短暫轉染所產生的抗體(0.75-2.0 ml)。使用固定在塗有抗生蛋白鏈菌素之粒子上的生物素標記抗IgG親和抗體分子(Abcam)、在光碟(CD)微型實驗室(Gyros)上、經由Fc區捕捉抗體。將親和抗體試劑短暫渦旋且用PBS-吐溫20(0.01% v/v)稀釋至0.1 mg/ml之最終工作濃度(working concentration)。接著使用雷射誘導螢光、經由標記ALEXA 647之Fab2抗人類IgG κ 輕鏈分子偵測抗體。藉由短暫渦旋且藉由在13000 rpm下離心4分鐘來製備標記ALEXA 647之偵測劑。將標記之Fab2偵測劑添加至未標記Fab2中，使用Rexcip F偵測試劑稀釋劑(Gyros)分別稀釋至75 nM及1.5 μ M之最終濃度。相對於抗CD23單株抗體標準曲線，抗體定量範圍介於0.244-250 μ g/ml之間。藉由組織培養基(Freestyle 293表現培養基，氧化異丙烯F68(Pluronic F68)及遺傳黴素(Geneticin)，Invitrogen))連續稀釋抗體來產生抗CD23(1 mg/ml)標準曲線。

在一些情況下，使用固定蛋白質A管柱純化抗體分子且藉由讀取280 nm下之吸光度進行定量，且需要時，在下述

實例所述之分析法中評估該純化抗體分子。

10.3 IL-4結合ELISA

使用下列方法測試此等 mAbdAb 在直接結合 ELISA 中對 IL-4 之結合。

用含於 NaHCO_3 中之 $5 \mu\text{g/ml}$ 人類 IL-4 (在 GSK 製備) 塗佈 96 孔高結合培養盤且在 4°C 下儲存隔夜。用含有 0.05% 之吐溫-20 的 Tris 緩衝鹽水 (TBST) 洗滌培養盤兩次。在各孔中添加 $100 \mu\text{L}$ 阻斷溶液 (含有 1% BSA 之 TBST 緩衝液) 且培養盤在室溫下培育至少 1 小時。越過培養盤的經純化 mAbdAb 於阻斷溶液中連續稀釋。在 1 小時培育之後，洗滌培養盤 3 次。山羊抗人類 κ 輕鏈特異性過氧化酶結合抗體 (Sigma A7164) 於阻斷溶液中稀釋至 $1 \mu\text{g/mL}$ 且向各孔中添加 $50 \mu\text{L}$ 。培養盤培育 1 小時。再進行 3 次洗滌步驟之後，向各孔中添加 $50 \mu\text{L}$ OPD (鄰苯二胺二鹽酸鹽) SigmaFast 受質溶液且約 5 分鐘後藉由添加 $25 \mu\text{L}$ 之 3 M 硫酸終止反應。使用鹼性終點方案、使用 VersaMax 可調微定量盤讀取器 (Molecular Devices) 在 490 nm 下讀取吸光度。

除均為純化物質之陽性對照物 (抗 IL-4 mAb) 及抗 IL13 陰性對照物 mAb 外，實驗使用直接來自組織培養液上清液中之 mAbdAb 來進行。此等數據展示於圖 17 中。

ELISA 結果顯示，此等短暫表現之抗 IL13 mAb-抗 IL4 dAb 大部分結合 IL-4，但觀測到 IL-4 結合活性的一些變化。純化的陽性對照物抗 IL-4 mAb 亦顯示結合至 IL-4，而純化的陰性對照物 mAb 顯示不結合至人類 IL-4。

實例 11-建構及測試包含 CDRH3 變體抗 IL-13 mAb 及突變 dAb 之抗原結合蛋白 (BPC1085、BPC1086 及 BPC1087)

11.1 建構及表現

使用編碼由抗 IL-13 mAb 及抗 IL-4 dAb 組成之重鏈的質體作為基本構築體以產生替代質體構築體。需要兩步選殖策略。在步驟 1 中，使用 Hind III 及 Spe I、經由限制性選殖將編碼 H 鏈之抗 IL13 mAb 組分之 V_H 的 DNA 序列置換為編碼另一人類化抗 IL13 抗體之 V_H (SEQ ID NO: 54) 的 DNA 序列。在步驟 2 中，經由定點突變誘發使編碼 mAb dAb 之抗 IL4 dAb (DOM9-155-154, SEQ ID NO: 80) 組分中之 Kabat 位置 89 處之白胺酸的密碼子突變成麩醯胺酸。由此產生之所有重鏈 DNA 序列皆於 SEQ ID NO: 96、98 及 100 中給出。表 9 提供所建構及所表現之分子清單。

表 9-所建構及所表現之抗體概述

標識符	替代名稱	連接子	分子描述	蛋白質 SEQ ID NO:
BPC1085	829H-GS(TVAAPSGS) ₂ -154 (89Q) 或 829H-GS(TVAAPSGS) ₂ -256	GS(TVAAPSGS) ₂	H鏈：抗人類IL-13 mAb重鏈Y100B_V-GS(TVAAPSGS) ₂ -DOM9-155-256	96
			L鏈：抗人類IL-13 mAb輕鏈	24
BPC1086	829H-GS(TVAAPSGS) ₃ -154 (89Q) 或 829H-GS(TVAAPSGS) ₃ -256	GS(TVAAPSGS) ₃	H鏈：抗人類IL-13 mAb重鏈Y100B_V-GS(TVAAPSGS) ₃ -DOM9-155-256	98
			L鏈：抗人類IL-13 mAb輕鏈	24

BPC1087	829H- GS(TVAAPSGS) ₄ - 154 (89Q) 或 829H- GS(TVAAPSGS) ₄ - 256	GS(TVAAPSGS) ₄	H鏈：抗人類IL-13 mAb重鏈Y100B_V- GS(TVAAPSGS) ₄ - DOM9-155-256	100
			L鏈：抗人類IL-13 mAb輕鏈	24

使用 293fectin(Invitrogen, 12347019)將編碼 BPC1085、BPC1086及 BPC1087 mAb dAb 之重鏈及輕鏈表現質體共轉染入 HEK 2936E 細胞中。24 小時後將胰化蛋白飼料添加至各細胞培養液中且 72 小時後收集細胞。在結合分析法測試之前使用蛋白質 A 管柱純化抗體。

使用蛋白質 A 親和法純化 BPC1085、BPC1086 及 BPC1087 mAb dAb。在 AKTA Xpress 系統上使用 1 ml 蛋白質 A 管柱 (GE Healthcare)，用 PBS (Gibco/Invitrogen) 平衡管柱且使用 Pierce IgG 溶離物溶離抗體。使用 1 M 參(羥甲基)胺基甲烷緩衝液(一般而言 5-10% v/v)中和溶離份。彙集抗體溶離份且經由尺寸排阻層析法分析聚集度且使用分光光度計藉由在 280 nm 下讀取 OD 進行定量。

對此等抗體與描述於表 10 中之類似 mAb dAb (2222、2223、2230 及 2231) 進行比較。此等類似 mAb dAb 包含：

- i) 與 BPC1085、BPC1086 及 BPC1087 中所用之 dAb 一致的 dAb，例外之處為位置 89，在 BPC2222、BPC2223、BPC2230 及 BPC2231 中，其為「L」且在 BPC1085、BPC1086 及 BPC1087 中，其為「Q」，
- ii) 相同連接子，
- iii) 與 BPC1085、BPC1086 及 BPC1087 中所用之 IL-13 mAb

序列一致的IL-13 mAb序列，例外之處為位置100B，在BPC2222、BPC2223、BPC2230及BPC2231中，其為「Y」且在BPC1085、6及7中，其為「V」。

表 10：

標識符	mAb	連接子	dAb	重鏈	輕鏈
BPC2222	A1L1	GS(TVAAPSGS) ₁	DOM9-155-154	135	24
BPC2223	A1L1	GS(TVAAPSGS) ₂	DOM9-155-154	136	24
BPC2230	A1L1	GS(TVAAPSGS) ₃	DOM9-155-154	137	24
BPC2231	A1L1	GS(TVAAPSGS) ₄	DOM9-155-154	138	24

使用蛋白質A親和法純化BPC2222、2223、2230及2231 mAbdAb。在AKTA Xpress系統上使用1 ml蛋白質A管柱(GE Healthcare)，用PBS(Gibco/Invitrogen)平衡管柱且使用Pierce IgG溶離物溶離抗體。使用1 M參(羥甲基)胺基甲烷緩衝液(一般而言5-10% v/v)中和溶離份。彙集抗體溶離份且經由尺寸排阻層析法分析聚集度且使用分光光度計藉由在280 nm下讀取OD進行定量。

BPC2222、2223、2230及2231顯示聚集度介於30-40%之間，聚集物溶離早於10分鐘。

如經由尺寸排阻層析法所評估，構築體BPC1085、1086及1087相較於BPC2222、2223、2230及2231顯示較低聚集度。此等分子之SEC概況展示於圖3-9中。

11.2 IL-4結合ELISA

根據實例10.3中所述方法測試純化BPC1085、BPC1086及BPC1087 mAbdAb在直接結合ELISA中對IL-4之結合。

此等數據展示於圖10中。ELISA結果證實此等純化

mAbdAb結合至IL-4。陽性對照物抗IL-4 mAb及BPC2231亦顯示結合至IL-4，而陰性對照物mAb(抗IL-13 mAb)顯示不結合至人類IL-4。此指示在此ELISA中當連接子長度自GS(TVAAPSGS)增加至GS(TVAAPSGS)₂₋₄時，dAb效能增加。

11.3 在TF-1細胞增殖生物分析法中對IL-4之中和

在TF-1細胞生物分析法中測試純化BPC1085、BPC1086及BPC1087對人類IL-4之中和程度。

TF-1細胞回應於許多不同細胞激素(包括人類IL-4)而增殖。此等細胞對於IL-4之增殖反應因此可用於量測IL-4之生物活性且隨後已開發一種分析法以測定mAbdAb中和IL-4之效能(抑制IL-4生物活性)。

該分析法在無菌條件下於無菌96孔組織培養盤中進行且所有測試孔皆一式兩份進行。將約2.2 ng/ml經重組大腸桿菌表現之人類IL-4與各種稀釋度之mAbdAb(通常為560 nM以3倍稀釋度滴定至0.009 nM)以120 µl總體積在37°C下預培育1小時。無關特異性之抗體作為陰性對照(抗IL13 mAb)以類似方式滴定。接著將50 µl此等樣品添加至含於無菌96孔組織培養盤中之50 µl TF-1細胞(每毫升 2×10^5 個細胞之濃度)中。因此最終100 µl分析體積含有各種稀釋度之mAb(270 nM以3倍稀釋度滴定至0.005 nM之最終濃度)、重組大腸桿菌表現之人類IL-4(1.1 ng/ml之最終濃度)及TF-1細胞(每毫升 1×10^5 個細胞之最終濃度)。分析盤在含濕氣CO₂培育箱中在37°C下培育約4天。接著使用Promega之

「CellTitre 96®非放射性細胞增殖分析法」(產品目錄第G4100號)、如製造商說明書中所述來測定細胞增殖量。96孔盤中之樣品的吸光度於讀盤器中在570 nm下讀取。此等數據輸入Excel試算表，對一式兩份測試孔之值求平均值且減去平均背景值(無mAb-dAb及無IL-4測試孔)。

mAbdAb中和重組經大腸桿菌表現之人類IL-4生物活性的能力表述為將一定量之人類IL-4(1.1 ng/ml)的生物活性中和50%所需之mAb-dAb濃度(=ND₅₀)。所需mAbdAb之濃度越低，則中和能力越強。使用Excel中之Robosage函數來計算本文提供之ND₅₀數據(表11)。此等數據圖示於圖11中。

抗IL-4 mAb及DOM9-155-154(SEQ ID NO : 80)作為中和人類及石蟹獼猴IL-4的陽性對照物而包括於TF-1細胞生物分析法中。另外，對無關抗原具有特異性之dAb(模擬dAb)亦作為中和人類或石蟹獼猴IL-4的陰性對照物而包括於TF-1細胞生物分析法中。

此等測試重複若干次且圖11展示此等實驗之一的結果。根據數據集計算ND₅₀值。ND₅₀值為能夠將IL-4之生物活性中和50%之mAbdAb、或mAb或dAb的濃度。

平均ND₅₀值及測試次數(n)展示於表11中。

表 11

分子	平均ND ₅₀ 值及標準偏差(nM)	重複次數
BPC1085	9.21	3
BPC1086	4.32	3
BPC1087	3.59	3
抗IL-4 mAb	1.95	2
DOM9-155-154	0.98	2
陰性對照dAb	不中和	2

此等數據證實，純化 BPC1085、BPC1086 及 BPC1087 mAbdAb 中和人類及石蟹獼猴 IL-4 之生物活性。抗 IL-4 mAb 及 DOM9-155-154 亦中和了人類及石蟹獼猴 IL-4 之生物活性，而陰性 dAb(模擬 dAb)在相同生物分析法中未展示中和作用。

所有三種 mAbdAb 皆展示良好效能，且根據中和分析法顯而易見 dAb 效能隨連接子長度增加而增加的明顯趨勢(儘管較粗糙的 ELISA 未偵測此效能差異)。陰性對照物抗 IL-4 mAb 在相同生物分析法中未展示中和作用。

11.5 在 TF-1 細胞增殖生物分析法中對人類 IL-13 之中和

在如下所述之 TF-1 細胞生物分析法中測試純化 BPC1085、BPC1086 及 BPC1087 對人類 IL-13 之中和程度。

TF-1 細胞回應於許多不同細胞激素(包括人類 IL-13)而增殖。此等細胞對於 IL-13 之增殖反應因此可用於量測 IL-13 之生物活性且隨後已開發一種分析法以測定 mAbdAb 中和 IL-13 之效能(抑制 IL-13 生物活性)。

該分析法在無菌條件下於無菌 96 孔組織培養盤中進行且

所有測試孔皆一式兩份進行。將約 14 ng/ml 經重組大腸桿菌表現之人類 IL-4 與各種稀釋度(通常為 560 nM 以 3 倍稀釋度滴定至 0.009 nM)之 mAbdAb 以 120 μ l 總體積在 37°C 下預培育 1 小時。無關特異性之抗體及 dAb 作為陰性對照物(分別為抗 IL-4 mAb 及 DOM9-155-154)以類似方式滴定。接著將 50 μ l 此等樣品添加至含於無菌 96 孔組織培養盤中之 50 μ l TF-1 細胞(每毫升 2×10^5 個細胞之濃度)中。因此最終 100 μ l 分析體積含有各種稀釋度之 mAbdAb(270 nM 以 3 倍稀釋度滴定至 0.005 nM 之最終濃度)、重組大腸桿菌表現之人類 IL-13(7 ng/ml 之最終濃度)及 TF-1 細胞(每毫升 1×10^5 個細胞之最終濃度)。分析盤在含濕氣 CO₂ 培育箱中在 37°C 下培育約 4 天。接著使用 Promega 之「CellTitre 96® 非放射性細胞增殖分析法」(產品目錄第 G4100 號)、如製造商說明書中所述來測定細胞增殖量。96 孔盤中之樣品的吸光度於讀盤器中在 570 nm 下讀取。此等數據輸入 Excel 試算表，對一式兩份測試孔之值求平均值且減去平均背景值(無 mAb-dAb 及無 IL-13 測試孔)。

mAbdAb 中和重組大腸桿菌表現之人類 IL-13 生物活性的能力表述為將一定量之人類 IL-13(7 ng/ml)的生物活性中和 50% 所需之 mAb-dAb 濃度(=ND₅₀)。所需 mAbdAb 之濃度越低，則中和能力越強。使用 Excel 中之 Robosage 函數來計算本文提供之 ND₅₀ 數據(表 12)。此等數據圖示於圖 12 中。

抗 IL-13 mAb(SEQ ID NO: 22 & 24)作為中和人類 IL-13 的陽性對照物而包括於 TF-1 細胞生物分析法中。另外，抗

IL-4 mAb亦作為陰性對照物而包括在內。

圖 12 展示 TF-1 細胞中和分析法之結果。根據數據集計算 ND_{50} 值。 ND_{50} 值為能夠將 IL-13 之生物活性中和 50% 之 mAbdAb 或 mAb 或 dAb 的濃度。

平均 ND_{50} 值及測試次數展示於表 12 中。

表 12

分子	平均 ND_{50} 值及標準偏差(nM)	重複次數
BPC1085	0.88	1
BPC1086	1.01	1
BPC1087	1.14	1
抗IL-13 mAb	5.01	1
抗IL-4 mAb	不中和	1

此等數據證實，純化 BPC1085、BPC1086 及 BPC1087 mAbdAb 中和重組人類及石蟹獼猴 IL-13 之生物活性。陰性對照物抗 IL-4 mAb 在相同生物分析法中未展示中和作用。

實例 12 抗 IL-13 mAb 輕鏈之再人類化

12.1 再人類化

將鼠類抗體 6A1 (其輕鏈於 SEQ ID NO: 59 中表示) 之輕鏈 CDR 再接枝於新架構上以改良某些抗 IL-13 mAb-抗 IL-4 dAb 分子 (BPC1085) 之表現。使用基於 PCR 之策略及重疊寡核苷酸來重新建構密碼子優化之輕鏈可變區序列 (概述於表 13 中)。PCR 引子設計成合併信號序列 (SEQ ID NO: 56) 且包括 HindIII 及 BsiWI 限制性位點，該等 HindIII 及 BsiWI 限制性位點設計成框住 V_L 域且允許選殖入含有人類 κ C 區的 pTT 及 Rln 哺乳動物表現載體中。表 13 概述已建構之再人

類化輕鏈。

表 13

輕鏈名稱	描述	主鏈	反突變	核苷酸序列 SEQ ID NO:	胺基酸序列 SEQ ID NO:
P0	抗IL-13 808VL κ輕鏈	IGKV1_39+JK2	N/A	108	109
P1	抗IL-13 809VL κ輕鏈	IGKV1_39+JK2	I2V+Q3L	110	111
Q0		IGKV3_20+JK2	N/A	112	113
Q1		IGKV3_20+JK2	I2V、V3L、 L4M、E1D、 R45K、I58V	114	115

12.2 分子表現於HEK 293 6E細胞中

首先以mAb形式檢驗再人類化輕鏈之表現性質。使用293fectin(Invitrogen, 12347019)將編碼A1Y100BVAL1 (SEQ ID NO: 54)重鏈、現有輕鏈(SEQ ID NO: 24)及再人類化輕鏈之質體短暫共轉染入HEK 293 6E細胞中。小規模(2×0.75 ml培養體積)表現質體以產生抗體。24小時後將胰化蛋白飼料添加至細胞培養液中且再過72小時後收集細胞。表14概述已建構及表現之所有mAb。

表 14

抗體ID	分子描述	蛋白質 SEQ ID NO:
A1Y100BVAL1	H鏈：抗人類IL-13 Y100b_V mAb	54
	L鏈：586抗人類IL-13 mAb	24
BPC3208	H鏈：抗人類IL-13 Y100b_V mAb	54
	L鏈：P0再人類化抗人類IL-13 mAb	108
BPC3211	H鏈：抗人類IL-13 Y100b_V mAb	54

	L鏈：P1再人類化抗人類IL-13 mAb	110
BPC3219	H鏈：抗人類IL-13 Y100b_V mAb	54
	L鏈：Q0再人類化抗人類IL-13 mAb	112
BPC3220	H鏈：抗人類IL-13 Y100b_V mAb	54
	L鏈：Q1再人類化抗人類IL-13 mAb	114

使用 Gyrolab 工作站、經由定量免疫分析法評估直接來自組織培養液上清液中之抗體的表現。含有再人類化輕鏈（分別表示為 P0 及 P1）之抗體 BPC3208 及 BPC3211 相較於 A1Y100BVAL1 mAb 展示改良之表現產量。Q0 及 Q1 輕鏈（BPC3219 及 BPC3220）不改良抗 IL-13 mAb 之表現。表現數據呈現於表 15 中。

表 15

抗體ID	細胞上清液中之總產量(μg)
A1Y100BVAL1	19.9
BPC3208	111.0
BPC3211	115.0
BPC3219	16.0
BPC3220	18.3

12.3 mAb-dAb 表現於 HEK 293 6E 細胞中

因為 BPC3208 及 BPC3211 之再人類化輕鏈使抗 IL-13 mAb 之表現改良，所以其在抗 IL-13mAb-抗 IL-4dAb 之情形下檢驗。使用 293fectin(Invitrogen, 12347019) 將再人類化輕鏈 P0 及 P1 及 586(L1) 輕鏈與 829H-GS(TVAAPSGS)₂-256 重鏈 (SEQ ID NO: 96, 詳情概述於表 16 中) 共轉染入 HEK 293 6E 細胞中。質體在 50 至 500 ml 規模上受表現以產生抗體分子。24 小時後將胰化蛋白饋料添加至細胞培養液中且再過 48 小時後收集細胞。使用固定蛋白質 A 管柱純化抗體且藉

由讀取280 nm下之吸光度進行定量且需要時，在下述實例所述之分析法中評估該純化抗體分子。如圖13及14中所說明，經由尺寸排阻層析法(SEC)分析BPC3214及BPC3215。

表 16

抗體ID	替代名稱	連接子	分子描述	蛋白質 SEQ ID NO:	DNA SEQ ID NO:
BPC1085	829H- GS(TVAAPSGS) ₂ -256	GS(TVAAPSGS) ₂	H鏈：抗人類IL-13 mAb重鏈 Y100B_V- GS(TVAAPSGS) ₂ - DOM9-155-256	96	97
			L鏈：586抗人類IL-13 mAb輕鏈	24	25
BPC3214	808H- GS(TVAAPSGS) ₂ -256	GS(TVAAPSGS) ₂	H鏈：抗人類IL-13 mAb重鏈 Y100B_V- GS(TVAAPSGS) ₂ - DOM9-155-256	96	97
			L鏈：P0再人類化抗人類IL-13 mAb	108	109
BPC3215	809H- GS(TVAAPSGS) ₂ -256	GS(TVAAPSGS) ₂	H鏈：抗人類IL-13 mAb重鏈 Y100B_V- GS(TVAAPSGS) ₂ - DOM9-155-256	96	97
			L鏈：P1再人類化抗人類IL-13 mAb	110	111

與以mAb形式觀測之結果一致，含有再人類化輕鏈之mAbdAb(BPC3214及BPC3215)相較於BPC1085展示改良之表現。代表性表現數據概述於表17中。

表 17

抗體ID	純化mAbdAb之產量(μg/ml)
BPC1085	5.6
BPC3214	9.8
BPC3215	7.2

12.4 人類IL-13結合ELISA

經由直接結合ELISA測試純化BPC3214及BPC3215相較於BPC1085(描述於實例10中)對人類IL-13的結合。抗IL-13 mAb A1Y100BVAL1及抗IL-4 mAb亦分別作為陽性及陰性對照物加以檢驗。用5 $\mu\text{g/ml}$ 經重組大腸桿菌表現之人類IL-13(批號: GRITS31061)以50微升/孔塗佈96孔高結合培養盤且在+4°C下培育隔夜。隨後所有步驟皆在室溫下進行。用含有0.05%吐溫20之磷酸鹽緩衝鹽水洗滌該等培養盤3次。向各孔中添加100 μL 阻斷溶液(含有1% BSA、0.05%吐溫-20之磷酸鹽緩衝鹽水)且在室溫下培育該等培養盤至少1小時。接著進行另一洗滌步驟。越過培養盤之純化抗體於阻斷溶液中連續稀釋。培育1小時之後,洗滌培養盤。山羊抗人類 κ 輕鏈特異性過氧化酶結合抗體(Sigma A7164)於阻斷溶液中稀釋至0.75 $\mu\text{g/mL}$ 且向各孔中添加50 μL 。將該等培養盤培育1小時。再進行兩次洗滌步驟之後,向各孔中添加50 μl OPD(鄰苯二胺二鹽酸鹽)SigmaFast受質溶液且藉由添加50 μL 之3 M硫酸終止反應。使用鹼性終點方案、使用VersaMax微定量盤讀取器(Molecular Devices)在490 nm下讀取吸光度。此等數據展示於圖15中。直接結合ELISA證實BPC3214及BPC3215結合至人類IL-13。BPC3214及BPC3215展示與BPC1085類似之IL-13結合效能。陽性對照物抗IL-13 mAb A1Y100BVAL1亦展示結合至重組IL-13,而陰性對照物抗IL-4 mAb顯示不結合至人類IL-13。

12.5 人類IL-4結合ELISA

在直接結合ELISA中亦測試純化BPC3214及BPC3215對重組大腸桿菌表現之人類IL-4的結合。如實例4中所述進行ELISA，用5 µg/ml經重組大腸桿菌表現之人類IL-4以50微升/孔塗佈96孔高結合培養盤且在+4°C下培育隔夜。此等數據展示於圖16中。直接結合ELISA證實BPC3214及BPC3215結合至人類IL-4。亦檢驗BPC1085。BPC3214展示與BPC1085類似之IL-4結合效能。陽性對照物抗IL-4 mAb亦展示結合至重組IL-4，而陰性對照物抗IL-13mAb A1Y100BVAL1顯示不結合至人類IL-4。

實例13-包含初始IL-13 mAb CDRH3之mAbdAb (BPC2222、BPC2223及BPC2230-2231)對IL-13及IL-4之結合親和力，如經由BIAcore™分析所評估

方法

蛋白質A藉由一級胺偶聯固定在C1晶片上；此表面用作欲測試之抗體分子的捕捉表面。重組大腸桿菌表現之人類IL13在256、64、16、4及1 nM下使用，重組大腸桿菌表現之人類IL4在64、16、4、1及0.25 nM下使用，0 nM(亦即僅用緩衝液)用作IL4與IL13結合之結合曲線的雙重參照。用100 mM磷酸再生蛋白質A表面。使用HBS-EP作為操作緩衝液在25°C下操作該分析法。針對Biacore T100分析軟體固有之1:1模型擬合數據。

結合至人類IL13之結果展示於表18中且結合至人類IL4之結果展示於表19中。

表 18

分子名稱	分子描述	ka(M/s)	kd(1/s)	K _D (nM)
BPC2222	586H-GSTVAAPSGS-154	1.31E+06	4.93E-04	0.376
BPC2223	586H-GS(TVAAPSGS)2-154	1.32E+06	4.90E-04	0.372
BPC2230	586H-GS(TVAAPSGS)3-154	1.31E+06	4.88E-04	0.373
BPC2231	586H-GS(TVAAPSSGS)4-154	1.30E+06	5.13E-04	0.394

表 19

分子名稱	分子描述	ka(M/s)	kd(1/s)	K _D (nM)
BPC2222	586H-TVAAPSGS-154	1.06E+05	1.09E-04	1.027
BPC2223	586H-TVAAPSGSx2-154	8.59E+06	1.56E-04	0.018
BPC2230*	586H-TVAAPSGSx3-154	2.48E+07	2.48E-04	0.010
BPC2231*	586H-TVAAPSSGSx4-154	4.03E+07	2.31E-04	0.006

*BPC2230及2231之結合速率(on-rate)超出Biacore之靈敏度，但未能精確分析此數據之事實說明，與IL4可能以快結合速率、高親和力相互作用。

實例14-包含初始IL-13 mAb CDRH3之mAbdAb (BPC2222、BPC2231)及包含變體抗IL-13 mAb CDRH3之mAbdAb (BPC1085-1087)對IL-13及IL-4的結合親和力，如經由BIAcore™分析所評估

方法

蛋白質A藉由一級胺偶聯固定在CM5晶片上；此表面用作欲測試之抗體分子的捕捉表面。重組大腸桿菌表現之人類IL13僅在256 nM下使用，重組大腸桿菌表現之人類IL4在64、16、4、1 nM下使用，0 nM(亦即僅用緩衝液)用作IL4與IL13結合之結合曲線的雙重參照。用50 mM NaOH再生蛋白質A表面。使用HBS-EP作為操作緩衝液在25℃下操

作該分析法。針對Biacore T100分析軟體固有之1:1模型擬合數據。

結合至人類IL13之結果展示於表20中，且結合至人類IL4之結果展示於表21中。

表 20

分子名稱	ka(M/s)	kd(1/s)	K _D (nM)
BPC2222	1.64E+05	5.15E-05	0.314
BPC2231	5.36E+08	1.16E-03	0.002
BPC1085	1.87E+07	8.97E-04	0.048
BPC1086	7.99E+07	1.64E-03	0.021
BPC1087	9.86E+07	1.79E-03	0.018

BPC1086及BPC1087之結合速率超出Biacore之靈敏度，但未能精確分析此數據之事實說明，與IL4可能以快結合速率、高親和力相互作用。

表 21

分子名稱	ka(M/s)	kd(1/s)	K _D (nM)
BPC2222	1.44E+06	4.44E-04	0.308
BPC2231	1.56E+06	4.95E-04	0.316
BPC1085	1.20E+06	6.39E-05	0.053
BPC1086	1.28E+06	6.57E-05	0.051
BPC1087	1.13E+06	6.42E-05	0.057

實例 15- 包含許多變體抗 IL-13 mAb CDRH3 之 mAbdAb (BPC1085、BPC1090-BPC1095、及 BPC1108-BPC1119) 對 IL-4 的結合親和力，如經由BIAcore™分析所評估方法(人類IL-4結合親和力)

蛋白質A藉由一級胺偶聯固定在CM5晶片上；此表面用

作欲測試之抗體分子的捕捉表面。

重組大腸桿菌表現之人類IL4在64、16、4、1及0.25 nM下使用。所有結合曲線皆以0 nM進樣(亦即僅用緩衝液)作為雙重參照。

用50 mM NaOH再生蛋白質A表面。使用HBS-EP作為操作緩衝液在25℃下操作該分析法。針對Biacore T100分析軟體固有之1:1模型擬合數據。

結合至人類IL4之結果展示於表22中。

表 22

分子名稱	ka (M/s)	kd (1/s)	K _D (nM)
BPC1085	1.07E+07	8.34E-04	0.078
BPC1090	4.34E+06	4.16E-04	0.096
BPC1091	6.05E+06	1.02E-03	0.168
BPC1092	2.27E+06	3.89E-03	1.713
BPC1093	3.84E+06	2.11E-04	0.055
BPC1094	1.46E+06	3.04E-03	2.078
BPC1095	6.78E+06	3.18E-02	4.687
BPC1108	4.38E+06	1.23E-03	0.281
BPC1109	1.20E+06	1.77E-01	147.300
BPC1110	1.07E+06	1.73E-03	1.626
BPC1111	2.98E+06	1.11E-04	0.037
BPC1112*	1.14E+08	3.31E+00	28.980
BPC1113	未顯示結合	未顯示結合	未顯示結合
BPC1114	3.89E+06	2.55E-03	0.656
BPC1115**	1.44E+08	3.29E-01	2.292
BPC1116	6.82E+06	2.74E-03	0.402
BPC1117	3.95E+06	9.13E-04	0.231
BPC1118	6.39E+06	2.58E-03	0.405
BPC1119	未顯示結合	未顯示結合	未顯示結合

*BPC1112數據具有正解離速率(off-rate)，此係由於機器可能因解離速率如此之迅速而不能計算真實解離速率所致，此外，此構築體之結合速率超出Biacore可量測之程度，但構築體對IL4之結合極其不良。

*BPC1115亦具有不可能存在之結合速率，其在BIAcore計算親和力之範圍外。

實例 16- 包含再人類化輕鏈之 mAbdAb(BPC3214 及 BPC3215)相較於包含初始輕鏈之 mAbdAb(BPC1085)對 IL-13 的結合親和力，如經由 BIAcore™ 分析所評估

方法(人類及石蟹獼猴 IL-13 結合親和力)

蛋白質 A 藉由一級胺偶聯固定在 CM5 晶片上；此表面用作欲測試之抗體分子的捕捉表面。

重組大腸桿菌表現之人類 IL13 及石蟹獼猴 IL13 在 64、16、4、1 及 0.25 nM 下使用。所有結合曲線皆以 0 nM 進樣(亦即僅用緩衝液)作為雙重參照。

用 50 mM NaOH 再生蛋白質 A 表面。使用 HBS-EP 作為操作緩衝液在 25°C 下操作該分析法。針對 Biacore T100 分析軟體固有之 1:1 模型擬合數據。

結合至人類及石蟹獼猴 IL13 之結果展示於表 23 中。

表 23

分子名稱	ka (M/s)	kd (1/s)	K _D (nM)	註解
結合至人類 IL13				
BPC3214	7.749E+05	7.18E-05	0.093	
BPC3215	8.220E+05	5.23E-05	0.064	
BPC1085	8.652E+05	6.34E-05	0.073	

結合至石蟹獼猴IL13				
BPC3214*	3.214E+05	5.07E-06	0.015770	不可能存在之解離速率
BPC3215*	3.283E+05	3.13E-06	0.009546	不可能存在之解離速率
BPC1085*	3.552E+05	5.19E-10	0.000001	不可能存在之解離速率

*石蟹獼猴 IL13 結合至 BPC3214、BPC3215 及 BPC1085 之解離速率 (ka) 超出 Biacore T100 之靈敏度，此指示解離速率極慢且相互作用可能具有極高親和力。

實例 17-對含有或不含有突變 dAb 之 mAbdAb 的著重點研究

將許多 mAbdAb 置於 PBS 或 50 mM 乙酸鹽緩衝液中且在 37°C 下培育多達 14 天。接著針對可見沈澱物之存在、可溶性聚集物及黏附直至濃度穩定性對其進行分析。

結果說明，包含突變 dAb 之 mAbdAb (BPC2222、2223、2230、2231) 在表現上類似於包含非突變 dAb 之 mAbdAb (BPC1085、1086、1087)，如依據溶液中蛋白質濃度無變化所指示，兩類 mAbdAb 在 PBS 與乙酸鹽緩衝液中、在 37°C 下之兩週培育期間均顯示穩定。此外，注意到溶液中之聚集物的含量無變化或變化極小且未觀測到沈澱物。

實例 18-PK 評估

在各別研究中研究 BPC1085、BPC1086 及 BPC1087 靜脈內投與大鼠之後的藥物動力學。亦研究 BPC1085 靜脈內投與石蟹獼猴後的 PK。

發現所有三種分子在大鼠中及 BPC1085 在猴中之 PK 與標準 mAb 之 PK 一致。

序 列 概 述 (表 24)

描述	序 列 標 識 符 (SEQ ID NO)	
	胺 基 酸 序 列	聚 核 苷 酸 序 列
抗IL13 A1，CDRH1	1	-
抗IL13 A1，CDRH2	2	-
抗IL13 A1，CDRH3	3	-
CDRH3替代物	4	-
CDRH3替代物	5	-
CDRH3替代物	6	-
CDRH3替代物	7	-
CDRH3替代物	8	-
CDRH3替代物	9	-
CDRH3替代物	10	-
CDRH3替代物	11	-
CDRH3替代物	12	-
CDRH3替代物	13	-
CDRH3替代物	14	-
CDRH3替代物	15	-
CDRH3替代物	16	-
CDRH3替代物	17	-
CDRH3替代物	18	-
抗IL13 L1，CDRL1	19	-
抗IL13 L1，CDRL2	20	-
抗IL13 L1，CDRL3	21	-
抗IL13 A1 (重鏈)	22	23
抗IL13 L1 (輕鏈)	24	25
抗IL13人類化變體A1 S95 Trp (重鏈)	26	27
抗IL13人類化變體A1 I96 Val (重鏈)	28	29
抗IL13人類化變體A1 Y97 Phe (重鏈)	30	31
抗IL13人類化變體A1 D98 Glu (重鏈)	32	33
抗IL13人類化變體A1 H100A Ala (重鏈)	34	35
抗IL13人類化變體A1 H100A Glu (重鏈)	36	37
抗IL13人類化變體A1 H100A Gln (重鏈)	38	39

抗IL13人類化變體A1 H100A Arg (重鏈)	40	41
抗IL13人類化變體A1 H100A Ser (重鏈)	42	43
抗IL13人類化變體A1 H100A Thr (重鏈)	44	45
抗IL13人類化變體A1 H100A Val (重鏈)	46	47
抗IL13人類化變體A1 Y100B Ala (重鏈)	48	49
抗IL13人類化變體A1 Y100B Ile (重鏈)	50	51
抗IL13人類化變體A1 Y100B Trp (重鏈)	52	53
抗IL13人類化變體A1 Y100B Val (重鏈)	54	55
信號序列	56	-
人類IL13	57	-
鼠類6A1 VH	58	-
鼠類6A1 VL	59	-
替代CDRH1 (Chothia及Kabat編號)	60	-
替代CDRH1 (Chothia及Kabat編號)	61	-
A1Y100BA1a H-TVAAPS-210 (重鏈)	62	63
A1 Y100BI1e H-TVAAPS-210 (重鏈)	64	65
A1Y100BT1p H-TVAAPS -210 (重鏈)	66	67
A1Y100BV1a H-TVAAPS-210 (重鏈)	68	69
A1Y100BA1a H-ASTKGPS-210 (重鏈)	70	71
A1 Y100BI1e H-ASTKGPS-210 (重鏈)	72	73
A1Y100BT1p H-ASTKGPS-210 (重鏈)	74	75
A1Y100BV1a H-ASTKGPS-210 (重鏈)	76	77
DOM9-155-25	78	
DOM9-155-147	79	
DOM9-155-154	80	
DOM9-112-210	81	
連接子	82	
連接子	83	
連接子	84	
連接子	85	
連接子	86	
連接子	87	
147-TVAAPS-586 Y100B V重鏈	88	
147-ASTKG-586 Y100B V重鏈	89	

154-TVAAPS-586 Y100B V 重鏈	90	
154- ASTKG -586 Y100B V 重鏈	91	
連接子	92	
連接子	93	
DOM9-155-154 L89Q(aka DOM9-155-256)	94	95
829H-GS(TVAAPSGS) ₂ -154 L89Q	96	97
829H-GS(TVAAPSGS) ₃ -154 L89Q	98	99
829H-GS(TVAAPSGS) ₄ -154 L89Q	100	101
829H-(TVAAPS) ₂ GS-154 L89Q	102	103
829H-(TVAAPS) ₃ GS-154 L89Q	104	105
829H-(TVAAPS) ₄ GS-154 L89Q	106	107
P0	108	109
P1	110	111
Q0	112	113
Q1	114	115
586H-TVAAPS-154 (H鏈)	116	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154(89G)	117	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154(89S)	118	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154(89H)	119	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154(89M)	120	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154(89A)	121	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154(89T)	122	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154(89C)	123	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154(89R)	124	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS- DOM9-155-154(89W)	125	

抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154(89E)	126	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154(89K)	127	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154(89D)	128	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154(89N)	129	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154(89Y)	130	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154(89V)	131	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154(89I)	132	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154(89F)	133	
抗人類IL-13 mAb重鏈Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154(89P)	134	
抗IL-13 mAb重鏈GS(TVAAPSGS) ₁ -DOM9-155-154	135	-
抗IL-13 mAb重鏈GS(TVAAPSGS) ₂ -DOM9-155-154	136	-
抗IL-13 mAb重鏈GS(TVAAPSGS) ₃ -DOM9-155-154	137	-
抗IL-13 mAb重鏈GS(TVAAPSGS) ₄ -DOM9-155-154	138	
GS(TVAAPSGS) ₁	139	
GS(TVAAPSGS) ₂	140	
GS(TVAAPSGS) ₃	141	
GS(TVAAPSGS) ₄	142	
GS(TVAAPSGS) ₅	143	
GS(TVAAPSGS) ₆	144	
(TVAAPS) ₂ (GS) ₁	145	
(TVAAPS) ₃ (GS) ₁	146	

序列

SEQ ID NO: 1

DTYMH

SEQ ID NO: 2

TIDPANGNTKYVPKFQG

SEQ ID NO: 3

SIYDDYHYDDYYAMDY

SEQ ID NO: 4

WIYDDYHYDDYYAMDY

SEQ ID NO: 5

SVYDDYHYDDYYAMDY

SEQ ID NO: 6

SIFDDYHYDDYYAMDY

SEQ ID NO: 7

SIYEDYHYDDYYAMDY

SEQ ID NO: 8

SIYDDYAYDDYYAMDY

SEQ ID NO: 9

SIYDDYHYDDYYAMDY

SEQ ID NO: 10

SIYDDYQYDDYYAMDY

SEQ ID NO: 11

SIYDDYRYDDYYAMDY

SEQ ID NO: 12

SIYDDYSYDDYYAMDY

SEQ ID NO: 13

SIYDDYTYDDYYAMDY

SEQ ID NO: 14

SIYDDYVYDDYYAMDY

SEQ ID NO: 15

SIYDDYHADDYYAMDY

SEQ ID NO: 16

SIYDDYHIDDYYAMDY

SEQ ID NO: 17

SIYDDYHWDDYYAMDY

SEQ ID NO: 18

SIYDDYHVDDYYAMDY

SEQ ID NO: 19

RSSQNIVHINGNTYLE

SEQ ID NO: 20

KISDRFS

SEQ ID NO: 21

FQGSHPWT

SEQ ID NO: 22

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHVVRQAPGGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSED TAVYYCARSIYDDYHYDDYYAMDYWGQGTLVTVSSASTKG

PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 23

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAAGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTGTTCCCCCCTAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTACGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 24

DIVMTQSPLSLPVTPGEPASISCRSSQNIVHINGNTYLEWYLQKPGQSPRLLIYKISDRFSGVPD
RFGSGSGTDFTLKISRVEADDDVGIYYCFQGSHVPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 25

GACATCGTGATGACCCAGTCTCCTCTGAGCCTCCCCGTGACCCCCGGCGAACCAGCCAGCATCTC
CTGCAGAAGCAGCCAGAACATCGTGACATCAACGGCAACACCTACCTGGAGTGGTACCTGCAAA
AGCCCCGGCCAGAGCCCCAGGCTGCTGATCTACAAGATCAGCGACAGGTTTCAGCGGCGTGCCCGAT
AGGTTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAAGATCAGCAGGGTGGAGGCCGACGA
CGTGGGCATCTACTACTGCTTCCAGGGCAGCCACGTCCCCTGGACTTTCGGACAGGGCACCAAGC
TGGAGATTAAGCGTACGGTGGCCGCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCTG
AAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAACCTTCTACCCCCGGGAGGCCAAGGTGCA
GTGGAAGGTGGACAATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCA
AGGACTCCACCTACAGCCTGAGCAGCACCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAG
GTGTACGCCTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGG
CGAGTGC

SEQ ID NO: 26

QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARWIYDDYHYDDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVMSHEALHNHYTQKSLSLSPGK

SEQ ID NO: 27

CAGGTGCAGCTCGTGACAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGGAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGTGGATCTACGACGACTACCACTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC



CAAGGTGGACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTTCCTGTTCCCCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCGAGAACAATAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 28

QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHVVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSVYDDYHYDDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPQVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 29

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTACGAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCGTCTACGACGACTACCACTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTTCCTGTTCCCCCCAAGCCTAAGGACACCCTGATG

ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCGAGAACAACCTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCAGAAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 30

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSIFDDYHYDDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPQVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSFSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 31

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTACGAGCAGCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTTTGACGACTACCACTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTGTTCCCCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT

ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGCACCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACCCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 32

QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHVVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDVAVYYCARSIYEDYHYDDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPDKTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 33

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTACGAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGAGGACTACCACTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCCTGTTCCCCCCTAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGCACCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCTATCGAGAAAACCATCAGCAAGGC

CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTCAGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCAGAAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 34

QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSYDDYAYDDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPETVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEALHNHYTQKSLSLSPGK

SEQ ID NO: 35

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACGCGTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCTCCCGCCAGCAGCAAGAGCACCAGCGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCGAACCAGTACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGCACCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG

AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 36

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDVAVYYCARSIYDDYEYDDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 37

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACGAGTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCCTGTTCCCCCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGCTGCT

CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 38

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDITYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSYDDYQYDDYYAMDYWGQGTTLTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPETVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVMSHEALHNHYTQKSLSLSPGK

SEQ ID NO: 39

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTACGAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCTCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCTCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCGAGAACAACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTACGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG



SEQ ID NO: 40

QVQLVQSGAEVKKPGSSVKVSCASGFYIKDTYMHVWRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDVAVYYCARSIYDDYRYDDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

SEQ ID NO: 41

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGT CAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGA ACTGAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACAGGTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTGTTCCCCC CAAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGTCACCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCC CAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCGAGAACA ACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTT CAGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 42

QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSIYDDYSYDDYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK

SEQ ID NO: 43

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACTCCTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCTCCCTGGCCCCCAGCAGCAAGAGCACCAGCGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCTAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCGAGAACAATAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCAGAGAGCCTGAGCCTGTCCCCTGGCAAG



SEQ ID NO: 44

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDVAVYYCARSYDDYTYDDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 45

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAAGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACACGTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTGTTCCCCCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCAGAACAACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 46

QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSYDDYVYDDYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPQVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 47

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTACGAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACGTGTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCTCCCTGGCCCCCAGCAGCAAGAGCACCAGCGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCGAACCAGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCTCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGTGTCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 48

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSYDDYHADDYYAMDYWGQGTLLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 49

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAACAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACGCGGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGTCACCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCAGAACAACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 50

QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSYDDYHIDDYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEALHNHYTQKSLSLSPGK

SEQ ID NO: 51

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACATTGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCTCCCGTGGCCCCAGCAGCAAGAGCACCAGCGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCTCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCGAGAACAATACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCAGAAAGAGCCTGAGCCTGTCCCCTGGCAAG



SEQ ID NO: 52

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDVAVYYCARSIYDDYHWDDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSVMSVMEALHNHYTQKSLSLSPGK

SEQ ID NO: 53

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACTGGGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTGTTCCCCCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGTCACCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCAGAACAACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 54

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDVAVYYCARSIYDDYHVDYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPQVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 55

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAAGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACC GCCTACATGGAAGTGAAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACGTGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCTCCCTGGCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCTAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCGAGAACAACTACAAGACACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCAGAAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 56

MGWSCIIILFLVATATGVHS

SEQ ID NO: 57

GPVPPSTALRELIEELVNITQNQKAPLCNGSMVWSINLTAGMYCAALES LINVSGCSAIEKTQRM
LSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLHLKKL FREGRFN

SEQ ID NO: 58

EIQ LQQSVAELVRPGASVRLSCTASGFYIKDTYMHWVIQRPEQGLEWIGTIDPANGNTKYVPKFQ
GKATITADTSSNTAYLRLSSLTSEDTAIYYCARSIYDDYHYDDYAMDYWGQTSVTVSS

SEQ ID NO: 59

DVLMTQTPLSLPVS LGDQASISCRSSQNIVHINGNTYLEWYLQKPGQSPKLLIYKISDRFSGVPD
RFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHVPWTFGGGTKLEIK

SEQ ID NO: 60

FYIKDTYMH

SEQ ID NO: 61

GFYIKDTYMH

SEQ ID 62: A1Y100BA1a H-TVAAPS-210(蛋白質序列)

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSED TAVYYCARSIYDDYHADDYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
TVAAPSEVQLLES GGGGLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWIISSGTETY
YADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGLTVTVSS

SEQ ID 63: A1Y100BA1a H-TVAAPS-210(DNA 序列)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACGCGGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCTAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCTTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCTAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCGAGAACAATAAAGACACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTACGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
ACCGTGGCCGCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGG
CAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTACCTTCAGGAACTTCGGCATGGGCTGGGTCA
GGCAGGCCCCCGCAAGGGCCTGGAGTGGGTGAGCTGGATCATCAGCTCCGGCACCGAGACCTAC
TACGCCGACAGCGTGAAGGGCAGGTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTACCT
GCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCAGGT
TCGACTACTGGGGACAGGGGACCCTGGTGAAGTGTGAGCAGC

SEQ ID 64: A1Y100BI1e H-TVAAPS-210(蛋白質序列)

QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHVWRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSYDDYHIDYYAMDYWGQGLTVTVSSASTKG
PSVFLPAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM

ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
TVAAPSEVQLLESGGGLVQPGGSLRLS CAASGFTFRNFGMGWVRQAPGKGLEWVSWIISSGTETY
YADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGLTVTVSS

SEQ ID 65: A1Y100BIle H-TVAAPS-210(DNA 序列)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAAGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACATTGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCTAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCCTGTTCCCCCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
ACCGTGGCCGCCCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGG
CAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTCACCTTCAGGAACTTCGGCATGGGCTGGGTCA
GGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCTGGATCATCAGCTCCGGCACCGAGACCTAC
TACGCCGACAGCGTGAAGGGCAGGTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTACCT
GCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCAGGT
TCGACTACTGGGGACAGGGGACCCTGGTGACTGTGAGCAGC

SEQ ID 66: A1Y100BTrp H-TVAAPS-210(蛋白質序列)

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSED TAVYYCARSIYDDYHWDDYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPQVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSQSVMEALHNHYTQKSLSLSPGK
TVAAPSEVQLLES GGGLVQPGGSLRLS CAASGFTFRNFGMGWVRQAPGKGLEWVSWI ISSGTETY
YADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCAKSLGRFDYWGQGLTVTVSS

SEQ ID 67: A1Y100BTrp H-TVAAPS-210(DNA序列)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACC GCCTACATGGAAGTGAAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACTGGGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCTAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTACGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCAGAAAGAGCCTGAGCCTGTCCCCTGGCAAG
ACCGTGGCCGCCCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGG

CAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTCACCTTCAGGAACTTCGGCATGGGCTGGGTCA
 GGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCTGGATCATCAGCTCCGGCACCAGACCTAC
 TACGCCGACAGCGTGAAGGGCAGGTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTACCT
 GCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCAGGT
 TCGACTACTGGGGACAGGGGACCCTGGTGACTGTGAGCAGC

SEQ ID 68: A1Y100B Val H-TVAAPS-210(蛋白質序列)

QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHVWRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDVAVYYCARSIYDDYHVDYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
 TVAAPSEVQLLESGGLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWIISSGTETY
 YADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGLTVTVSS

SEQ ID 69: A1Y100B Val H-TVAAPS-210(DNA序列)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACC GCCTACATGGAAGTGAAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACGTCGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTGTTCCCCCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA

ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTACGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
ACCGTGGCCGCCCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGG
CAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTACCTTCAGGAACTTCGGCATGGGCTGGGTCA
GGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCTGGATCATCAGCTCCGGCACCGAGACCTAC
TACGCCGACAGCGTGAAGGGCAGGTTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTACCT
GCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCAGGT
TCGACTACTGGGGACAGGGGACCCTGGTGAAGTGTGAGCAGC

SEQ ID 70: A1Y100BA1a H-ASTKGPS-210(蛋白質序列)

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSIDDDYHADDYAMDYWGQGLTLTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTEPVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVMSHEALHNHYTQKSLSLSPGK
ASTKGPSSEVQLLESGGGLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWIISSGTET
YYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGLTLTVSS

SEQ ID 71: A1Y100BA1a H-ASTKGPS-210(DNA序列)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTACGAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACGCGGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCTCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG

CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGATATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCGAGAACAACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTACGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACCCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
 GCCAGCACCAAGGGCCCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGGCGGCTGGTGCAGCCCGG
 CGGCAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTACCTTCAGGAACCTCGGCATGGGCTGGG
 TCAGGCAGGCCCCCGCAAGGGCCTGGAGTGGGTGAGCTGGATCATCAGCTCCGGCACCGAGACC
 TACTACGCCGACAGCGTGAAGGGCAGGTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTA
 CCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCA
 GGTTCGACTACTGGGGACAGGGGACCCTGGTGACTGTGAGCAGC

SEQ ID 72: A1Y100BIle H- ASTKGPS -210(蛋白質序列)

QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHVVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDVAVYYCARSIDDDYHIDDDYAMDYWGQGLTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVSMHEALHNHYTQKSLSLSPGK
 ASTKGPSSEVQLLESGLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWIISSTET
 YYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGLTLTVSS

SEQ ID 73: A1Y100BIle H- ASTKGPS -210(DNA序列)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGGAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACATTGACGACT

ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCTCCCTGGCCCCCAGCAGCAAGAGCACCAGCGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGTCACCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGATATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCGAGAACAACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGTGT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
GCCAGCACCAAGGGCCCCCTCGGAAGTGACGCTCCTGGAGAGCGCGCGGCCCTGGTGCAGCCCGG
CGGCAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTCACCTTCAGGAACCTCGGCATGGGCTGGG
TCAGGCAGGCCCCCGCAAGGGCCTGGAGTGGGTGAGTGGATCATCAGCTCCGGCACCGAGACC
TACTACGCCGACAGCGTGAAGGGCAGGTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTA
CCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCA
GGTTCGACTACTGGGGACAGGGGACCCTGGTGAAGTGTGAGCAGC

SEQ ID 74: A1Y100BTrp H- ASTKGPS -210(蛋白質序列)

QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDVAVYYCARSYDDYHWDDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
ASTKGPSEVQLLESGLLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWIISSGTET
YYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGLTVTVSS

SEQ ID 75: A1Y100BTrp H- ASTKGPS -210(DNA 序列)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACTGGGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTTCTGTTCCCCCCTAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGATATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCGAGAACAACCTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTACGTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACCCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
 GCCAGCACCAAGGGCCCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGCCTGGTGCAGCCCGG
 CGGCAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTACCTTCAGGAACTTCGGCATGGGCTGGG
 TCAGGCAGGCCCCCGCAAGGGCCTGGAGTGGGTGAGCTGGATCATCAGCTCCGGCACCGAGACC
 TACTACGCCGACAGCGTGAAGGGCAGGTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTA
 CCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCA
 GGTTCGACTACTGGGGACAGGGGACCCTGGTGACTGTGAGCAGC

SEQ ID 76: A1Y100BVal H- ASTKGPS -210(蛋白質序列)

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDITYMHVVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDVAVYYCARSIDDDYHVDYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLM

ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPVLDSDGSEFLYSKLTVDKSRWQQGNVFSVSMHEALHNHYTQKSLSLSPGK
ASTKGPSSEVQLLESGGGLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWIISSGTET
YYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGLTVTVSS

SEQ ID 77: A1Y100BVal H- ASTKGPS -210(DNA 序列)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACGTGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCTCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
GCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCTAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGATATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGTGTCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCAGAGAGCCTGAGCCTGTCCCCTGGCAAG
GCCAGCACCAAGGGCCCCCTCGGAAGTGACGCTCCTGGAGAGCGGCGGCGGCTGGTGCAGCCCGG
CGGCAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTACCTTCAGGAACCTTCGGCATGGGCTGGG
TCAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCTGGATCATCAGCTCCGGCACCGAGACC
TACTACGCCGACAGCGTGAAGGGCAGGTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTA
CCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCA
GGTTCGACTACTGGGGACAGGGGACCCTGGTGAAGTGTGAGCAGC



SEQ ID NO: 78=DOM9-155- 25

DIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASTLD SGVPSRFSGS
GSGTDFTLTISSLQPEDFATYYCLQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 79=DOM9-155-147

DIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLYEGVPSRFSGS
GSGTDFTLTISSLQPEDFATYYCLQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 80=DOM9-155-154

DIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVPSRFSGS
GSGTDFTLTISSLQPEDFATYYCLQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 81=DOM9-112-210

EVQLLESGGGLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWIISSGTETYYADSVK
GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGT LVTVSS

SEQ ID NO: 82(G4S連接子)

GGGS

SEQ ID NO: 83(連接子)

TVAAPS

SEQ ID NO: 84(連接子)

ASTKGPT

SEQ ID NO: 85(連接子)

ASTKGPS

SEQ ID NO: 86(連接子)

GS

SEQ ID NO: 87(連接子)

TVAAPSGS

SEQ ID NO: 88=147-TVAAPS-586 Y100B V (重鏈)

DIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLYEGVPSRFSGS
 GSGTDFTLTISSSLQPEDFATYYCLQEGWGPPTFGQGTKVEIKRGSTVAAPSQVQLVQSGAEVKKP
 GSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQGRVTITADESTSTA
 YMELSSLRSEDTAVYYCARSIIYDDYHVDDYYAMDYWGQGTLLVTVSSASTKGPSVFPLAPSSKSTS
 GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
 VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDV
 SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
 VLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 89=147-ASTKG-586 Y100B V (重鏈)

DIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLYEGVPSRFSGS
 GSGTDFTLTISSSLQPEDFATYYCLQEGWGPPTFGQGTKVEIKRGSASTKGPSQVQLVQSGAEVKK
 PGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQGRVTITADESTST
 AYMELSSLRSEDTAVYYCARSIIYDDYHVDDYYAMDYWGQGTLLVTVSSASTKGPSVFPLAPSSKST
 SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC
 NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDV
 VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
 PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP
 PVLDSDGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 90=154-TVAAPS-586 Y100B V (重鏈)

DIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVPSRFSGS
 GSGTDFTLTISSSLQPEDFATYYCLQEGWGPPTFGQGTKVEIKRGSTVAAPSQVQLVQSGAEVKKP
 GSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQGRVTITADESTSTA
 YMELSSLRSEDTAVYYCARSIIYDDYHVDDYYAMDYWGQGTLLVTVSSASTKGPSVFPLAPSSKSTS
 GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
 VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDV
 SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
 VLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 91=154-ASTKG-586 Y100B V (重鏈)

DIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVPSRFGSGS
 GSGTDFTLTISLQPEDFATYYCLQEGWGPPTFGQGTKVEIKRGSASTKGPSQVQLVQSGAEVKK
 PGSSVKVSCKASGFYIKDTYMHWVRQAPGGGLEWMGTIDPANGNTKYVPKFQGRVTITADESTST
 AYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGLTVTVSSASTKGPSVFPLAPSSKST
 SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYIC
 NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
 VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
 PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTP
 PVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

SEQ ID NO: 92(連接子)

GSTVAAPS

SEQ ID NO: 93(連接子)

GSTVAAPSGS

SEQ ID NO: 94**DOM9-155-154 L89Q(aka DOM9-155-256)**

DIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVPS
 RFSGSGSGTDFTLTISLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 95**DOM9-155-154 L89Q(aka DOM9-155-256)**

GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACC
 ATTACCTGCAGGGCCAGCAGGCCCATCAGCGACTGGCTGCACTGGTACCAACAGAAGCCC
 GGCAAGGCTCCCAAGCTGCTGATCGCCTGGGCCAGCAGCCTGCAGGGAGGCGTGCCCGAGC
 AGGTTTAGCGGCAGCGGCAGCGGCACCGACTTCACCCTCACCATCTCTTCCCTGCAGCCC
 GAGGACTTCGCCACCTACTACTGCCAGCAGGAGGGCTGGGGGCCCCCTACTTTTCGGCCAG
 GGCACCAAGGTGGAGATCAAGAGG

SEQ ID NO: 96**829H-GS(TVAAPSGS)₂-154 L89Q**

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKY
VPKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARSIIYDDYHVDDYYAMDYWGQGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
PSTRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLT
VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGSTVAAPSGSTVAAPSGSDIQMT
QSPSSLSASVGDRTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVPSRFS
SGSGSGTDFTLTITSSSLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 97
829H-GS(TVAAPSGS)₂-154 L89Q

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTG
AGCTGCAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCT
CCTGGCCAGGGCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTAC
GTGCCCCAAGTTCCAGGGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTAC
ATGGAACTGAGCAGCCTGAGGTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATC
TACGACGACTACCACGTCGACGACTACTACGCCATGGACTACTGGGGACAGGGCACACTA
GTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCTCCCGTGGCCCCCAGCAGC
AAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAA
CCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCC
GTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGC
CTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGAC
AAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTGCCCC
GAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCCTGAG
GTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGG
GAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAT
TGGCTGAACGGCAAGGAGTACAAGTGTAAAGGTGTCCAACAAGGCCCTGCCTGCCCCATC
GAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCC
CCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTC
TACCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCGAGAACCAACTACAAG
ACCACCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTG



GACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCTCCGTGATGCACGAGGCCCTG
CACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAGGGATCTACCGTGGCA
GCACCATCCGGATCTACCGTAGCAGCACCATCCGGATCCGACATCCAGATGACCCAGAGC
CCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATTACCTGCAGGGGCCAGCAGG
CCCATCAGCGACTGGCTGCACTGGTACCAACAGAAGCCCGGCAAGGCTCCCAAGCTGCTG
ATCGCCTGGGCCAGCAGCCTGCAGGGAGGCGTGCCCAGCAGGTTTAGCGGCAGCGGCAGC
GGCACCAGACTTCACCCTCACCATCTCTTCCCTGCAGCCCGAGGACTTCGCCACCTACTAC
TGCCAGCAGGAGGGCTGGGGGCCCCCTACTTTCGGCCAGGGCACCAAGGTGGAGATCAAG
AGG

SEQ ID NO: 98**829H-GS(TVAAPSGS)₃-154 L89Q**

QVQLVQSGAEVKKPGSSSVKVSCKASGFYIKDTYMHVVRQAPGQGLEWMGTIDPANGNTKY
VPKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDY YAMDYWGQGL
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
ELLGGPSVFLFPPKPKDTLMISRTPPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV
DKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGKGSTVAAPSGSTVAAPSGSTVAAPSG
SDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVP
SRFSGSGSGTDFTLT ISSLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 99**829H-GS(TVAAPSGS)₃-154 L89Q**

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTG
AGCTGCAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCT
CCTGGCCAGGGCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTAC
GTGCCCAAGTTCCAGGGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTAC
ATGGAAGTGAAGCAGCCTGAGGTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATC
TACGACGACTACCACGTCGACGACTACTACGCCATGGACTACTGGGGACAGGGCACACTA
GTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCTCCCTGGCCCCCAGCAGC
AAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAA
CCGGTGACCGTGTCTTGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCC

GTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGC
CTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGAC
AAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTGCCCC
GAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAG
GTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGG
GAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAT
TGGCTGAACGGCAAGGAGTACAAGTGTAAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATC
GAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCC
CCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTC
TACCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAATAACAAG
ACCACCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTG
GACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCTCCGTGATGCACGAGGCCCTG
CACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAGGGATCTACCGTGGCA
GCACCATCAGGATCTACCGTGGCAGCACCATCAGGTTCAACAGTAGCTGCTCCTTCTGGA
TCCGACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTG
ACCATTACCTGCAGGGCCAGCAGGCCCATCAGCGACTGGCTGCACTGGTACCAACAGAAG
CCCGGCAAGGCTCCCAAGCTGCTGATCGCCTGGGCCAGCAGCCTGCAGGGAGGCGTGCCC
AGCAGGTTTAGCGGCAGCGGCAGCGGCACCGACTTCACCCTCACCATCTCTTCCCTGCAG
CCCAGGACTTCGCCACCTACTACTGCCAGCAGGAGGGCTGGGGGGCCCCCTACTTTTCGGC
CAGGGCACCAAGGTGGAGATCAAGAGG

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QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKY
VPKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARSIIYDDYHVDDYYAMDYWGQGLT
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSQSVMHENHNTQKSLSLSPGKGSTVAAPSGSTVAAPSGSTVAAPSG
STVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
SSLQGGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 101**829H-GS(TVAAPSGS)₄-154 L89Q**

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTG
AGCTGCAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCT
CCTGGCCAGGGCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTAC
GTGCCCAAGTTCCAGGGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTAC
ATGGAACTGAGCAGCCTGAGGTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATC
TACGACGACTACCACGTCGACGACTACTACGCCATGGACTACTGGGGACAGGGCACAATA
GTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCTCCCTGGCCCCCAGCAGC
AAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAA
CCGGTGACCGTGTCTTGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCC
GTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGC
CTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGAC
AAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTGCCCC
GAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCTCCCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAG
GTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGG
GAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCAGGAT
TGGCTGAACGGCAAGGAGTACAAGTGTAAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATC
GAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCC
CCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTC
TACCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCGAGAACAATACTACAAG
ACCACCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTG
GACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCTCCGTGATGCACGAGGCCCTG
CACAATCACTACACCAGAAGAGCCTGAGCCTGTCCCCTGGCAAGGGATCTACCGTGGCA
GCACCATCAGGATCTACCGTGGCAGCACCATCAGGTTCAACAGTAGCTGCTCCTTCTGGT
TCAACAGTAGCTGCTCCTTCTGGATCCGACATCCAGATGACCCAGAGCCCCAGCAGCCTG
AGCGCCAGCGTGGGCGACAGGGTGACCATTACCTGCAGGGCCAGCAGGCCCATCAGCGAC
TGGCTGCACTGGTACCAACAGAAGCCCGGCAAGGCTCCCAAGCTGCTGATCGCCTGGGCC
AGCAGCCTGCAGGGAGGCGTGCCCAGCAGGTTTAGCGGCAGCGGCAGCGGCACCGACTTC
ACCCTCACCATCTCTTCCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGGAG
GGCTGGGGGCCCCCTACTTTCGGCCAGGGCACCAAGGTGGAGATCAAGAGG

SEQ ID NO: 102
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QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKY
VPKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARSIYDDYHVDDYYAMDYWGQGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
PSTRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKTVAAPSTVAAPSGSDIQMTQSPSSL
SASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVPSRFSGSGSGTDF
TLTISSLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR

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CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTG
AGCTGCAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCT
CCTGGCCAGGGCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTAC
GTGCCCAAGTTCCAGGGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTAC
ATGGAAGTGAAGCAGCCTGAGGTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATC
TACGACGACTACCACGTGACGACTACTACGCCATGGACTACTGGGGACAGGGCACACTA
GTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTCCCCCTGGCCCCCAGCAGC
AAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAA
CCGGTGACCGTGTCTTGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCC
GTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGC
CTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGAC
AAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTGCCCC
GAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCTAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAG
GTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGG
GAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAT
TGGCTGAACGGCAAGGAGTACAAGTGTAAAGGTGTCCAACAAGGCCCTGCCTGCCCCATC
GAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCC
CCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTC

TACCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACACTACAAG
ACCACCCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTG
GACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCTCCGTGATGCACGAGGCCCTG
CACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCTGGCAAGACCGTGGCAGCACCA
TCCACCGTAGCAGCACCATCCGGATCCGACATCCAGATGACCCAGAGCCCCAGCAGCCTG
AGCGCCAGCGTGGGCGACAGGGTGACCATTACCTGCAGGGCCAGCAGGCCCATCAGCGAC
TGGCTGCACTGGTACCAACAGAAGCCCGGCAAGGCTCCCAAGCTGCTGATCGCCTGGGCC
AGCAGCCTGCAGGGAGGCGTGCCAGCAGGTTTAGCGGCAGCGGCAGCGGCACCGACTTC
ACCCTCACCATCTCTTCCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGGAG
GGCTGGGGGGCCCCCTACTTTCGGCCAGGGCACCAAGGTGGAGATCAAGAGG

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QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHVVRQAPGQGLEWMGTIDPANGNTKY
VPKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARSYDDYHVDDYYAMDYWGQGLT
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKTVAAPSTVAAPSTVAAPSGSDIQMT
QSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPKAPKLLIAWASSLQGGVPSRFSGS
GSGTDFTLTISSLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 105**829H-(TVAAPS)₃GS-154 L89Q**

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTG
AGCTGCAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCT
CCTGGCCAGGGCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTAC
GTGCCCAAGTTCCAGGGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTAC
ATGGAAGTGAAGCAGCCTGAGGTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATC
TACGACGACTACCACGTCGACGACTACTACGCCATGGACTACTGGGGACAGGGCACACTA
GTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGC
AAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAA

CCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCC
GTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGC
CTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGAC
AAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTGCCCCC
GAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAG
GTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGG
GAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAT
TGGCTGAACGGCAAGGAGTACAAGTGTAAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATC
GAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCC
CCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTC
TACCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACCTACAAG
ACCACCCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTG
GACAAGAGCAGATGGCAGCAGGGCAACGTGTTTACGCTGCTCCGTGATGCACGAGGCCCTG
CACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAGACCGTGGCAGCACCA
TCAACCGTGGCAGCACCATCAACAGTAGCTGCTCCTTCTGGATCCGACATCCAGATGACC
CAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATTACCTGCAGGGCC
AGCAGGCCCCATCAGCGACTGGCTGCACTGGTACCAACAGAAGCCCGGCAAGGCTCCCAAG
CTGCTGATCGCCTGGGCCAGCAGCCTGCAGGGAGGCGTGCCCAGCAGGTTTAGCGGCAGC
GGCAGCGGCACCGACTTCACCCTCACCATCTCTTCCCTGCAGCCCGAGGACTTCGCCACC
TACTACTGCCAGCAGGAGGGCTGGGGGCCCCCTACTTTCGGCCAGGGCACCAAGGTGGAG
ATCAAGAGG

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QVQLVQSGAEVKKPGSSVKVSKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKY
VPKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGLT
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS DGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKTVAAPSTVAAPSTVAAPSTVAAPSG
SDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVP

SRFSGSGSGTDFTLTISSLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 107
829H-(TVAAPS)₄GS-154 L89Q

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTG
AGCTGCAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCT
CCTGGCCAGGGCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTAC
GTGCCCCAAGTTCCAGGGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTAC
ATGGAACTGAGCAGCCTGAGGTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATC
TACGACGACTACCACGTGACGACTACTACGCCATGGACTACTGGGGACAGGGCACACTA
GTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGC
AAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAA
CCGGTGACCGTGTCTTGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCC
GTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGC
CTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGAC
AAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTGCCCCC
GAGCTGCTGGGAGGCCCCAGCGTGTTCTTGTTCCCCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAG
GTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGG
GAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAT
TGGCTGAACGGCAAGGAGTACAAGTGTAAAGGTGTCCAACAAGGCCCTGCCTGCCCCTATC
GAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCC
CCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTC
TACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACCTACAAG
ACCACCCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTG
GACAAGAGCAGATGGCAGCAGGGCAACGTGTTCAGCTGCTCCGTGATGCACGAGGCCCTG
CACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAGACCGTGGCAGCACCA
TCAACCGTGGCAGCACCATCAACAGTAGCTGCTCCTTCTACAGTAGCTGCTCCTTCTGGA
TCCGACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTG
ACCATTACCTGCAGGGCCAGCAGGCCCATCAGCGACTGGCTGCACTGGTACCAACAGAAG
CCCGGCAAGGCTCCCAAGCTGCTGATCGCCTGGGCCAGCAGCCTGCAGGGAGGCGTGCCC
AGCAGGTTTAGCGGCAGCGGCAGCGGCACCGACTTCACCCTCACCATCTCTTCCCTGCAG
CCCGAGGACTTCGCCACCTACTACTGCCAGCAGGAGGGCTGGGGGCCCCCTACTTTCGGC
CAGGGCACCAAGGTGGAGATCAAGAGG

SEQ ID NO: 108

DIQMTQSPSSLSASVGDRVITITCRSSQNIVHINGNTYLEWYQQKPGKAPKLLIYKISDRFSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCFQGSHVPWTFGQGTKLEIKRTVAAPSVFI FPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 109

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGACAGCGACATCCA
GATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACTATCACCTGCAGGA
GCAGCCAGAACATCGTGACATCAACGGCAACACCTACCTCGAGTGGTACCAGCAGAAACCCGGG
AAGGCCCCCAAGCTGCTGATCTACAAGATCAGCGACAGGTTAGCGGCGTGCCAGCAGGTTTAG
CGGCTCCGGCTCAGGCACCGATTTACCCCTGACCATTAGCAGCCTGCAGCCCCGAGGACTTCGCCA
CCTACTACTGCTTCCAGGGCTCTCACGTCCCCTGGACCTTCGGCCAGGGCACCAAGCTGGAGATC
AAGCGTACGGTGGCCGCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCTGAAGAGCGG
CACCGCCAGCGTGGTGTGTCTGCTGAACAACCTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGG
TGGACAATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACTCC
ACCTACAGCCTGAGCAGCACCCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGC
CTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGC

SEQ ID NO: 110

DVLMTQSPSSLSASVGDRVITITCRSSQNIVHINGNTYLEWYQQKPGKAPKLLIYKISDRFSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCFQGSHVPWTFGQGTKLEIKRTVAAPSVFI FPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 111

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGACAGCGACGTGCT
GATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACTATCACCTGCAGGA
GCAGCCAGAACATCGTGACATCAACGGCAACACCTACCTCGAGTGGTACCAGCAGAAACCCGGG
AAGGCCCCCAAGCTGCTGATCTACAAGATCAGCGACAGGTTAGCGGCGTGCCAGCAGGTTTAG
CGGCTCCGGCTCAGGCACCGATTTACCCCTGACCATTAGCAGCCTGCAGCCCCGAGGACTTCGCCA
CCTACTACTGCTTCCAGGGCTCTCACGTCCCCTGGACCTTCGGCCAGGGCACCAAGCTGGAGATC
AAGCGTACGGTGGCCGCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCTGAAGAGCGG
CACCGCCAGCGTGGTGTGTCTGCTGAACAACCTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGG

TGGACAATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACTCC
ACCTACAGCCTGAGCAGCACCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGC
CTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGC

SEQ ID NO: 112

EIVLTQSPGTLSSLSPGERATLSCRSSQNIVHINGNTYLEWYQQKPGQAPRLLIYKISDRFSGIPD
RFSGSGSGTDFTLTISRLEPEDFAVYYCFQGSHPVWTFGQGTKLEIKRTVAAPSVFIFPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 113

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGACAGCGAGATCGT
GCTGACCCAGAGCCCTGGCACACTGAGCCTGAGCCCCGAGAGAGGGCCACCCTGAGCTGCAGGT
CTAGCCAGAACATCGTGCACATCAACGGCAACACCTACCTGGAGTGGTATCAGCAGAAGCCCGGC
CAGGCCCCCAGGCTGCTGATCTACAAGATCAGCGACAGGTTTACGCGGCATCCCCGACAGGTTTAG
CGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATTAGCAGGCTGGAGCCCCGAGGACTTCGCCG
TGTACTIONGCTTCCAGGGGAGCCACGTGCCCTGGACCTTCGGCCAGGGCACCAAGCTCGAAATC
AAGCGTACGGTGGCCGCCCCCAGCGTGTTTATCTTCCCCCCCAGCGATGAGCAGCTGAAGAGCGG
CACCGCCAGCGTGGTGTGTCTGCTGAACAACCTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGG
TGGACAATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACTCC
ACCTACAGCCTGAGCAGCACCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGC
CTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGC

SEQ ID NO: 114

DVLTMTQSPGTLSSLSPGERATLSCRSSQNIVHINGNTYLEWYQQKPGQAPKLLIYKISDRFSGVDP
RFSGSGSGTDFTLTISRLEPEDFAVYYCFQGSHPVWTFGQGTKLEIKRTVAAPSVFIFPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 115

GACGTGCTGATGACCCAGAGCCCTGGCACACTGAGCCTGAGCCCCGAGAGAGGGCCACCCTGAG
CTGCAGGTCTAGCCAGAACATCGTGCACATCAACGGCAACACCTACCTGGAGTGGTATCAGCAGA
AGCCCGGCCAGGCCCCCAAGCTGCTGATCTACAAGATCAGCGACAGGTTTACGCGGCGTGCCCGAC
AGGTTTACGCGCAGCGGCAGCGGCACCGACTTCACCCTGACCATTAGCAGGCTGGAGCCCCGAGGA

CTTCGCCGTGTACTACTGCTTCCAGGGGAGCCACGTGCCCTGGACCTTCGGCCAGGGCACCAAGC
TCGAAATCAAGCGTACGGTGGCCGCCCGCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCTG
AAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCA
GTGGAAGGTGGACAATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCA
AGGACTCCACCTACAGCCTGAGCAGCACCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAG
GTGTACGCCTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGG
CGAGTGC

SEQ ID NO:116=586H-TVAAPS-154(鏈)

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSYDDYHYDDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
TVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGG
VPSRFSGSGSGTDFTLTISLQPEDFATYYCLQEGWGPPTFGQGTKVEIKR

SEQ ID NO:117

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSYDDYHVDDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
SSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCGQEGWGPPTFGQGTKVEIKR

SEQ ID NO:118

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSYDDYHVDDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT

VPSSSLGTQTYICNVNHKPSNTKVDDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
SSLQGGVPSRFSFGSGSGTDFTLTISLQPEDFATYYCSQEGWGPPTFGQGTKVEIKR

SEQ ID NO:119

QVQLVQSGAEVKKPGSSVKVSCASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDVAVYYCARSIYDDYHVDDYYAMDYWGQGTLLTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
SSLQGGVPSRFSFGSGSGTDFTLTISLQPEDFATYYCHQEGWGPPTFGQGTKVEIKR

SEQ ID NO:120

QVQLVQSGAEVKKPGSSVKVSCASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDVAVYYCARSIYDDYHVDDYYAMDYWGQGTLLTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
SSLQGGVPSRFSFGSGSGTDFTLTISLQPEDFATYYCMQEGWGPPTFGQGTKVEIKR

SEQ ID NO:121

QVQLVQSGAEVKKPGSSVKVSCASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDVAVYYCARSIYDDYHVDDYYAMDYWGQGTLLTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE

SNGQPENNYKTTTPVLDSGSEFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
SSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCAQEGWGPPTFGQGTKVEIKR

SEQ ID NO:122

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSIYDDYHVDYYAMDYWGQGTTLTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSGSEFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
SSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCTQEGWGPPTFGQGTKVEIKR

SEQ ID NO:123

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSEDTAVYYCARSIYDDYHVDYYAMDYWGQGTTLTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
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SEQ ID NO:146

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【圖式簡單說明】

圖 1：曲線圖展示包含 Y100B 變體之 mAbdAb 在 TF-1 細胞增殖分析法中中和人類 IL-13 之能力；

圖 2：曲線圖展示包含 Y100B 變體之 mAbdAb 在 TF-1 細胞增殖分析法中中和人類 IL-13 之能力；

圖 3：BPC2222 之 SEC 跡線；

圖 4：BPC2223 之 SEC 跡線；

圖 5：BPC2230 之 SEC 跡線；

圖 6：BPC2231 之 SEC 跡線；

圖 7：BPC1085 之 SEC 跡線；

圖 8：BPC1086 之 SEC 跡線；

圖 9：BPC1087 之 SEC 跡線；

圖 10：曲線圖展示純化 mAbdAb(BPC1085、BPC1086 及 BPC1087)對人類 IL-4 之結合，如 ELISA 所測定。IL-4 對照物 mAb 標示為「帕考珠單抗(pascolizumab)」；

圖 11：曲線圖展示純化 mAbdAb(BPC1085、BPC1086 及 BPC1087)在 TF-1 細胞生物分析法中對人類 IL-4 之中和程度。IL-4 對照物 mAb 標示為「帕考珠單抗」；

圖 12：曲線圖展示純化 mAbdAb(BPC1085、BPC1086 及 BPC1087)在 TF-1 細胞生物分析法中對人類 IL-13 之中和程度。IL-4 對照物 mAb 標示為「帕考珠單抗」；

圖 13：BPC3214 之 SEC 概況；

圖 14：BPC3215 之 SEC 概況；

圖 15：曲線圖展示純化 mAbdAb BPC3214、BPC3215、

BPC1085及對照物 mAb A1Y100BVAL1及抗 IL-4 mAb對人類 IL-13之結合，如 ELISA所測定。IL-4對照物 mAb標示為「帕考珠單抗」；

圖 16：曲線圖展示純化 mAbdAb BPC3214、BPC3215、BPC1085及對照 mAb A1Y100BVAL1及抗 IL-4 mAb對人類 IL-4之結合，如 ELISA所測定。IL-4對照 mAb標示為「帕考珠單抗」；及

圖 17：曲線圖展示短暫表現之 mAbdAb對重組大腸桿菌表現之人類 IL-4之結合，如 ELISA所測定。IL-4對照物 mAb標示為「帕考珠單抗」。

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Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met Asp Tyr
1 5 10 15

<210> 19
<211> 16
<212> PRT
<213> 小鼠屬

<400> 19
Arg Ser Ser Gln Asn Ile Val His Ile Asn Gly Asn Thr Tyr Leu Glu
1 5 10 15

<210> 20
<211> 7
<212> PRT
<213> 小鼠屬

<400> 20
Lys Ile Ser Asp Arg Phe Ser
1 5

<210> 21
<211> 9
<212> PRT
<213> 小鼠屬

<400> 21
Phe Gln Gly Ser His Val Pro Trp Thr
1 5

<210> 22
<211> 455
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 22
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Tyr Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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
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
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 Arg Glu Glu Gln Tyr		
290	295	300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
305	310	315
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 Asp Glu Leu 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
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		
450	455	

<210> 23
<211> 1365
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 23
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc cgggcagcag cgtgaaggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcaactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact accactacga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg cctgcccc 720
gagctgctgg gagccccag cgtgttcctg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggctgaacg gcaaggagta caagtgtgag gtgtccaaca aggcctgcc tgcccctatc 1020
gagaaaaacca tcagcaaggc caagggccag ccagagagc ccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggcttc 1140
taccccagcg acatcgccgt ggagtgggag agcaacggcc agcccagaaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa ggcctgagc ctgtcccctg gcaag 1365

<210> 24
<211> 219
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 24
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly

1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Asn Ile Val His Ile
20 25 30
Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asp Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Asp Asp Val Gly Ile Tyr Tyr Cys Phe Gln Gly
85 90 95
Ser His Val Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 25
<211> 657
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 25
gacatcgtga tgaccagtc tcctctgagc ctccccgtga cccccggcga accagccagc 60
atctcctgca gaagcagcca gaacatcgtg cacatcaacg gcaacaccta cctggagtgg 120
tacctgcaaa agccccggcca gagccccagg ctgctgatct acaagatcag cgacaggttc 180
agcggcgtgc ccataggtt cagcggcagc ggcagcggca ccgacttcac cctgaagatc 240
agcaggttgaggaggcga cgtgggcac tactactgct tccagggcag ccacgtcccc 300
tggactttcg gacagggcac caagctggag attaagcgta cgggtggccgc cccagcgtg 360

ttcatcttcc cccccagcga tgagcagctg aagagcggca ccgccagcgt ggtgtgtctg 420
ctgaacaact tctacccccg ggaggccaag gtgcagtgga aggtggacaa tgccctgcag 480
agcggcaaca gccaggagag cgtgaccgag caggacagca aggactccac ctacagcctg 540
agcagcaccc tgacctgag caaggccgac tacgagaagc acaaggtgta cgcctgtgag 600
gtgaccacc accggcctgtc cagccccgtg accaagagct tcaaccgggg cgagtgc 657

<210> 26
<211> 455
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 26
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Ile Tyr Asp Asp Tyr His Tyr Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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
450 455

<210> 27
<211> 1365
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 27
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc cgggcagcag cgtgaaggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcaactgggt caggcaggct 120
cctggccagg gcttgagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgccaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240

atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggtggatc 300
tacgacgact accactacga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc ccccagcagc 420
aagagcacca gcgcgggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccgggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gagccccag cgtgttctg tccccccca agcctaagga caccctgatg 780
atcagcagaa ccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggctgaacg gcaaggagta caagtgtgta gtgtccaaca aggccctgcc tgcccctatc 1020
gagaaaaacca tcagcaaggc caagggccag ccagagagc ccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccacagcg acatcgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200
accaccccc ctgtgtgga cagcgtatgc agctttcttc tgtacagaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtccctg gcaag 1365

<210> 28
<211> 455
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 28
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Val Tyr Asp Asp Tyr His Tyr Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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
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
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 Arg	Glu Glu Gln Tyr
290	295	300
Asn Ser Thr Tyr Arg Val	Val Ser Val Leu Thr Val	Leu His Gln Asp
305	310	315
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 Asp	Glu Leu 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
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	
450	455	

<210> 29
 <211> 1365
 <212> DNA
 <213> 人工序列

<220>
 <223> 人類化

<400> 29

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cagggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggcct ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgccaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcgtc 300
tacgaagact accactacga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc cccagcgtgt tccccctggc cccagcagc 420
aagagcacca gggggggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gagccccag cgtgttcctg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggacctgag 840
gtgaagttca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggctgaacg gcaaggagta caagtgtaa gtgtccaaca aggcctgcc tgccctatc 1020
gagaaaacca tcagcaaggc caagggccag cccagagagc cccaggtgta caccctgcc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccaccagc acatcgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gacctgagc ctgtccctg gcaag 1365
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<210> 30
 <211> 455
 <212> PRT
 <213> 人工序列

<220>
 <223> 人類化

<400> 30

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

1	5	10	15
Ser Val Lys	Val Ser Cys Lys Ala	Ser Gly Phe Tyr Ile	Lys Asp Thr
20	25	30	
Tyr Met His	Trp Val Arg Gln Ala	Pro Gly Gln Gly Leu	Glu Trp Met
35	40	45	
Gly Thr Ile	Asp Pro Ala Asn Gly	Asn Thr Lys Tyr Val	Pro Lys Phe
50	55	60	
Gln Gly Arg	Val Thr Ile Thr Ala	Asp Glu Ser Thr Ser	Thr Ala Tyr
65	70	75	80
Met Glu Leu	Ser Ser Leu Arg Ser	Glu Asp Thr Ala Val	Tyr Tyr Cys
85	90	95	
Ala Arg Ser	Ile Phe Asp Asp Tyr	His Tyr Asp Asp Tyr	Tyr Ala Met
100	105	110	
Asp Tyr Trp	Gly Gln Gly Thr Leu	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 Arg Glu	Glu Gln Tyr
290	295	300	
Asn Ser Thr	Tyr Arg Val 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 Asp Glu	Leu 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
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser		400
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		
450	455	

- <210> 31
- <211> 1365
- <212> DNA
- <213> 人工序列

- <220>
- <223> 人類化

<400> 31
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gectggagtg gatgggcact atcgaccccc ccaacggcaa caccaagtac 180
gtgccaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tttgacgact accactacga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gggcggcgac agccgccctg ggtgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcgccct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccocag cgtgttcctg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggctgaacg gcaaggagta caagtgtgag gtgtccaaca aggcctgcc tgccccatc 1020
gagaaaacca tcagcaaggc caagggccag ccagagagc ccaggtgta caccctgcc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggcttc 1140
taccacagcg acatcgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200

accaccccc ctgtgctgga cagcgatggc agctttctcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtcccctg gcaag 1365

<210> 32
<211> 455
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 32
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Glu Asp Tyr His Tyr Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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
450 455

- <210> 33
- <211> 1365
- <212> DNA
- <213> 人工序列

- <220>
- <223> 人類化

<400> 33
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc cgggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgccaagt tccagggcag ggtgaccatc accgcgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgcctgt actattgcgc caggagcatc 300
tacgaggact accactacga cgactactac gccatggact actggggaca gggcacacta 360

gtgaccgtgt ccagcgccag caccaagggc cccagcgtgt tccccctggc ccccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgtctcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctggggcacc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttcctg ttcccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtgttgatg tgagccacga ggacctgag 840
gtgaagtca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtctaacg gcaaggagta caagtgaag gtgtccaaca aggcctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag cccagagagc cccaggtgta caccctgcc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggg gaagggcttc 1140
taccacagcg acatcgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct cctgatgca cgaggccctg 1320
cacaatcact acaccagaa gacctgagc ctgtcccctg gcaag 1365

- <210> 34
- <211> 455
- <212> PRT
- <213> 人工序列

- <220>
- <223> 人類化

<400> 34
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr Ala Tyr Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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
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
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 Arg Glu Glu Gln Tyr		
290	295	300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
305	310	315
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 Asp Glu Leu 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
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		
450	455	

<210> 35

<211> 1365
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 35
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgccaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattggcg caggagcatc 300
tacgacgact acgcgtacga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcttgaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcgccct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaagggtg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttcctg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggctgaacg gcaaggagta caagtgtgag gtgtccaaca aggccctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag cccagagagc cccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccaccagc acatcgccgt ggagtgggag agcaacggcc agcccagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtcccctg gcaag 1365

<210> 36
<211> 455
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 36
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr

20							25					30					
Tyr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met		
35							40					45					
Gly	Thr	Ile	Asp	Pro	Ala	Asn	Gly	Asn	Thr	Lys	Tyr	Val	Pro	Lys	Phe		
50							55					60					
Gln	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Ser	Thr	Ala	Tyr		
65							70					75				80	
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
85							90					95					
Ala	Arg	Ser	Ile	Tyr	Asp	Asp	Tyr	Glu	Tyr	Asp	Asp	Tyr	Tyr	Ala	Met		
100							105					110					
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	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	Arg	Glu	Glu	Gln	Tyr		
290							295					300					
Asn	Ser	Thr	Tyr	Arg	Val	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	Asp	Glu	Leu	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
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser		400
	405	410
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser		415
	420	425
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser		430
	435	440
Leu Ser Leu Ser Pro Gly Lys		445
	450	455

<210> 37
<211> 1365
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 37
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact acgagtacga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcgccac agccgccttg ggctgccttg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcgccct gtacagcctg agcagcgttg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaagggtg agcccaagag ctgtgacaag acccacacct gccccccctg cctgcccc 720
gagctgctgg gaggccccag cgtgttcttg tccccccca agcctaagga caccctgatg 780
atcagcagaa ccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagttca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtgtaacg gcaaggagta caagtgtgag gtgtccaaca aggccctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag ccagagagc ccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccagcagc acatcgccgt ggagtgggag agcaacggcc agcccagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320

cacaatcact acaccagaa gagcctgagc ctgtcccctg gcaag 1365

<210> 38
<211> 455
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 38
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr Gln Tyr Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr		
290	295	300
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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		
450	455	

- <210> 39
- <211> 1365
- <212> DNA
- <213> 人工序列

- <220>
- <223> 人類化

<400> 39
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaaggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcaact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccgaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcadc 300
tacgacgact accagtacga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc cccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480

ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggacccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttcctg ttcccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggctgaacg gcaaggagta caagtgtgag gtgtccaaca aggccctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag ccagagagc ccagggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggg gaagggttc 1140
taccacagcg acatgcctgt ggagtgggag agcaacggcc agcccagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctget ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtcccctg gcaag 1365

<210> 40
<211> 455
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 40
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr Arg Tyr Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr			
	290	295	300
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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			
	450	455	

<210> 41

<211> 1365

<212> DNA

<213> 人工序列

<220>

<223> 人類化

<400> 41

caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaaggtg 60
agctgcaagg cctccggett ctacatcaag gacacctaca tgcaactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccagtg tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact acaggtacga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttcctg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagttca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtgaacg gcaaggagta caagtgtgag gtgtccaaca aggcctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag ccagagagc cccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccacagcg acatgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa ggcctgagc ctgtccctg gcaag 1365

<210> 42

<211> 455

<212> PRT

<213> 人工序列

<220>

<223> 人類化

<400> 42

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35	40	45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe		
50	55	60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr		
65	70	75
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys		
85	90	95
Ala Arg Ser Ile Tyr Asp Asp Tyr Ser Tyr Asp Asp Tyr Tyr Ala Met		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Leu 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
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
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 Arg Glu Glu Gln Tyr		
290	295	300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
305	310	315
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 Asp Glu Leu 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
450 455

<210> 43
<211> 1365
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 43
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaaggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcaact atcgaccccg ccaacggcaa caccaagtac 180
gtgccaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact actcctacga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcgccac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttcctg ttccccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagttca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtgaacg gcaaggagta caagtgtgag gtgtccaaca aggccctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag cccagagagc cccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggg gaagggttc 1140
taccacagcg acatcgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct cgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtccctg gcaag 1365

<210> 44
 <211> 455
 <212> PRT
 <213> 人工序列

<220>
 <223> 人類化

<400> 44

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1           5           10           15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
          20           25           30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
          35           40           45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
          50           55           60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
          65           70           75           80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
          85           90           95
Ala Arg Ser Ile Tyr Asp Asp Tyr Thr Tyr Asp Asp Tyr Tyr Ala Met
          100          105          110
Asp Tyr Trp Gly Gln Gly Thr Leu 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

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275	280	285
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr		
290	295	300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
305	310	315
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu		320
	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 Asp Glu Leu 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		
450	455	

<210> 45
<211> 1365
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 45
caggtgcagc tcgtgcagag cggcgcgcaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcaact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccgaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact acacgtacga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgcag caccaagggc cccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccttg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgctctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600



ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttcctg ttcccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtgaacg gcaaggagta caagtgtgag gtgtccaaca aggccctgcc tgccccatc 1020
gagaaaacca tcagcaaggc caagggccag ccagagagc ccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccacagcg acatcgccgt ggagtgggag agcaacggcc agcccagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agctttcttc tgtacagaa gctgaccgtg 1260
gacaagacga gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagectgagc ctgtcccctg gcaag 1365

<210> 46
<211> 455
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 46
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr Val Tyr Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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	Arg	Glu	Glu	Gln	Tyr				
290								295					300						
Asn	Ser	Thr	Tyr	Arg	Val	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	Asp	Glu	Leu	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													
450								455											

- <210> 47
- <211> 1365
- <212> DNA
- <213> 人工序列

<220>

<223> 人類化

<400> 47

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caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgccaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact acgtgtacga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaagggtg agccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttcctg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggctgaacg gcaaggagta caagtgtgag gtgtccaaca aggccctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag ccagagagc ccaggtgta caccctgcc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccacagcg acatcgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtccctg gcaag 1365

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<210> 48

<211> 455

<212> PRT

<213> 人工序列

<220>

<223> 人類化

<400> 48

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1           5           10          15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
      20           25          30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
      35           40          45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe

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50	55	60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr		
65	70	75
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys		
85	90	95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Ala Asp Asp Tyr Tyr Ala Met		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Leu 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
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
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 Arg Glu Glu Gln Tyr		
290	295	300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
305	310	315
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 Asp Glu Leu 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
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		
450	455	

<210> 49
<211> 1365
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 49
cagggtgcagc tcgtgcagag cggcgcgcaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcact atcgaccccc ccaacggcaa caccaagtac 180
gtgcccgaag tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact accacgcgga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc cccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccttg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcgccct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gagggcccag cgtgttcctg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtgatg tgagccacga ggaccctgag 840
gtgaagttea actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtctgaacg gcaaggagta caagtgaag gtgtccaaca aggcctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag cccagagagc cccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccccagcg acatcgccgt ggagtgggag agcaacggcc agcccagaaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtcccctg gcaag 1365

<210> 50
<211> 455

<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 50
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Ile Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr



290 295 300
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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
450 455

<210> 51
<211> 1365
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 51
caggtgcagc tcgtgcagag cggcgcgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcaact atcgaccccg ccaacggcaa caccaagtac 180
gtgccaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact accacattga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc cccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720

gagctgctgg gaggccccag cgtgttcctg ttcccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggctgaacg gcaaggagta caagtgtgag gtgtccaaca aggcctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag cccagagagc cccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggcttc 1140
taccacagcg acatcgccgt ggagtgggag agcaacggcc agcccagaaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct cctgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtccctg gcaag 1365

- <210> 52
- <211> 455
- <212> PRT
- <213> 人工序列

- <220>
- <223> 人類化

<400> 52
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Trp Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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	Arg	Glu	Glu	Gln	Tyr			
290							295					300						
Asn	Ser	Thr	Tyr	Arg	Val	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	Asp	Glu	Leu	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												
450							455											

- <210> 53
- <211> 1365
- <212> DNA
- <213> 人工序列

- <220>
- <223> 人類化

<400> 53

cagggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaaggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccaggt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact accactggga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttctg tttccccca agcctaagga caccctgatg 780
atcagcagaa cccccagggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagttca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtgaacg gcaaggagta caagtgtgag gtgtccaaca aggccctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag ccagagagc ccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggg gaagggett 1140
taccacagcg acatcgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa ggcctgagc ctgtccctg gcaag 1365

<210> 54

<211> 455

<212> PRT

<213> 人工序列

<220>

<223> 人類化

<400> 54

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr

65		70		75		80									
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85						90					95	
Ala	Arg	Ser	Ile	Tyr	Asp	Asp	Tyr	His	Val	Asp	Asp	Tyr	Tyr	Ala	Met
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	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	Arg	Glu	Glu	Gln	Tyr
	290						295				300				
Asn	Ser	Thr	Tyr	Arg	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	Asp	Glu	Leu	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		
450	455	

<210> 55
<211> 1365
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 55
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccagt tccagggcag ggtgaccatc accgcgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgcctgt actattgcgc caggagcatc 300
tacgacgact accacgtcga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcgccac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcgccct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaagggtg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttcttg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtget gcaccaggat 960
tggtgaacg gcaaggagta caagtgtgag gtgtccaaca aggcctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag ccagagagc ccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccacagcg acatcgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agctttcttc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctget ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa ggcctgagc ctgtcccctg gcaag 1365

<210> 56
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 信號序列

<400> 56
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15
Val His Ser

<210> 57
<211> 112
<212> PRT
<213> 智人

<400> 57
Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Glu Leu Ile Glu Glu Leu
1 5 10 15
Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly Ser Met
20 25 30
Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala Leu Glu
35 40 45
Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr Gln Arg
50 55 60
Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln Phe Ser
65 70 75 80
Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe Val Lys
85 90 95
Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg Phe Asn
100 105 110

<210> 58
<211> 125
<212> PRT
<213> 小鼠屬

<400> 58
Glu Ile Gln Leu Gln Gln Ser Val Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15
Ser Val Arg Leu Ser Cys Thr Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Ile Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile

35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80
Leu Arg Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Tyr Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120 125

<210> 59
<211> 112
<212> PRT
<213> 小鼠属

<400> 59
Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15
Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Asn Ile Val His Ile
20 25 30
Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Ile Ser Asp Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95
Ser His Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 60
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 突变 CDR

<400> 60

Phe Tyr Ile Lys Asp Thr Tyr Met His
1 5

<210> 61
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 突變 CDR

<400> 61
Gly Phe Tyr Ile Lys Asp Thr Tyr Met His
1 5 10

<210> 62
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 62
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Ala Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Glu Val Gln
 450 455 460
 Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg
 465 470 475 480
 Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asn Phe Gly Met Gly
 485 490 495

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Trp Ile
500 505 510
Ile Ser Ser Gly Thr Glu Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg
515 520 525
Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met
530 535 540
Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Ser
545 550 555 560
Leu Gly Arg Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
565 570 575
Ser

<210> 63
<211> 1731
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 63
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cctggccagg gcctggagtg gatgggcaat atcgaccccg ccaacggcaa caccaagtac 180
gtgcccagt tccagggcag ggtgaccatc accgcccgtg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgcccgtg actattgcgc caggagcatc 300
tacgacgact accacgcgga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ctagcgccag caccaagggc cccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccttg ggctgccttg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgttg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaagggtg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttctctg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagttca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtctgaacg gcaaggagta caagtgtgag gtgtccaaca aggcctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag cccagagagc cccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggcttc 1140
taccagcagc acatcgccgt ggagtgggag agcaacggcc agcccagaaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260

gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtcccctg gcaagaccgt ggccgcccc 1380
tcggaagtgc agctcctgga gagcggcggc ggccctggtgc agcccggcgg cagcctgagg 1440
ctgagctgcg ccgctagcgg cttcaccttc aggaacttcg gcatgggctg ggtcaggcag 1500
gccccggca agggcctgga gtgggtcagc tggatcatca gctccggcac cgagacctac 1560
tacgccgaca gcgtgaaggg caggttcacc atcagccgcg acaacagcaa gaacaccctg 1620
tacctgcaga tgaacagcct gagggccgag gacaccgcg tctactactg cgccaagagc 1680
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- <210> 64
- <211> 577
- <212> PRT
- <213> 人工序列

- <220>
- <223> 人類化

<400> 64
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1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Ile Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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



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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 Arg Glu Glu Gln Tyr
                      290                      295                      300
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Glu Val Gln
                      450                      455                      460
Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg
465                      470                      475                      480
Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asn Phe Gly Met Gly
                      485                      490                      495
Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Trp Ile
                      500                      505                      510
Ile Ser Ser Gly Thr Glu Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg
                      515                      520                      525
Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met
                      530                      535                      540
Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Ser
545                      550                      555                      560

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Leu Gly Arg Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
565 570 575

Ser

- <210> 65
- <211> 1731
- <212> DNA
- <213> 人工序列

- <220>
- <223> 人類化

<400> 65

caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
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cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgccccagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcattc 300
tacgacgact accacattga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ctagcgccag caccaagggc cccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gagggccag cgtgttcctg tccccccca agcctaagga caccctgatg 780
atcagcagaa ccccgagggt gacctgtgtg tgggtggatg tgagccacga ggaccctgag 840
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gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggctgaacg gcaaggagta caagtgtgag gtgtccaaca aggccctgcc tgccccctac 1020
gagaaaacca tcagcaaggc caagggccag cccagagagc cccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
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accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtccctg gcaagaccgt ggccgcccc 1380
tcggaagtgc agctcctgga gagcggcggc ggccctggtg agcccgggcg cagcctgagg 1440
ctgagctgcg ccgctagcgg cttcaccttc aggaacttcg gcatgggctg ggtcaggcag 1500
gccccggca agggcctgga gtgggtcagc tggatcatca gctccggcac cgagacctac 1560
tacgccgaca gcgtgaaggg caggttcacc atcagccgag acaacagcaa gaacaccctg 1620
tacctgcaga tgaacagcct gagggccgag gacaccgccg tctactactg cgccaagagc 1680
ctgggcaggt tcgactactg gggacagggg accctggtga ctgtgagcag c 1731

<210> 66
 <211> 577
 <212> PRT
 <213> 人工序列

<220>
 <223> 人類化

<400> 66

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1           5           10           15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
      20           25           30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
      35           40           45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50           55           60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65           70           75           80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
      85           90           95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Trp Asp Asp Tyr Tyr Ala Met
      100          105          110
Asp Tyr Trp Gly Gln Gly Thr Leu 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

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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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Glu Val Gln
 450 455 460
 Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg
 465 470 475 480
 Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asn Phe Gly Met Gly
 485 490 495
 Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Trp Ile
 500 505 510
 Ile Ser Ser Gly Thr Glu Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg
 515 520 525
 Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met
 530 535 540
 Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Ser
 545 550 555 560
 Leu Gly Arg Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 565 570 575
 Ser

<210> 67

<211> 1731

<212> DNA

<213> 人工序列

<220>

<223> 人類化

<400> 67

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cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgccaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact accactggga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ctagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
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aagaagggtg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttctg ttcccccca agcctaagga caccctgatg 780
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tacgccgaca gcgtgaaggg caggttcacc atcagcccg acaacagcaa gaacaccctg 1620
tacctgcaga tgaacagcct gagggccgag gacaccgcc totactactg cgccaagagc 1680
ctgggcaggt tcgactactg gggacagggg accctggtga ctgtgagcag c 1731

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<210> 68

<211> 577

<212> PRT

<213> 人工序列

<220>

<223> 人類化

<400> 68

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Glu Val Gln
450 455 460
Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg
465 470 475 480
Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asn Phe Gly Met Gly
485 490 495
Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Trp Ile
500 505 510
Ile Ser Ser Gly Thr Glu Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg
515 520 525
Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met
530 535 540
Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Ser
545 550 555 560
Leu Gly Arg Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
565 570 575
Ser

<210> 69
<211> 1731
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 69
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc cgggcagcag cgtgaaggtg 60

agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcaact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccgaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
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tacgacgact accacgtcga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcgccac agccgccttg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
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atcagcagaa cccccaggtg gacctgtgtg gtggtggatg tgagccacga ggacctgag 840
gtgaagtica actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
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gcccccgca agggcctgga gtgggtcagc tggatcatca gctccggcac cgagacctac 1560
tacgccgaca gcgtgaaggg caggttcacc atcagccgcg acaacagaa gaacacctg 1620
tacctgcaga tgaacagcct gagggccag gacaccgcc tctactactg cgccaagagc 1680
ctgggcagggt tcgactactg gggacagggg accctggtga ctgtgagcag c 1731

- <210> 70
- <211> 578
- <212> PRT
- <213> 人工序列

- <220>
- <223> 人類化

<400> 70
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Ala Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Ala Ser Thr Lys Gly Pro Ser Glu Val
450 455 460
Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
465 470 475 480
Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asn Phe Gly Met
485 490 495
Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Trp
500 505 510
Ile Ile Ser Ser Gly Thr Glu Thr Tyr Tyr Ala Asp Ser Val Lys Gly
515 520 525
Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
530 535 540
Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys
545 550 555 560
Ser Leu Gly Arg Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
565 570 575
Ser Ser

- <210> 71
- <211> 1734
- <212> DNA
- <213> 人工序列

- <220>
- <223> 人類化

<400> 71
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaaggtg 60
agctgcaagg cctccggett ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgccaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact accacgcgga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc ccccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgccttgaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540

gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtagg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gagggcccag cgtgttctctg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtgtaacg gcaaggagta caagtgtgag gtgtccaaca aggccctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag cccagagagc cccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccacagcg atatcgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtccctg gcaaggccag caccaagggc 1380
ccctcggaag tgcagctcct ggagagcggc ggcgccctgg tgcagcccgg cggcagcctg 1440
aggctgagct ggcgcgctag cggcttcacc ttcaggaact tcggcatggg ctgggtcagg 1500
caggcccccg gcaagggcct ggagtgggtc agctggatca tcagctccgg caccgagacc 1560
tactacgccg acagcgtgaa gggcaggttc accatcagcc gcgacaacag caagaacacc 1620
ctgtacctgc agatgaacag cctgagggcc gaggacaccg ccgtctacta ctgcgccaag 1680
agcctgggca ggttcgacta ctggggacag gggaccctgg tgactgtgag cagc 1734

<210> 72
<211> 578
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 72
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Ile Asp Asp Tyr Tyr Ala Met
100 105 110

Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	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
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
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	Arg	Glu	Glu	Gln	Tyr	290	295	300
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	305	310	315
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	Asp	Glu	Leu	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
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	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Glu	Val	450	455	460

Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
465 470 475 480
Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asn Phe Gly Met
485 490 495
Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Trp
500 505 510
Ile Ile Ser Ser Gly Thr Glu Thr Tyr Tyr Ala Asp Ser Val Lys Gly
515 520 525
Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
530 535 540
Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys
545 550 555 560
Ser Leu Gly Arg Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
565 570 575
Ser Ser

<210> 73
<211> 1734
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 73
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggtt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagt gatgggcaact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccagt tccagggcag ggtgaccatc accccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgcctgt actattgcgc caggagcatc 300
tacgacgact accacattga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaagggtg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttcctg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggctgaacg gcaaggagta caagtgtgtaag gtgtccaaca aggcctgcc tgcccctatc 1020

gagaaaacca tcagcaaggc caagggccag cccagagagc cccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccocagcg atatcgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa ggcctgagc ctgtccctg gcaaggccag caccaagggc 1380
ccctcggaag tgcagctcct ggagagcggc ggcggcctgg tgcagcccgg cggcagcctg 1440
aggtgagct gcgcgctag cggcttcacc ttcaggaact tcggcatggg ctgggtcagg 1500
caggcccccg gcaagggcct ggagtgggtc agctggatca tcagctccgg caccgagacc 1560
tactacgccg acagcgtgaa gggcaggttc accatcagcc gcgacaacag caagaacacc 1620
ctgtacctgc agatgaacag cctgagggcc gaggacaccg ccgtctacta ctgcgccaag 1680
agcctgggca ggttcgacta ctggggacag gggaccctgg tgactgtgag cagc 1734

<210> 74
<211> 578
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 74
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Trp Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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

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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 Arg Glu Glu Gln Tyr
      290                      295                      300
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Ala Ser Thr Lys Gly Pro Ser Glu Val
      450                      455                      460
Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
465                      470                      475                      480
Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asn Phe Gly Met
      485                      490                      495
Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Trp
      500                      505                      510
Ile Ile Ser Ser Gly Thr Glu Thr Tyr Tyr Ala Asp Ser Val Lys Gly
      515                      520                      525

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Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
530 535 540
Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys
545 550 555 560
Ser Leu Gly Arg Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
565 570 575
Ser Ser

- <210> 75
- <211> 1734
- <212> DNA
- <213> 人工序列

- <220>
- <223> 人類化

<400> 75
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc cgggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcaact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccagtg tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact accactggga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgcag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaagggtg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gagggcccag cgtgttctctg ttcccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggacctgag 840
gtgaagttca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtgaacg gcaaggagta caagtgtgag gtgtccaaca aggccctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag ccagagagc cccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccacagcg atatcgccgt ggagtgggag agcaacggcc agcccagaaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agctttcttc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtccctg gcaaggccag caccaagggc 1380
ccctcggaag tgcagctcct ggagagcggc ggccggcctg tgcagcccgg cggcagcctg 1440
aggctgagct gcgcgctag cggcttcacc ttcaggaact tcggcatggg ctgggtcagg 1500

caggcccccg gcaagggcct ggagtgggtc agctggatca tcagctccgg caccgagacc 1560
tactacgccg acagcgtgaa gggcaggttc accatcagcc gcgacaacag caagaacacc 1620
ctgtacctgc agatgaacag cctgagggcc gaggacaccg ccgtctacta ctgcgccaag 1680
agcctgggca ggttcgacta ctggggacag gggaccctgg tgactgtgag cagc 1734

<210> 76
<211> 578
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 76
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Ala Ser Thr Lys Gly Pro Ser Glu Val
 450 455 460
 Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu
 465 470 475 480
 Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asn Phe Gly Met
 485 490 495
 Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Trp
 500 505 510
 Ile Ile Ser Ser Gly Thr Glu Thr Tyr Tyr Ala Asp Ser Val Lys Gly
 515 520 525
 Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 530 535 540
 Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys
 545 550 555 560
 Ser Leu Gly Arg Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
 565 570 575
 Ser Ser

<210> 77

<211> 1734

<212> DNA

<213> 人工序列

<220>

<223> 人類化

<400> 77

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caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccagtg tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact accacgtcga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccgggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaagggtg agccccagag ctgtgacaag acccacacct gccccccctg cctgcccc 720
gagctgctgg gaggccccag cgtgttcctg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtgaacg gcaaggagta caagtgtgag gtgtccaaca aggccctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag ccagagagc ccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggg gaagggttc 1140
taccocagcg atatcgccgt ggagtgggag agcaacggcc agcccagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agctttcttc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtcccctg gcaaggccag caccaagggc 1380
ccctcggaag tgcagctcct ggagagcggc ggcggcctgg tgcagcccgg cggcagcctg 1440
aggctgagct gcgccctag cggcttcacc ttcagggaact tcggcatggg ctgggtcagg 1500
caggcccccg gcaagggcct ggagtgggtc agctggatca tcagctccgg caccgagacc 1560
tactacgccg acagcgtgaa gggcaggttc accatcagcc gcgacaacag caagaacacc 1620
ctgtacctgc agatgaacag cctgagggcc gaggaacccg ccgtctacta ctgcgccaag 1680
agcctgggca ggttcgacta ctggggacag gggaccctgg tgactgtgag cagc 1734

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<210> 78

<211> 108

<212> PRT

<213> 智人

<400> 78

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Ser Asp Trp
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Ala Trp Ala Ser Thr Leu Asp 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 Leu Gln Glu Gly Trp Gly Pro Pro
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 79

<211> 108

<212> PRT

<213> 智人

<400> 79

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Ser Asp Trp
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Ala Trp Ala Ser Ser Leu Tyr Glu 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 Leu Gln Glu Gly Trp Gly Pro Pro
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 80

<211> 108

<212> PRT

<213> 智人

<400> 80

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1             5             10             15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Ser Asp Trp
          20             25             30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
          35             40             45
Ala Trp Ala Ser Ser Leu Gln Gly 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 Leu Gln Glu Gly Trp Gly Pro Pro
          85             90             95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
          100             105

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<210> 81

<211> 116

<212> PRT

<213> 智人

<400> 81

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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 Arg Asn Phe
          20             25             30
Gly Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35             40             45
Ser Trp Ile Ile Ser Ser Gly Thr Glu 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 Tyr Cys
          85             90             95
Ala Lys Ser Leu Gly Arg Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
          100             105             110
Thr Val Ser Ser
          115

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<210> 82

<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 82
Gly Gly Gly Gly Ser
1 5

<210> 83
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 83
Thr Val Ala Ala Pro Ser
1 5

<210> 84
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 84
Ala Ser Thr Lys Gly Pro Thr
1 5

<210> 85
<211> 7
<212> PRT
<213> 人工序列

<220>

<223> 連接子

<400> 85

Ala Ser Thr Lys Gly Pro Ser
1 5

<210> 86

<211> 2

<212> PRT

<213> 人工序列

<220>

<223> 連接子

<400> 86

Gly Ser
1

<210> 87

<211> 8

<212> PRT

<213> 人工序列

<220>

<223> 連接子

<400> 87

Thr Val Ala Ala Pro Ser Gly Ser
1 5

<210> 88

<211> 571

<212> PRT

<213> 人工序列

<220>

<223> 人類化

<400> 88

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

1	5	10	15
Asp Arg Val Thr	Ile Thr Cys Arg	Ala Ser Arg Pro	Ile Ser Asp Trp
20	25	30	
Leu His Trp Tyr	Gln Gln Lys Pro	Gly Lys Ala Pro	Lys Leu Leu Ile
35	40	45	
Ala Trp Ala Ser	Ser Leu Tyr Glu	Gly Val Pro Ser	Arg Phe Ser Gly
50	55	60	
Ser Gly Ser Gly	Thr Asp Phe Thr	Leu Thr Ile Ser	Ser Ser Leu Gln Pro
65	70	75	80
Glu Asp Phe Ala	Thr Tyr Tyr Cys	Leu Gln Glu Gly	Trp Gly Pro Pro
85	90	95	
Thr Phe Gly Gln	Gly Thr Lys Val	Glu Ile Lys Arg	Gly Ser Thr Val
100	105	110	
Ala Ala Pro Ser	Gln Val Gln Leu	Val Gln Ser Gly	Ala Glu Val Lys
115	120	125	
Lys Pro Gly Ser	Ser Val Lys Val	Ser Cys Lys Ala	Ser Gly Phe Tyr
130	135	140	
Ile Lys Asp Thr	Tyr Met His Trp	Val Arg Gln Ala	Pro Gly Gln Gly
145	150	155	160
Leu Glu Trp Met	Gly Thr Ile Asp	Pro Ala Asn Gly	Asn Thr Lys Tyr
165	170	175	
Val Pro Lys Phe	Gln Gly Arg Val	Thr Ile Thr Ala	Asp Glu Ser Thr
180	185	190	
Ser Thr Ala Tyr	Met Glu Leu Ser	Ser Ser Leu Arg	Ser Glu Asp Thr Ala
195	200	205	
Val Tyr Tyr Cys	Ala Arg Ser Ile	Tyr Asp Asp Tyr	His Val Asp Asp
210	215	220	
Tyr Tyr Ala Met	Asp Tyr Trp Gly	Gln Gly Thr Leu	Val Thr Val Ser
225	230	235	240
Ser Ala Ser Thr	Lys Gly Pro Ser	Val Phe Pro Leu	Ala Pro Ser Ser
245	250	255	
Lys Ser Thr Ser	Gly Gly Thr Ala	Ala Leu Gly Cys	Leu Val Lys Asp
260	265	270	
Tyr Phe Pro Glu	Pro Val Thr Val	Ser Trp Asn Ser	Gly Ala Leu Thr
275	280	285	
Ser Gly Val His	Thr Phe Pro Ala	Val Leu Gln Ser	Ser Ser Gly Leu Tyr
290	295	300	
Ser Leu Ser Ser	Val Val Thr Val	Pro Ser Ser Ser	Leu Gly Thr Gln
305	310	315	320
Thr Tyr Ile Cys	Asn Val Asn His	Lys Pro Ser Asn	Thr Lys Val Asp
325	330	335	
Lys Lys Val Glu	Pro Lys Ser Cys	Asp Lys Thr His	Thr Cys Pro Pro
340	345	350	
Cys Pro Ala Pro	Glu Leu Leu Gly	Gly Pro Ser Val	Phe Leu Phe Pro

355	360	365
Pro Lys Pro Lys Asp Thr	Leu Met Ile Ser Arg Thr	Pro Glu Val Thr
370	375	380
Cys Val Val Val Asp Val	Ser His Glu Asp Pro Glu Val	Lys Phe Asn
385	390	395
Trp Tyr Val Asp Gly Val	Glu Val His Asn Ala Lys Thr	Lys Pro Arg
405	410	415
Glu Glu Gln Tyr Asn Ser Thr	Tyr Arg Val Val Ser Val	Leu Thr Val
420	425	430
Leu His Gln Asp Trp Leu Asn Gly	Lys Glu Tyr Lys Cys Lys Val	Ser
435	440	445
Asn Lys Ala Leu Pro Ala Pro	Ile Glu Lys Thr Ile Ser Lys Ala	Lys
450	455	460
Gly Gln Pro Arg Glu Pro Gln	Val Tyr Thr Leu Pro Pro Ser Arg	Asp
465	470	475
Glu Leu Thr Lys Asn Gln Val	Ser Leu Thr Cys Leu Val Lys Gly	Phe
485	490	495
Tyr Pro Ser Asp Ile Ala Val	Glu Trp Glu Ser Asn Gly Gln Pro	Glu
500	505	510
Asn Asn Tyr Lys Thr Thr Pro	Pro Val Leu Asp Ser Asp Gly Ser	Phe
515	520	525
Phe Leu Tyr Ser Lys Leu Thr	Val Asp Lys Ser Arg Trp Gln Gln	Gly
530	535	540
Asn Val Phe Ser Cys Ser Val	Met His Glu Ala Leu His Asn His	Tyr
545	550	555
Thr Gln Lys Ser Leu Ser Leu	Ser Pro Gly Lys	
565	570	

<210> 89
<211> 572
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 89
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Ser Asp Trp
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

35	40	45
Ala Trp Ala Ser Ser Leu Tyr Glu 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
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Glu Gly Trp Gly Pro Pro		
85	90	95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Gly Ser Ala Ser		
100	105	110
Thr Lys Gly Pro Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val		
115	120	125
Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe		
130	135	140
Tyr Ile Lys Asp Thr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln		
145	150	155
Gly Leu Glu Trp Met Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys		
165	170	175
Tyr Val Pro Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser		
180	185	190
Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr		
195	200	205
Ala Val Tyr Tyr Cys Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp		
210	215	220
Asp Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val		
225	230	235
Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser		
245	250	255
Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys		
260	265	270
Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu		
275	280	285
Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu		
290	295	300
Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr		
305	310	315
Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val		
325	330	335
Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro		
340	345	350
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe		
355	360	365
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val		
370	375	380
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe		

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385              390              395              400
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
              405              410              415
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
              420              425              430
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
              435              440              445
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
              450              455              460
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
465              470              475              480
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
              485              490              495
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
              500              505              510
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
              515              520              525
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
              530              535              540
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
545              550              555              560
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
              565              570

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<210> 90

<211> 571

<212> PRT

<213> 人工序列

<220>

<223> 人類化

<400> 90

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1              5              10              15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Ser Asp Trp
              20              25              30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
              35              40              45
Ala Trp Ala Ser Ser Leu Gln Gly 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

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65	70	75	80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Glu Gly Trp Gly Pro Pro			
85	90	95	
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Gly Ser Thr Val			
100	105	110	
Ala Ala Pro Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys			
115	120	125	
Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr			
130	135	140	
Ile Lys Asp Thr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly			
145	150	155	160
Leu Glu Trp Met Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr			
165	170	175	
Val Pro Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr			
180	185	190	
Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala			
195	200	205	
Val Tyr Tyr Cys Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp			
210	215	220	
Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser			
225	230	235	240
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser			
245	250	255	
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp			
260	265	270	
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr			
275	280	285	
Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr			
290	295	300	
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln			
305	310	315	320
Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp			
325	330	335	
Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro			
340	345	350	
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro			
355	360	365	
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr			
370	375	380	
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn			
385	390	395	400
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg			
405	410	415	
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val			

420 425 430
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
435 440 445
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
450 455 460
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
465 470 475 480
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
485 490 495
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
500 505 510
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
515 520 525
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
530 535 540
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
545 550 555 560
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
565 570

<210> 91
<211> 572
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 91
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Ser Asp Trp
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Ala Trp Ala Ser Ser Leu Gln Gly 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 Leu Gln Glu Gly Trp Gly Pro Pro
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Gly Ser Ala Ser

100	105	110
Thr Lys Gly Pro Ser Gln Val	Gln Leu Val Gln Ser Gly	Ala Glu Val
115	120	125
Lys Lys Pro Gly Ser Ser Val	Lys Val Ser Cys Lys Ala	Ser Gly Phe
130	135	140
Tyr Ile Lys Asp Thr Tyr Met	His Trp Val Arg Gln Ala	Pro Gly Gln
145	150	155
Gly Leu Glu Trp Met Gly Thr	Ile Asp Pro Ala Asn Gly	Asn Thr Lys
165	170	175
Tyr Val Pro Lys Phe Gln Gly	Arg Val Thr Ile Thr Ala	Asp Glu Ser
180	185	190
Thr Ser Thr Ala Tyr Met Glu	Leu Ser Ser Leu Arg Ser	Glu Asp Thr
195	200	205
Ala Val Tyr Tyr Cys Ala Arg	Ser Ile Tyr Asp Asp Tyr	His Val Asp
210	215	220
Asp Tyr Tyr Ala Met Asp Tyr	Trp Gly Gln Gly Thr Leu	Val Thr Val
225	230	235
Ser Ser Ala Ser Thr Lys Gly	Pro Ser Val Phe Pro Leu	Ala Pro Ser
245	250	255
Ser Lys Ser Thr Ser Gly Gly	Thr Ala Ala Leu Gly Cys	Leu Val Lys
260	265	270
Asp Tyr Phe Pro Glu Pro Val	Thr Val Ser Trp Asn Ser	Gly Ala Leu
275	280	285
Thr Ser Gly Val His Thr Phe	Pro Ala Val Leu Gln Ser	Ser Gly Leu
290	295	300
Tyr Ser Leu Ser Ser Val Val	Thr Val Pro Ser Ser Ser	Leu Gly Thr
305	310	315
Gln Thr Tyr Ile Cys Asn Val	Asn His Lys Pro Ser Asn	Thr Lys Val
325	330	335
Asp Lys Lys Val Glu Pro Lys	Ser Cys Asp Lys Thr His	Thr Cys Pro
340	345	350
Pro Cys Pro Ala Pro Glu Leu	Leu Gly Gly Pro Ser Val	Phe Leu Phe
355	360	365
Pro Pro Lys Pro Lys Asp Thr	Leu Met Ile Ser Arg Thr	Pro Glu Val
370	375	380
Thr Cys Val Val Val Asp Val	Ser His Glu Asp Pro Glu	Val Lys Phe
385	390	395
Asn Trp Tyr Val Asp Gly Val	Glu Val His Asn Ala Lys	Thr Lys Pro
405	410	415
Arg Glu Glu Gln Tyr Asn Ser	Thr Tyr Arg Val Val Ser	Val Leu Thr
420	425	430
Val Leu His Gln Asp Trp Leu	Asn Gly Lys Glu Tyr Lys	Cys Lys Val
435	440	445
Ser Asn Lys Ala Leu Pro Ala	Pro Ile Glu Lys Thr Ile	Ser Lys Ala

450						455										460
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	
465						470					475					480
Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	
				485						490					495	
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	
				500						505					510	
Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	
			515					520					525			
Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	
		530					535					540				
Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	
545					550					555					560	
Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys					
				565						570						

<210> 92
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 连接子

<400> 92
Gly Ser Thr Val Ala Ala Pro Ser
1 5

<210> 93
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 连接子

<400> 93
Gly Ser Thr Val Ala Ala Pro Ser Gly Ser
1 5 10

<210> 94
<211> 108
<212> PRT
<213> 智人

<220>
<223> 突變 dAb

<400> 94
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Ser Asp Trp
20 25 30
Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Ala Trp Ala Ser Ser Leu Gln Gly 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 Glu Gly Trp Gly Pro Pro
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 95
<211> 324
<212> DNA
<213> 智人

<400> 95
gacatccaga tgaccagag cccagcagc ctgagcgcca gcgtgggcga cagggtgacc 60
attacctgca gggccagcag gcccatcagc gactggctgc actggtacca acagaagccc 120
ggcaaggctc ccaagctgct gatcgcttg gccagcagcc tgcagggagg cgtgcccagc 180
aggtttagcg gcagcggcag cggcaccgac ttcacctca ccatctcttc cctgcagccc 240
gaggacttgc ccacctacta ctgccagcag gagggctggg ggccccctac ttctggccag 300
ggcaccaagg tggagatcaa gagg 324

<210> 96
<211> 581
<212> PRT
<213> 人工序列

<220>

<223> 人類化

<400> 96

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300

Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Gly Ser Thr Val Ala Ala Pro Ser Gly
450 455 460
Ser Thr Val Ala Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser
465 470 475 480
Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
485 490 495
Arg Ala Ser Arg Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys
500 505 510
Pro Gly Lys Ala Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln
515 520 525
Gly Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
530 535 540
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
545 550 555 560
Cys Gln Gln Glu Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys
565 570 575
Val Glu Ile Lys Arg
580

<210> 97
<211> 1743
<212> DNA
<213> 人工序列

<220>

<223> 人類化

<400> 97

caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
 agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
 cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
 gtgcccgaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
 atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
 tacgacgact accacgtcga cgactactac gccatggact actggggaca gggcacacta 360
 gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
 aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
 ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
 gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
 ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
 aagaagggtg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
 gagctgctgg gaggccccag cgtgttctg tttccccca agcctaagga caccctgatg 780
 atcagcagaa cccccagggt gacctgtgtg gtggtggatg tgagccacga ggacctgag 840
 gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
 gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
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 cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggcttc 1140
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 accaccccc ctgtgctgga cagcgatggc agctttcttc tgtacagcaa gctgaccgtg 1260
 gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
 cacaatcact acaccagaa gagcctgagc ctgtccctg gcaagggatc taccgtggca 1380
 gcaccatcog gatctaccgt agcagcacca tccggatccg acatccagat gaccagagc 1440
 cccagcagcc tgagcgccag cgtgggcgac aggggtgacca ttacctgcag ggccagcagg 1500
 cccatcagcg actggctgca ctggtaccaa cagaagccc gcaaggctcc caagctgctg 1560
 atgcctggg ccagcagcct gcagggagc gtcccagca ggtttagcgg cagcggcagc 1620
 ggcaccgact tcaccctcac catctcttc ctgcagccc aggacttcgc cacctactac 1680
 tgccagcagg agggctgggg gccccctact ttggccagg gcaccaaggt ggagatcaag 1740
 agg 1743

<210> 98

<211> 589

<212> PRT

<213> 人工序列

<220>

<223> 人類化

<400> 98

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Gly Ser Thr Val Ala Ala Pro Ser Gly
450 455 460
Ser Thr Val Ala Ala Pro Ser Gly Ser Thr Val Ala Ala Pro Ser Gly
465 470 475 480
Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
485 490 495
Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Ser Asp
500 505 510
Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
515 520 525
Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Arg Phe Ser
530 535 540
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
545 550 555 560
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Glu Gly Trp Gly Pro
565 570 575
Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
580 585

<210> 99
<211> 1767
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 99
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60

agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcagget 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact accacgtcga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccttg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttcttg tccccccca agcctaagga caccctgatg 780
atcagcagaa ccccgagggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagttea actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtgaacg gcaaggagta caagtgtgag gtgtccaaca aggccctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag ccagagagc ccaggtgta caccctgcc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggg gaagggttc 1140
taccccagcg acatcgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtccctg gcaagggatc taccgtggca 1380
gcaccatcag gatctaccgt ggcagcacca tcaggttcaa cagtagctgc tccttctgga 1440
tcgacatcc agatgacca gagccccagc agcctgagcg ccagcgtggg cgacagggtg 1500
accattacct gcagggccag caggcccatc agcgactggc tgcactggta ccaacagaag 1560
cccggcaagg ctcccaagct gctgatcgcc tgggccagca gcctgcaggg aggcgtgccc 1620
agcaggttta gcggcagcgg cagcggcacc gacttcaccc tcaccatctc ttccctgcag 1680
cccaggact tcgccaccta ctactgccag caggagggtt gggggccccc tactttcggc 1740
cagggcacca aggtggagat caagagg 1767

- <210> 100
- <211> 597
- <212> PRT
- <213> 人工序列

- <220>
- <223> 人類化

<400> 100
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30

201107345

Tyr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
35				40				45							
Gly	Thr	Ile	Asp	Pro	Ala	Asn	Gly	Asn	Thr	Lys	Tyr	Val	Pro	Lys	Phe
50				55				60							
Gln	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Ser	Thr	Ala	Tyr
65				70				75				80			
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
85				90				95							
Ala	Arg	Ser	Ile	Tyr	Asp	Asp	Tyr	His	Val	Asp	Asp	Tyr	Tyr	Ala	Met
100				105				110							
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	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	Arg	Glu	Glu	Gln	Tyr
290				295				300							
Asn	Ser	Thr	Tyr	Arg	Val	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	Asp	Glu	Leu	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 Gly Ser Thr Val Ala Ala Pro Ser Gly
450 455 460
Ser Thr Val Ala Ala Pro Ser Gly Ser Thr Val Ala Ala Pro Ser Gly
465 470 475 480
Ser Thr Val Ala Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser
485 490 495
Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
500 505 510
Arg Ala Ser Arg Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys
515 520 525
Pro Gly Lys Ala Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln
530 535 540
Gly Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
545 550 555 560
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
565 570 575
Cys Gln Gln Glu Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys
580 585 590
Val Glu Ile Lys Arg
595

- <210> 101
- <211> 1791
- <212> DNA
- <213> 人工序列

- <220>
- <223> 人類化

<400> 101
caggtgcagc tcgtgcagag cggcgcgaa gtgaaaaagc ccggcagcag cgtgaaggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcaactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcaact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240

atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact accacgtcga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc cccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttcctg ttcccccca agcctaagga caccctgatg 780
atcagcagaa cccccaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtgtaacg gcaaggagta caagtgaag gtgtccaaca aggccctgcc tgcccctatc 1020
gagaaaaacca tcagcaaggc caagggccag cccagagagc cccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggg gaagggett 1140
taccacagcg acatcgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtcccctg gcaagggatc taccgtggca 1380
gcaccatcag gatctaccgt ggcagcacca tcaggttcaa cagtagctgc tccttctggt 1440
tcaacagtag ctgctccttc tggatccgac atccagatga cccagagccc cagcagcctg 1500
agcgccagcg tggcgacag ggtgaccatt acctgcaggg ccagcaggcc catcagcgac 1560
tggtgcaact ggtaccaaca gaagcccggc aaggctccca agctgctgat cgctggggc 1620
agcagcctgc agggaggcgt gccagcagg tttagcggca gcggcagcgg caccgacttc 1680
accctcacca tctcttcct gcagcccag gacttcgcca cctactactg ccagcaggag 1740
ggctgggggc ccctacttt cggccagggc accaaggtgg agatcaagag g 1791

- <210> 102
- <211> 577
- <212> PRT
- <213> 人工序列

- <220>
- <223> 人類化

<400> 102
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe

50	55	60
Gln Gly Arg Val Thr	Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr	
65	70	75
Met Glu Leu Ser Ser	Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys	80
85	90	95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Leu 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
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
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 Arg Glu Glu Gln Tyr		
290	295	300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
305	310	315
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 Asp Glu Leu 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
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser		400

	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	Thr	Val	Ala	Ala	Pro	Ser	Thr	Val	Ala
	450							455						460	
Ala	Pro	Ser	Gly	Ser	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu
	465							470						475	
Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Arg
								485						490	
Pro	Ile	Ser	Asp	Trp	Leu	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala
								500						505	
Pro	Lys	Leu	Leu	Ile	Ala	Trp	Ala	Ser	Ser	Leu	Gln	Gly	Gly	Val	Pro
								515						520	
Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile
								530						535	
Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Glu
								545						550	
Gly	Trp	Gly	Pro	Pro	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys
								555						560	
								565						570	
														575	

Arg

<210> 103
<211> 1731
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 103
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcagget 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgccccagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact accacgtcga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540

gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gagggcccag cgtgttcctg ttcccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagttca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggctgaacg gcaaggagta caagtgaag gtgtccaaca aggcctgcc tgcctctatc 1020
gagaaaacca tcagcaaggc caagggccag ccagagagc ccaggtgta caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccocagcg acatcgccgt ggagtgggag agcaacggcc agcccgagaa caactacaag 1200
accaccccc ctgtgctgga cagcgtggc agcttcttcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtcccctg gcaagaccgt ggcagcacca 1380
tccaccgtag cagcaccatc cggatccgac atccagatga ccagagccc cagcagcctg 1440
agcgccagcg tgggcgacag ggtgaccatt acctgcaggg ccagcaggcc catcagcgac 1500
tggctgcaact ggtaccaaca gaagcccggc aaggctccca agctgctgat cgcctgggcc 1560
agcagcctgc agggaggcgt gccagcagg tttagcggca gcggcagcgg caccgacttc 1620
accctcacca tctcttcct gcagcccgag gacttcgcca cctactactg ccagcaggag 1680
ggctgggggc cccctacttt cggccagggc accaaggtgg agatcaagag g 1731

- <210> 104
- <211> 583
- <212> PRT
- <213> 人工序列

- <220>
- <223> 人類化

<400> 104
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met

100	105	110
Asp Tyr Trp Gly Gln Gly Thr Leu 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
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
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 Arg Glu Glu Gln Tyr		
290	295	300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
305	310	315
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 Asp Glu Leu 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
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 Thr Val Ala Ala Pro Ser Thr Val Ala		

450 455 460
Ala Pro Ser Thr Val Ala Ala Pro Ser Gly Ser Asp Ile Gln Met Thr
465 470 475 480
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
485 490 495
Thr Cys Arg Ala Ser Arg Pro Ile Ser Asp Trp Leu His Trp Tyr Gln
500 505 510
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser
515 520 525
Leu Gln Gly Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
530 535 540
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
545 550 555 560
Tyr Tyr Cys Gln Gln Glu Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly
565 570 575
Thr Lys Val Glu Ile Lys Arg
580

<210> 105
<211> 1749
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 105
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgcactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcaact atcgaccccg ccaacggcaa caccaagtac 180
gtgcccagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgcgc caggagcatc 300
tacgacgact accacgtoga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc ccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaaggtgg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttcctg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccaggt gacctgtgtg gtggtgatg tgagccacga ggaccctgag 840
gtgaagttea actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900

gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtgaacg gcaaggagta caagtgttaag gtgtccaaca aggccctgcc tgcccctatc 1020
gagaaaacca tcagcaaggc caagggccag cccagagagc cccagggtga caccctgccc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggcttc 1140
taccacagcg acatcgccgt ggagtgggag agcaacggcc agcccagaaa caactacaag 1200
accaccccc ctgtgctgga cagcgatggc agctttcttc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa ggcctgagc ctgtccctg gcaagaccgt ggcagcacca 1380
tcaaccgtgg cagcaccatc aacagtagct gctccttctg gatccgacat ccagatgacc 1440
cagagcccca gcagcctgag cgcagcgtg ggcgacaggg tgaccattac ctgcagggcc 1500
agcaggccca tcagcgactg gctgcactgg taccaacaga agcccggcaa ggctcccaag 1560
ctgctgatcg cctgggccag cagcctgcag ggaggcgtgc ccagcagggt tagcggcagc 1620
ggcagcggca ccgacttcac cctcaccatc tcttcctgc agcccagga cttcgccacc 1680
tactactgcc agcaggaggg ctggggggccc octactttcg gccagggcac caaggtggag 1740
atcaagagg 1749

- <210> 106
- <211> 589
- <212> PRT
- <213> 人工序列

- <220>
- <223> 人類化

<400> 106
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala
 450 455 460
 Ala Pro Ser Thr Val Ala Ala Pro Ser Thr Val Ala Ala Pro Ser Gly
 465 470 475 480
 Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
 485 490 495

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Ser Asp
500 505 510
Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
515 520 525
Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Arg Phe Ser
530 535 540
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
545 550 555 560
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Glu Gly Trp Gly Pro
565 570 575
Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
580 585

<210> 107
<211> 1767
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 107
caggtgcagc tcgtgcagag cggcgccgaa gtgaaaaagc ccggcagcag cgtgaagggtg 60
agctgcaagg cctccggctt ctacatcaag gacacctaca tgactgggt caggcaggct 120
cctggccagg gcctggagtg gatgggcact atcgaccccg ccaacggcaa caccaagtac 180
gtgccaagt tccagggcag ggtgaccatc accgccgatg agagcaccag caccgcctac 240
atggaactga gcagcctgag gtctgaggac accgccgtgt actattgogc caggagcatc 300
tacgacgact accacgtcga cgactactac gccatggact actggggaca gggcacacta 360
gtgaccgtgt ccagcgccag caccaagggc cccagcgtgt tccccctggc cccagcagc 420
aagagcacca gcggcggcac agccgccctg ggctgcctgg tgaaggacta cttccccgaa 480
ccggtgaccg tgtcctggaa cagcggagcc ctgaccagcg gcgtgcacac cttccccgcc 540
gtgctgcaga gcagcggcct gtacagcctg agcagcgtgg tgaccgtgcc cagcagcagc 600
ctgggcaccc agacctacat ctgtaacgtg aaccacaagc ccagcaacac caaggtggac 660
aagaagggtg agcccaagag ctgtgacaag acccacacct gccccccctg ccctgcccc 720
gagctgctgg gaggccccag cgtgttcctg tccccccca agcctaagga caccctgatg 780
atcagcagaa cccccgaggt gacctgtgtg gtggtggatg tgagccacga ggaccctgag 840
gtgaagtcca actggtacgt ggacggcgtg gaggtgcaca atgccaagac caagcccagg 900
gaggagcagt acaacagcac ctaccgggtg gtgtccgtgc tgaccgtgct gcaccaggat 960
tggtgaacg gcaaggagta caagtgtgag gtgtccaaca aggcctgcc tgccctatc 1020
gagaaaacca tcagcaaggc caagggccag cccagagagc cccaggtgta caccctgcc 1080
cctagcagag atgagctgac caagaaccag gtgtccctga cctgcctggt gaagggttc 1140
taccacagcg acatcgccgt ggagtgggag agcaacggcc agcccagaa caactacaag 1200

accaccccc ctgtgctgga cagcgatggc agctttctcc tgtacagcaa gctgaccgtg 1260
gacaagagca gatggcagca gggcaacgtg ttcagctgct ccgtgatgca cgaggccctg 1320
cacaatcact acaccagaa gagcctgagc ctgtcccctg gcaagaccgt ggcagcacca 1380
tcaaccgtgg cagcaccatc aacagtagct gctccttcta cagtagctgc tccttctgga 1440
tccgacatcc agatgaccca gagccccagc agcctgagcg ccagcgtggg cgacagggtg 1500
accattacct gcagggccag caggcccatc agcgactggc tgcactggta ccaacagaag 1560
cccggcaagg ctcccaagct gctgatcgcc tgggccagca gcctgcaggg aggcgtgccc 1620
agcaggttta gcggcagcgg cagcggcacc gacttcaccc tcaccatctc ttccctgcag 1680
cccgaggact tcgccacctc ctactgccag caggagggtt gggggccccc tactttcggc 1740
cagggcacca aggtggagat caagagg 1767

- <210> 108
- <211> 219
- <212> PRT
- <213> 人工序列

- <220>
- <223> 人類化

<400> 108
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Asn Ile Val His Ile
20 25 30
Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Ile Ser Asp Arg Phe Ser Gly Val Pro
50 55 60
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly
85 90 95
Ser His Val Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu

180 185 190
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 109
<211> 714
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 109
atgggctggt cctgcatcat cctgtttctg gtggccaccg ccaccggcgt gcacagcgac 60
atccagatga cccagagccc cagcagcctg agcgccagcg tgggcgacag ggtgactatc 120
acctgcagga gcagccagaa catcgtgcac atcaacggca acacctacct cgagtggtag 180
cagcagaaac ccgggaaggc cccaagctg ctgatctaca agatcagcga caggttcagc 240
ggcgtgcccc gcaggttttag cggtccggc tcaggcaccc atttcaccct gaccattagc 300
agcctgcagc ccagggaactt cgccacctac tactgtctcc agggctctca cgtcccctgg 360
accttcggcc agggcaccaa gctggagatc aagcgtacgg tggccgcccc cagcgtgttc 420
atcttcccc ccagcgatga gcagctgaag agcggcaccc ccagcgtggt gtgtctgctg 480
aacaacttct acccccggga ggccaaggtg cagtggaagg tggacaatgc cctgcagagc 540
ggcaacagcc aggagagcgt gaccgagcag gacagcaagg actccaccta cagcctgagc 600
agcaccctga cctgagcaa ggccgactac gagaagcaca aggtgtacgc ctgtgaggtg 660
accaccagg gcctgtccag ccccgtagcc aagagcttca accggggcga gtgc 714

<210> 110
<211> 219
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 110
Asp Val Leu Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Asn Ile Val His Ile
20 25 30

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

- <210> 111
- <211> 714
- <212> DNA
- <213> 人工序列
- <220>
- <223> 人類化

<400> 111
atgggctggt cctgcatcat cctgtttctg gtggccaccg ccaccggcgt gcacagcgac 60
gtgctgatga cccagagccc cagcagcctg agcgccagcg tgggcgacag ggtgactatc 120
acctgcagga gcagccagaa catcgtgcac atcaacggca acacctacct cgagtggtag 180
cagcagaaac ccgggaaggc cccaagctg ctgatctaca agatcagcga caggttcagc 240
ggcgtgcccc gcaggttttag cggtccggc tcaggcaccg atttcacct gaccattagc 300
agcctgcagc ccgaggactt cgccacctac tactgcttcc agggctctca cgccccctgg 360
accttcggcc agggcaccaa gctggagatc aagcgtagcg tggccgcccc cagcgtgttc 420
atcttcccc ccagcgatga gcagctgaag agcggcaccg ccagcgtggt gtgtctgctg 480

aacaacttct acccccggga ggccaaggtg cagtggaagg tggacaatgc cctgcagagc 540
 ggcaacagcc aggagagcgt gaccgagcag gacagcaagg actccaccta cagcctgagc 600
 agcacccctga ccctgagcaa ggccgactac gagaagcaca aggtgtacgc ctgtgaggtg 660
 acccaccagg gcctgtccag ccccgtagacc aagagcttca accggggcga gtgc 714

<210> 112

<211> 219

<212> PRT

<213> 人工序列

<220>

<223> 人類化

<400> 112

Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Gly	Thr	Leu	Ser	Leu	Ser	Pro	Gly
1				5				10					15		
Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ser	Ser	Gln	Asn	Ile	Val	His	Ile
			20					25					30		
Asn	Gly	Asn	Thr	Tyr	Leu	Glu	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala
			35				40					45			
Pro	Arg	Leu	Leu	Ile	Tyr	Lys	Ile	Ser	Asp	Arg	Phe	Ser	Gly	Ile	Pro
			50				55					60			
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile
65				70						75					80
Ser	Arg	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Phe	Gln	Gly
			85							90				95	
Ser	His	Val	Pro	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys
			100					105					110		
Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu
			115					120					125		
Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe
			130				135					140			
Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln
145				150						155					160
Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser
			165						170				175		
Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu
			180					185					190		
Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser
			195					200					205		
Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys					
			210					215							

<210> 113
<211> 714
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 113
atgggctggt cctgcatcat cctgtttctg gtggccaccg ccaccggcgt gcacagcgag 60
atcgtgctga cccagagccc tggcacactg agcctgagcc ccggagagag ggccaccctg 120
agctgcaggt ctagccagaa catcgtgcac atcaacggca acacctacct ggagtgggtat 180
cagcagaagc ccggccaggc ccccaggctg ctgatctaca agatcagcga caggttcagc 240
ggcatccccg acaggttttag cggcagcggc agcggcaccg acttcaccct gaccattagc 300
aggctggagc ccgaggactt cgccgtgtac tactgcttcc aggggagcca cgtgccctgg 360
accttcggcc agggcaccaa gctcgaaatc aagcgtacgg tggccgcccc cagcgtgttc 420
atcttcccc ccagcgatga gcagctgaag agcggcaccg ccagcgtggt gtgtctgctg 480
aacaacttct acccccggga ggccaagggt cagtggaagg tggacaatgc cctgcagagc 540
ggcaacagcc aggagagcgt gaccgagcag gacagcaagg actccaccta cagcctgagc 600
agcacctga ccctgagcaa ggccgactac gagaagcaca aggtgtacgc ctgtgaggtg 660
accaccagg gcctgtccag ccccgtagcc aagagcttca accggggcga gtgc 714

<210> 114
<211> 219
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 114
Asp Val Leu Met Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Gln Asn Ile Val His Ile
20 25 30
Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45
Pro Lys Leu Leu Ile Tyr Lys Ile Ser Asp Arg Phe Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Phe Gln Gly
85 90 95
Ser His Val Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 115
<211> 657
<212> DNA
<213> 人工序列

<220>
<223> 人類化

<400> 115
gacgtgctga tgaccagag ccctggcaca ctgagcctga gccccggaga gagggccacc 60
ctgagctgca ggtctagcca gaacatcgtg cacatcaacg gcaacaccta cctggagtgg 120
tatcagcaga agcccgcca gcccccaag ctgctgatct acaagatcag cgacaggttc 180
agcggcgtgc ccgacaggtt tagcggcagc ggcagcggca ccgactcac cctgaccatt 240
agcaggctgg agcccgagga cttcgccgtg tactactgct tccaggggag ccacgtgcc 300
tggaccttcg gccagggcac caagctcgaa atcaagcgta cgggtggccgc cccagcgtg 360
ttcatcttcc cccccagcga tgagcagctg aagagcggca ccgccagcgt ggtgtgtctg 420
ctgaacaact tctacccccg ggaggccaag gtgcagtgga aggtggacaa tgccctgcag 480
agcggcaaca gccaggagag cgtgaccgag caggacagca aggactccac ctacagcctg 540
agcagcacco tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgtgag 600
gtgaccacc accggcctgtc cagccccgtg accaagagct tcaaccgggg cgagtgc 657

<210> 116
<211> 571

<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 116
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Tyr Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Gly Ser Asp
450 455 460
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
465 470 475 480
Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Ser Asp Trp Leu
485 490 495
His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Ala
500 505 510
Trp Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Arg Phe Ser Gly Ser
515 520 525
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
530 535 540
Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Glu Gly Trp Gly Pro Pro Thr
545 550 555 560
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
565 570

<210> 117
<211> 577
<212> PRT
<213> 人工序列

<220>

<223> 人類化

<400> 117

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala
 450 455 460
 Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
 465 470 475 480
 Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
 485 490 495
 Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
 500 505 510
 Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
 515 520 525
 Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
 530 535 540
 Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gly Gln Glu
 545 550 555 560
 Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 565 570 575
 Arg

<210> 118

<211> 577

<212> PRT

<213> 人工序列

<220>

<223> 人類化

<400> 118

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala
450 455 460
Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
465 470 475 480
Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
485 490 495
Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
500 505 510
Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
515 520 525
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
530 535 540
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ser Gln Glu
545 550 555 560
Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
565 570 575
Arg

<210> 119
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 119

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser			
1	5	10	15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr			
20	25	30	
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met			
35	40	45	
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe			
50	55	60	
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr			
65	70	75	80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys			
85	90	95	
Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met			
100	105	110	
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr			
290	295	300	
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala
450 455 460
Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
465 470 475 480
Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
485 490 495
Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
500 505 510
Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
515 520 525
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
530 535 540
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys His Gln Glu
545 550 555 560
Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
565 570 575
Arg

<210> 120
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 120
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala
450 455 460
Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
465 470 475 480
Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
485 490 495
Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
500 505 510
Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
515 520 525
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
530 535 540
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Met Gln Glu
545 550 555 560
Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
565 570 575
Arg

<210> 121
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 121
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala
450 455 460
Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
465 470 475 480
Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
485 490 495
Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
500 505 510
Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
515 520 525
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
530 535 540
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Glu
545 550 555 560
Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
565 570 575
Arg

<210> 122
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 122
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe		
50	55	60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr		
65	70	75
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys		
85	90	95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Leu 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
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
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 Arg Glu Glu Gln Tyr		
290	295	300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
305	310	315
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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala
450 455 460
Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
465 470 475 480
Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
485 490 495
Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
500 505 510
Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
515 520 525
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
530 535 540
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Thr Gln Glu
545 550 555 560
Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
565 570 575
Arg

<210> 123
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 123
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala
 450 455 460
 Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
 465 470 475 480
 Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
 485 490 495
 Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
 500 505 510
 Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
 515 520 525
 Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
 530 535 540
 Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Cys Gln Glu
 545 550 555 560
 Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 565 570 575
 Arg

<210> 124

<211> 577

<212> PRT

<213> 人工序列

<220>

<223> 人類化

<400> 124

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80

Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	85	90	95
Ala	Arg	Ser	Ile	Tyr	Asp	Asp	Tyr	His	Val	Asp	Asp	Tyr	Tyr	Ala	Met	100	105	110
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	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
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
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	Arg	Glu	Glu	Gln	Tyr	290	295	300
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	305	310	315
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	Asp	Glu	Leu	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
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 Thr Val Ala Ala Pro Ser Thr Val Ala
450 455 460
Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
465 470 475 480
Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
485 490 495
Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
500 505 510
Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
515 520 525
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
530 535 540
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Arg Gln Glu
545 550 555 560
Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
565 570 575
Arg

<210> 125
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 125
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met		
100	105	110
Asp Tyr Trp Gly Gln Gly Thr Leu 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
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
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 Arg Glu Glu Gln Tyr		
290	295	300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
305	310	315
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 Asp Glu Leu 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
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 Thr Val Ala Ala Pro Ser Thr Val Ala
 450 455 460
 Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
 465 470 475 480
 Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
 485 490 495
 Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
 500 505 510
 Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
 515 520 525
 Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
 530 535 540
 Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Trp Gln Glu
 545 550 555 560
 Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 565 570 575
 Arg

<210> 126

<211> 577

<212> PRT

<213> 人工序列

<220>

<223> 人類化

<400> 126

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr			
290	295	300	
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala			
450	455	460	

Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
465 470 475 480
Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
485 490 495
Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
500 505 510
Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
515 520 525
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
530 535 540
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Glu Gln Glu
545 550 555 560
Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
565 570 575
Arg

<210> 127
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 127
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala
 450 455 460
 Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
 465 470 475 480

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
485 490 495
Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
500 505 510
Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
515 520 525
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
530 535 540
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Lys Gln Glu
545 550 555 560
Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
565 570 575
Arg

<210> 128
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 128
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala
 450 455 460
 Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
 465 470 475 480
 Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
 485 490 495

Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
500 505 510
Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
515 520 525
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
530 535 540
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Asp Gln Glu
545 550 555 560
Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
565 570 575
Arg

<210> 129
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 129
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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	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	Arg	Glu	Glu	Gln	Tyr	290	295	300
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	305	310	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	Asp	Glu	Leu	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	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	Thr	Val	Ala	Ala	Pro	Ser	Thr	Val	Ala	450	455	460
Ala	Pro	Ser	Gly	Ser	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	465	470	480
Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Arg	485	490	495
Pro	Ile	Ser	Asp	Trp	Leu	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	500	505	510

Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
515 520 525
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
530 535 540
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Asn Gln Glu
545 550 555 560
Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
565 570 575
Arg

<210> 130
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 130
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr			
290	295	300	
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala			
450	455	460	
Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu			
465	470	475	480
Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg			
485	490	495	
Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala			
500	505	510	
Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro			
515	520	525	

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
530 535 540
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Tyr Gln Glu
545 550 555 560
Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
565 570 575
Arg

<210> 131
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 131
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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	Arg	Glu	Glu	Gln	Tyr			
	290				295					300								
Asn	Ser	Thr	Tyr	Arg	Val	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	Asp	Glu	Leu	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	Thr	Val	Ala	Ala	Pro	Ser	Thr	Val	Ala			
	450					455					460							
Ala	Pro	Ser	Gly	Ser	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu			
	465				470					475					480			
Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Arg			
		485						490					495					
Pro	Ile	Ser	Asp	Trp	Leu	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala			
		500						505					510					
Pro	Lys	Leu	Leu	Ile	Ala	Trp	Ala	Ser	Ser	Leu	Gln	Gly	Gly	Val	Pro			
	515					520						525						
Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile			
	530					535							540					

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Val Gln Glu
 545 550 555 560
 Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 565 570 575
 Arg

<210> 132
 <211> 577
 <212> PRT
 <213> 人工序列

<220>
 <223> 人類化

<400> 132
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr		
	290	295 300
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala		
	450	455 460
Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu		
465	470	475 480
Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg		
	485	490 495
Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala		
	500	505 510
Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro		
	515	520 525
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile		
	530	535 540
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ile Gln Glu		
545	550	555 560

Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
565 570 575
Arg

<210> 133
<211> 577
<212> PRT
<213> 人工序列

<220>
<223> 人類化

<400> 133
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala
 450 455 460
 Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
 465 470 475 480
 Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
 485 490 495
 Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
 500 505 510
 Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
 515 520 525
 Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
 530 535 540
 Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Glu
 545 550 555 560
 Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 565 570 575

Arg

<210> 134

<211> 577

<212> PRT

<213> 人工序列

<220>

<223> 人類化

<400> 134

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1           5           10           15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
      20           25           30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
      35           40           45
Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
      50           55           60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
      65           70           75           80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
      85           90           95
Ala Arg Ser Ile Tyr Asp Asp Tyr His Val Asp Asp Tyr Tyr Ala Met
      100           105           110
Asp Tyr Trp Gly Gln Gly Thr Leu 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

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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 Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Thr Val Ala Ala Pro Ser Thr Val Ala
450 455 460
Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
465 470 475 480
Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
485 490 495
Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
500 505 510
Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro
515 520 525
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
530 535 540
Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Pro Gln Glu
545 550 555 560
Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
565 570 575
Arg

<210> 135
 <211> 573
 <212> PRT
 <213> 人工序列

<220>
 <223> 人類化

<400> 135
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Tyr Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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

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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 Arg Glu Glu Gln Tyr
      290                      295                      300
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Gly Ser Thr Val Ala Ala Pro Ser Gly
      450                      455                      460
Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
      465                      470                      475                      480
Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Ser Asp
      485                      490                      495
Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
      500                      505                      510
Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Arg Phe Ser
      515                      520                      525
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
      530                      535                      540
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Glu Gly Trp Gly Pro
      545                      550                      555                      560
Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
      565                      570

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<210> 136

<211> 581

<212> PRT

<213> 人工序列

<220>

<223> 人類化

<400> 136

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
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 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Tyr Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
290 295 300
Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Gly Ser Thr Val Ala Ala Pro Ser Gly
450 455 460
Ser Thr Val Ala Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser
465 470 475 480
Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
485 490 495
Arg Ala Ser Arg Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys
500 505 510
Pro Gly Lys Ala Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln
515 520 525
Gly Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
530 535 540
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
545 550 555 560
Cys Leu Gln Glu Gly Trp Gly Pro Pro Thr Phe Gly Gln Gly Thr Lys
565 570 575
Val Glu Ile Lys Arg
580

- <210> 137
- <211> 589
- <212> PRT
- <213> 人工序列

<220>

<223> 人類化

<400> 137

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Tyr Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300

Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Gly Ser Thr Val Ala Ala Pro Ser Gly
450 455 460
Ser Thr Val Ala Ala Pro Ser Gly Ser Thr Val Ala Ala Pro Ser Gly
465 470 475 480
Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
485 490 495
Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Ser Asp
500 505 510
Trp Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
515 520 525
Ile Ala Trp Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Arg Phe Ser
530 535 540
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
545 550 555 560
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Glu Gly Trp Gly Pro
565 570 575
Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
580 585

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- <211> 597
- <212> PRT
- <213> 人工序列
- <220>

<223> 人類化

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 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Tyr Ile Lys Asp Thr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Thr Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Val Pro Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Ile Tyr Asp Asp Tyr His Tyr Asp Asp Tyr Tyr Ala Met
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu 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 Arg Glu Glu Gln Tyr
 290 295 300
 Asn Ser Thr Tyr Arg Val 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 Asp Glu Leu 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 Gly Ser Thr Val Ala Ala Pro Ser Gly
450 455 460
Ser Thr Val Ala Ala Pro Ser Gly Ser Thr Val Ala Ala Pro Ser Gly
465 470 475 480
Ser Thr Val Ala Ala Pro Ser Gly Ser Asp Ile Gln Met Thr Gln Ser
485 490 495
Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
500 505 510
Arg Ala Ser Arg Pro Ile Ser Asp Trp Leu His Trp Tyr Gln Gln Lys
515 520 525
Pro Gly Lys Ala Pro Lys Leu Leu Ile Ala Trp Ala Ser Ser Leu Gln
530 535 540
Gly Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
545 550 555 560
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
565 570 575
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Val Glu Ile Lys Arg
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Gly Ser Thr Val Ala Ala Pro Ser Gly Ser
35 40

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1 5 10 15

201107345

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20 25 30
Gly Ser Thr Val Ala Ala Pro Ser Gly Ser Thr Val Ala Ala Pro Ser
35 40 45
Gly Ser
50

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<211> 14
<212> PRT
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<220>
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1 5 10

<210> 146
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Thr Val Ala Ala Pro Ser Thr Val Ala Ala Pro Ser Thr Val Ala Ala
1 5 10 15
Pro Ser Gly Ser
20

發明專利說明書

(本說明書格式、順序及粗體字，請勿任意更動，※記號部分請勿填寫)

※申請案號：99116859

※申請日：99.5.26

※IPC 分類：A61K; C07K; A61P

一、發明名稱：(中文/英文)

免疫球蛋白

IMMUNOGLOBULINS

C07K 16/40 (2006.01)

C07K 16/46

A61K 39/395 (2006.01)

二、中文發明摘要：

本發明係關於一種人類IL-13之抗原結合蛋白(包括抗IL-13抗體及抗IL-3/抗IL-4 mAbdAb)、一種含有該等抗原結合蛋白之醫藥調配物，及此等抗原結合蛋白用於治療及/或預防發炎疾病(諸如哮喘或IPF)的用途。

三、英文發明摘要：

The present invention relates to antigen binding proteins to human IL-13, including anti-IL-13 antibodies and anti-IL-3/anti-IL-4 mAbdAbs, pharmaceutical formulations containing them and to the use of such antigen binding proteins in the treatment and/or prophylaxis of inflammatory diseases such as asthma or IPF.

七、申請專利範圍：

1. 一種抗原結合蛋白，其結合人類IL-13且其包含CDRH3
SIYDDYHYDDYYAMDY(SEQ ID NO: 3)，其中CDRH3包
含一或多個下列取代：
 - g) 位置1中之S95取代為色胺酸(W)
 - h) 位置2中之I96取代為纈胺酸(V)
 - i) 位置3中之Y97取代為苯丙胺酸(F)
 - j) 位置4中之D98取代為麩醯胺酸(E)
 - k) 位置7中之H100A取代為丙胺酸(A)、麩胺酸(E)、麩醯
胺酸(Q)、精胺酸(R)、絲胺酸(S)、蘇胺酸(T)或纈胺酸
(V)及
 - l) 位置8中之Y100B取代為丙胺酸(A)、異白胺酸(I)、色
胺酸(W)或纈胺酸(V)。
2. 如請求項1之抗原結合蛋白，其中CDRH3之位置8中之
Y100B取代為選自以下之胺基酸：丙胺酸(A)、異白胺酸
(I)、色胺酸(W)或纈胺酸(V)。
3. 如請求項1或2之抗原結合蛋白，其結合人類IL-13且其包
含選自以下所示的CDRH3序列：SEQ ID NO: 4、SEQ ID
NO: 5、SEQ ID NO: 6、SEQ ID NO: 7、SEQ ID NO: 8及
SEQ ID NO: 9、SEQ ID NO: 10、SEQ ID NO: 11、SEQ
ID NO: 12、SEQ ID NO: 13、SEQ ID NO: 14及SEQ ID
NO: 15、SEQ ID NO: 16、SEQ ID NO: 17及SEQ ID NO:
18。
4. 如請求項1或2之抗原結合蛋白，其中該抗原結合蛋白進

一步包含下列CDR序列：

CDRH1：SEQ ID NO: 1；

CDRH2：SEQ ID NO: 2；

CDRL1：SEQ ID NO:19；

CDRL2：SEQ ID NO: 20；及

CDRL3：SEQ ID NO: 21。

5. 如請求項1或2之抗原結合蛋白，其中該抗原結合蛋白包含下列CDR：

CDRH1：SEQ ID NO: 1；

CDRH2：SEQ ID NO: 2；

CDRH3：SEQ ID NO: 18；

CDRL1：SEQ ID NO: 19；

CDRL2：SEQ ID NO: 20；及

CDRL3：SEQ ID NO: 21。

6. 如請求項1或2之抗原結合蛋白，其中該抗原結合蛋白包含下列CDR：

CDRH1：SEQ ID NO: 1；

CDRH2：SEQ ID NO: 2；

CDRH3：SEQ ID NO: 17；

CDRL1；SEQ ID NO: 19；

CDRL2：SEQ ID NO: 20；及

CDRL3：SEQ ID NO: 21。

7. 如請求項1或2之抗原結合蛋白，其中該抗原結合蛋白包含下列CDR：

CDRH1 : SEQ ID NO: 1 ;

CDRH2 : SEQ ID NO: 2 ;

CDRH3 : SEQ ID NO: 16 ;

CDRL1 : SEQ ID NO: 19 ;

CDRL2 : SEQ ID NO: 20 ; 及

CDRL3 : SEQ ID NO: 21 。

8. 如請求項1或2之抗原結合蛋白，其中該抗原結合蛋白包含下列CDR：

CDRH1 : SEQ ID NO:1 ;

CDRH2 : SEQ ID NO: 2 ;

CDRH3 : SEQ ID NO:15 ;

CDRL1 : SEQ ID NO:19 ;

CDRL2 : SEQ ID NO:20 ; 及

CDRL3 : SEQ ID NO:21 。

9. 如請求項1或2之抗原結合蛋白，其中該抗原結合蛋白包含抗體。

10. 如請求項1或2之抗體，其中該抗體為人類化抗體。

11. 如請求項1或2之抗原結合蛋白，其中該抗體為IgG同型抗體。

12. 如請求項1或2之抗原結合蛋白，其包含選自以下之重鏈：SEQ ID NO: 26、SEQ ID NO: 28、SEQ ID NO: 30、SEQ ID NO: 32、SEQ ID NO: 34、SEQ ID NO: 36、SEQ ID NO: 38、SEQ ID NO: 40、SEQ ID NO: 42、SEQ ID NO: 44、SEQ ID NO: 46、SEQ ID NO: 48、SEQ ID NO:

50、SEQ ID NO: 52及SEQ ID NO: 54；及SEQ ID NO: 24、108、110、112及114之輕鏈。

13. 如請求項12之抗原結合蛋白，其包含選自SEQ ID NO: 48、SEQ ID NO: 50、SEQ ID NO: 52及SEQ ID NO: 54之重鏈；及SEQ ID NO: 108及110之輕鏈。

14. 如請求項13之抗原結合蛋白，其包含SEQ ID NO: 54之重鏈及SEQ ID NO: 108之輕鏈。

15. 如請求項13之抗原結合蛋白，其包含SEQ ID NO: 54之重鏈及SEQ ID NO: 110之輕鏈。

16. 如請求項1或2之抗體，其包含突變Fc區，從而降低該抗體之ADCC及/或補體活化作用。

17. 如請求項1或2之抗原結合蛋白，其能夠結合至IL-13且其亦能夠結合至IL-4及IL-5中至少一者。

18. 如請求項17之抗原結合蛋白，其包含至少一種選自SEQ ID NO: 78、79、80、81及94之dAb。

19. 如請求項18之抗原結合蛋白，其包含選自以下任一者之重鏈：SEQ ID NO: 62、64、66、68、70、72、74、76、96、98、100、102、104、106及117-138；及SEQ ID NO: 24、108、110、112及114之輕鏈。

20. 如請求項19之抗原結合蛋白，其包含選自以下任一者之重鏈：SEQ ID NO: 96、98、100、102、104、106；及SEQ ID NO: 24、108及110之輕鏈。

21. 如請求項20之抗原結合蛋白，其包含：SEQ ID NO: 96之重鏈及SEQ ID NO: 24之輕鏈，或SEQ ID NO: 96之重鏈

及SEQ ID NO: 108之輕鏈，或SEQ ID NO: 96之重鏈及SEQ ID NO: 110之輕鏈，或SEQ ID NO: 98之重鏈及SEQ ID NO: 24之輕鏈，或SEQ ID NO: 98之重鏈及SEQ ID NO: 108之輕鏈，或SEQ ID NO: 98之重鏈及SEQ ID NO: 110之輕鏈，或SEQ ID NO: 100之重鏈及SEQ ID NO: 24之輕鏈，或SEQ ID NO: 100之重鏈及SEQ ID NO: 108之輕鏈，或SEQ ID NO: 100之重鏈及SEQ ID NO: 110之輕鏈。

22. 一種重組轉型或轉染之宿主細胞，其包含第一及第二載體，該第一載體包含編碼如請求項1至21中任一項之抗原結合蛋白之重鏈的聚核苷酸且該第二載體包含編碼如請求項1至21中任一項之抗原結合蛋白之輕鏈的聚核苷酸。
23. 一種醫藥組合物，其包含如請求項1至21中任一項之抗原結合蛋白及醫藥學上可接受之載劑。
24. 一種如請求項1至21中任一項之抗原結合蛋白的用途，係用於製備供治療或預防以下病症的藥劑：過敏性哮喘、嚴重哮喘、難治性哮喘、脆性哮喘、夜間哮喘、經前哮喘、抗類固醇哮喘、類固醇依賴型哮喘、阿斯匹靈誘發型哮喘、成年發作型哮喘、小兒哮喘、異位性皮膚炎、過敏性鼻炎、克隆氏病(Crohn's disease)、COPD；纖維變性疾病或病症，諸如特發性肺纖維化、進行性全身性硬化、肝纖維化；肝肉芽瘤、血吸蟲病、利什曼體病(leishmaniasis)；細胞週期調節疾病，諸如霍奇金氏病

(Hodgkins disease)、B細胞慢性淋巴細胞白血病。

25. 一種降低免疫球蛋白單可變域之聚集的方法，其包含步驟：

- a) 量測免疫球蛋白單可變域之聚集程度；
- b) 使kabat位置89突變成麩醯胺酸；
- c) 量測該突變免疫球蛋白單可變域之聚集程度；

其中保留結合活性，且該突變免疫球蛋白單可變域之聚集程度低於未突變免疫球蛋白單可變域之聚集程度。

26. 一種人類VK dAb，其來源於選自以下之生殖系架構：
IGKV1-17、IGKV1D-17、IGKV1/OR2-108、IGKV1-6、
IGKV5-2、IGKV1D-42、IGKV2-24、IGKV2-28、
IGKV2-30、IGKV2-40、IGKV2D-29、IGKV2D-30、
IGKV2D-24及IGKV6-21，其中該人類VK dAb之殘基
89(kabat編號)為麩醯胺酸。

27. 一種免疫球蛋白單可變域，其包含SEQ ID NO: 94之序列。

八、圖式：

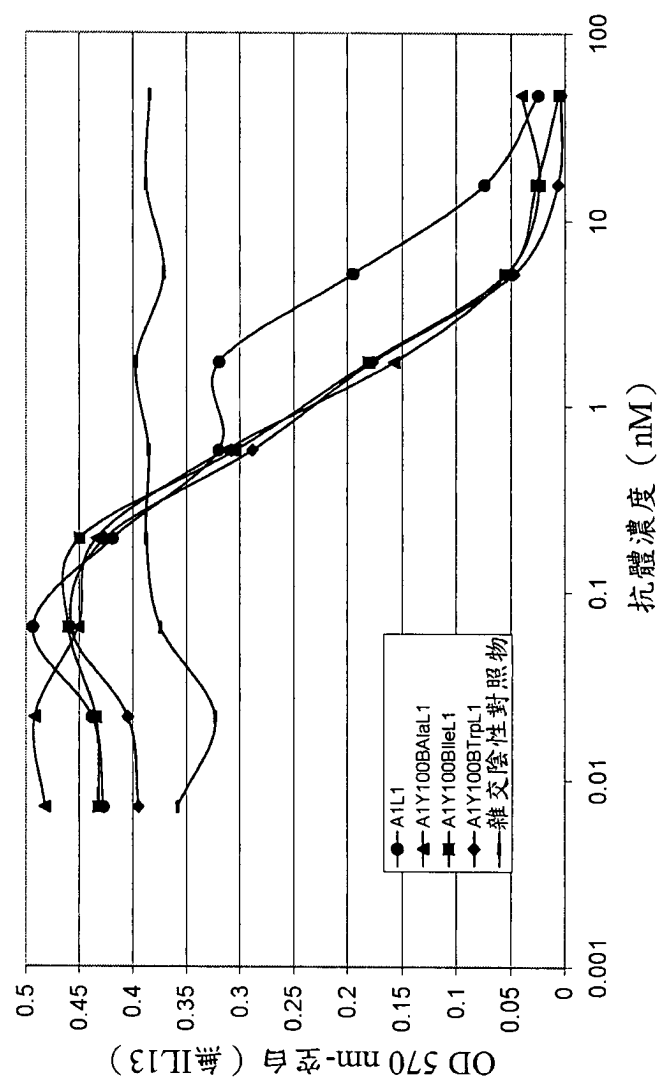


圖1

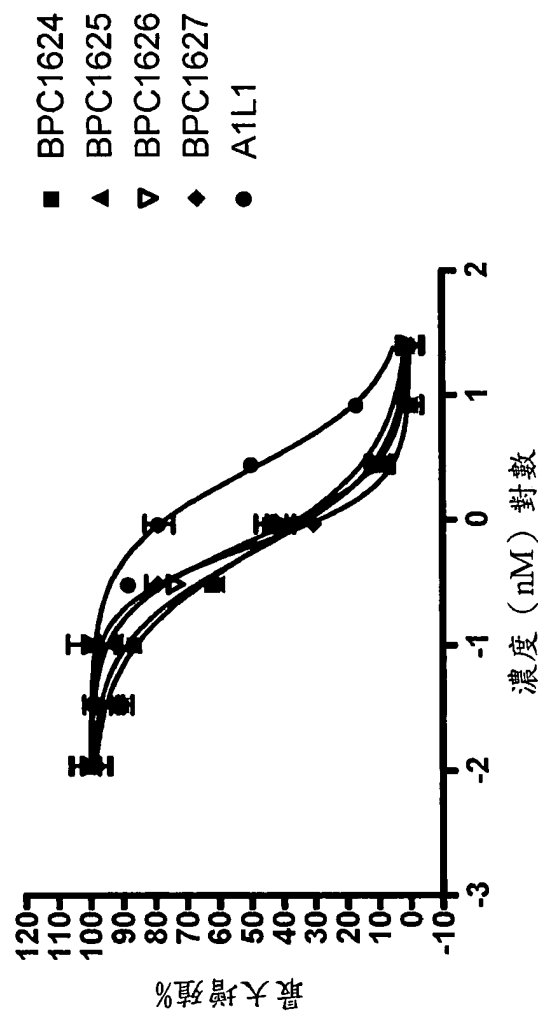


圖2

BPC2222

標準SEC等強度梯度

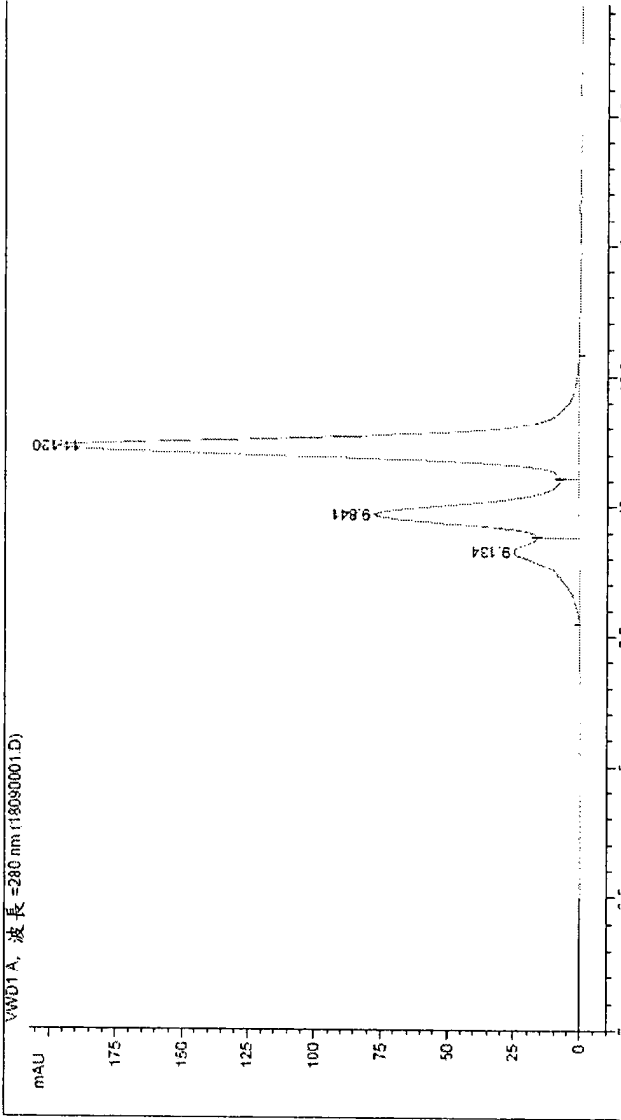


圖3

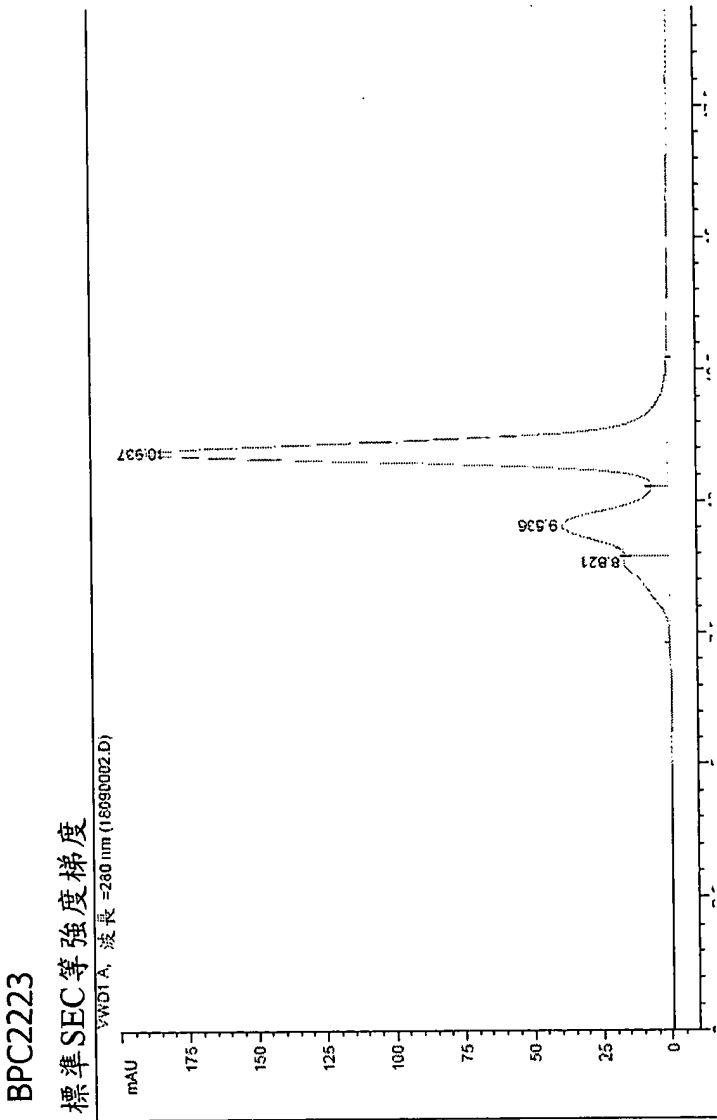


圖4

BPC 2230

標準SEC等強度梯度

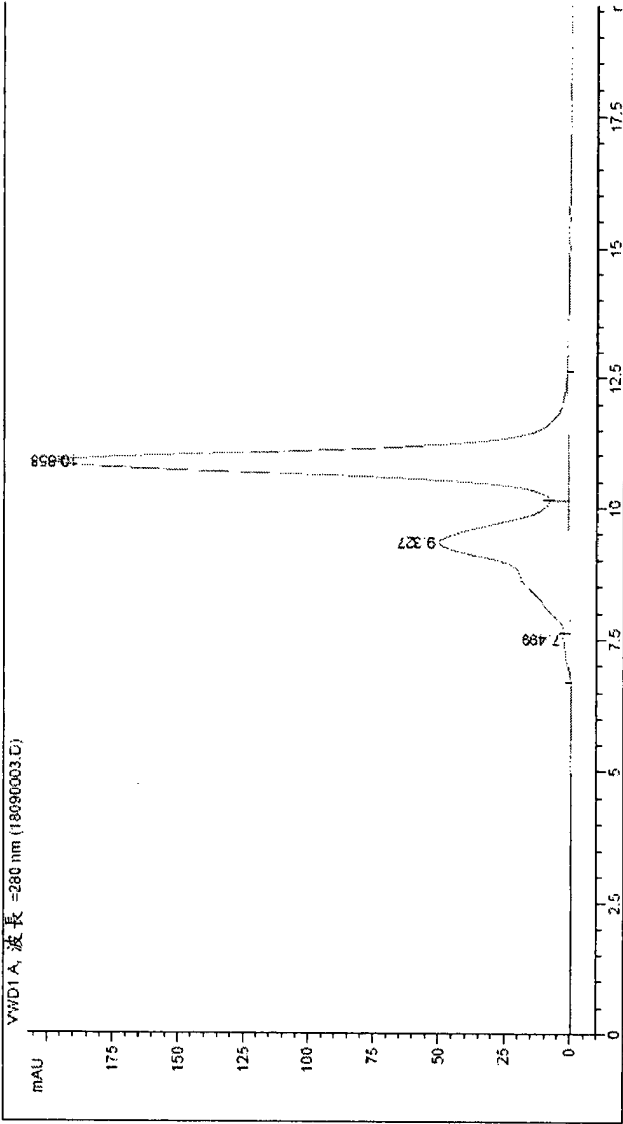


圖5

BPC2231
標準SEC等強度梯度

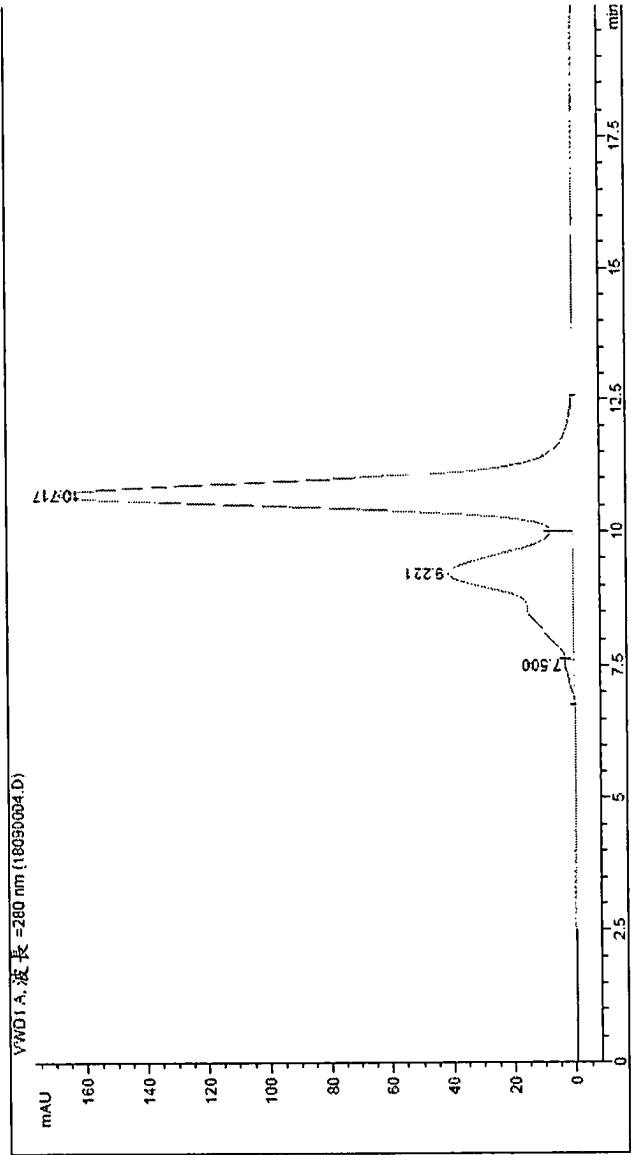


圖6

BPC1085
標準SEC等強度梯度

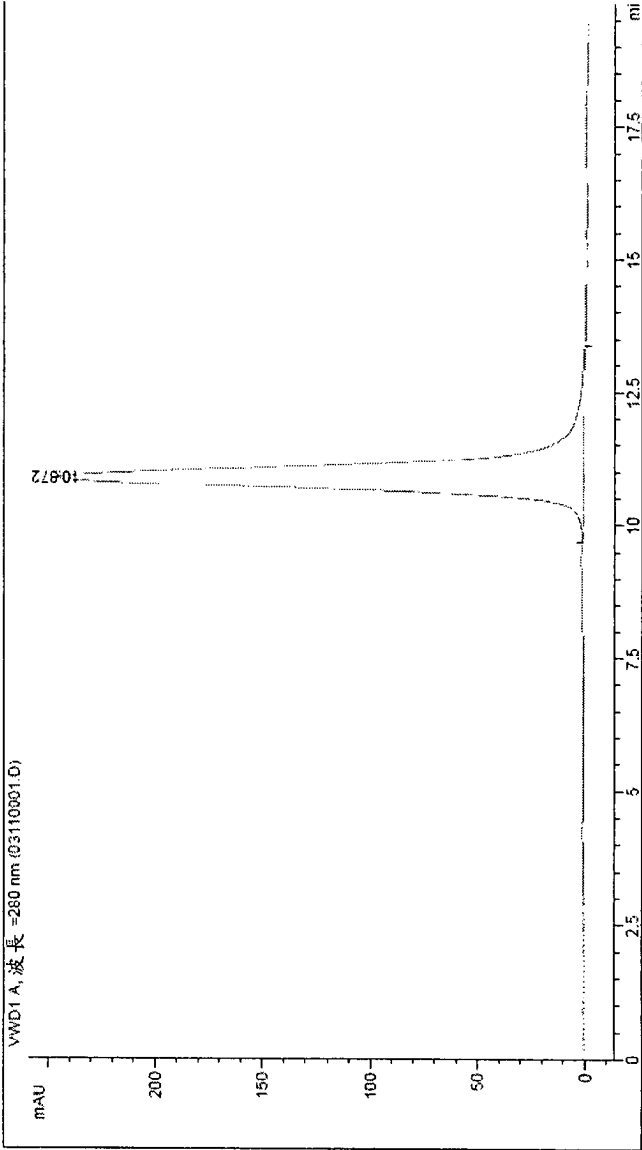


圖7

BPC1086
標準SEC等強度梯度

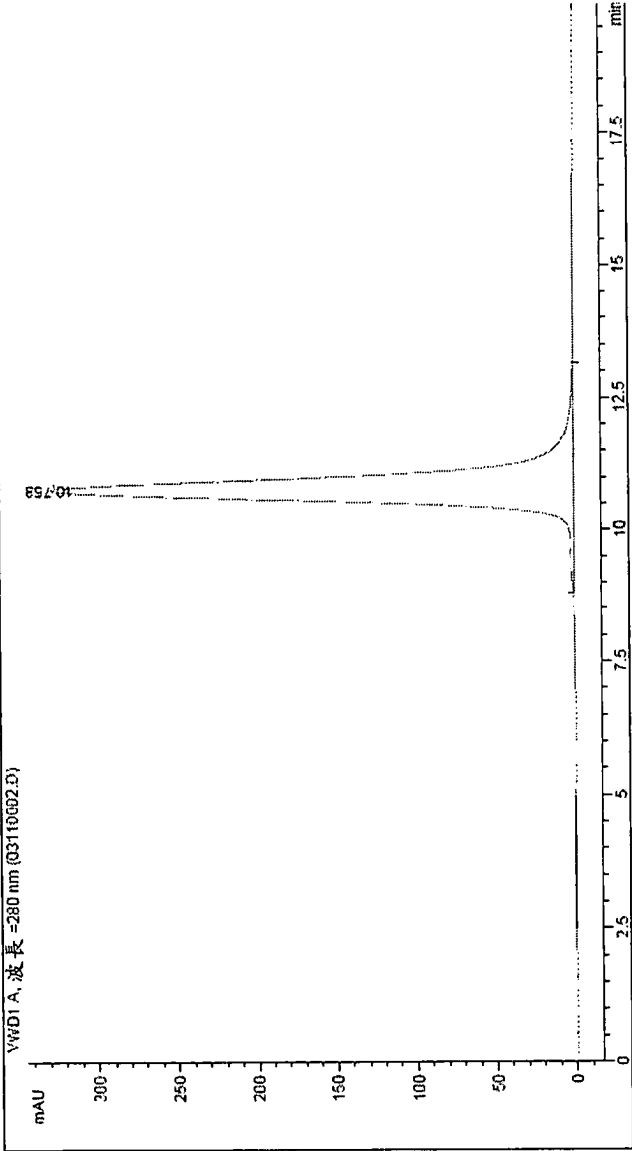


圖8

BPC1087
標準SEC等強度梯度

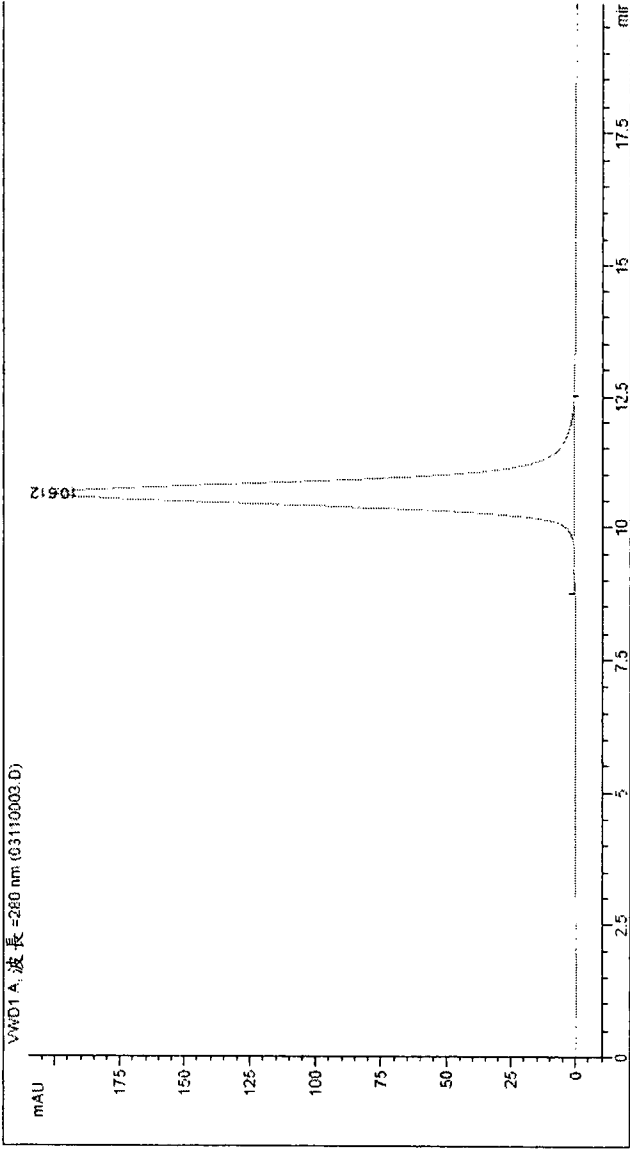


圖9

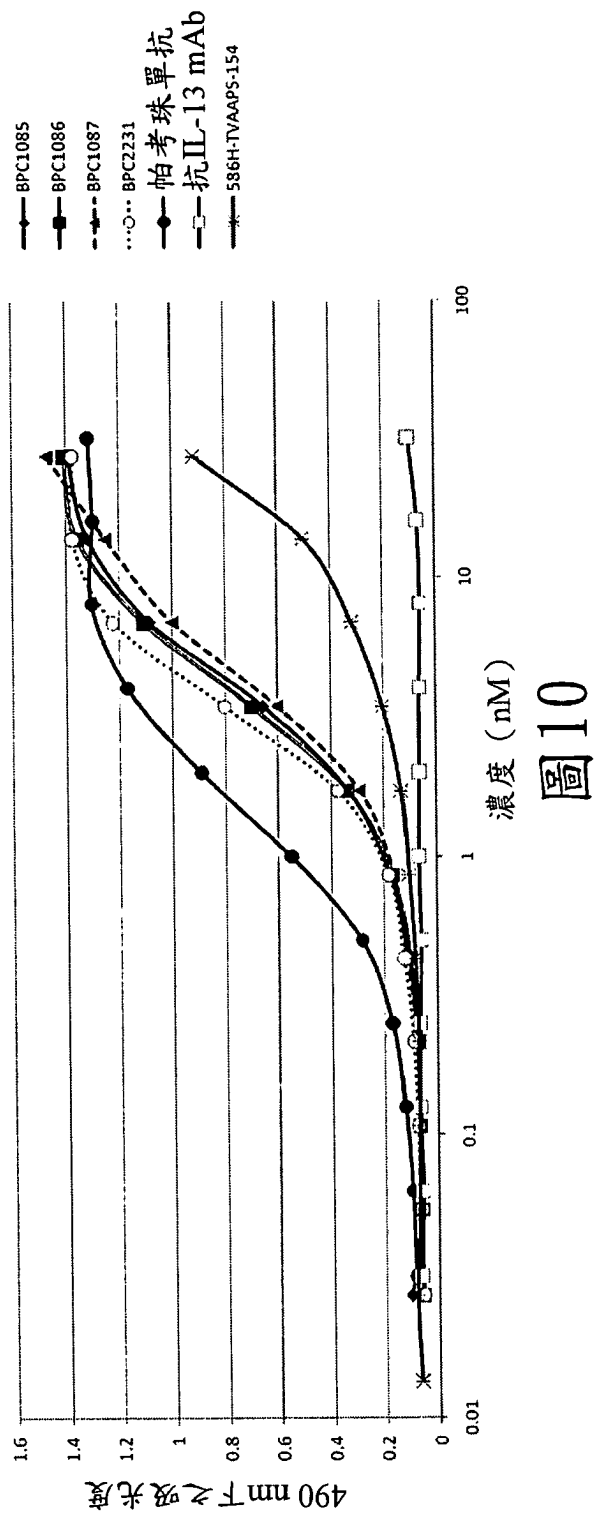


圖10

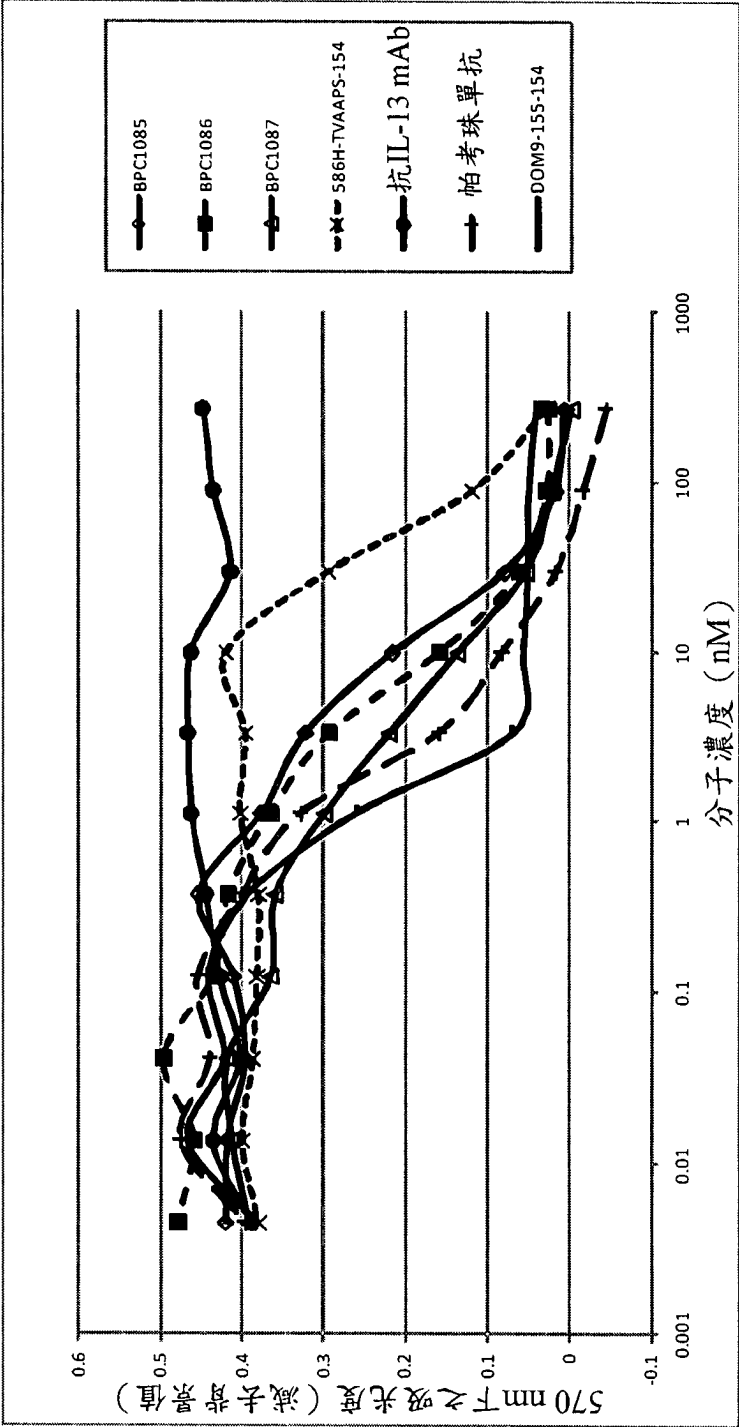


圖 11

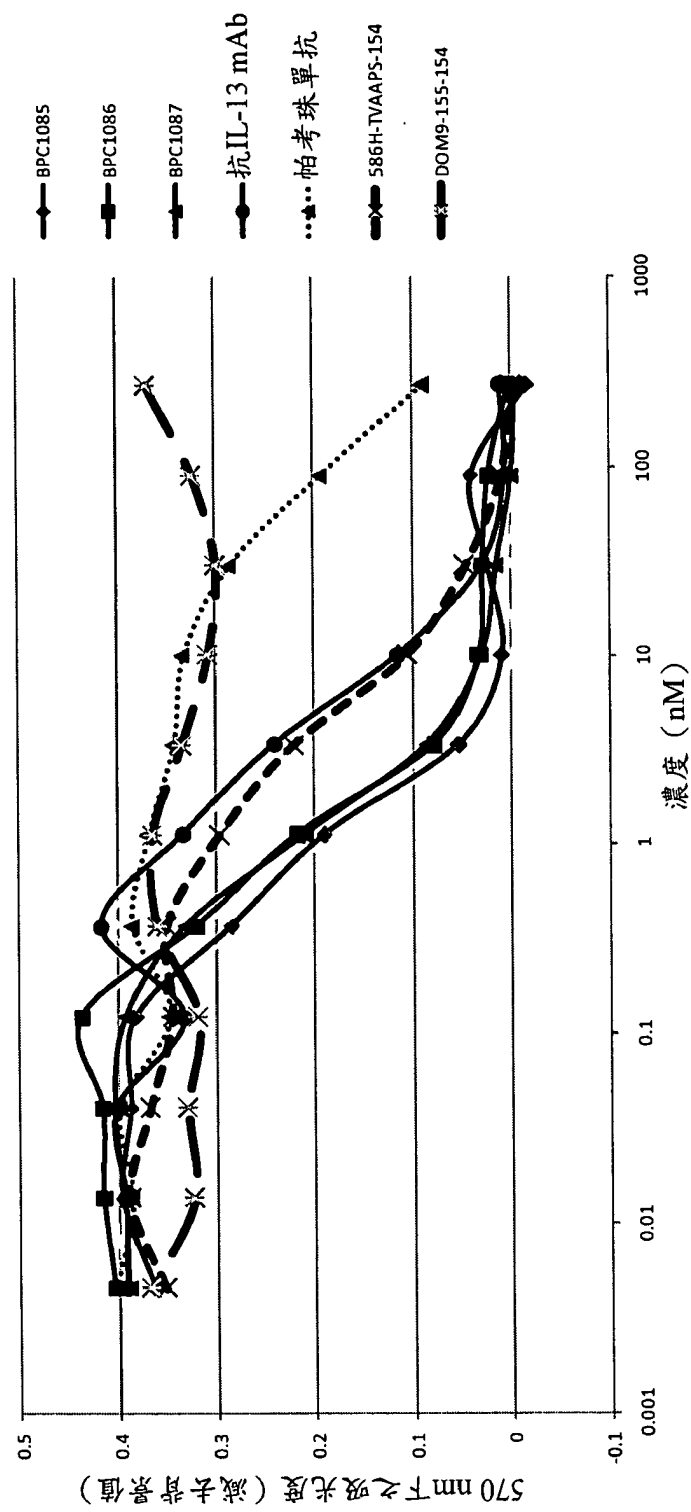


圖12

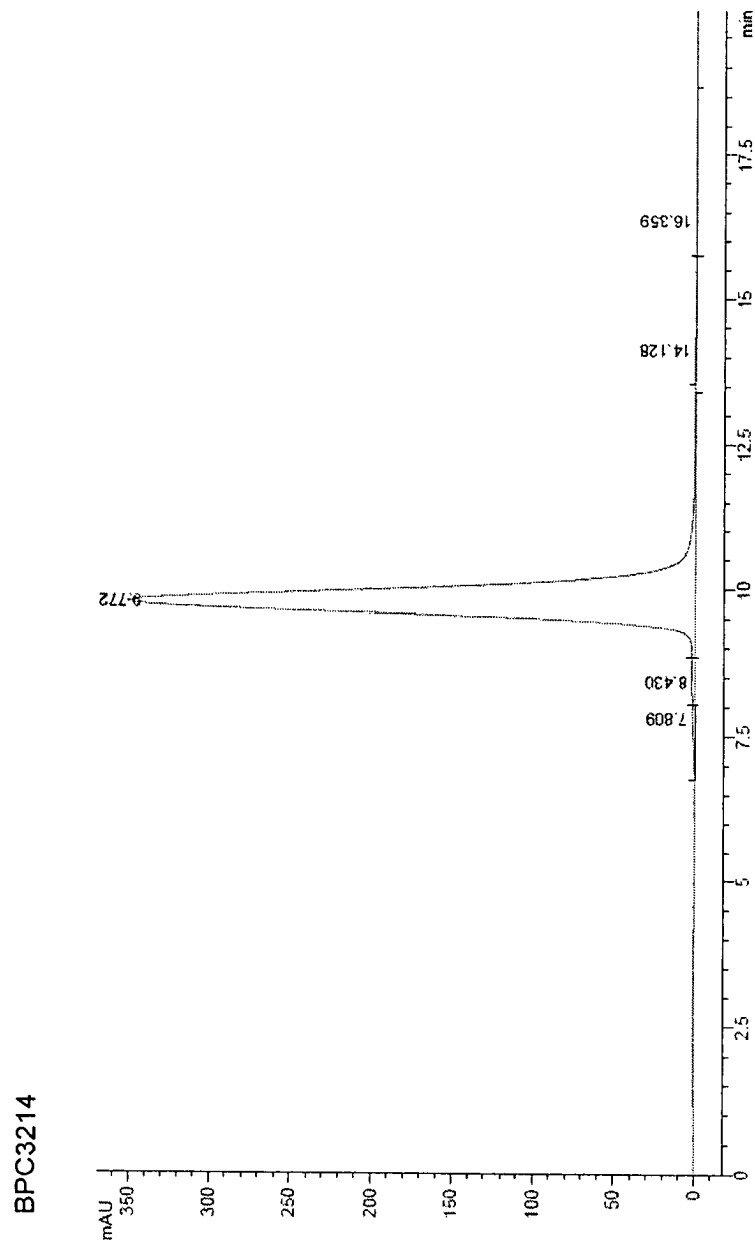


圖 13

BPC3215

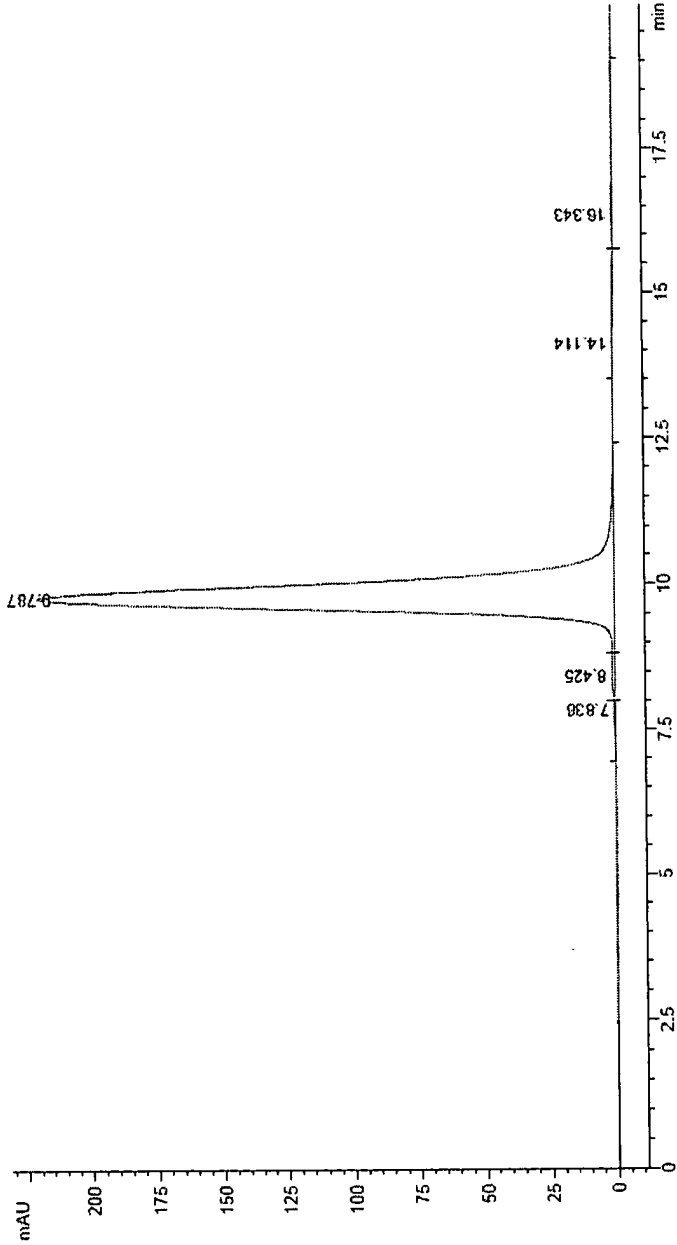


圖14

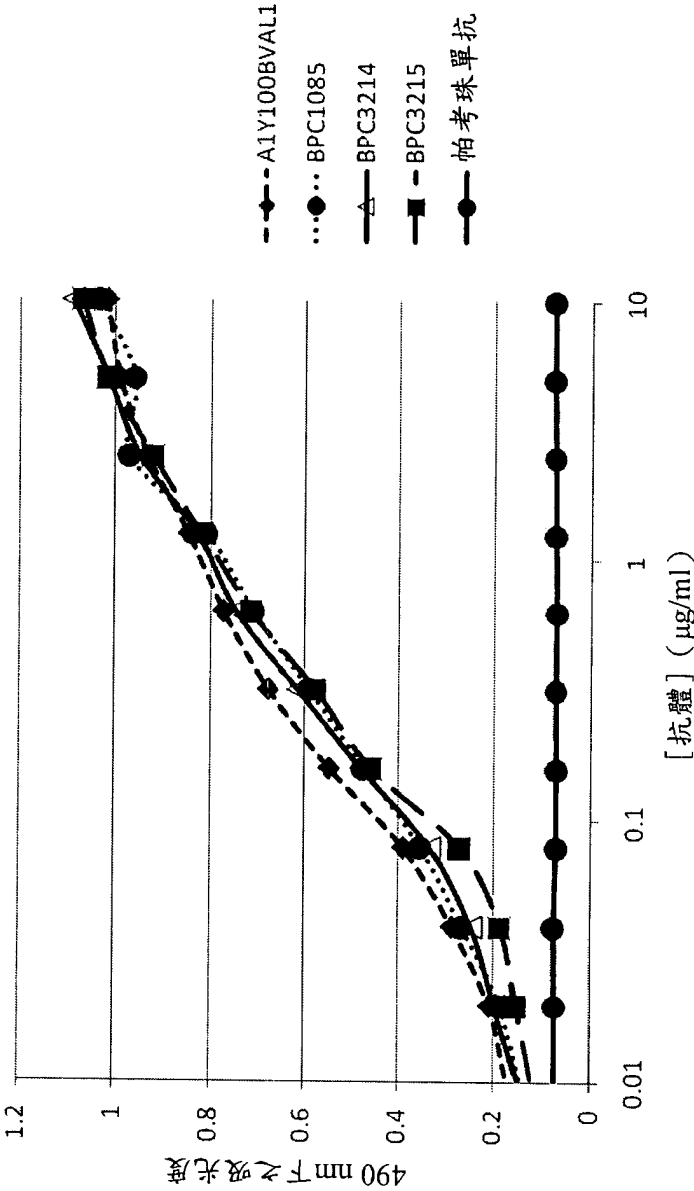


圖15

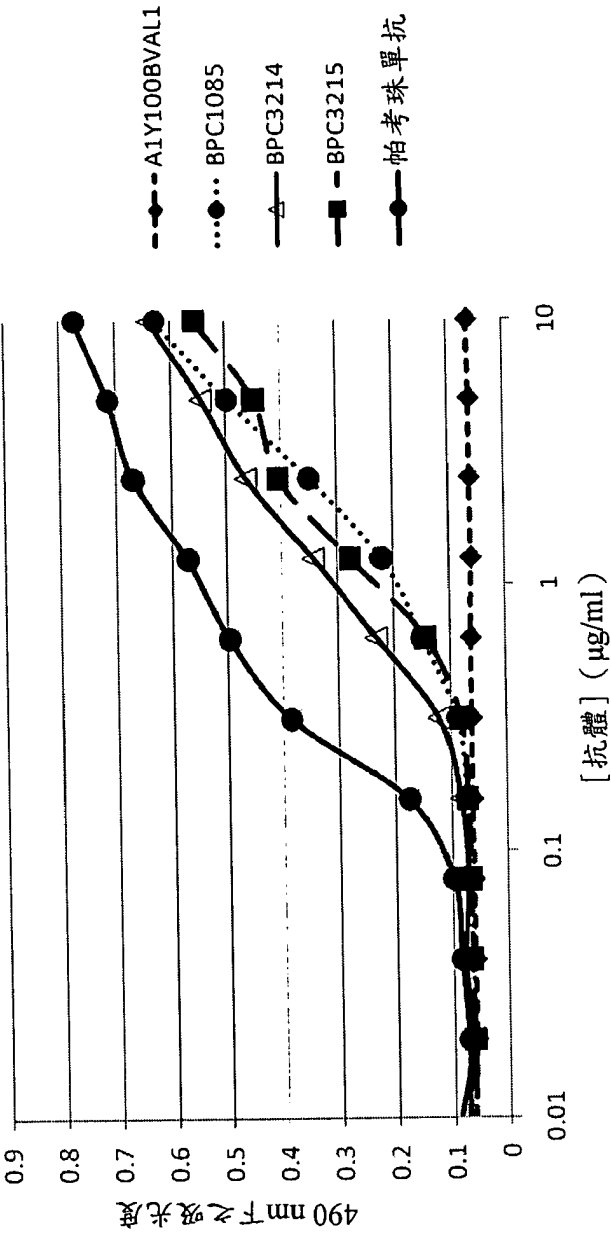


圖16

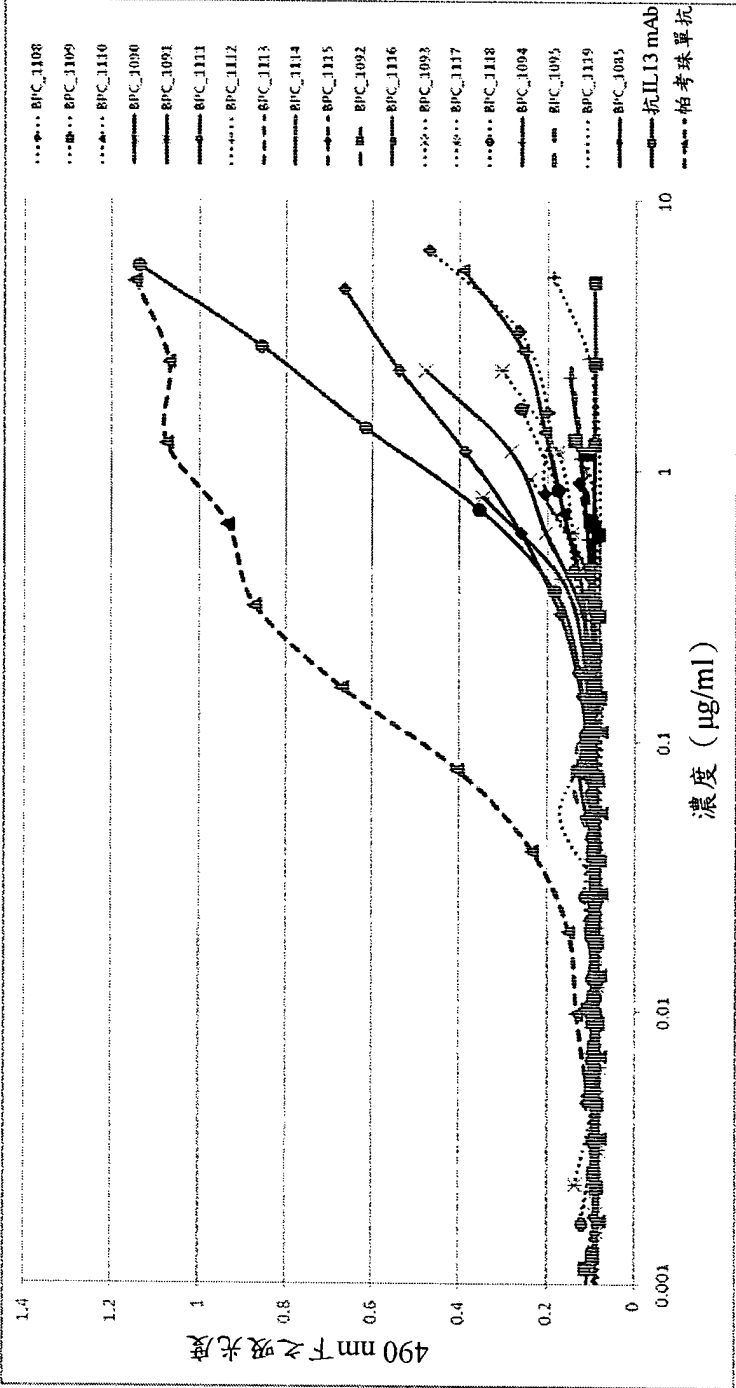


圖17

四、指定代表圖：

(一)本案指定代表圖為：第(17)圖。

(二)本代表圖之元件符號簡單說明：

(無元件符號說明)

五、本案若有化學式時，請揭示最能顯示發明特徵的化學式：

(無)