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(54)名稱

ＴＮＦ拮抗物及以其作為有效成分之ＴＮＦ阻礙劑

(57)摘要

本發明係關於提供一種腫瘤壞死因子突變體蛋白質、換言之 TNF-R1 或 TNF-R2 特異性腫瘤壞死因子突變體蛋白質、及以此作為有效成分之腫瘤壞死因子阻礙劑或腫瘤壞死因子製劑作為課題者。藉由提供 1 或 2 個以上的序列號碼 1 所示胺基酸序列中自 N 末端第 29、31、32、145、146 及 147 個胺基酸殘基、或第 84 至 89 個胺基酸殘基由其他胺基酸殘基取代之腫瘤壞死因子突變體蛋白質、及以此為作為有效成分的腫瘤壞死因子阻礙劑或腫瘤壞死因子製劑解決前述課題。

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六、發明說明：

【發明所屬之技術領域】

本發明係關於對於腫瘤壞死因子（以下於本說明書中以「TNF」略稱）突變體蛋白質，尤其以TNF受體TNF-R1或TNF-R2爲特異性之TNF拮抗劑或TNF增效物（agonist）、及以這些作爲有效成分之TNF阻礙劑或TNF製劑者。

【先前技術】

由TNF因可對於多種腫瘤細胞發揮極強力的抗腫瘤作用得知，其可被期待作爲抗癌劑使用。然而，TNF因具有細胞障礙活性故對於活體的副作用極大，故無法作爲醫藥品利用。又，TNF由癌症或感染症等病人活體內所產生，而引起發炎反應，且因情況有可能成爲病情惡化之因子。因此，可望開發出可調節TNF作用之方法。作爲調節TNF作用之方法，可舉出將與TNF結合之抗體投與於活體內，中和TNF活性之方法，且已開發出以該抗體作爲有效成分之醫藥品。然而，該方法有著因TNF而喪失所有有益活體防禦能之顧慮。

因此，作爲TNF受體，已知有分子量55k道爾頓之TNF受體（以下稱爲「TNF-R1」）及分子量75k道爾頓之TNF受體（以下稱爲「TNF-R2」）。Van Ostade X、Tavernier J、Prange T、Fiers W、Localization of the active site of human tumour necrosis factor(hTNF) by mutational analysis、The ENBO Journal ，1991年，第10卷，第4號

，第827至836頁中揭示，未與老鼠TNF-R2結合之來自人類α型TNF（以下稱爲「TNF-α」），可發揮與雙方受體結合之老鼠TNF-α相異之生物作用。然而，僅與選自任一TNF-R1或TNF-R2者結合之TNF突變體蛋白質，可期待發揮與過去TNF所具有的生物作用相異之作用。

製作僅與選自任一TNF-R1或TNF-R2者結合者，即製作受體特異性TNF突變體蛋白質時，Van Ostade X等於上述文獻中，對於各TNF-α之與TNF-R1或TNF-R2之結合部位的突變導入法做調查。其結果揭示，對於TNF-α之自N末端第29至第34個、第86個及第146個的胺基酸殘基之突變導入，可減低對TNF-R2的結合力、及對143至145個的胺基酸殘基之突變導入，可減低對TNF-R1的結合力。換言之，自N末端第32個精胺酸（R）突變成色胺酸（W），自N末端第86個絲胺酸（S）突變成蘇胺酸（T）之TNF-α突變體蛋白質可保持對TNF-R1的結合力下，顯著減低對TNF-R2的結合力。且，參照特開平6-256395號公報、特開平7-285997號公報、Zhang XM、Weber I、Chen MJ、Site-directed mutational analysis of human tumor necrosis factor-alpha receptor binding site and structure-functional relationship、Journal of Biological Chemistry、1992年，第267卷，第33號，第24069至24075頁、及Loetscher H、Stueber D、Banner D、Mackay F、Lesslauer W、Human tumor necrosis factor alpha (TNF alpha) mutants with exclusive specificity for the 55-kDa or 75-kDa TNF

receptors、The Journal of Biological Chemistry，1993年，第268卷，第35號，第26350至26357頁，欲賦予受體特異性於TNF突變體蛋白質上，自TNF-α的N末端第29至第34、81至89、或第143至第147個胺基酸殘基上導入突變爲佳。且，上述文獻中，已做成受體特異性之TNF-α突變體蛋白質，即爲保持作爲這些TNF之活性的增效物（agonist）。這些可望作爲具有TNF藥效之TNF製劑而被利用。

另一方面，作爲TNF的活性較爲弱或完全無的TNF突變體蛋白質，尤其以TNF拮抗物因與任一TNF受體做選擇性地結合，故可僅與殘留活體內所產生的TNF之TNF受體做選擇性結合。然而，上述文獻中並未揭示任一TNF受體上具有特異性拮抗活性之TNF突變體蛋白質，故期待受體特異性的TNF拮抗物之開發。

【發明內容】

有鑑於相關情況，本發明爲提供一種TNF突變體蛋白質，即TNF-R1或TNF-R2特異性TNF拮抗物、及以這些作爲有效成分之TNF阻礙劑作爲課題。

本發明者等欲得到TNF受體的一種之TNF-R1或TNF-R2特異性TNF拮抗物，製造各種TNF突變體蛋白質，進行篩選。結果成功地得到僅TNF-R1之結合力比野生型TNF顯著覺弱的TNF突變體蛋白質，或得到僅與TNF-R2的結合力比野生型TNF顯著較弱的TNF變異體蛋白質。這些TNF突變體蛋白質係爲可拮抗阻礙TNF與僅任一TNF受體結合的

TNF拮抗物，或可選擇性地與僅任一的TNF受體結合，確認顯示如TNF作用之TNF拮抗物，進而完成本發明。

即，本發明係爲藉由提供對於TNF-R1或TNF-R2爲特異性之TNF拮抗物或TNF增效物（agonist)、及以該蛋白質作爲有效成分之TNF阻礙劑解決上述課題者。

本發明所謂的TNF-R1特異性，表示與TNF-R2的結合力顯著地弱，其結果主要與TNF-R1結合的能力較爲顯著。TNF-R2特異性，表示與TNF-R1的結合力顯著地弱，其結果主要與TNF-R2結合的能力較爲顯著。本發明所謂的TNF拮抗物，表示雖與TNF受體結合，但與野生型TNF相比活性較弱或完全無顯示的蛋白質。本發明的TNF拮抗物爲，與TNF-R1或TNF-R2之任一受體的結合力越強時，另一方對受體之結合則越弱爲佳。

對本發明的TNF-R1或TNF-R2特異性之TNF拮抗物爲，編碼具有序列表中序列號碼1所示胺基酸序列之TNF-α的DNA上，於所望位置上將NNS序列（N表示鹼基爲A、T、G或C，S表示鹼基爲G或C）依據常法PCR技術等進行導入，藉由噬菌體顯式法（phage display）選出具有所望特性之克隆而得到。又，取代TNF-α，1或2個以上選自自序列表的序列號碼1所示的胺基酸序列之N末端的第11、65、90、98、112、128個離胺酸爲欠缺、或由其他胺基酸殘基取，較佳爲具有序列表之序列號碼2至4的鹼基序列所記載的胺基酸之TNF離胺酸轉化體（以下稱爲「離胺酸轉化體」）作爲基團亦可。具體而言，首先欲變化對TNF-R1或

TNF-R2之結合力，序列表的序列號碼1所示的胺基酸序列、或序列表中序列號碼2至4的鹼基序列所記載的胺基序列中，將這些自N末端第29、31、32、145、146及147的胺基酸殘基以隨機的胺基酸取代（序列表的序列號碼5）、或將這些自N末端的第84、85、86、87、88及89個胺基酸殘基以隨機的胺基酸取代（序列表的序列號碼7）時，使用常法的寡聚DNA合成技術、PCR技術、DNA連接技術等，製造出編碼上述位置的胺基酸殘基之密碼子由NNS取代之TNF突變體蛋白質之DNA（序列表的序列號碼6或8）。所得之DNA於製造噬菌體基因庫時，插入噬菌粒（phagemid）載體，表現蛋白質後，將與TNF-R1（具有GENBANK M58286所揭示的胺基酸之蛋白質）或TNF-R2蛋白質（具有GENBANK M55994所揭示的胺基酸之蛋白質）結合之噬菌體克隆，使用利用表面電漿共振原理的機器等進行鑲嵌法而選擇出。對於所得之克隆與另一方受體（TNF-R2或TNF-R1）之結合性進行調查，選出對於2個受體的結合力間有差距的克隆，選擇出TNF-α或TNF離胺酸轉化體之2分之1、較佳爲10分之1、更佳爲1000分之1，最佳爲選出對片面受體之結合力爲消失的可檢測水準以下的克隆。將所選出的克隆，使用來自人類喉頭癌之細胞株Hep-2細胞（ATCC CCL-23）或來自老鼠繡結細胞的細胞株L-M細胞（ATCC CCL-1.2）等TNF標的細胞之公知生化檢測方法進行生物活性的測定。其結果，活性較低者，例如可選出TNF-α之2分之1、較佳爲10分之1、更佳爲1000分之1，最

佳爲選出細胞障礙活性消失的可檢測水準以下的噬菌體克隆。

如此所得之本發明TNF拮抗物爲具有序列表中序列號碼1所示的胺基酸序列之TNF-α、或具有序列表中序列號碼2至4的鹼基序列所記載的胺基酸序列之TNF離胺酸轉化體的自N末端的第29、31、32、145、146及147個之胺基酸殘基或第84或89個的胺基酸殘基之一部份或全部由其他胺基酸或終止密碼子取代者。這些TNF轉化體蛋白質雖與任一的TNF-R1或TNF-R2進行特異性結合，但完全未顯示比野生型TNF更低的活性。換言之，因TNF-R1或TNF-R2爲特異性TNF拮抗物，故投與於活體時，與TNF-R1或TNF-R2的任一方做選擇性結合，使得活體內所產生的TNF會阻礙所選出者與TNF受體之結合。因此，藉由投與對活體內所產生的TNF爲過剩量之本發明拮抗物，僅可控制爲活體內所產生的TNF作用介著任一方的TNF受體之TNF活性。作爲本發明的TNF-R1特異性TNF拮抗物，可舉出序列號碼1所示的胺基酸序列中，自N末端的第29個胺基酸殘基爲精胺酸、組胺酸或絲胺酸、第31個由精胺酸、天冬醯胺、麩胺酸、脯胺酸或絲胺酸、第32個由組胺酸、蛋胺酸、蘇胺酸或酪胺酸、第145個由丙胺酸、天冬醯胺、天冬胺酸或絲胺酸、第146個由天冬醯胺、甘胺酸蛋胺酸或絲胺酸、及第147個由丙胺酸、天冬醯胺、脯胺酸、蘇胺酸或終止密碼子所取代、或第84個由丙胺酸、蘇胺酸、絲胺酸或甘胺酸、第85個由脯胺酸、蘇胺酸甘胺酸、第86個由丙胺酸

、甘胺酸、蘇胺酸或脯胺酸、第87個由酪胺酸、異亮胺酸或組胺酸、第88個由麩胺酸、天冬醯胺或絲胺酸、及第89個由精胺酸、組胺酸或麩胺酸所取代之TNF突變體蛋白質。例如，具有序列表中序列號碼9至13或序列號碼19至22所示的胺基酸序列之TNF突變體蛋白質爲佳，作爲本發明的TNF-R2特異性TNF拮抗物，可舉出第145個由丙胺酸、離胺酸或精胺酸、第146個由麩胺酸、天冬醯胺、天冬胺酸或蘇胺酸、及第147個由蘇胺酸或天冬胺酸所取代之TNF突變物蛋白質，例如具有序列表中序列號碼14至18所示的胺基酸序列之TNF突變物蛋白質爲佳。

另一方面，檢索本發明的TNF拮抗務實，雖與TNF-R1做特異性結合者保持著活性，但得到活性降低較少的TNF突變物蛋白質。這些蛋白質因欠缺對TNF-R2的結合能，可被企求爲可發揮與野生型TNF相異的生物活性。可推測如此蛋白質作爲TNF增效物（agonist)進行作用，序列表中序列號碼1所示的胺基酸中自N末端的第29個由亮胺酸、麩胺酸、蘇胺酸或離胺酸、第31個由精胺酸、甘胺酸、絲胺酸或丙胺酸、第32個由色胺酸、酪胺酸、天冬胺酸或甘胺酸、第146個由麩胺酸、丙胺酸或絲胺酸、及第147個由絲胺酸、精胺酸或蘇胺酸所取代、或第84個由蘇胺酸、絲胺酸或天冬醯胺、第85個由絲胺酸、離胺酸、脯胺酸、酪胺酸、精胺酸、蘇胺酸、組胺酸、麩胺酸、天冬胺酸或丙胺酸、第86個由組胺酸、蘇胺酸、亮胺酸、天冬醯胺、丙胺酸、纈胺酸、離胺酸、絲胺酸、麩胺酸、甘胺酸、精胺酸或

天冬胺酸、第88個由絲胺酸、脯胺酸、蘇胺酸、天冬醯胺、丙胺酸、甘胺酸、精胺酸或麩胺酸、及第89個由天冬胺酸、組胺酸、離胺酸、甘胺酸、絲胺酸、脯胺酸、丙胺酸、麩胺酸、苯基丙胺酸或精胺酸所取代之TNF突變體蛋白質，例如以具有序列表中序列號碼37至59所示的胺基酸序列之TNF離胺酸突變體蛋白質爲佳。

本發明所謂的TNF離胺酸轉化體，本發明者欲使TNF-α的生物活性不要減低而結合於水溶性高分子上時，使自TNF-α的胺基酸序列之N末端第11、65、90、98、112及128個胺基酸殘基的1或2個以上之離胺酸殘基被其他胺基酸殘基取代或欠缺（參照歐洲公開專利EP1354893號說明書）。具有序列表中序列號碼2至4的鹼基序列所記載之胺基酸序列的TNF離胺酸轉化體，與TNF-α比較爲具有同等或同等以上的活性，實質上對於TNF-R1及TNF-R2的結合力亦相等。因此，該發明的TNF-R1或TNF-R2特異性TNF拮抗體結合於水溶性高分子上所成之複合體利用於醫藥品時，蛋白質部份未具有離胺酸殘基、或離胺酸殘基數經減低的TNF離胺酸轉化體較佳。序列表中的序列號碼9至22所示的上述本發明TNF拮抗體、或序列表中序列號碼37至59所示的上述本發明的TNF增效物（agonist），係以TNF離胺酸轉化體爲準所製造出，因完全未具有離胺酸殘基或僅具有1個離胺酸殘基，故對於與水溶性高分子製造複合體而言爲較佳例子。且，若不將本發明的TNF突變體蛋白質與水溶性高分子結合時，序列表中序列號碼9至22或37至59

所示的胺基酸序列中自N末端第11、65、90、98、112及128個胺基酸殘基的1或2個以上可爲與野生型TNF相同之離胺酸殘基、或所有皆爲離胺酸殘基亦可。

本發明的TNF突變體蛋白質爲，使用編碼這些的DNA，例如具有序列表中序列號碼23至36或60至82所示的鹼基序列中任一之DNA，依據常法的基因工學技術製造出。即，因應必須，編碼本發明的TNF突變體蛋白質之DNA中任一藉由PCR反應增幅後，插入蛋白質表現用之質體載體後導入如大腸桿菌等之宿主而進行轉形，由所得之轉形體選出可生產目的蛋白質的克隆，培養該克隆後可得到所望量。由轉形體的培養物採出蛋白質時，可使用透析、鹽析、過濾、濃縮、離心分離、沈澱分離、膠體過濾層析法、離子交換層析法、疏水性層析法、親和層析法、層析焦集法、膠體電泳法、等電點電泳等一般法純化蛋白質，若必要可適宜地組合這些方法使用。

本發明的TNF突變體蛋白質因可提高活體內的安定性，故可人爲地結合於適當的水溶性高分子上。本發明所使用的水溶性高分子實質上爲水溶性，換言之對活體爲無害且難成爲抗原之非蛋白質性者爲佳。具體而言，例如可舉出與聚乙烯醇、聚乙二醇、聚乙烯吡咯烷酮、聚丙二醇等單獨聚合物、乙二醇與乙烯醇、丙二醇等之共聚物或這些衍生物等之合成高分子、或elsinan、葡聚醣、羥基乙基纖維素、聚三葡萄糖(pullulan)、甲基纖維素等天然高分子。其中以較容易得到之分子量一致的調製物之觀點來看，聚

乙二醇的單獨聚合物、具乙二醇與其他水溶性高分子之高聚合物及這些之衍生物爲佳。且，水溶性高分子之分子量的平均分子量一般爲選自500至100,000道爾頓，較佳爲1,000至50,000道爾頓之範圍內爲佳。使用分子量經均勻化之水溶性高分子時，以對蛋白質的結合反應爲首，例如可任意藉由沈澱分離、膠體過濾層析法等之一般方法進而分離分子量。又，水溶性高分子的形狀可使用任一直鏈構造及支鏈構造者，但由立體障礙的觀點來看使用支鏈構造亦佳。雖依據水溶性高分子的種類或複合物的最終用途有所不同，但若水溶性高分子的分子量低於上述範圍時，難以改善體內動態，相反地，若高於上述範圍，複合體的生理活性會過低，無法作爲醫藥品使用。

有關欲將對於TNF突變體蛋白質之水溶性高分子的結合，藉由對於游離胺基酸進行特異性反應而形成共鍵結的試藥，使另外活化之水溶性高分子反應於蛋白質上，或藉由具有對於游離胺基酸爲特異性反應之官能基的多官能試驗，交聯蛋白質與水溶性高分子即可。作爲反應方法，可依據歐洲公開專利EP1354893號說明書所記載的方法進行。又，亦可使用該領域中常用的方法，例如特開昭62-289522號公報等所記載的酯鍵結法、醯胺鍵結法等。蛋白質部份與水溶性高分子之間所形成的鍵結以藉由經安定共鍵結所形成的醯胺結合法所得者爲佳。

雖反應方法依物質而有所不同，但反應開始時蛋白質與水溶性的高分子之比率爲，莫耳比爲1：0.1至1：100，

較佳爲1：0.5至1：50，最佳爲1：1至1：10的範圍。一般而言，若低於該範圍時蛋白質彼此間的結合較爲顯著，相反地高於該範圍時水溶性高分子彼此間的結合會較明顯。任一皆會降低反應與反應後的純化效率，一般以上述範圍內爲較佳。反應時的溫度、pH及反應時間設定爲蛋白質較難失活或分解，且不佳的副反應爲較小爲佳，具體而言反應溫度爲0至100℃，較佳爲20至40℃，pH爲0.1至12，較佳爲5至9，反應時間爲0.1至50小時，較佳爲10小時以內完成。如此所得之TNF突變體蛋白質與水溶性高分子複合體可與純化TNF突變體蛋白質時相同方法下純化出，對應最終所使用的型態，例如藉由濃縮、鹽析、離心分離、冷凍乾燥等方法得到液狀或固狀。

本發明的TNF突變體蛋白質、或與這些的水溶性高分子之複合體可極適用於治療及/或預防敏感性疾病、或緩和發炎症狀等之TNF阻礙劑或TNF製劑上。本發明中所謂的敏感性疾病爲，單獨投與本發明的TNF阻礙劑或TNF製劑、或與其他藥劑同時投與而治療、預防、或緩和症狀之所有疾病而言，具體而言爲活體內的TNF過剩表現或過剩投與所引起的各種疾病、TNF過剩表現所引起的各種疾病、或因TNF的腫瘤壞死作用之治療效果被確認之各種疾病，作爲各疾病例如可舉出，結腸癌、直腸癌、胃癌、甲狀腺癌、舌癌、膀胱癌、絨毛癌、肝癌、子宮癌、煙頭癌、肺癌、乳癌、惡性黑色瘤、神經芽細胞瘤、卵巢瘤、睪丸瘤、骨肉瘤、胰臟瘤、副腎臟瘤、甲狀腺瘤、腦瘤、惡性

黑色瘤、菌狀息肉症等固體腫瘤、白血病、淋巴瘤等血液系腫瘤、潰瘍性大腸炎、克隆病、慢性關節風濕、過敏症、乾癬等自身免疫疾病、惡病質、慢性及急性發炎、關節炎、敗血病、播種性血管內凝固症候群、移植排斥反應、急性移植物對抗宿主反應、感染、腦中風、虛血症、急性呼吸困難症候群、血管再狹窄、腦障礙、AIDS、SARS、骨病、斑塊性動脈硬化、川崎病、白塞病、全身性紅斑性狼瘡、多發性器官衰竭、癌疾、髓膜炎、劇烈性肝炎、阿茲海默症等。因此，本發明的TNF阻礙劑或TNF製劑於治療及/或預防這些病症、或緩和發炎等症狀時，可適合作爲醫藥品等多樣化用途使用。

藉由將TNF並用本發明的TNF拮抗劑時，可選擇性發揮與本發明的TNF增效物（agonist)相同的作用，即可藉由TNF-R1或TNF-R2之TNF活性做選擇性地發揮。作爲TNF，可爲TNF-α或TNF-β、這些突變體蛋白質、或這些與水溶性高分子之複合體。本發明的TNF拮抗物與TNF的添加量可配合患者的症狀做適當的設定即可，但欲藉由單方的受體使TNF活性無法實質地發揮時，添加本發明的TNF-R1或TNF-R2特異性TNF拮抗物與TNF的莫耳比爲100,000倍以上，較佳爲500,000倍以上爲佳。又，既使未達到上述莫耳比，藉由單方的受體之TNF活性亦可部份性地被抑制，故可期待可發揮與一般相異的TNF作用、或減輕TNF的副作用。因此，TNF拮抗物與TNF的莫耳比可選自1至1,000,000倍，較佳爲10至1,000,000倍，更佳爲100至

1,000,000倍。

雖依作爲適用對象的敏感性疾病之種類或症狀而不同，但含有本發明的TNF突變體蛋白質之TNF阻礙劑或TNF製劑，配合投與途徑，作爲1次用量，投與其有效成分爲0.25ng/kg體重以上，較佳爲2.5ng至400mg/kg體重，依據用途可調製出萃取劑、萬靈藥、下氣道吸入劑、膠囊劑、顆粒劑、眼科用緩釋劑、丸劑、眼用軟膏劑、口腔黏膜貼劑、懸浮劑、乳劑、硬膏劑、塞劑、散劑、錠劑、糖漿劑、浸漬劑、煎劑、注射劑、點滴劑、酊劑、眼藥水、點耳劑、點鼻劑、口含劑、軟膏劑、貼劑、芳香水劑、鼻用噴霧劑、擦劑、液狀精華液、乳液劑等型態。

本發明的TNF阻礙劑或TNF製劑的適用及較適投與量的決定，可將患者血液中的TNF及可溶性TNF受體（TNF-R1或TNF-R2）濃度、患部組織之細胞表面的TNF受體表現數等，以常法的酵素化驗、流動細胞計算法或鍵結化驗法進行測定爲佳。

本發明的TNF阻礙劑或TNF製劑亦包含投藥單位型態之藥劑，所謂該投藥單位型態之藥劑爲，表示含有例如相當於一次用量或其整數倍（至4倍量）或約數（至1/40倍）的量之本發明TNF突變體蛋白質所成，經適合投藥的物理性分離之一體化劑型的藥劑。作爲如此投藥單位型態之藥劑，例如可舉出膠囊劑、顆粒劑、丸劑、塞劑、散劑、錠劑、注射劑、點藥劑、貼劑等。

本發明的TNF阻礙劑或TNF製劑中可添加作爲有效成

分之本發明TNF突變體蛋白質以外，例如可添加賦形劑、軟膏基劑、溶解劑、矯味劑、除臭劑、著色劑、乳化劑等藥劑一般所通用的適當調劑用藥。又，以不違背本發明的目的之範圍內，與TNF突變體蛋白質同時作爲有效成分的其他成分而言，例如可添加外皮用殺菌消毒劑、創藥保護劑、消炎劑等外皮用藥、維他命A劑、維他命B劑、維他命C劑、維他命D劑、維他命E劑、維他命K劑等維他命劑、鈣劑、無機製劑、醣類劑、有機酸製劑、蛋白胺基酸製劑、臟器至劑等滋養強健藥劑、葉綠素製劑、色素製劑等細胞賦活用藥、烷基化劑、代謝拮抗劑、抗腫瘤性抗生素製劑、抗腫瘤性植物成分至劑等抗腫瘤藥劑、抗組織胺劑等過敏用劑、抗結核病菌劑、合成抗菌劑、抗病毒劑等化學治療法、且更可添加1種或數種賀爾蒙劑、抗生素劑、生化製劑等本發明TNF突變體蛋白質以外的製劑。

且本發明的TNF阻礙劑或TNF製劑可同時組合使用作爲免疫助劑的放線菌素D（Actinomycin D）、醋葡醛內酯（Aceglatone）、Ifosfamide、烏苯美司（ubenimex）、依託泊苷（etoposide）、enocitabin、鹽酸阿克拉霉素（Aclarubicin Hydrochloride）、鹽酸伊達比星（Idamycin Hydrochlorid）、鹽酸伊利諾迪肯（irinotecan Hydrochloride）、鹽酸表柔比星（epirubicin hydrochloride）、鹽酸吉西他濱（gemcitabine hydrochloride）、鹽酸柔紅黴素（Daunomycin hydrochloride）、鹽酸阿霉素（doxorubicin hydrochloride

）、鹽酸氮芥-N-氧化物、鹽酸尼莫司汀（Nimustine hydrochloride）、鹽酸吡柔比星（pirarubicin hydrochloride）、falsol hydrochloride水合物、鹽酸平陽霉素（Bleomycin Hydrochloride）、鹽酸甲基下肼（Procarbazine hydrochloride）、鹽酸米托蒽醌（Mitoxantrone hydrochloride）、卡波醌（Carboquone）、卡鉑（Carboplatin）、卡莫氟（Carmofur）、泰莫西芬檸檬酸鹽（tamoxifen citrate）、托瑞米芬檸檬酸鹽（Toremifene Citrate）、克速鎮（Krestin）、甲基乙醯氧孕前酮乙酸鹽(medroxyprogesterone acetate)、環磷琉胺（Cyclophosphamide）、順一雙氨雙氯鉑（Cisplatin）、裂摺菌素（Schizophyllum）、賽達命（Cytarabine）、Cytarabine ocfosfate、淨司他丁替美（Zinostatin Stimalamer）、酒石酸長春瑞賓（Vinorelbine tartrate）、索布佐生（Sobuzoxane）、氮烯咪胺（Dacarbazine）、塞替派（Thiotepa）、Tegafur、Tegafur・尿嘧啶、TEGAFUR GIMERACIL OTERACILPOTASSIUM、去氧氟尿苷(Doxifluridine)、多西紫衫醇(Docetaxel)、全反式維甲酸(all-trans-Retinoic Acid)、新制癌菌素（Neocarzinostatin）、奈達鉑.（nedaplatin）、紫杉醇（Paclitaxel）、白卡羅他邁（Bicalutamide）、溶鏈菌製劑（Picibanil）、羥基脲（Hydroxycarbamide）、白消安（busulfan）、氟尿嘧啶、氟他胺（Flutamide）、噴司他丁（Pentostatin）、卟吩姆鈉（Porfimer Sodium）、絲裂霉

素C（Mitomycin C）、二溴甘露醇（Mitobronitol）、甲氨喋呤（Methotrexate）、巯嘌呤（Mercaptopurine）、6-巯嘌呤（6-Mercaptopurine）核苷酸、硫酸博萊霉素（Bleomycin Sulfate）、硫酸長春新鹼（Vincristine Sulfate）、硫酸長春地辛（Vindesine Sulfate）、硫酸長春鹼（Vinblastine Sulfate）、培洛霉素（Peplomycin Sulfate）、香菇多醣(Lentinan)的抗腫瘤藥劑等。又，同時使用干擾素、間白素等生物素、胰島素等賀爾蒙、及對於這些的抗體、結合蛋白質、增效物（agonist)、拮抗物、阻礙劑或可溶性受體時，可得到僅任一單方無法容易達成，且可相乘之效果。

本發明的TNF阻礙劑或TNF製劑，不僅適用於經口途徑，亦適用於非經口途徑下可有效地發揮敏感性疾病之治療・預防效果。依據感受性疾病的種類或症狀不同，具體而言，例如觀察患者症狀或使用後之經過下，將每體重1kg爲0.01至1,000mg/天，較佳爲0.1至100mg/天之本發明TNF拮抗物或TNF增效物（agonist)，因應其需要分爲數次以1至7次/週的頻率下進行1星期至1年之經口投與，或藉由皮內、皮下、肌肉內、靜脈內、鼻腔內、直腸內、腹腔內等非經口途徑，或藉由注射或點滴。本發明的TNF突變蛋白質與水溶性高分子之複合體，其爲安定且難由血液中的蛋白酶等分解，且於活體的滯留時間比TNF-α或TNF突變體蛋白質更顯著長，藉由投與途徑可達到10倍以上，故對於同一敏感性患者而言使用於同一途徑上時，其可達到

投與量顯著減少之效果。

【實施方式】

以下，依據實驗例對本發明做更詳細說明。

實驗例1：編碼TNF突變體蛋白質之DNA基因庫的製作及篩選

依據常法，以歐洲公開專利EP1354893號說明書所記載的實施例2所揭示的人類TNF離胺酸轉化體、即編碼TNF-α的第11、65、90、98、112及128個離胺酸殘基各可由蛋胺酸、絲胺酸、脯胺酸、精胺酸、天冬醯胺、脯胺酸取代之蛋白質的DNA（序列表中的序列號碼2）作爲鑄型，使用序列表中序列號碼83及84所表示的寡核苷酸引子，依據常法進行PCR，且使用所得之PCR產物作爲鑄模與序列表中序列號碼85及86所示寡核苷酸引子，依據常法進行PCR，得到編碼自N末端第29、31、32、145、146、147的胺基酸殘基由任意胺基酸取代之序列表中序列號碼5所示TNF變異體蛋白質之DNA（序列表中序列號碼6）。又，同樣地將人類TNF離胺酸轉化體DNA（序列表中序列號碼2）作爲鑄型，使用序列表中的序列號碼85及87所示寡核苷酸引子，依據常法進行PCR，進一步使用所得之PCR產物與序列表中之序列號碼88所示寡核苷酸引子，依據常法進行PCR，得到編碼自N末端第84至89的胺基酸由任意胺基酸取代之序列表中序列號碼7所示蛋白質之DNA（序列表中

序列號碼8）。

這些DNA可依據常法，導入質體載體pCANTAB5E（Amersham Biosciencese公司製作），得到自N末端第29、31、32、145、146、147的胺基酸殘基全部由任意胺基酸殘基取代之TNF突變體蛋白質、或表現第84至89個胺基酸殘基全部由任意胺基酸殘基取代之TNF突變體蛋白質的質體基因庫。對於該基因庫，藉由使用利用TNF-R1（具有GENBANK M58286所揭示的胺基酸序列之蛋白質）固定於感應探針（sensor tip）之商品的表面電漿共鳴之檢測機（商品名『BIACORE 2000』由Biacore股份有限公司販賣）進行3次重複的鑲嵌法，得到結合於TNF-R1之噬菌體克隆，又同樣地藉由固定TNF-R2（具有GENBANK M55994所揭示的胺基酸序列之蛋白質）之感應探針，得到結合於TNF-R2的噬菌體克隆。

利用對於結合於TNF-R1的克隆而言爲固定TNF-R2之感應探針的上述表面電漿共鳴之檢測機器，及利用對於結合於TNF-R2的克隆而言爲固定TNF-R1的感應探針的上述表面電漿共鳴之檢測機器，測定對受體的結合力，選出對受體的結合力具有差距的克隆。且，以所得的噬菌體克隆之DNA作爲鑄型，使用序列表中序列號碼89（具有限制酶NdeI切斷部位，開始密碼子、及TNF突變體蛋白質的5'-末端附近的鹼基序列）及序列號碼90（具有限制酶BamHI切斷部位，開始密碼子、及TNF突變體蛋白質的3'-末端附近的鹼基序列）所表示的寡核苷酸作爲引子，依據常法的

PCR，增幅於引子序列爲特異性之DNA後，藉由限制酶NdeI及BamHI消化後作爲DNA片段。

將所得之DNA片段，依據常法導入具有T7啓動子區、T7末端區、盤尼西林耐性基因區及ColE1・Ori區之質體載體（商品名『pet-3a』，Nova gene公司）的上述限制酶部位。且，將所得之質體導入大腸桿菌BL21DE3株，得到生產TNF突變體蛋白質之大腸桿菌。依據常法，培養所得之大腸桿菌後，藉由離心分離回收菌體，以TES緩衝液（pH8.0）（20mM Tris HCl、10Mm 伸乙二胺4乙酸、及0.5M氯化鈉）洗淨2次後，加入含有0.2mg/ml的溶菌酶之TES緩衝液（pH8.0），依據常法以超音波處理後進行離心分離，回收含有生產的TNF突變體蛋白質之殘餘部份。於此加入含有1（w/v）%之triton X-100之TES緩衝液，攪拌後經離心分離除去澄清液之操作進行3次，於所得之沈澱物中加入含有8M鹽酸胍鹽及50mM的二硫代蘇糖醇的50mM Tris HCl緩衝液（pH7.0），室溫遮光下攪拌16小時，經離心分離後回收澄清液。於此徐徐加入少量含有100倍量的1M Tris、0.9（w/v）%氯化鈉、0.4ML-精胺酸鹽酸鹽、2.5mM還原型谷胱胺肽、0.5mM氧化型谷胱胺肽、0.05（w/v）% Tween20的水溶液並攪拌後，於4℃下放置16小時。將此加入4倍量的0.1（w/v）%牛血清白蛋白之磷酸食鹽緩衝液（pH7.2），將pH由6.5調整至7.5後，依據常法藉由Q-Sepharose（Pharmacia公司製作）、MonoQ HR5/5（Pharmacia公司製作）、Superlose12 HR 10/30（

Pharmacia公司製作）及/或抗TNF-α抗體管柱層析法，依次純化出各TNF突變體蛋白質。所得之TNF突變體蛋白質以使用適當的以HEp-2細胞或L-M細胞爲標的細胞之生物檢驗方法對其細胞障礙活性進行調查。又，依據常法的DNA排序法，解讀各克隆的DNA突變導入部位之鹼基序列，調查哪個胺基酸殘基或終止密碼子被取代。又，對於細胞障礙性及對受體的結合力之評估方法爲，藉由與上述相同方法，以大腸桿菌所產生的重組型TNF-α作爲對照組，其次如下設定。

「4」：結合力或細胞障礙活性與重組型TNF-α相比爲提高至2倍以上。

「3」：結合力或細胞障礙活性與重組型TNF-α相比幾乎相等（0.5至2倍）。

「2」：結合力或細胞障礙活性與重組型TNF-α相比爲降低至0.5至0.1倍以下。

「1」：結合力或細胞障礙活性與重組型TNF-α相比爲降低至0.001至0.1倍以下。

「0」：結合力或細胞障礙活性與重組型TNF-α相比爲降低至0.001倍以下。

「-」：無測定

結果如表1（第29、31、32、145、146及147的胺基酸殘基被取代之TNF突變體）及表2（第84至89個胺基酸殘基被取代之TNF突變體）所示。

表 1

克隆號碼	生物檢驗		受體結合力		突變位置與突變後的胺基酸殘基及其密碼子						備註
	HEp-2	L-M	TNF-R1	TNF-R2	29	31	32	145	146	147	
TNF-α (對照)	3	3	3	3	Leu	Arg	Arg	Ala	Glu	Ser	配列號碼1
					ctg	cgc	cgg	gcc	gag	tct	
TNT離胺酸轉化體	3	3	3	3	Leu	Arg	Arg	Ala	Glu	Ser	配列號碼2
					ctg	cgc	cgg	gcc	gag	tct	
1	3	2	3	1	Gln	Arg	Trp	Ala	Glu	Ser	配列號碼37
					cag	agg	tgg	gcc	gag	tct	配列號碼60
2	4	3	3	2	Thr	Gly	Tyr	Ala	Glu	Ser	配列號碼38
					acg	ggg	tac	gcc	gag	tct	配列號碼61
3	4	1	3	1	Leu	Ser	Asp	Ala	Ala	Arg	配列號碼39
					tcc	agc	gac	gcc	gcc	cgc	配列號碼62
4	3	—	3	0	Lys	Ala	Gly	Ala	Ser	Thr	配列號碼40
					aag	gcc	ggc	gct	tcg	acg	配列號碼63
5	0	0	3	0	Arg	Ser	His	Ser	Gly	Thr	配列號碼 9
					agg	tcg	cac	tcg	ggc	acc	配列號碼23
6	1	—	3	1	Ser	Arg	Tyr	Ser	Met	stop	配列號碼10
					tcg	cgg	tac	tcc	atg	tag	配列號碼24
7	1	—	2	1	His	Asn	Thr	Asp	Ser	Asn	配列號碼11
					cac	aac	acg	gac	tcc	aac	配列號碼25
8	1	—	2	1	Arg	Glu	His	Asn	Asn	Ala	配列號碼12
					cgc	gag	cac	aac	aac	gcg	配列號碼26
9	1	—	2	1	Ser	Pro	Met	Ala	Asn	Pro	配列號碼13
					agc	ccc	atg	gcc	aac	ccc	配列號碼27
10	1	1	1	4	Leu	Arg	Arg	Lys	Asp	Thr	配列號碼14
					ctg	cgc	cgg	aag	gac	acg	配列號碼28
11	0	0	0	3	Leu	Arg	Arg	Arg	Thr	Asp	配列號碼15
					ctg	cgc	cgg	cgg	acg	gac	配列號碼29
12	1	1	1	3	Leu	Arg	Arg	Arg	Glu	Thr	配列號碼16
					ctg	cgc	cgg	agg	gag	acg	配列號碼30
13	2	2	2	4	Leu	Arg	Arg	Ala	Asp	Asp	配列號碼17
					ctg	cgc	cgg	gcc	gac	gac	配列號碼31
14	2	2	2	3	Leu	Arg	Arg	Ala	Asn	Asp	配列號碼18
					ctg	cgc	cgg	gcc	aac	gac	配列號碼32

表 2

克隆號碼	生物檢驗		受體		突變位置與突變後的胺基酸殘基及其密碼子						備註
	HEp-2	L-M	TNF-R1	TNF-R2	84	85	86	87	88	89	
TNF-α (對照)	3	3	3	3	Ala	Val	Ser	Tyr	Gln	Thr	配列號碼 1
					gcc	gtc	tcc	tac	cag	acc	
15	2	2	2	1	Thr	Asn	His	Tyr	Ser	Asn	
					acc	aac	cac	tac	tcg	aac	
16	4	4	4	2	Ser	Ser	Thr	Tyr	Pro	Asp	配列號碼 41
					agc	tcg	acc	tac	ccc	gac	配列號碼 64
17	4	4	3	1	Ser	Lys	Thr	Tyr	Thr	His	配列號碼 42
					tcg	aag	acc	tac	acc	cac	配列號碼 65
18	4	4	4	1	Ser	Pro	Leu	Tyr	Pro	Lys	配列號碼 43
					tcc	ccc	ctg	tac	ccc	aag	配列號碼 66
19	4	4	4	1	Ser	Tyr	Asn	Tyr	Asn	Gly	配列號碼 44
					tcc	acc	aac	tac	aac	ggc	配列號碼 67
20	3	4	3	2	Ser	Ser	Ala	Tyr	Ala	Ser	配列號碼 45
					tcc	agc	gcg	tac	gcg	agc	配列號碼 68
21	4	4	4	1	Thr	Ser	Ala	Tyr	Gly	Pro	配列號碼 46
					tcg	tcg	gcc	tac	ggg	ccg	配列號碼 69
22	4	4	3	1	Ser	Arg	Val	Tyr	Thr	Ala	配列號碼 47
					tcg	cgc	gtg	tac	acc	gcc	配列號碼 70
23	4	4	4	1	Thr	Thr	Ala	Tyr	Ser	Gly	配列號碼 48
					acg	acg	gcg	tac	agc	ggc	配列號碼 71
24	4	4	4	1	Thr	His	Lys	Tyr	Pro	Gln	配列號碼 49
					acg	cac	aag	tac	ccg	cag	配列號碼 72
25	4	3	4	1	Ser	Lys	Thr	Tyr	Ser	His	配列號碼 50
					agc	aag	acc	tac	tcc	cac	配列號碼 73
26	4	2	4	1	Ser	Ser	His	Tyr	Arg	Phe	配列號碼 51
					tcg	tcc	cac	tac	agg	ttc	配列號碼 74
27	3	4	3	2	Thr	Pro	Ala	Tyr	Pro	Arg	配列號碼 52
					acc	ccc	gcc	tac	ccc	cgg	配列號碼 75
28	3	3	3	1	Thr	Lys	Ser	Tyr	Ser	Lys	配列號碼 53
					acg	aag	tcc	tac	tcc	aag	配列號碼 76
29	4	4	3	1	Thr	Glu	Gln	Tyr	Ser	His	配列號碼 54
					acc	gag	cag	tac	tcc	cac	配列號碼 77
30	4	4	3	2	Thr	Pro	Gly	Tyr	Pro	Ser	配列號碼 55
					acg	ccc	cag	tac	ccg	tcc	配列號碼 78
31	4	4	4	3	Ser	Lys	Thr	Tyr	Ser	His	配列號碼 56
					agc	aag	acc	tac	tcc	cac	配列號碼 79
32	3	4	4	2	Thr	Asp	Arg	Tyr	Ser	Ser	配列號碼 57
					acg	gac	cgc	tac	agc	agc	配列號碼 80
33	3	3	4	1	Asn	His	Arg	Tyr	Gln	Asp	配列號碼 58
					aac	cac	agg	tac	cag	gac	配列號碼 81
34	4	3	3	2	Ser	Ala	Asp	Tyr	Pro	His	配列號碼 59
					tcc	gcg	gac	tac	ccc	cac	配列號碼 82
35	0	0	4	0	Thr	Pro	Ala	Ile	Asn	Arg	配列號碼 19
					acc	ccc	gcc	atc	aac	cgg	配列號碼 33
36	1	1	3	1	Ala	Pro	Gly	Tyr	Ser	His	配列號碼 20
					gcg	ccc	ggc	tac	tcc	cac	配列號碼 34
37	1	1	3	1	Ser	Thr	Thr	His	Asn	Gln	配列號碼 21
					agc	acc	acc	cac	aac	cag	配列號碼 35
38	1	1	3	1	Gly	Gly	Pro	Tyr	Gln	Arg	配列號碼 22
					ggc	ggc	ccg	tac	cag	cgg	配列號碼 36

如表1所示，對照組的TNF-α與TNF離胺酸轉化體幾

乎顯示相同程度的細胞障礙活性及對TNF受體的結合力。又，對於以TNF離胺酸轉化體爲準所製作出TNF突變體蛋白質，克隆號碼1至4的TNF突變體蛋白質與對TNF-R1之結合力相等，對TNF-R2的結合力較爲弱，使用HEp-2細胞及L-M細胞的生化檢驗中顯示細胞障礙活性。另一方面，克隆號碼第5至9的TNF突變體蛋白質爲，對TNF-R1之結合力爲同等或同等以下，對TNF-R2的結合力極爲弱，使用HEp-2細胞及L-M細胞的生化檢驗中所顯示的細胞障礙活性極爲減弱。由該結果得知，這些克隆皆可判斷爲TNF-R1特異性之TNF突變體蛋白質，其中克隆號碼1至4的TNF突變體蛋白質爲TNF-R1特異性之TNF增效物（agonist)、克隆號碼5至9的TNF突變體蛋白質爲TNF-R1特異性TNF拮抗物。又，克隆號10至14的TNF突變體蛋白質，其對TNF-R2的結合力與對照組的重組型TNF-α比較爲同等或同等以上，對TNF-R1的結合力極爲弱，使用HEp-2細胞及L-M細胞的生化檢驗中顯示細胞障礙活性極爲減弱。由該結果得知，克隆號碼10至14的TNF突變體蛋白質係爲TNF-R2特異性之TNF拮抗物。

又，如表2所示，與對照組的TNF離胺酸轉化體比較，克隆號碼16至34的TNF突變體蛋白質對TNF-R1的結合力爲同等或同等以上，對TNF-R2的結合力爲同等或同等以下，使用HEp-2細胞及L-M細胞的生化檢驗中顯示幾乎相等的細胞障礙活性。另一方面，克隆號碼35至38的TNF突變體蛋白質對TNF-R1的結合力爲同等，對TNF-R2的結合力極

爲弱，生化檢驗下細胞障礙活性極爲減弱。其結果得知，這些克隆爲TNF-R1特異性TNF突變體蛋白質者，克隆號碼16至34的TNF突變體蛋白質爲TNF-R1特異性TNF增效物（agonist)、克隆號碼35至38的TNF突變體蛋白質爲TNF-R1變異性TNF拮抗物。

實驗例2：TNF拮抗阻礙活性

對於上述號碼35至38的TNF拮抗物，更詳細調查拮抗阻礙活性。使用含有10ng/ml以基因工學技術常法所製造出的重組型人類TNF-α與下述表3之濃度的TNF拮抗物之培養基，測定僅多量TNF-R1表現於細胞膜表面之HEp-2細胞、或表現TNF-R1及TNF-R2之L-M細胞（TNF-R1的表現量比HEp-2少）的生存率（值越小TNF的細胞障礙活性更強）。

表3

TNF拮抗物 (ng/ml)		TNF-α (ng/ml)	生存率(%)	
			HEp-2	L-M
0		10	9	17
克隆號碼35	1,000	10	10	43
	10,000	10	18	58
	100,000	10	86	61
	500,000	10	103	64
克隆號碼36	1,000	10	12	43
	10,000	10	13	54
	100,000	10	38	63
	500,000	10	74	59
克隆號碼37	1,000	10	11	42
	10,000	10	18	51
	100,000	10	43	59
	500,000	10	75	72
克隆號碼38	1,000	10	11	42
	10,000	10	22	47
	100,000	10	72	58
	500,000	10	95	70

如表3所示，顯示較強細胞障礙活性之10ng/lm的重組型人類TNF-α存在下，HEp-2細胞的生存率爲，藉由100,000ng/ml以上濃度的TNF拮抗物之添加，由9%生存率對各提供於實驗的各克隆分別增加至86%、38%、43%或72%，重組型人類TNF-α的細胞障礙作用被部份性地遮斷。且TNF拮抗物500,000ng/ml的濃度中，生存率分別爲103%、74%、75%、95%，TNF-α的細胞障礙作用幾乎被遮斷。另一方面，藉由TNF拮抗物之添加，L-M細胞中生存率由17%於1,000ng/ml濃度下分別提高至43%、43%、51

%、47%，但於500,000ng/ml的濃度下生存率僅回復至64%、59%、72%、70%。該結果得知，克隆號碼35至38的TNF拮抗物，對於僅使TNF-R1豐富表現之HEp-2細胞而言，欲遮斷TNF的作用必須爲較高濃度之TNF突變體蛋白質，HEp-2細胞因未表現TNF-R2，故藉由高濃度的TNF拮抗物可完全遮斷TNF作用，相對於此，對於表現TNF-R1及TNF-R2雙方的L-M細胞而言，藉由TNF-R1的TNF作用因TNF-R1的表現數較爲少故較容易遮蔽，而藉由TNF-R2無法遮蔽TNF作用，故既使藉由高濃度的TNF拮抗物亦無法遮斷TNF-α的細胞障礙作用。然而，該結果表示本發明的TNF拮抗物具TNF-R1特異性。

實驗例3：TNF突變體蛋白質與水溶性高分子的複合體之調製

藉由實驗例1的方法所得之14種類的TNF拮抗物（克隆號碼5至14、35至38）或23種類的TNF增效物（agonist)（克隆號碼1至4、16至34）溶解於磷酸緩衝液生理食鹽水（pH7.2）至濃度0.1至1mg/ml後，加入作爲水溶性高分子將經單甲氧基N-琥珀銑酵亞胺丙酸鹽活化的聚乙二醇（m-PAG-SPA，平均分子量5,000道爾頓）至莫耳比爲蛋白質之3倍，經37℃下反應30分鐘。其次，於反應混合物中加入ε-胺基己酸至莫耳比爲水溶性高分子的10倍量，暫時靜置後停止反應後，反應混合物以陰離子交換層析管柱（商品名『Mono S』，Amersham Biosciencese公司製作）進行

HPLC分離，除去未與蛋白質結合之聚乙二醇，得到本發明的結合TNF突變體蛋白質於水溶性高分子的複合體。將其中的14種類TNF拮抗物，提供於使用HEp-2細胞之實驗例2所記載的競爭試驗，同樣地測定TNF拮抗阻礙活性時，判斷具有未與聚乙二醇結合之各TNF拮抗物約70%之TNF拮抗阻礙活性。

實驗例4：急性毒性試驗

依據常法，使用8週齡的雄性老鼠（體重20至25g），實驗1所得之14種類TNF拮抗物（克隆號碼5至14、35至38）或23種類的TNF增效物（agonist)（克隆號碼1至4、16至34）、或實驗例3的方法所得之14種類的TNF拮抗物或23種類的TNF增效物（agonist)與聚乙二醇結合所得之任一複合體，藉由經皮、經口或腹腔途徑進行注射投與時，TNF拮抗物及與此與聚乙二醇結合之複合體的LD_{50}，對於任一投與途徑皆爲100mg/kg體重以上。此表示作爲本發明的TNF突變體蛋白質及此與聚乙二醇結合的複合體對人類或牛等家畜進行投與之醫藥品，或添加於醫藥品使用時具有安全性。

以下繼本發明的實施型態時以實施例說明本發明。

實施例1：液劑

作爲安定劑於含有1%（w/w）人血清白蛋白之生理食鹽水中溶解任一之實驗例1的方法所得之14種類的TNF拮抗

物（克隆號碼5至14、35至38）、23種類的TNF增效物（agonist)（克隆1至4、16至34）或實驗例3的方法所得之14種類的TNF拮抗物與聚乙二醇結合之複合體至100mg/ml，依據常法經精密過濾得到滅菌的溶劑。

本品可作爲治療或預防、及緩和以惡性腫瘤、病毒性疾病、細菌感染症、細菌感染症、發炎性疾病及免疫性疾病爲主之敏感性疾病的症狀時之注射劑、眼藥劑及點鼻劑等使用。

實施例2：液劑

作爲安定劑於含有1%（w/w）人血清白蛋白之生理食鹽水中溶解任一之實驗例1的方法所得之14種類的TNF拮抗物（克隆號碼5至14、35至38）、23種類的TNF增效物（agonist)（克隆1至4、16至34）或實驗例3的方法所得之14種類的TNF拮抗物與聚乙二醇結合之複合體至10mg/ml，重組人類TNF-α至1μg/ml，依據常法經精密過濾得到滅菌的溶劑。

本品可作爲治療或預防、及緩和以惡性腫瘤、病毒性疾病、細菌感染症、細菌感染症、發炎性疾病及免疫性疾病爲主之敏感性疾病的症狀時之注射劑、眼藥劑及點鼻劑等使用。

實施例3：乾燥注射劑

作爲安定劑於含有1%（w/w）之純明膠的100ml生理

食鹽水中，溶解任一之實驗例3的方法所得之14種類的TNF拮抗物（克隆號碼5至14、35至38）與聚乙二醇結合之1g複合體、0.1mg的歐洲公開專利EP1354893號說明書之實施例2所得的生理活性複合體（具有本案說明書的序列表中序列表2所示的鹼基序列所記載的胺基酸序列之TNF離胺酸轉化體、與聚二醇之複合體），依據常法經精密過濾進行滅菌，以每1ml分裝於管瓶（vial）中，經冷凍乾燥、密栓後得到乾燥注射劑。

本品可作爲治療或預防、及緩和以惡性腫瘤、病毒性疾病、細菌感染症、細菌感染症、發炎性疾病及免疫性疾病爲主之敏感性疾病的症狀時之注射劑、眼藥劑及點鼻劑等使用。

實施例4：軟膏劑

滅菌蒸餾水中溶解的羧基乙稀聚合物（商品名『Hibiswako』，和光純藥工業股份有限公司）與除去熱源的高純度海藻糖（商品名『Torha』，林原股份有限公司製造）至各濃度爲1.4%（w/w）及2.0%（w/w）後，均勻混合任一適量的由實施例1方法所得之14種類的TNF拮抗物（克隆號碼5至14、35至38）或23種類的TNF增效物（agonist)（克隆號碼1至4、16至34），調製至pH7.2，得到每1g中含有10μg的TNF拮抗物或TNF增效物（agonist)之漿狀物。

具有優良延展性與安定性之本品，可適用於惡性腫瘤

、病毒性疾病、或細菌感染症、或因TNF所引起的發炎、過敏等疾病的治療、預防上之軟膏。

實施例5：錠劑

無水結晶性α-麥芽糖粉末（商品名『faintose』，林原股份有限公司製造）中均勻混合適量的任一由實施例3方法所得之14種類的TNF拮抗物（克隆號碼5至14、35至38）與聚乙二醇之複合物、對於此的莫耳比爲1/10,000之歐洲公開專利EP1354893號說明書的實施例2之方法所得的具有TNF活性之生理活性複合體（具有本案說明書的序列表中序列號碼2所示的鹼基序列所記載的胺基酸序列之TNF離胺酸轉化體、與聚乙二醇之複合體），所得之混合物依據常法打錠得到每錠（約200mg）中含有約10mg的具有TNF拮抗活性之生理活性複合體、及約1μg的具有TNF活性之生理活性複合體之錠劑。

具有攝取性、安定性優良的本品，可有用作爲治療、預防惡性腫瘤、病毒性感染、細菌感染症、發炎及免疫性疾病爲主的敏感性疾病上之錠劑。

產業上可利用性

如上所述，本發明的TNF拮抗物或以此作爲有效成分的TNF阻礙劑，可抑制藉由TNF-R1或TNF-R2之TNF作用，故於醫藥品的領域下，例如具有抗腫瘤劑、抗病毒疾病劑、抗感染症劑、發炎疾病劑、免疫疾病劑等之多樣化用途

。又，對於TNF-R1爲特異性結合之TNF增效物（agonist）可望其可發揮與野生型TNF相異的生物作用。且本發明的TNF突變體蛋白質藉由與聚乙二醇等水溶性高分子之結合可提高活體內的安定性，故極有利地使用於醫藥品上。

序列表

<110> Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo
Tadanori Mayumi
Yasuo Tsutsumi
Shinsaku Nakagawa
<120> TNF拮抗物及以其作爲有效成分之TNF阻礙劑
<130> W01042
<160> 90

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<211> 157
<212> PRT
<213> 人類

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Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Lys Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Ala Val Ser Tyr Gln Thr Lys Val Asn Leu Leu Ser Ala
85 90 95
Ile Lys Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

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1 5 10 15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
85 90 95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

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<211> 471
<212> DNA
<213> 人造序列

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  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc cgg gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Arg Val Asn Leu Leu Ser Ala
                 85                  90                  95
atc gcc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc ctc 336
Ile Ala Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Leu
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag acc 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Thr
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
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145                 150                 155
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<210> 4
<211> 471
<212> DNA
<213> 人造序列

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  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc gac gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
atc gcc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc ctc 336
Ile Ala Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Leu
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag acc 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Thr
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
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<211> 157
<212> PRT
<213> 人造序列

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

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<211> 471
<212> DNA
<213> 人造序列

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Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
gta gca aac cct caa gct gag ggg cag ctc cag tgg nns aac nns nns 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Xaa Asn Xaa Xaa
20 25 30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
85 90 95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
nns nns nns ggg cag gtc tac ttt ggg atc att gcc ctg
Xaa Xaa Xaa Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 7
<211> 157
<212> PRT
<213> 人造序列

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1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30

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Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
          35                  40                  45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
      50                  55                  60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
  65                  70                  75                  80
Ser Arg Ile Xaa Xaa Xaa Xaa Xaa Xaa Pro Val Asn Leu Leu Ser Ala
                  85                  90                  95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
             100                 105                 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
         115                 120                 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
     130                 135                 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
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<211> 471
<212> DNA
<213> 人造序列

<400> 8

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Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc nns nns nns nns nns nns ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Xaa Xaa Xaa Xaa Xaa Xaa Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
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<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 5

<400> 9

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

```
                85                  90                  95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
Ser Gly Thr Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
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<211> 146
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No.6

<400> 10

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

<210> 11
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No.7

<400> 11

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

<210> 12
<211> 157
<212> PRT

<213> 人造序列

<220>
<223> 克隆 No. 8

<400> 12
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Arg Asn Glu His
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Asn Asn Ala Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 13
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 9

<400> 13
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Ser Asn Pro Met
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Asn Pro Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 14
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 10

<400> 14
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60

```
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
Lys Asp Thr Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 15
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No.11

<400> 15

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

<210> 16
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No.12

<400> 16

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

<210> 17
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 13

<400> 17
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Asp Asp Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 18
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 14

<400> 18
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Asn Asp Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 19
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 35

<400> 19
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu

```
          35                  40                  45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
      50                  55                  60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
Ser Arg Ile Thr Pro Ala Ile Asn Arg Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 20
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No.36

<400> 20

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

<210> 21
<211> 157
<212> PRT
<213>

<220>
<223> 克隆 No.37

<400> 21

```
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
            20                  25                  30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
Ser Arg Ile Ser Thr Thr His Asn Gln Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
```

145 150 155

<210> 22
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 38

<400> 22
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Gly Gly Pro Tyr Gln Arg Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 23
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 5

<400> 23
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
gta gca aac cct caa gct gag ggg cag ctc cag tgg agg aac tcg cac 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Arg Asn Ser His
20 25 30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
85 90 95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
tcg ggc acc ggg cag gtc tac ttt ggg atc att gcc ctg
Ser Gly Thr Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 24

<211> 441
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 6

<400> 24
```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
 1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg tcg aac cgg tac 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Ser Asn Arg Tyr
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
tcc atg tag
Ser Met
145
```

<210> 25
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 7

<400> 25
```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
 1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg cac aac aac acg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp His Asn Asn Thr
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
```

```
gac tcc aac ggg cag gtc tac ttt ggg atc att gcc ctg
Asp Ser Asn Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 26
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 8

<400> 26

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg cgc aac gag cac 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Arg Asn Glu His
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
aac aac gcg ggg cag gtc tac ttt ggg atc att gcc ctg
Asn Asn Ala Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 27
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 9

<400> 27

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg agc aac ccc atg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Ser Asn Pro Met
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
```

```
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc aac ccc ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Asn Pro Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 28
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No.10

<400> 28

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
aag gac acg ggg cag gtc tac ttt ggg atc att gcc ctg
Lys Asp Thr Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 29
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No.11

<400> 29

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
```

```
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
cgg acg gac ggg cag gtc tac ttt ggg atc att gcc ctg
Arg Thr Asp Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 30
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 12

```
<400> 30
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
agg gag acg ggg cag gtc tac ttt ggg atc att gcc ctg
Arg Glu Thr Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 31
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 13

```
<400> 31
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
```

```
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gac gac ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Asp Asp Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 32
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 14

<400> 32

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc aac gac ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Asn Asp Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 33
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 35

<400> 33

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
```

```
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc acc ccc gcc atc aac cgg ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Thr Pro Ala Ile Asn Arg Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 34
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 36

<400> 34

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc gcg ccc ggc tac tcc cac ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Pro Gly Tyr Ser His Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 35
<211> 471
<212> DNA
<213> 人造序列

<220>

<223> 克隆 No. 37

<400> 35

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc agc acc acc cac aac cag ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ser Thr Thr His Asn Gln Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 36
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 38

<400> 36

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc ggc ggc ccg tac cag cgg ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Gly Gly Pro Tyr Gln Arg Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 37

<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 1

<400> 37
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Gln Asn Arg Trp
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 38
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 2

<400> 38
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Thr Asn Gly Tyr
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 39
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 3

<400> 39
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Ser Asp
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60

```
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
Ala Ala Arg Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 40
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No.4

<400> 40

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

<210> 41
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No.16

<400> 41

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

<210> 42
<211> 157
<212> PRT

<213> 人造序列

<220>
<223> 克隆 No.17

<400> 42
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Ser Lys Thr Tyr Thr His Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 43
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No.18

<400> 43
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Ser Pro Leu Tyr Pro Lys Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 44
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No.19

<400> 44
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80

Ser Arg Ile Ser Tyr Asn Tyr Asn Gly Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 45
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 20

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

<210> 46
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 21

<400> 46
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Thr Ser Ala Tyr Gly Pro Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 47
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 22

<400> 47
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Ser Arg Val Tyr Thr Ala Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 48
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 23

<400> 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Thr Thr Ala Tyr Ser Gly Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 49
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 24

<400> 49
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Thr His Lys Tyr Pro Gln Pro Val Asn Leu Leu Ser Ala
85 90 95

Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 50
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 25

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

<210> 51
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 26

<400> 51
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Ser Ser His Tyr Arg Phe Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 52
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 27

<400> 52
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Thr Pro Ala Tyr Pro Arg Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 53
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 28

<400> 53
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Thr Lys Ser Tyr Ser Lys Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 54
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 29

<400> 54
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
Ser Arg Ile Thr Glu Gln Tyr Ser His Pro Val Asn Leu Leu Ser Ala
85 90 95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110

```
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 55
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No.30

<400> 55

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

<210> 56
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No.31

<400> 56

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

<210> 57
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No.32

<400> 57

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

<210> 58
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 33

<400> 58

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

<210> 59
<211> 157
<212> PRT
<213> 人造序列

<220>
<223> 克隆 No. 34

<400> 59

```
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
Ser Arg Ile Ser Ala Asp Tyr Pro His Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
```

```
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 60
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 1

<400> 60

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg cag aac agg tgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Gln Asn Arg Trp
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 61
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 2

<400> 61

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg acg aac ggg tac 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Thr Asn Gly Tyr
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
```

```
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 62
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 3

<400> 62

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg tcc aac agc gac 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Ser Asp
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gcc cgc ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Ala Arg Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 63
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 4

<400> 63

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg aag aac gcc ggc 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Lys Asn Ala Gly
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc gcc gtc tcc tac cag acc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ala Val Ser Tyr Gln Thr Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
```

atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
gct tcg acg ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Ser Thr Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 64
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 16

<400> 64
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
agc cgc atc agc tcg acc tac ccc gac ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ser Ser Thr Tyr Pro Asp Pro Val Asn Leu Leu Ser Ala
85 90 95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 65
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 17

<400> 65
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile

```
 65                  70                  75                  80
agc cgc atc tcg aag acc tac acc cac ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ser Lys Thr Tyr Thr His Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 66
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No.18

<400> 66

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc tcc ccc ctg tac ccc aag ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ser Pro Leu Tyr Pro Lys Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 67
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No.19

<400> 67

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
```

```
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc tcc acc aac tac aac ggc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ser Tyr Asn Tyr Asn Gly Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 68
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 20

<400> 68

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc tcc agc gcg tac gcg agc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ser Ser Ala Tyr Ala Ser Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 69
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 21

<400> 69

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
```

```
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc tcg tcg gcc tac ggg ccg ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Thr Ser Ala Tyr Gly Pro Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 70
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 22

<400> 70

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc tcg cgc gtg tac acc gcc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ser Arg Val Tyr Thr Ala Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 71
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 23

<400> 71

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
```

```
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc acg acg gcg tac agc ggc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Thr Thr Ala Tyr Ser Gly Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 72
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 24

<400> 72

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc acg cac aag tac ccg cag ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Thr His Lys Tyr Pro Gln Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 73
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 25

<400> 73
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
agc cgc atc agc aag acc tac tcc cac ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ser Lys Thr Tyr Ser His Pro Val Asn Leu Leu Ser Ala
85 90 95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 74
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 26

<400> 74
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
1 5 10 15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80
agc cgc atc tcg tcc cac tac agg ttc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ser Ser His Tyr Arg Phe Pro Val Asn Leu Leu Ser Ala
85 90 95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
100 105 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
115 120 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
130 135 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145 150 155

<210> 75
<211> 471
<212> DNA

<213> 人造序列

<220>
<223> 克隆 No. 27

<400> 75
```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc acc ccc gcc tac ccc cgg ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Thr Pro Ala Tyr Pro Arg Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 76
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 28

<400> 76
```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc acg aag tcc tac tcc aag ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Thr Lys Ser Tyr Ser Lys Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 77
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 29

<400> 77
```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc acc gag cag tac tcc cac ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Thr Glu Gln Tyr Ser His Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 78
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 30

<400> 78
```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
             20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
         35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
     50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
 65                  70                  75                  80
agc cgc atc acg ccc cag tac ccg tcc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Thr Pro Gly Tyr Pro Ser Pro Val Asn Leu Leu Ser Ala
                 85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
```

```
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 79
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No.31

<400> 79

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc agc aag acc tac tcc cac ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ser Lys Thr Tyr Ser His Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 80
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No.32

<400> 80

```
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc acg gac cgc tac agc agc ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Thr Asp Arg Tyr Ser Ser Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
```

```
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 81
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 33

```
<400> 81
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc aac cac agg tac cag gac ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Asn His Arg Tyr Gln Asp Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 82
<211> 471
<212> DNA
<213> 人造序列

<220>
<223> 克隆 No. 34

```
<400> 82
gtc aga tca tct tct cga acc ccg agt gac atg cct gta gcc cat gtt 48
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Met Pro Val Ala His Val
  1               5                  10                  15
gta gca aac cct caa gct gag ggg cag ctc cag tgg ctg aac cgc cgg 96
Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
            20                  25                  30
gcc aat gcc ctc ctg gcc aat ggc gtg gag ctg aga gat aac cag ctg 144
Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
        35                  40                  45
gtg gtg cca tca gag ggc ctg tac ctc atc tac tcc cag gtc ctc ttc 192
Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
    50                  55                  60
tcg ggc caa ggc tgc ccc tcc acc cat gtg ctc ctc acc cac acc atc 240
Ser Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65                  70                  75                  80
agc cgc atc tcc gcg gac tac ccc cac ccc gtc aac ctc ctc tct gcc 288
Ser Arg Ile Ser Ala Asp Tyr Pro His Pro Val Asn Leu Leu Ser Ala
                85                  90                  95
```

```
atc cgc agc ccc tgc cag agg gag acc cca gag ggg gct gag gcc aac 336
Ile Arg Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Asn
            100                 105                 110
ccc tgg tat gag ccc atc tat ctg gga ggg gtc ttc cag ctg gag ccg 384
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Pro
        115                 120                 125
ggt gac cga ctc agc gct gag atc aat cgg ccc gac tat ctc gac ttt 432
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
    130                 135                 140
gcc gag tct ggg cag gtc tac ttt ggg atc att gcc ctg
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
145                 150                 155
```

<210> 83
<211> 87
<212> DNA
<213> 人造序列
<220>
<223> 具NNS配列的寡核苷酸作爲引子(突變於第29、31、及32個胺基酸殘基)

<400> 83
gacatgcctg tagcccatgt tgtagcaaac cctcaagctg aggggcagct ccagtggnns 60
aacnnsnnsg ccaatgccct cctggcc

<210> 84
<211> 57
<212> DNA
<213> 人造序列
<220>
<223> 具NNS配列的寡核苷酸作爲引子(突變於第145至147個胺基酸殘基)

<400> 84
cagggcaatg atcccaaagt agacctgccc snnsnnsnna aagtcgagat agtcggg

<210> 85
<211> 65
<212> DNA
<213> 人造序列
<220>
<223> 藉由5'-末端的寡核苷酸將PCR增幅的DNA插入噬菌粒載體中

<400> 85
cccagccggc catggccgtc agatcatctt ctcgaacccc gagtgacatg cctgtagccc 60
atgtt

<210> 86
<211> 62
<212> DNA
<213> 人造序列
<220>
<223> 藉由3'-末端的寡核苷酸將PCR增幅的DNA插入噬菌粒載體中

<400> 86
ggcaccggcg cacctgcggc cgcagatcca ccaccaccca gggcaatgat cccaaagtag 60
ac

<210> 87
<211> 87
<212> DNA
<213> 人造序列
<220>
<223> 具有NNS序列的寡核苷酸作爲反義引子(突變胺基酸殘基於第84-89位置上)

<400> 87
ctggcagggg ctgcggatgg cagagaggag attgacgggs nnsnnsnnsn nsnnsnngat 60
gcggctgatg gtgtgggtga ggagcac

<210> 88

<211> 218
<212> DNA
<213> 人造序列
<220>
<223> 藉由3'-末端的寡核苷酸將PCR增幅的DNA插入噬菌粒載體中

<400> 88
ggcaccggcg cacctgcggc cgcagatcca ccaccaccca gggcaatgat cccaaagtag 60
acctgcccag actcggcaaa gtcgagatag tcgggccgat tgatctcagc gctgagtcgg 120
tcacccggct ccagctggaa gacccctccc agatagatgg gctcatacca ggggttggcc 180
tcagcccccc ctggggtctc cctctggcag gggctgcg

<210> 89
<211> 38
<212> DNA
<213> 人造序列
<220>
<223> 藉由5'-末端的寡核苷酸將PCR增幅的DNA插入表現載體中

<400> 89
tatacatatg gtcagatcat cttctcgaac cccgagtg

<210> 90
<211> 35
<212> DNA
<213> 人造序列
<220>
<223> 藉由3'-末端的寡核苷酸將PCR增幅的DNA插入表現載體中

<400> 90
aaggatccct acagggcaat gatcccaaag tagac

201122103

分割案

發明專利說明書

（本申請書格式、順序，請勿任意更動，※記號部分請勿填寫）

※申請案號：100101936

※申請日期：94.1.4　※IPC分類：C12N 15/28 (2006.01)
C07K 14/525 (2006.01)

原申請案號：094100160

一、發明名稱：（中文／英文）

TNF拮抗物及以其作爲有效成分之TNF阻礙劑

二、中文發明摘要：

本發明係關於提供一種腫瘤壞死因子突變體蛋白質、換言之TNF-R1或TNF-R2特異性腫瘤壞死因子突變體蛋白質、及以此作爲有效成分之腫瘤壞死因子阻礙劑或腫瘤壞死因子製劑作爲課題者。藉由提供1或2個以上的序列號碼1所示胺基酸序列中自N末端第29、31、32、145、146及147個胺基酸殘基、或第84至89個胺基酸殘基由其他胺基酸殘基取代之腫瘤壞死因子突變體蛋白質、及以此爲作爲有效成分的腫瘤壞死因子阻礙劑或腫瘤壞死因子製劑解決前述課題。

三、英文發明摘要：

七、申請專利範圍：

1.一種腫瘤壞死因子突變體蛋白質，其特徵爲序列表中序列號碼1所示的胺基酸序列中，自N末端第29個爲亮胺酸、麩胺酸、蘇胺酸或離胺酸、

第31個爲精胺酸、甘胺酸、絲胺酸或丙胺酸

第32個爲色胺酸、酪胺酸、天冬胺酸或甘胺酸、

第146個爲麩胺酸、丙胺酸或絲胺酸、及

第147個爲絲胺酸、精胺酸或蘇胺酸取代、或

第84個爲蘇胺酸、絲胺酸或天冬醯胺、

第85個爲絲胺酸、離胺酸、脯胺酸、酪胺酸、精胺酸、蘇胺酸、組胺酸、麩胺酸、天冬胺酸或丙胺酸、

第86個爲組胺酸、蘇胺酸、亮胺酸、天冬醯胺、丙胺酸、纈胺酸、離胺酸、絲胺酸、麩胺酸、甘胺酸、精胺酸或天冬胺酸、

第88個爲絲胺酸、脯胺酸、蘇胺酸、天冬醯胺、丙胺酸、甘胺酸、精胺酸或麩胺酸、及

第89個爲天冬胺酸、組胺酸、離胺酸、甘胺酸、絲胺酸、脯胺酸、丙胺酸、麩胺酸、苯丙胺酸或精胺酸取代，

且對於腫瘤壞死因子具有增效作用者。

2.如申請專利範圍第1項之腫瘤壞死因子突變體蛋白質，其爲序列表中序列個碼37至59所示之任一胺基酸序列、或選自自這些胺基酸序列的N末端第11、65、90、98、112及128個之胺基酸殘基的1或2個以上的胺基酸殘基爲離胺酸殘基之蛋白質，且對於腫瘤壞死因子具有增效作用者

。

3.如申請專利範圍第1項或第2項之腫瘤壞死因子突變體蛋白質，其與水溶性高分子結合。

4.如申請專利範圍第3項之腫瘤壞死因子突變體蛋白質，其中水溶性高分子爲聚乙二醇。

5.一種腫瘤壞死因子阻礙劑，其特徵爲含有如申請專利範圍第1項或第2項之腫瘤壞死因子突變體蛋白質。

四、指定代表圖：

（一）本案指定代表圖為：無

（二）本代表圖之元件符號簡單說明：無

五、本案若有化學式時，請揭示最能顯示發明特徵的化學式：無