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(54)名稱
細胞傷害誘導治療劑

(57)摘要

本發明找到一種新的多專一性抗原結合分子，其包含:含有具 Glypican3 結合活性之抗體可變區之域、及含有具 T 細胞受體複合體結合活性之抗體可變區之域，且維持優良的細胞傷害活性與高安全性。本發明之分子對於表現 Glypican3 之細胞、組織呈強細胞傷害性，故能製造用以治療或預防各種癌之新的醫藥組合物。



【發明摘要】

【中文發明名稱】 細胞傷害誘導治療劑

【中文】

本發明找到一種新的多專一性抗原結合分子，其包含：含有具Glypican3結合活性之抗體可變區之域、及含有具T細胞受體複合體結合活性之抗體可變區之域，且維持優良的細胞傷害活性與高安全性。本發明之分子對於表現Glypican3之細胞、組織呈強細胞傷害性，故能製造用以治療或預防各種癌之新的醫藥組合物。

【指定代表圖】 無

【代表圖之符號簡單說明】 無

【發明說明書】

【中文發明名稱】 細胞傷害誘導治療劑

【技術領域】

【0001】 本發明係關於多專一性抗原結合分子及其利用等。

【先前技術】

【0002】 抗體在血漿中之安定性高、副作用也少，因此作為醫藥品受到重視(非專利文獻1及非專利文獻2)。抗體不只有結合於抗原之作用、致效劑作用、拮抗劑作用，尚已知會誘導ADCC(Antibody Dependent Cytotoxicity：抗體依存性傷害活性)、ADCP(Antibody Dependent Cell phagocytosis：抗體依存性細胞吞噬作用)、CDC(補體依存性細胞傷害活性)這些利用效應子細胞之細胞傷害活性(也稱為效應子機能)，並發揮針對癌細胞之抗腫瘤效果(非專利文獻3)。藉由使抗體之Fc區結合於存在於NK細胞或巨噬體等效應子細胞上的Fc受體，使得該等效應子細胞對於抗體所結合之標的癌細胞發揮之細胞傷害，為ADCC。補體複合體會結合於抗體之構造中所存在之補體結合部位。存在於該複合體中之補體成分會在抗體所結合之細胞之細胞膜上形成孔，藉此促進水或離子流入細胞內並引起細胞受破壞的細胞傷害，為CDC。至今已有多種呈現優異之抗腫瘤效果之治療用抗體作為癌治療為目的之醫藥品被開發出來(非專利文獻4)，但既有的治療用抗體雖認為具有優異的作用，但是藉由如此的抗體的投予獲得之治療成績尚未令人滿意。

【0003】 抗體為了展現ADCC、ADCP、CDC，抗體之Fc區必須和NK細胞、巨噬體等效應子細胞存在之抗體受體(FcγR)及各種補體成分結合。於人，就FcγR之蛋白質家族而言，有人報告了FcγRIa、FcγRIIa、FcγRIIb、FcγRIIIa、FcγRIIIb

之同功型(isoform)，其各自的副型(allotype)也有人報告 (非專利文獻5)。該等同功型之中，FcγRIa、FcγRIIa、FcγRIIIa在細胞內域(domain)帶有稱為ITAM (Immunoreceptor Tyrosine-based Activation Motif) 之域，會傳達活化信號。另一方面，只有FcγRIIb在細胞內域帶有稱為ITIM (Immunoreceptor Tyrosine-based Inhibitory Motif) 之域，並抑制信號傳達。已知所有的FcγR均會因免疫複合體等而交聯(crosslink)而傳達信號(非專利文獻6)。實際上，當抗體對於癌細胞發揮效應子機能時，在癌細胞膜上結合之多個抗體之Fc區，效應子細胞膜上之FcγR會成為簇集，以效應子細胞傳達活化信號。其結果，會發揮殺細胞效果，但此時FcγR之交聯會受限於存在癌細胞附近的效應子細胞，故免疫活化只在癌細胞局部發生。(非專利文獻7)

【0004】 天然型之免疫球蛋白係以可變區和抗原結合，並以不變區和FcγR、FcRn、FcαR、FcεR這些受體、補體結合。於IgG之Fc區交互作用之結合分子之一即FcRn會和抗體之重鏈各結合1分子，故據報告:針對IgG型之抗體1分子會結合2分子之FcRn。但是FcγR和FcRn等不同，FcγR是於抗體之鉸鏈區及CH2域交互作用，針對IgG型之抗體1分子只結合1分子(非專利文獻8)。又，通常天然型之IgG型之抗體係利用其可變區(Fab)認識1個抗原決定基並結合，故只能結合於1個抗原。另一方面，已知癌、發炎涉及多種蛋白質，有時蛋白質彼此會串音(crosstalk)。例如，於免疫疾病，已知涉及數種發炎性細胞介素(TNF、IL1、IL6)(非專利文獻9)。又，已知癌獲得藥劑耐性之機制之一為活化其他受體(非專利文獻10)。在如此的情形，認識1個抗原決定基之通常之抗體無法妨礙多數蛋白質。

【0005】 作為妨礙多數標靶之分子，已有人研究以1分子結合2種以上之抗原之抗體(Bispecific抗體，雙專一性抗體)。藉由改良天然型之IgG型之抗體，可賦予向不同的2個抗原(第1抗原與第2抗原)之結合活性(非專利文獻11)。所以，不只有以1個分子中和2種以上之抗原之作用，尚有藉由將帶有細胞傷害活性之細

胞和癌細胞予以交聯而提高抗腫瘤活性之作用。至今，就Bispecific抗體之分子形態而言，已有人報告：在抗體之N末端、C末端附加抗原結合部位之分子(DVD-Ig、scFv-IgG)、抗體之2個Fab區具有不同序列之分子(共通L鏈Bispecific抗體及混成融合瘤(hybridhybridoma))、一個Fab區認識2個抗原之分子(Two-in-one IgG)、CH3區之迴圈部位成為新抗原結合部位之分子(Fcab)(非專利文獻12及非專利文獻13)。Bispecific抗體皆以Fc區和FcγR交互作用，故保存抗體之效應子機能。因此針對Bispecific抗體認識之任一抗原，會和FcγR同時結合，並對於表現抗原之細胞呈現ADCC活性。

【0006】 Bispecific抗體所認識之抗原若均為在癌專一性地表現的抗原，則結合於任一抗原均對於癌細胞顯示細胞傷害活性，能期待比起認識一個抗原的通常的抗體醫藥品有更有效率的抗腫瘤效果。但是Bispecific抗體所認識之抗原之中若有任一抗原在正常組織也表現時、為表現於免疫細胞之細胞時，會因為和FcγR之交聯而造成正常組織之傷害、細胞介素之放出(非專利文獻14)。其結果誘導強副作用。

【0007】 作為Bispecific抗體之一，從1980年代已知有將T細胞作為效應子細胞而動員之細胞傷害作為其抗腫瘤效果之機制的抗體即T細胞重定向抗體(T cell-redirecting抗體)(非專利文獻15、16、17)。和將NK細胞、巨噬體作為效應子細胞而動員之ADCC作為其抗腫瘤效果之機制的抗體不同，T細胞重定向抗體係針對T細胞上之T細胞受體(TCR)複合體之構成次單元之任一者的抗體，尤其是包括結合於CD3 epsilon鏈之抗體、與結合於標的癌細胞上之抗原之抗體的bi-specific抗體。T細胞重定向抗體藉由同時結合於CD3 epsilon鏈與癌抗原，使T細胞接近癌細胞。其結果，據認為因T細胞帶有的細胞傷害作用對於癌細胞發揮抗腫瘤效果。

【0008】 已知係作為T細胞重定向抗體之一之Catumaxomab，以2個Fab分

別和在癌抗原(EpCAM)與T細胞表現之CD3 ϵ 鏈結合。Catumaxomab藉由同時結合癌抗原與CD3 ϵ ，會誘導T細胞所為之細胞傷害活性，藉由同時結合於癌抗原與Fc γ R，會誘導NK細胞、巨噬體等抗原提示細胞所致之細胞傷害活性。藉由利用2種細胞傷害活性，Catumaxomab進行腹腔內投予時，在惡性腹水症顯示高治療效果，於歐洲已獲認可(非專利文獻18)。又，已有人報告利用Catumaxomab投予而出現對於癌細胞反應之抗體之例，顯見會誘導獲得免疫(非專利文獻19)。由此結果，可期待具有T細胞所致之細胞傷害活性以及介由Fc γ R之NK細胞、巨噬體等細胞所致作用兩者之抗體(尤其稱為三官能(trifunctional)抗體)能有強抗腫瘤效果與獲得免疫誘導，故受人重視。

【0009】 但是trifunctional抗體即使在癌抗原不存在時仍會同時結合於CD3 ϵ 與Fc γ R，故即使於癌細胞不存在的環境仍會使表現CD3 ϵ 之T細胞與表現Fc γ R之細胞交聯，而大量產生各種細胞介素。由於如此的癌抗原非依存性的各種細胞介素的產生誘導，目前，trifunctional抗體之投予限於腹腔內(非專利文獻20)，由於嚴重的細胞介素風暴(storm)樣的副作用，極難進行全身投予。實際上，在對於非小細胞肺癌患者進行catumaxomab之全身投予所為之第一期臨床試驗，係以5 μ g/body的極低用量作為最大容許投予量，據報告更多用量的投予會引起各種嚴重的副作用(非專利文獻21)。

如上，習知技術之Bispecific抗體，因為第一抗原即癌抗原(EpCAM)與第二抗原即CD3 ϵ 之兩者的抗原會同時結合於Fc γ R，故在分子結構上不可能避免Fc γ R與第2抗原之CD3 ϵ 之同時結合所致的如此的副作用。

【0010】 另一方面，由於BiTE(bispecific T-cell engager)與catumaxomab不同，不具有對抗Fc γ 受體之結合部位，所以，不會發生癌抗原非依存地表現於T細胞與NK細胞或巨噬體等之受體交聯的情形。是以，顯示當投予catumaxomab時觀察到的癌抗原非依存性的細胞介素的誘導並不會發生。但是BiTE係欠缺Fc

區之低分子量型之改造抗體分子，故比起通常使用於當做治療用抗體的IgG型抗體，會存在對於患者投予之BiTE的血中半衰期顯著短的問題。實際上，對於活體投予之BiTE之血中半衰期據顯示為數小時左右(非專利文獻22、23)，於blinatumomab之臨床試驗係使用迷你泵浦持續進行靜脈內投予，而投予blinatumomab。如此的投予對於患者不僅是便利性顯著不佳的投予法，而且也存在由於機器故障等造成的醫療事故的風險，不能稱得上是理想的治療方法。

【0011】 近年來，藉由使用對於FcγR之結合活性減小的Fc區，已提供:維持BiTE帶有之強抗腫瘤活性、及不誘導癌抗原非依存性細胞介素風暴等這些在安全性上優良之性質，而且帶有長血中半衰期之新的多胜肽聯合體(專利文獻1)。

另一方面，使習知技術之雙專一性抗體表現時，係使2種H鏈與2種L鏈表現，故其組合據認為有10種組合。其中，有目的之結合專一性之組合為1種。故，為了取得目的之雙專一性抗體，須從10種抗體精製出1種目的抗體，效率極差且困難。

作為解決此問題之方法，已有人報告:藉由對於IgG之H鏈之CH3區施加胺基酸取代，而使異種H鏈之組合，例如使對抗抗原A之H鏈與對抗抗原B之H鏈優先分泌之方法(專利文獻2、3、4、5、6、7及非專利文獻24、25)。此等據報告有:利用 "knob；突起"與"hole；空隙"之物理性障礙之方法、利用電荷排斥之方法。

為了以更良好效率獲得目的分子，據報告:使用即便胺基酸序列相同，仍可結合於2種不同抗原之L鏈之方法(專利文獻8、9)。但是由於使用共通L鏈，對於抗原之親和性(affinity)可能大幅降低，難找出維持向抗原之親和性的共通L鏈。

[先前技術文獻]

[專利文獻]

【0012】 [專利文獻1] WO2012/073985

[專利文獻2] WO96/27011

[專利文獻3] WO2006/106905

[專利文獻4] WO2007/147901

[專利文獻5] WO2009/089004

[專利文獻6] WO2010/129304

[專利文獻7] WO2013/065708

[專利文獻8] WO98/050431

[專利文獻9] WO2006/109592

[非專利文獻]

【0013】 [非專利文獻1] Nat. Biotechnol. (2005) 23, 1073-1078

[非專利文獻2] Eur J Pharm Biopharm. (2005) 59 (3), 389-396

[非專利文獻3] Drug Des Devel Ther (2009) 3, 7-16

[非專利文獻4] Clin Cancer Res. (2010) 16 (1), 11-20

[非專利文獻5] Immunol. Lett. (2002) 82, 57-65

[非專利文獻6] Nat. Rev. Immunol. (2008) 8, 34-47

[非專利文獻7] Ann. Rev. Immunol. (1988). 6. 251-81

[非專利文獻8] J. Bio. Chem., (20001) 276, 16469-16477

[非專利文獻9] Nat. Biotech., (2011) 28, 502-10

[非專利文獻10] Endocr Relat Cancer (2006) 13, 45-51

[非專利文獻11] MAbs. (2012) Mar 1, 4(2)

[非專利文獻12] Nat. Rev. (2010) 10, 301-316

[非專利文獻13] Peds (2010), 23(4), 289-297

[非專利文獻14] J. Immunol. (1999) Aug 1, 163(3), 1246-52

[非專利文獻15] Nature (1985) 314 (6012), 628-31

[非專利文獻16] Int J Cancer (1988) 41 (4), 609-15.

[非專利文獻17] Proc Natl Acad Sci USA (1986) 83 (5), 1453-7

[非專利文獻18] Cancer Treat Rev. (2010) Oct 36(6), 458-67

[非專利文獻19] Future Oncol. (2012) Jan 8(1), 73-85

[非專利文獻20] Cancer Immunol Immunother. (2007) 56(9), 1397-406

[非專利文獻21] Cancer Immunol Immunother. (2007) 56 (10), 1637-44

[非專利文獻22] Cancer Immunol Immunother. (2006) 55(5), 503-14

[非專利文獻23] Cancer Immunol Immunother. (2009) 58(1), 95-109

[非專利文獻24] Protein Engineering. (1996) vol.9, p.617-621

[非專利文獻25] Nature Biotechnology. (1998) vol.16, p.677-681

【發明內容】

(發明欲解決之課題)

【0014】 本發明有鑑於上述情況，目的為提供:為使T細胞接近目標癌細胞，藉由T細胞所為之對於包括Glypican3表現細胞之目標癌組織之細胞傷害活性來治療癌且產生效率高之分子型即多專一性抗原結合分子、該抗原結合分子之製造方法、及含有該抗原結合分子作為有效成分之醫藥組合物。

(解決課題之方式)

【0015】 本案發明人等找到:一種新的多專一性抗原結合分子，在含有結合於Glypican3之抗體可變區之域與含有結合於T細胞受體複合體之抗體可變區之域找到能使針對兩抗原之親和性提高之共通L鏈，藉此成為產生效率高之分子型，而且維持著BiTE等T細胞重定向抗體帶有之強抗腫瘤活性與不誘導癌抗原非依存的細胞介素風暴等之安全性上之優良性質，且帶有長血中半衰期。再者，發現:具有共通L鏈之多專一性抗原結合分子能將Glypican3表現癌細胞作為目標而帶來細胞傷害。本案發明人等基於此發現，得知:本發明之多專一性抗原結合

分子會傷害包含Glypican3表現癌細胞之癌組織。

【0016】 亦即，本發明提供以下：

[1] 一種多專一性抗原結合分子，包含下列域且(1)之可變區與(2)之可變區所含之L鏈可變區為共通之胺基酸序列；

(1)含有具Glypican3結合活性之抗體可變區之域、

(2)含有具T細胞受體複合體結合活性之抗體可變區之域、及

(3)含有對於Fc γ 受體之結合活性降低之Fc區之域；

細胞傷害活性比起Glypican3結合域由序列編號47及48構成且T細胞受體複合體結合域由序列編號49及50構成之雙專一性抗體(GPC3_ERY22_rCE115)為同等或更高。

[2] 如[1]之多專一性抗原結合分子，其中，細胞傷害活性為T細胞依存的細胞傷害活性。

[3] 如[1]或[2]之多專一性抗原結合分子，其中，T細胞受體複合體結合活性為對於T細胞受體之結合活性。

[4] 如[1]至[3]中任一項之多專一性抗原結合分子，其中，T細胞受體複合體結合活性為對於CD3 ϵ 鏈之結合活性。

[5] 如[1]至[4]中任一項之多專一性抗原結合分子，其中，[1]記載之(1)之抗體可變區係包括選自下列(a1)~(a5)中任一H鏈CDR1、CDR2及CDR3之組合之抗體可變區、或與其在機能上為同等之抗體可變區；

(a1) CDR1、CDR2及CDR3和序列編號：40所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(a2) CDR1、CDR2及CDR3和序列編號：197所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(a3) CDR1、CDR2及CDR3和序列編號：206所含之CDR1、CDR2及CDR3

區之胺基酸序列相同

(a4) CDR1、CDR2及CDR3和序列編號：211所含之CDR1、CDR2及CDR3

區之胺基酸序列相同

(a5) CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3

區之胺基酸序列相同。

[6] 如[1]至[4]中任一項之多專一性抗原結合分子，其中，[1]記載之(2)之抗體可變區係包括選自下列(b1)~(b15)中之任一H鏈CDR1、CDR2及CDR3之胺基酸序列之組合之抗體可變區、或與其在機能上為同等之抗體可變區；

(b1) CDR1、CDR2及CDR3和序列編號：52所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b2) CDR1、CDR2及CDR3和序列編號：103所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b3) CDR1、CDR2及CDR3和序列編號：122所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b4) CDR1、CDR2及CDR3和序列編號：128所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b5) CDR1、CDR2及CDR3和序列編號：129所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b6) CDR1、CDR2及CDR3和序列編號：132所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b7) CDR1、CDR2及CDR3和序列編號：142所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b8) CDR1、CDR2及CDR3和序列編號：144所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b9) CDR1、CDR2及CDR3和序列編號：164所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b10) CDR1、CDR2及CDR3和序列編號：168所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b11) CDR1、CDR2及CDR3和序列編號：421所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b12) CDR1、CDR2及CDR3和序列編號：424所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b13) CDR1、CDR2及CDR3和序列編號：426所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b14) CDR1、CDR2及CDR3和序列編號：429所含之CDR1、CDR2及CDR3區之胺基酸序列相同

(b15) CDR1、CDR2及CDR3和序列編號：430所含之CDR1、CDR2及CDR3區之胺基酸序列相同。

[7] 如[1]至[4]中任一項之多專一性抗原結合分子，其中，[1]記載之(1)及(2)之抗體可變區係包括選自下列(c1)~(c19)中之任一H鏈 CDR1、CDR2及CDR3之組合之抗體可變區、或與其在機能上為同等之抗體可變區；

(c1) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：40所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：52所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(c2) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：40所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：421所含之CDR1、CDR2及CDR3區之

胺基酸序列相同;

(c3) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：40所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：426所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c4) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：40所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：429所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c5) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：40所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：430所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c6) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：197所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：128所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c7) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：206所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：142所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c8) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：206所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：144所含之CDR1、CDR2及CDR3區之

胺基酸序列相同;

(c9) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:206所含之CDR1、CDR2及CDR3區之胺基酸序列相同,[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:164所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c10) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:206所含之CDR1、CDR2及CDR3區之胺基酸序列相同,[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:168所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c11) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:211所含之CDR1、CDR2及CDR3區之胺基酸序列相同,[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:142所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c12) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:211所含之CDR1、CDR2及CDR3區之胺基酸序列相同,[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:144所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c13) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:211所含之CDR1、CDR2及CDR3區之胺基酸序列相同,[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:164所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c14) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:211所含之CDR1、CDR2及CDR3區之胺基酸序列相同,[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:168所含之CDR1、CDR2及CDR3

區之胺基酸序列相同;

(c15) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：103所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c16) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：122所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c17) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：129所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c18) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：132所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(c19) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：424所含之CDR1、CDR2及CDR3區之胺基酸序列相同。

[8] 如[5]至[7]中任一項之多專一性抗原結合分子，其中， CDR1、CDR2及CDR3係依據Kabat編號之CDR1、CDR2及CDR3區。

[9] 如[1]至[4]中任一項之多專一性抗原結合分子，其中，[1]記載之(1)之抗

體可變區係包括選自下列(a1)~(a5)中之任一H鏈可變區之抗體可變區、或與其在機能上為同等之抗體可變區;

- (a1) H鏈可變區為序列編號：40之胺基酸序列
- (a2) H鏈可變區為序列編號：197之胺基酸序列
- (a3) H鏈可變區為序列編號：206之胺基酸序列
- (a4) H鏈可變區為序列編號：211之胺基酸序列
- (a5) H鏈可變區為序列編號：215之胺基酸序列。

[10] 如[1]至[4]中任一項之多專一性抗原結合分子，其中，[1]記載之(2)之抗體可變區係包括選自下列(b1)~(b15)中之任一H鏈可變區之抗體可變區、或與其在機能上為同等之抗體可變區;

- (b1) H鏈可變區為序列編號：52之胺基酸序列
- (b2) H鏈可變區為序列編號：103之胺基酸序列
- (b3) H鏈可變區為序列編號：122之胺基酸序列
- (b4) H鏈可變區為序列編號：128之胺基酸序列
- (b5) H鏈可變區為序列編號：129之胺基酸序列
- (b6) H鏈可變區為序列編號：132之胺基酸序列
- (b7) H鏈可變區為序列編號：142之胺基酸序列
- (b8) H鏈可變區為序列編號：144之胺基酸序列
- (b9) H鏈可變區為序列編號：164之胺基酸序列
- (b10) H鏈可變區為序列編號：168之胺基酸序列
- (b11) H鏈可變區為序列編號：421之胺基酸序列
- (b12) H鏈可變區為序列編號：424之胺基酸序列
- (b13) H鏈可變區為序列編號：426之胺基酸序列
- (b14) H鏈可變區為序列編號：429之胺基酸序列

(b15) H鏈可變區為序列編號：430之胺基酸序列。

[11] 如[1]至[4]中任一項之多專一性抗原結合分子，其中，[1]記載之(1)及(2)之抗體可變區係包括選自下列(c1)~(c19)中之任一H鏈可變區之組合之抗體可變區、或與其在機能上為同等之抗體可變區；

(c1) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：40之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：52之胺基酸序列；

(c2) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：40之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：421之胺基酸序列；

(c3) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：40之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：426之胺基酸序列；

(c4) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：40之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：429之胺基酸序列；

(c5) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：40之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：430之胺基酸序列；

(c6) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：197之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：128之胺基酸序列；

(c7) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：206之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：142之胺基酸序列；

(c8) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：206之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：144之胺基酸序列；

(c9) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：206之胺基酸

序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：164之胺基酸序列；

(c10) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：206之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：168之胺基酸序列；

(c11) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：211之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：142之胺基酸序列；

(c12) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：211之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：144之胺基酸序列；

(c13) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：211之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：164之胺基酸序列；

(c14) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：211之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：168之胺基酸序列；

(c15) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：215之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：103之胺基酸序列；

(c16) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：215之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：122之胺基酸序列；

(c17) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：215之胺基酸

序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：129之胺基酸序列；

(c18) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：215之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：132之胺基酸序列；

(c19) [1]記載之(1)之抗體可變區所含之H鏈可變區為序列編號：215之胺基酸序列，[1]記載之(2)之抗體可變區所含之H鏈可變區為序列編號：424之胺基酸序列。

[12] 如[1]至[11]中任一項之記載之多專一性抗原結合分子，其中，[1]記載之共通L鏈係包括選自下列(d1)~(d11)中之任一CDR1、CDR2及CDR3之組合之共通L鏈、或與其在機能上為同等之共通L鏈；

(d1) CDR1、CDR2及CDR3和序列編號：53所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(d2) CDR1、CDR2及CDR3和序列編號：223所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(d3) CDR1、CDR2及CDR3和序列編號：299所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(d4) CDR1、CDR2及CDR3和序列編號：301所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(d5) CDR1、CDR2及CDR3和序列編號：302所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(d6) CDR1、CDR2及CDR3和序列編號：304所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(d7) CDR1、CDR2及CDR3和序列編號：306所含之CDR1、CDR2及CDR3

區之胺基酸序列相同;

(d8) CDR1、CDR2及CDR3和序列編號：307所含之CDR1、CDR2及CDR3

區之胺基酸序列相同;

(d9) CDR1、CDR2及CDR3和序列編號：309所含之CDR1、CDR2及CDR3

區之胺基酸序列相同;

(d10) CDR1、CDR2及CDR3和序列編號：310所含之CDR1、CDR2及CDR3

區之胺基酸序列相同;

(d11) CDR1、CDR2及CDR3和序列編號：319所含之CDR1、CDR2及CDR3

區之胺基酸序列相同。

[13] 如[1]至[11]中任一項之多專一性抗原結合分子，其中，[1]記載之L鏈可變區係選自下列(d1)~(d11)中之任一L鏈胺基酸序列之可變區;

(d1) 由序列編號：53之胺基酸序列構成之L鏈

(d2) 由序列編號：223之胺基酸序列構成之L鏈

(d3) 由序列編號：299之胺基酸序列構成之L鏈

(d4) 由序列編號：301之胺基酸序列構成之L鏈

(d5) 由序列編號：302之胺基酸序列構成之L鏈

(d6) 由序列編號：304之胺基酸序列構成之L鏈

(d7) 由序列編號：306之胺基酸序列構成之L鏈

(d8) 由序列編號：307之胺基酸序列構成之L鏈

(d9) 由序列編號：309之胺基酸序列構成之L鏈

(d10) 由序列編號：310之胺基酸序列構成之L鏈

(d11) 由序列編號：319之胺基酸序列構成之L鏈。

[14] 如[1]至[4]中任一項之多專一性抗原結合分子，其中，[1]記載之(1)及(2)之抗體可變區、及共通L鏈可變區係包括選自下列(e1)~(e25)中之任一H鏈

CDR1、CDR2及CDR3、及L鏈CDR1、CDR2及CDR3之組合之抗體可變區、或與其在機能上為同等之抗體可變區;

(e1) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:197所含之CDR1、CDR2及CDR3區之胺基酸序列相同,[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:128所含之CDR1、CDR2及CDR3區之胺基酸序列相同,共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:53所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(e2) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:197所含之CDR1、CDR2及CDR3區之胺基酸序列相同,[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:128所含之CDR1、CDR2及CDR3區之胺基酸序列相同,共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:299所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(e3) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:197所含之CDR1、CDR2及CDR3區之胺基酸序列相同,[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:128所含之CDR1、CDR2及CDR3區之胺基酸序列相同,共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:310所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(e4) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:197所含之CDR1、CDR2及CDR3區之胺基酸序列相同,[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:128所含之CDR1、CDR2及CDR3區之胺基酸序列相同,共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:319所含之CDR1、CDR2及CDR3區之胺基酸序列相同;

(e5) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號:206所含之CDR1、CDR2及CDR3區之胺基酸序列相同,[1]記載之(2)之抗體可變區

所含之CDR1、CDR2及CDR3和序列編號：142所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：223所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e6) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：206所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：144所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：223所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e7) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：206所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：164所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：223所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e8) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：206所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：168所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：223所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e9) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：211所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：142所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：223所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e10) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：

第 20 頁，共 122 頁(發明說明書)

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211所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：142所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：299所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e11) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：211所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：144所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：223所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e12) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：211所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：164所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：223所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e13) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：211所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：168所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：223所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e14) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：103所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：53所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e15) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：103所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：299所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e16) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：103所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：301所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e17) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：103所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：302所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e18) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：103所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：304所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e19) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：103所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序

列編號：306所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e20) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：103所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：307所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e21) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：103所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：309所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e22) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：122所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：53所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e23) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：129所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：53所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e24) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：132所含之CDR1、CDR2及CDR3

區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：53所含之CDR1、CDR2及CDR3區之胺基酸序列相同；

(e25) [1]記載之(1)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：215所含之CDR1、CDR2及CDR3區之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：424所含之CDR1、CDR2及CDR3區之胺基酸序列相同，共通L鏈之抗體可變區所含之CDR1、CDR2及CDR3和序列編號：53所含之CDR1、CDR2及CDR3區之胺基酸序列相同。

[15] 如[1]至[4]中任一項之多專一性抗原結合分子，其中，[1]記載之(1)及(2)之抗體可變區、及共通L鏈可變區係包括選自下列(f1)~(f26)中之任一可變區之組合之抗體可變區、或與其在機能上為同等之抗體可變區；

(f1) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：197之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：128之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：53所含之可變區之胺基酸序列相同；

(f2) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：197之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：128之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：299所含之可變區之胺基酸序列相同；

(f3) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：197之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：128之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：310所含之可變區之胺基酸序列相同；

(f4) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：197之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：128之胺基

酸序列相同，共通L鏈之抗體可變區和序列編號：319所含之可變區之胺基酸序列相同;

(f5) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：206之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：142之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：223所含之可變區之胺基酸序列相同;

(f6) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：206之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：144之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：223所含之可變區之胺基酸序列相同;

(f7) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：206之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：164之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：223所含之可變區之胺基酸序列相同;

(f8) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：206之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：168之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：223所含之可變區之胺基酸序列相同;

(f9) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：211之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：142之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：223所含之可變區之胺基酸序列相同;

(f10) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：211之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：142之胺基

酸序列相同，共通L鏈之抗體可變區和序列編號：299所含之可變區之胺基酸序列相同;

(f11) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：211之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：144之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：223所含之可變區之胺基酸序列相同;

(f12) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：211之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：164之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：223所含之可變區之胺基酸序列相同;

(f13) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：211之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：168之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：223所含之可變區之胺基酸序列相同;

(f14) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：215之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：103之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：53所含之可變區之胺基酸序列相同;

(f15) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：215之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：103之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：299所含之可變區之胺基酸序列相同;

(f16) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：215之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：103之胺基

酸序列相同，共通L鏈之抗體可變區和序列編號：301所含之可變區之胺基酸序列相同;

(f17) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：215之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：103之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：302所含之可變區之胺基酸序列相同;

(f18) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：215之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：103之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：304所含之可變區之胺基酸序列相同;

(f19) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：215之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：103之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：306所含之可變區之胺基酸序列相同;

(f20) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：215之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：103之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：307所含之可變區之胺基酸序列相同;

(f21) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：215之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：103之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：309所含之可變區之胺基酸序列相同;

(f22) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：215之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：122之胺基

酸序列相同，共通L鏈之抗體可變區和序列編號：53所含之可變區之胺基酸序列相同；

(f23) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：215之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：129之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：53所含之可變區之胺基酸序列相同；

(f24) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：215之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：132之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：53所含之可變區之胺基酸序列相同；

(f25) [1]記載之(1)之抗體可變區所含之H鏈可變區和序列編號：215之胺基酸序列相同，[1]記載之(2)之抗體可變區所含之H鏈可變區和序列編號：424之胺基酸序列相同，共通L鏈之抗體可變區和序列編號：53所含之可變區之胺基酸序列相同；

(f26) 結合在和(f1)~(f25)中任一多專一性抗原結合分子所結合之Glypican3及T細胞受體複合體上之抗原決定基分別為重複之抗原決定基，且有共通L鏈。

[16] 如[1]至[15]中任一項之多專一性抗原結合分子，其中，[1]記載之(3)之Fc區為構成序列編號：23~26(IgG1~IgG4)記載之Fc區之胺基酸中任一胺基酸已變異之Fc區。

[17] 如[16]之多專一性抗原結合分子，其中，[1]記載之(3)之Fc區係選自依EU編號指定之下列胺基酸中之至少1個胺基酸已變異之Fc區；

220位、226位、229位、231位、232位、233位、234位、235位、236位、237位、238位、239位、240位、264位、265位、266位、267位、269位、270位、295位、296位、297位、298位、299位、300位、325位、327位、328位、329位、330

位、331位、332位。

[18] 如[16]之多專一性抗原結合分子，其中，[1]記載之(3)之Fc區係具有選自依EU編號指定之下列胺基酸中之至少1個胺基酸之Fc區；

234位之胺基酸為Arg、235位之胺基酸為Ala或Arg、239位之胺基酸為Lys、297位之胺基酸為Ala。

[19] 如[16]至[18]中任一項之多專一性抗原結合分子，其中，[1]記載之(3)之Fc區更具有為了促進形成由異二聚體構成之Fc區之胺基酸變異。

[20] 如[19]之多專一性抗原結合分子，其中，由異二聚體構成之Fc區為下列(g1)或(g2)之胺基酸序列之組合；

(g1)和具有序列編號：57之胺基酸序列之不變區之Fc區為相同胺基酸序列與和具有序列編號：58之胺基酸序列之不變區之Fc區為相同胺基酸序列之組合

(g2) 和具有序列編號：60或62之胺基酸序列之不變區之Fc區為相同胺基酸序列與和具有序列編號：61之胺基酸序列之不變區之Fc區為相同胺基酸序列之組合。

[21] 如[1]至[20]中任一項之多專一性抗原結合分子，其中，多專一性抗原結合分子為雙專一性抗體。

[22] 一種雙專一性抗體，係如以下(h1)~(h25)中任一者所記載：

(h1) 對於Glypican3有結合活性，對於由具有序列編號215之胺基酸序列之抗體H鏈可變區與具有序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，具有由具序列編號424之胺基酸序列之抗體H鏈可變區與具有序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號53之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h2) 對於Glypican3有結合活性，對於由具有序列編號215之胺基酸序列之抗體H鏈可變區與具有序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞

胞受體複合體有結合活性，並具有由具序列編號103之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號53之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h3) 對於Glypican3有結合活性，對於由具有序列編號215之胺基酸序列之抗體H鏈可變區與具有序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號103之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號299之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h4) 對於Glypican3有結合活性，對於由具有序列編號215之胺基酸序列之抗體H鏈可變區與具有序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號103之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號301之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h5) 對於Glypican3有結合活性，對於由具有序列編號215之胺基酸序列之抗體H鏈可變區與具有序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號103之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號302之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h6) 對於Glypican3有結合活性，對於由具有序列編號215之胺基酸序列之抗體H鏈可變區與具有序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號103之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號304之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h7) 對於Glypican3有結合活性，對於由具有序列編號215之胺基酸序列之抗

體H鏈可變區與具有序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具由具序列編號103之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號306之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h8) 對於Glypican3有結合活性，對於由具有序列編號215之胺基酸序列之抗體H鏈可變區與具有序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號103之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號307之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h9) 對於Glypican3有結合活性，對於由具有序列編號215之胺基酸序列之抗體H鏈可變區與具有序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號103之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具有序列編號309之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h10) 對於Glypican3有結合活性，對於由具有序列編號215之胺基酸序列之抗體H鏈可變區與具有序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號122之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈及具序列編號53之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h11) 對於Glypican3有結合活性，對於由具有序列編號215之胺基酸序列之抗體H鏈可變區與具有序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號129之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號53之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h12) 對於Glypican3有結合活性，對於由具有序列編號215之胺基酸序列之抗體H鏈可變區與具有序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號132之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號53之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h13) 對於Glypican3有結合活性，對於由具序列編號197之胺基酸序列之抗體H鏈可變區與具序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號128之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號299之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h14) 對於Glypican3有結合活性，對於由具序列編號197之胺基酸序列之抗體H鏈可變區與具序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號128之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號310之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h15) 對於Glypican3有結合活性，對於由具序列編號197之胺基酸序列之抗體H鏈可變區與具序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號128之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號319之胺基酸序列之抗體之共通L鏈之雙專一性抗體；

(h16) 對於Glypican3有結合活性，對於由具序列編號197之胺基酸序列之抗體H鏈可變區與具序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號128之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號53

之胺基酸序列之抗體之共通L鏈之雙專一性抗體;

(h17) 對於Glypican3有結合活性，對於由具序列編號211之胺基酸序列之抗體H鏈可變區與具序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號142之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號299之胺基酸序列之抗體之共通L鏈之雙專一性抗體;

(h18) 對於Glypican3有結合活性，對於由具序列編號211之胺基酸序列之抗體H鏈可變區與具序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號142之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號223之胺基酸序列之抗體之共通L鏈之雙專一性抗體;

(h19) 對於Glypican3有結合活性，對於由具序列編號211之胺基酸序列之抗體H鏈可變區與具序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號144之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具序列編號223之胺基酸序列之抗體之共通L鏈之雙專一性抗體;

(h20) 對於Glypican3有結合活性，對於由具序列編號206之胺基酸序列之抗體H鏈可變區與具序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號144之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具有序列編號223之胺基酸序列之抗體之共通L鏈之雙專一性抗體;

(h21) 對於Glypican3有結合活性，對於由具序列編號206之胺基酸序列之抗體H鏈可變區與具序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號142之胺基酸序列之抗體H鏈可變

區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具有序列編號223之胺基酸序列之抗體之共通L鏈之雙專一性抗體;

(h22) 對於Glypican3有結合活性，對於由具序列編號206之胺基酸序列之抗體H鏈可變區與具序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號164之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具有序列編號223之胺基酸序列之抗體之共通L鏈之雙專一性抗體;

(h23) 對於Glypican3有結合活性，對於由具序列編號206之胺基酸序列之抗體H鏈可變區與具序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具由由具序列編號168之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具有序列編號223之胺基酸序列之抗體之共通L鏈之雙專一性抗體;

(h24) 對於Glypican3有結合活性，對於由具序列編號211之胺基酸序列之抗體H鏈可變區與具序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具由具序列編號164之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具有序列編號223之胺基酸序列之抗體之共通L鏈之雙專一性抗體;

(h25) 對於Glypican3有結合活性，對於由具序列編號211之胺基酸序列之抗體H鏈可變區與具序列編號61之胺基酸序列之不變區構成之抗體H鏈、及T細胞受體複合體有結合活性，並具有由具序列編號168之胺基酸序列之抗體H鏈可變區與具序列編號60或62之胺基酸序列之不變區構成之抗體H鏈、及具有序列編號223之胺基酸序列之抗體之共通L鏈之雙專一性抗體。

[23] 一種核酸，編碼為如[1]至[20]中任一項之多專一性抗原結合分子、或[21]或[22]之雙專一性抗體。

[24] 一種載體，已導入如[23]之核酸。

[25] 一種細胞，包含如[23]之核酸、或如[24]之載體。

[26] 一種方法，係藉由培養如[25]之細胞，以製造如[1]至[20]中任一項多專一性抗原結合分子、或如[21]或[22]之雙專一性抗體。

[27] 一種多專一性抗原結合分子、或雙專一性抗體，係利用如[26]之方法製得。

[28] 一種醫藥組合物，包含如[1]至[20]中任一項之多專一性抗原結合分子、或如[21]或[22]之雙專一性抗體、及藥學上可容許之擔體。

[29] 如[28]之醫藥組合物，其誘導細胞傷害。

[30] 如[29]之醫藥組合物，其中，細胞傷害係T細胞依存的細胞傷害。

[31] 如[28]之醫藥組合物，其用在對於必要患者投予如[1]至[20]中任一項之多專一性抗原結合分子、或如[21]或[22]之雙專一性抗體。

【0017】 本發明係關於本發明之方法使用之套組，含有本發明之多專一性抗原結合分子或依本發明之製造方法製得之多專一性抗原結合分子。又，本發明係關於本發明之多專一性抗原結合分子或依本發明之製造方法製得之多專一性抗原結合分子之用途，使用在製造活化細胞傷害活性之醫藥組合物。又，本發明係關於用以使用在本發明之方法之本發明之多專一性抗原結合分子或依本發明之製造方法製得之多專一性抗原結合分子。在此，多專一性抗原結合分子包括本發明之雙專一性抗體。

【0018】 又，本發明係關於一種多專一性抗原結合分子，
含有下列域；

(1)含有具Glypican3結合活性之抗體可變區之域、及、

(2)含有具T細胞受體複合體結合活性之抗體可變區之域；

且(1)之可變區與(2)之可變區所含之L鏈可變區為共通之胺基酸序列。又，

本發明係關於(1)之域，亦即，該多專一性抗原結合分子所含之包含具Glypican3結合活性之抗體之重鏈及/或輕鏈之可變區之域。又，本發明係關於(2)之域，亦即，該多專一性抗原結合分子所含之含有具T細胞受體複合體結合活性之抗體可變區之域。(1)及(2)之域之詳情可為上述[1]~[22]記載者。該多專一性抗原結合分子也可為雙專一性抗體。又，該多專一性抗原結合分子也可更包括含有Fc區之域，該Fc區針對Fc γ 受體之結合活性也可降低。含有Fc區之域之詳情也可為例如上所述[1]~[22]記載者。又，本發明係關於：編碼為該多專一性抗原結合分子或該域之核酸、已導入該核酸之載體、包含該核酸或該載體之細胞、藉由培養該細胞而製造該多專一性抗原結合分子之方法、利用該方法製得之多專一性抗原結合分子或包含對於Glypican3或T細胞受體複合體有結合活性之抗體可變區之域。又，本發明係關於包含該多專一性抗原結合分子及藥學上可容許之擔體之醫藥組合物。該醫藥組合物可為誘導細胞傷患者，該細胞傷害可為T細胞依存的細胞傷害，該多專一性抗原結合分子可為對於必要之患者投予者。

又，本發明提供：一種多專一性抗原結合分子，其結合於和上述[14]之(e1)~(e25)中任一項之多專一性抗原結合分子所結合之Glypican3及T細胞受體複合體上之抗原決定基分別重複及/或競爭之抗原決定基，並提供一種多專一性抗原結合分子，其結合於和上述[15]之(f1)~(f25)中之任一多專一性抗原結合分子所結合之Glypican3及T細胞受體複合體上之抗原決定基分別重複及/或競爭之抗原決定基。

又，上述[20](g1)及(g2)中，2個Fc區之中，可為：前者之Fc區包括在對於Glypican3有結合活性之抗體H鏈，後者之Fc區包括在對於T細胞受體複合體有結合活性之抗體H鏈，也可：前者之Fc區包括在對於T細胞受體複合體有結合活性之抗體H鏈，後者之Fc區包括在對於Glypican3有結合活性之抗體H鏈。

(發明之效果)

【0019】 依本發明，可提供一種新的多專一性抗原結合分子，其為產生效率高之分子型，且維持BiTE帶有之強抗腫瘤活性、及不誘導癌抗原非依存的細胞介素風暴等之安全性上之優良性質，且有長血中半衰期。含有本發明之多專一性抗原結合分子作為有效成分之將細胞傷害活性予以活化之醫藥組合物，能將含有Glypican3表現癌細胞之癌組織作為目標而帶來細胞傷害，能治療或預防各種癌。對於患者而言，可提供安全性高而且身體的負擔少，便利性也高之理想之治療。

【圖式簡單說明】

【0020】

- 第1圖顯示:a： ERY22之示意圖、b： ERY27之示意圖。
- 第2圖顯示將NCI-H446作為目標細胞時，GPC3_ERY22_rCE115與GPC3_ERY27_hCE115之細胞傷害活性。黑菱(◆)代表GPC3_ERY22_rCE115，黑三角(▲)代表GPC3_ERY27_hCE115之細胞傷害活性。
- 第3圖顯示將PC-10作為目標細胞時，GPC3_ERY22_rCE115與GPC3_ERY27_hCE115之細胞傷害活性。黑菱(◆)代表GPC3_ERY22_rCE115，黑三角(▲)代表GPC3_ERY27_hCE115之細胞傷害活性。
- 第4圖顯示將NCI-H446作為目標細胞時，最適化抗體之細胞傷害活性。
- 第5圖顯示將NCI-H446作為目標細胞時，最適化抗體之細胞傷害活性。
- 第6圖顯示將NCI-H446作為目標細胞時，最適化抗體之細胞傷害活性。
- 第7圖顯示將NCI-H446作為目標細胞時，最適化抗體之細胞傷害活性。
- 第8圖顯示將NCI-H446作為目標細胞時，最適化抗體之細胞傷害活性。
- 第9圖顯示將NCI-H446作為目標細胞時，最適化抗體之細胞傷害活性。
- 第10圖顯示將PC-10作為目標細胞時，最適化抗體之活體內(in vivo)抗腫瘤效果。

第11圖顯示將NCI-H446作為目標細胞時，最適化抗體之活體內(in vivo)抗腫瘤效果。

第12圖顯示構成IgG1、IgG2、IgG3及IgG4之Fc區之胺基酸殘基與kabat之EU編號(本說明書也稱為EU INDEX)之關係圖。

第13-1圖顯示重鏈可變區序列與Kabat等各種編號。

第13-2圖顯示重鏈可變區序列與Kabat等各種編號。

第14圖顯示輕鏈可變區序列與Kabat等各種編號。

【實施方式】

【0021】 以下定義係為了容易了解本說明書說明之本發明而提供。

【0022】 抗體

本說明書中，抗體係指天然者或部分或完全合成所製造之免疫球蛋白。抗體可從其天然存在之血漿或血清等天然資源或產生抗體之融合瘤細胞之培養上清液單離，或可使用基因重組等方法部分或完全合成。抗體例如免疫球蛋白之同種型(isotype)及此等同種型之次類(subclass)為較佳例。人類免疫球蛋白已知有IgG1、IgG2、IgG3、IgG4、IgA1、IgA2、IgD、IgE、IgM9種類型(同種型(isotype))。本發明之抗體在該等同種型之中，可含IgG1、IgG2、IgG3、IgG4。

【0023】 製作具有所望結合活性之抗體之方法對於該技術領域之人士為公知。以下列舉製作和屬於GPI固定子(anchor)型受體家族之Glypican3(以下也稱為GPC3) (Int J Cancer. (2003) 103 (4), 455-65) 結合之抗體(抗GPC3抗體)之方法。和T細胞受體複合體結合的抗體也可依據下列例示適當製作。

【0024】 抗GPC3抗體可使用公知方法以多株或單株抗體之形式取得。抗GPC3抗體，宜製作哺乳動物來源的單株抗體。哺乳動物來源的單株抗體，包含由融合瘤產生者，及以基因工程的方法以含抗體基因之表現載體轉形而得之寄

主細胞所產生者等。

【0025】 單株抗體產生融合瘤，可使用公知技術依例如以下方式製作。亦即，使用GPC3蛋白質當做感作抗原，依通常之免疫方法將哺乳動物免疫。將獲得之免疫細胞以通常的細胞融合法與公知之母細胞融合。其次依照通常之篩選法，篩選單株抗體產生細胞，可選擇產生抗GPC3抗體之融合瘤。

【0026】 具體而言，單株抗體之製作係依例如以下所示方式實行。首先，藉由表現在RefSeq註冊編號NM_001164617.1 (序列編號：1)揭示其核苷酸序列之GPC3基因，取得當做抗體取得之感作抗原使用的以RefSeq註冊編號NP_001158089.1(序列編號：2)表示的GPC3蛋白質。亦即，藉由將編碼為GPC3之基因序列插入公知之表現載體，而將適當的寄主細胞轉形。從該寄主細胞中或培養上清液中以公知方法精製所望之人類GPC3蛋白質。為了從培養上清液中取得可溶型之GPC3，例如可使用表現序列編號：2表示之GPC3多胜肽序列當中，為了使GPC3留在細胞膜上使用之相當於GPI固定子序列之構成疏水性區之564-580胺基酸係缺失的蛋白質，以代替表現以序列編號：2表示之GPC3蛋白質。又，經精製的天然GPC3蛋白質也同樣可當做感作抗原使用。

【0027】 對於哺乳動物免疫時使用之感作抗原，可使用該精製GPC3蛋白質。GPC3之部分胜肽也可當做感作抗原使用。於此時，該部分胜肽可利用人類GPC3之胺基酸序列以化學合成取得。又，也可將GPC3基因之一部分納入表現載體使表現而取得。再者，使用蛋白質分解酵素將GPC3蛋白質分解也可取得，但是當做部分胜肽使用之GPC3胜肽之區域及大小不限於特別之態樣。較佳區域可從序列編號：2之胺基酸序列當中相當於524~563號胺基酸之胺基酸序列選擇任意序列，更佳為從相當於537~563號之胺基酸之胺基酸序列選擇任意序列。又，較佳為從序列編號：2之胺基酸序列之不包括相當於550~663號胺基酸之胺基酸序列之區域之胺基酸序列選擇任意序列。較佳為從序列編號：2之胺基酸序列中

相當於544~553號之胺基酸序列選擇任意序列，更佳為從相當於546~551號之胺基酸序列選擇任意序列。構成當做感作抗原之胜肽的胺基酸的數目至少為5以上，例如6以上或7以上較佳。更具體而言，可將8~50、較佳為10~30個殘基之胜肽當做感作抗原使用。

【0028】 又，將GPC3蛋白質之所望之部分多胜肽或胜肽與不同的多胜肽融合成的融合蛋白質可利用為感作抗原。為了製造當做感作抗原使用之融合蛋白質，例如可適當利用抗體之Fc片段或胜肽標籤(tag)等。表現融合蛋白質之載體，可藉由將編碼為所望之二種或更多種多胜肽片段之基因於框架內(inframe)融合，並將該融合基因以前述方式插入表現載體而製作。融合蛋白質之製作方法記載於Molecular Cloning 2nd ed. (Sambrook,J et al., Molecular Cloning 2nd ed., 9.47-9.58 (1989)Cold Spring Harbor Lab. press)。可當做感作抗原使用之GPC3之取得方法及使用其之免疫方法，在WO2003/000883、WO2004/022754、WO2006/006693等亦有具體記載。

【0029】 以該感作抗原免疫之哺乳動物不限於特定動物，宜考慮與細胞融合使用之母細胞之間的適合性選擇。一般的嚙齒類動物，例如小鼠、大鼠、倉鼠、或兔、猴等較佳。

【0030】 依公知方法將上述動物以感作抗原免疫。例如就一般方法而言，係藉由將感作抗原對於哺乳動物之腹腔內或皮下注射而投予以實施免疫。具體而言，將以PBS(Phosphate- Buffered Saline)或生理食鹽水等以適當稀釋倍率稀釋過的感作抗原，視所望與通常的佐劑例如佛洛依德完全佐劑混合並乳化後，將該感作抗原對於哺乳動物每4至21日投予數次。又，感作抗原免疫時可以使用適當擔體。尤其使用小分子量之部分胜肽當做感作抗原時，有時以結合有白蛋白、血藍蛋白(keyhole lympet hemocyanin)等擔體蛋白質的該感作抗原胜肽進行免疫為理想。

【0031】 又，產生所望抗體之融合瘤可使用DNA免疫並依以下方式製作。DNA免疫，係指在免疫動物中投予以能表現編碼為抗原蛋白質之基因的態樣構建之載體DNA的該免疫動物中，藉由感作抗原在該免疫動物之活體內表現，能提供免疫刺激之免疫方法。比起對於免疫動物投予蛋白質抗原之一般免疫方法，DNA免疫可期待如下的優越性。

一可維持如GPC3之膜蛋白質之構造而提供免疫刺激

一無需精製免疫抗原

【0032】 為了以DNA免疫獲得本發明之單株抗體，首先將表現GPC3蛋白質之DNA對於免疫動物投予。編碼為GPC3之DNA可利用PCR等公知方法合成。將獲得之DNA插入適當表現載體並對於免疫動物投予。表現載體例如可以理想地利用pcDNA3.1等市售表現載體。將載體對於活體投予之方法，可使用一般使用之方法。例如，可藉由將吸附有表現載體之金粒子以基因槍導入免疫動物個體之細胞內而實施DNA免疫。再者，認識GPC3之抗體之製作也可使用國際公開WO2003/104453記載之方法製作。

【0033】 以此方式將哺乳動物免疫，確認血清中與GPC3結合之抗體力價上升後，從哺乳動物採取免疫細胞以供細胞融合。較佳之免疫細胞尤佳為使用脾細胞。

【0034】 與前述免疫細胞融合之細胞，可使用哺乳動物之骨髓瘤細胞。骨髓瘤細胞宜具有為了篩選的適當選擇標記。選擇標記，係指能於特定培養條件下生存之(或無法生存)之形質。選擇標記中，次黃嘌呤-鳥嘌呤磷酸核糖轉移酶(hypoxanthine-guanine phosphoribosyl transferase)缺損(以下簡稱為HGPRT缺損)、或胸腺嘧啶激酶缺損(以下簡稱為TK缺損)等為公知。具HGPRT或TK缺損之細胞，具有次黃嘌呤-胺基喋呤-胸腺嘧啶感受性(以下簡稱為HAT感受性)。HAT感受性之細胞在HAT選擇培養基中無法合成DNA會死滅，但若與正常細胞

融合則會利用正常細胞之補救合成路徑(salvage pathway)繼續合成DNA，故能在HAT選擇培養基中增殖。

【0035】 HGPRT 缺損或 TK 缺損之細胞，各可以含 6 硫鳥嘌呤(thioguanine)、8 氮雜鳥嘌呤(以下簡稱為 8AG)、或 5' 溴去氧尿嘧啶之培養基選擇。於 DNA 中納入該等嘧啶類似物之正常細胞會死滅。另一方面，未納入該等嘧啶類似物之該等酵素缺損之細胞，能在選擇培養基中生存。其他稱為 G418 耐受性之選擇標記，係利用新黴素耐受性基因提供對於 2-去氧鏈黴胺(streptomycin)系抗生物質(慶大黴素(gentamycin 類似體)之耐受性。對細胞融合為理想的各種骨髓瘤細胞為公知。

【0036】 如此的骨髓瘤細胞例如可理想地使用 P3(P3x63Ag8.653)(J. Immunol.(1979)123 (4), 1548-1550)、P3x63Ag8U.1(Current Topics in Microbiology and Immunology (1978)81, 1-7)、NS-1(C. Eur. J. Immunol.(1976)6 (7), 511-519)、MPC-11(Cell(1976)8 (3), 405-415)、SP2/0(Nature (1978)276 (5685), 269-270)、FO(J. Immunol. Methods(1980)35 (1-2), 1-21)、S194/5.XX0.BU.1(J. Exp. Med.(1978)148 (1), 313-323)、R210(Nature(1979)277 (5692), 131-133)等。

【0037】 基本上可依照公知方法例如 Keller 與 Milstein 等人的方法(Methods Enzymol.(1981)73, 3-46)等，實施前述免疫細胞與骨髓瘤細胞之細胞融合。

更具體而言，可於例如細胞融合促進劑存在下於通常的營養培養液中實施前述細胞融合。融合促進劑可使用例如聚乙二醇(PEG)、仙台病毒(HVJ)等，為更提高融合效率，可視所望添加使用二甲基亞碲等輔助劑。

【0038】 免疫細胞與骨髓瘤細胞之使用比例可任意設定。例如相對於骨髓瘤細胞將免疫細胞定為 1 至 10 倍較佳。前述細胞融合使用之培養液，例如適於前述骨髓瘤細胞株增殖之 RPMI1640 培養液、MEM 培養液、此外，可使用該種細胞

培養使用之通常之培養液，再者，可理想地添加胎牛血清(FCS)等血清補液。

【0039】 將前述培養液中充分混合，並且將預先加溫至約37°C之PEG溶液(例如平均分子量1000至6000左右)以通常30至60%(w/v)之濃度添加。藉由將混合液緩慢混合，會形成所望之融合細胞(融合瘤)。接著，逐次添加上述列舉之適當培養液，反復實施離心並去除上清液之操作，可將對於融合瘤之生長不利的細胞融合劑等除去。

【0040】 以如此方式獲得之融合瘤，可藉由於通常之選擇培養液，例如HAT培養液(含次黃嘌呤、胺基喋呤、胸腺嘧啶之培養液)培養而選擇。為了使所望之融合瘤以外之細胞(非融合細胞)死滅，可使繼續進行使用上述HAT培養液之培養足夠時間(通常該足夠時間為數日至數週)。其次，以通常之極限稀釋法，實施產生所望抗體之融合瘤之篩選及單一選殖。

【0041】 以如此方式獲得之融合瘤，可利用因應細胞融合使用之骨髓瘤具有之選擇標記的選擇培養液而選擇。例如具HGPRT或TK缺損之細胞，可藉由以HAT培養液(含次黃嘌呤、胺基喋呤及胸腺嘧啶之培養液)培養而選擇。亦即，當使用HAT感受性骨髓瘤細胞於細胞融合時，可在HAT培養液中將成功與正常細胞細胞融合的細胞選擇性增殖。為了使所望融合瘤以外之細胞(非融合細胞)死滅，可以繼續使用上述HAT培養液之培養足夠時間。具體而言，一般可藉由數日至數週的培養而選擇所望之融合瘤。其次可利用通常之極限稀釋法，實施產生所望之抗體的融合瘤的篩選及單一選殖。

【0042】 所望之抗體之篩選及單一選殖，可依照基於公知抗原抗體反應之篩選方法而理想地實施。例如，結合於GPC3之單株抗體可以結合於在細胞表面表現的GPC3。如此的單株抗體例如可藉由FACS(fluorescence activated cell sorting)篩選。FACS係將與螢光抗體接觸之細胞以雷射光解析，並測定各個細胞發出之螢光，而可測定抗體對於細胞表面之結合的系統。

【0043】 為了利用FACS篩選產生本發明之單株抗體的融合瘤，首先要製備表現GPC3之細胞。用於篩選之較佳細胞為使GPC3強制表現之哺乳動物細胞。藉由以當做寄主細胞之未經轉形之哺乳動物細胞為對照，可以選擇性檢測抗體對於細胞表面之GPC3的結合活性。亦即，藉由選擇產生未結合於寄主細胞而結合於GPC3強制表現細胞的抗體的融合瘤，可以取得產生GPC3單株抗體之融合瘤。

【0044】 或抗體對於經固定化之GPC3表現細胞的結合活性可依據ELISA之原理評價。例如，將GPC3表現細胞固定化在ELISA平板的井。使融合瘤之培養上清液接觸井內之固定化細胞，以檢測結合於固定化細胞的抗體。單株抗體為小鼠來源時，與細胞結合之抗體可利用抗小鼠免疫球蛋白抗體檢測。該等篩選所選擇之產生具有對於抗原之結合能力的所望抗體的融合瘤，可利用極限稀釋法等選殖。

【0045】 以此方式製作之產生單株抗體之融合瘤可在通常之培養液中繼代培養。而且，該融合瘤可於液態氮中長期保存。

【0046】 將該融合瘤依照通常方法培養，可從其培養上清液取得所望之單株抗體。或可將融合瘤對於與其具適合性之哺乳動物投予使增殖，並從其腹水獲取單株抗體。前者之方法對於獲得高純度抗體為適當。

【0047】 從該融合瘤等抗體產生細胞選殖的抗體基因所編碼之抗體也可適當利用。藉由將經選殖的抗體基因納入適當載體並導入寄主，可以表現該基因所編碼的抗體。抗體基因之單離與對於載體之導入、及用於將寄主細胞轉形之方法，例如已由Vandamme等人確立 (Eur.J. Biochem.(1990)192 (3), 767-775)。下列所述重組抗體之製造方法亦為公知。

【0048】 例如，可從產生抗GPC3抗體之融合瘤細胞取得編碼為抗GPC3抗體之可變區(V區)之cDNA。為此，通常首先從融合瘤萃取全體RNA。用於從

細胞萃取mRNA之方法，例如可利用如下方法。

—胍(guanidine)超離心法(Biochemistry (1979) 18 (24), 5294-5299)

—AGPC法(Anal. Biochem. (1987) 162 (1), 156-159)

【0049】 萃取到的mRNA可使用mRNA Purification Kit (GE Health care bioscience製)等精製。或如QuickPrep mRNA Purification Kit (GE Health care bioscience製)等，也有用於從細胞直接萃取全體mRNA之市售套組。使用如此的套組，可從融合瘤取得mRNA。從獲得之mRNA使用反轉錄酵素可合成編碼為抗體V區之cDNA。cDNA可利用AMV Reverse Transcriptase First-strand cDNA Synthesis Kit(生化學工業社製)等合成。又，為了cDNA之合成及放大，可適當利用SMART RACE cDNA 放大套組(Clontech製)及使用PCR之5'-RACE法(Proc. Natl. Acad. Sci. USA (1988) 85 (23), 8998-9002、Nucleic Acids Res. (1989) 17 (8), 2919-2932)。又，在如此的cDNA合成之過程中，可在cDNA的兩末端導入後述適當的限制酶部位。

【0050】 從獲得之PCR產物精製目的之cDNA片段，其次與載體DNA連結。以如此方式製作重組載體，並導入大腸菌等，選擇群落(colony)後，從形成有該群落之大腸菌製備所望之重組載體。並且針對該重組載體是否具有目的cDNA之鹼基序列，可使用公知之方法例如二去氧核苷酸鏈終結法等確認。

【0051】 為了取得編碼為可變區之基因，利用使用可變區基因放大用引子之5'-RACE法係屬簡便。首先，以從融合瘤細胞萃取之RNA當做模板，合成cDNA，獲得5'-RACE cDNA庫。5'-RACE cDNA庫之合成可適當使用SMART RACE cDNA 放大套組等市售套組。

【0052】 以獲得之5'-RACE cDNA庫為模板，以PCR法將抗體基因放大。依據公知之抗體基因序列可設計小鼠抗體基因放大用之引子。此等引子為依免疫球蛋白之次類而各不相同的鹼基序列。因此，次類理想為預先使用Iso Strip小

鼠單株抗體同種型決定套組(Roche diagnostics)等市售套組決定。

【0053】 具體而言，當目的為取得例如編碼為小鼠IgG之基因時，可利用將編碼為當做重鏈之 $\gamma 1$ 、 $\gamma 2a$ 、 $\gamma 2b$ 、 $\gamma 3$ 、當做輕鏈之 κ 鏈與 λ 鏈的基因放大的引子。為了放大IgG之可變區基因，一般係利用於3'側之引子黏合有相當於接近可變區之恆定區之部分的引子。另一方面，5'側之引子係利用5' RACE cDNA庫製作套組所附帶的引子。

【0054】 利用如此放大之PCR產物，可再構成由重鏈與輕鏈之組合而成的免疫球蛋白。以再構成之免疫球蛋白對於GPC3之結合活性當做指標，可以篩選所望之抗體。例如目的為取得對抗GPC3之抗體時，抗體對於GPC3之結合，更佳為專一性的。與GPC3結合之抗體可藉由例如以下方式篩選；

(1)使從融合瘤獲得之含有由cDNA編碼之V區的抗體接觸GPC3表現細胞之步驟、

(2)檢測GPC3表現細胞與抗體之間的結合之步驟、及

(3)選擇與GPC3表現細胞結合之抗體之步驟。

【0055】 檢測抗體與GPC3表現細胞之間的結合的方法為公知。具體而言，可利用先前所述FACS等方法，檢測抗體與GPC3表現細胞間之結合。為了評價抗體之結合活性，可適當利用GPC3表現細胞之固定標本。

【0056】 以結合活性為指標之抗體之篩選方法，亦宜使用利用噬菌體載體之淘選法。從多株抗體表現細胞群，以重鏈與輕鏈之次類之庫的形式取得抗體基因時，利用噬菌體載體之篩選方法係屬有利。編碼為重鏈與輕鏈之可變區之基因，可藉由以適當連結子序列連結，而形成單鏈Fv(scFv)。藉由將編碼為scFv之基因插入噬菌體載體，可取得於表面表現scFv之噬菌體。該噬菌體與所望抗原接觸後，藉由回收與抗原結合之噬菌體，可以回收編碼為具目的結合活性之scFv的DNA。該操作可視需要反復實施，而將具所望之結合活性之scFv濃縮。

【0057】 獲得編碼為目的抗GPC3抗體之V區的cDNA後，將該cDNA以認識插入於該cDNA之兩末端的限制酶部位之限制酶消化者。較佳之限制酶，係認識構成抗體基因之鹼基序列中出現頻度低之鹼基序列並消化。再者，為了將1副本的消化片段以正確方向插入載體，宜插入提供附著末端之限制酶。藉由將以上述方式經消化之編碼為抗GPC3抗體之V區的cDNA插入適當表現載體，可以取得抗體表現載體。此時，若將編碼為抗體恆定區(C區)之基因、與編碼為前述V區之基因於框架內融合，則可取得嵌合抗體。在此，嵌合抗體係指恆定區與可變區之來源不同者。因此，除了小鼠—人類等的異種嵌合抗體，人類—人類同種嵌合抗體也包含在本發明之嵌合抗體。藉由預先在具恆定區之表現載體插入前述V區基因，可以構建嵌合抗體表現載體。具體而言，可於例如保持有編碼為所望之抗體恆定區(C區)之DNA的表現載體之5'側，適當配置消化前述V區基因之限制酶之限制酶認識序列。藉由將以相同組合之限制酶消化過的兩者於框架內融合，可以構建嵌合抗體表現載體。

【0058】 為了製造抗GPC3單株抗體，可以將抗體基因於由表現控制區控制之下表現的方式納入表現載體。用於表現抗體之表現控制區，例如包含增強子或啟動子。又，也可在胺基末端附加適當的信號序列，以使表現的抗體分泌到細胞外。後面記載之實施例係使用具胺基酸序列MGWSCILFLVATATGVHS (序列編號：3)之胜肽當做信號序列，但是也可加成其他適當的信號序列。將表現的多胜肽在上述序列之羧基末端部分切斷，切斷的多胜肽可以成熟多胜肽之形式分泌到細胞外。其次，藉由以該表現載體將適當的寄主細胞轉形，可以取得表現編碼為抗GPC3抗體之DNA的重組細胞。

【0059】 為了表現抗體基因，可將編碼為抗體重鏈(H鏈)及輕鏈(L鏈)之DNA納入分別的表現載體。藉由納入有H鏈與L鏈之載體，對於相同寄主細胞同時轉形(co-transfect)，可以表現具備H鏈與L鏈之抗體分子。或可將編碼為H鏈及

L鏈之DNA納入單一的表現載體，而將寄主細胞轉形（參照國際公開WO 94/11523）。

【0060】 用以藉由將經單離之抗體基因導入適當寄主而製作抗體之寄主細胞與表現載體的多數組合為公知。該等表現系均可應用於單離含有本發明之抗體可變區之域。真核細胞當做寄主細胞時，可適當使用動物細胞、植物細胞、或真菌細胞。具體而言，動物細胞例如以下細胞。

(1)哺乳類細胞、：CHO、COS、骨髓瘤、BHK(baby hamster kidney)、Hela、Vero等

(2)兩生類細胞：非洲爪蟾卵母細胞等

(3)昆蟲細胞：sf9、sf21、Tn5等

【0061】 或植物細胞以煙草(*Nicotiana tabacum*)等煙草 (*Nicotiana*)屬來源之細胞而得之抗體基因表現系為公知。植物細胞之轉形可以適當利用癒傷組織培養之細胞。

【0062】 又，真菌細胞可以利用如下的細胞。

酵母：啤酒酵母(*Saccharomyces cerevisiae*)等糖化酵母 (*Saccharomyces*)屬、甲醇同化酵母(*Pichia pastoris*)等*Pichia*屬

絲狀菌：黑麴黴(*Aspergillus niger*)等麴菌 (*Aspergillus*)屬

【0063】 又，利用原核細胞之抗體基因之表現系亦為公知。例如使用細菌細胞時，可以適當利用大腸菌(*E. coli*)、枯草菌等細菌細胞。於該等細胞中，以轉形導入含有目的抗體基因之表現載體。藉由將經轉形之細胞於體外培養，可從該轉形細胞之培養物獲取所望之抗體。

【0064】 重組抗體之產生，除了上述寄主細胞，尚可利用基因轉殖動物。亦即，從導入有編碼為所望抗體之基因的動物，可獲取該抗體。例如，抗體基因藉由於框架內插入編碼為乳汁中固有產生之蛋白質的基因內部，可以構建融

合基因。乳汁中分泌之蛋白質，例如可利用山羊 β 酪蛋白等。將含有插入有抗體基因之融合基因的DNA片段注入山羊胚，並將該經注入之胚胎導入雌山羊體內。從接受胚胎的山羊產生之基因轉殖山羊(或其子孫)所產之乳汁，可以取得所望之抗體與乳汁蛋白質之融合蛋白質。又，為了增加從基因轉殖山羊產生之含所望之抗體之乳汁量，可對於基因轉殖山羊投予荷爾蒙(Bio/Technology (1994), 12 (7), 699-702)。

【0065】 本說明書記載之抗原結合分子對於人類投予時，該抗原結合分子中之含有抗體可變區之域，可適當採用以降低對於人類之異種抗原性等為目的經人為改變過的基因重組型抗體來源的域。基因重組型抗體例如包含人類化(Humanized)抗體等。該等改造抗體可使用公知方法適當製造。

【0066】 本說明書記載之用於製作抗原結合分子中的含有抗體可變區之域所使用之抗體之可變區，通常由插入在4個框架區(FR)的3個互補性決定區(complementarity-determining region ; CDR)構成。CDR係實質上決定抗體之結合專一性之區域。CDR之胺基酸序列富有多樣性。另一方面，構成FR之胺基酸序列，即使在具有不同之結合專一性的抗體之間也常會顯示高度同一性。所以，一般可利用CDR之移植而將某抗體之結合專一性移植到其他抗體。

【0067】 人類化抗體也稱為再構成(reshaped)人類抗體。具體而言，將人類以外之動物例如小鼠抗體之CDR移植到人類抗體而成之人類化抗體等為公知。為了獲得人類化抗體之一般基因重組方法亦為已知。具體而言，就將小鼠抗體之CDR移植到人類FR的方法而言，例如Overlap Extension PCR為公知。於Overlap Extension PCR，係對於用於合成人類抗體FR之引子中，附加編碼為待移植之小鼠抗體之CDR的鹼基序列。引子各準備4個FR。一般將小鼠CDR移植到人類FR時，選擇與小鼠之FR具高同一性之人類FR時，對於維持CDR機能為有利。亦即，一般較佳為利用與相鄰於待移植之小鼠CDR的FR之胺基酸序列為高同一

性之胺基酸序列構成之人類FR。

【0068】 又，連結之鹼基序列可設計為彼此於框架內連接。藉由各引子，可個別合成人類FR。其結果，可獲得於各FR附加有編碼為小鼠CDR之DNA的產物。各產物之編碼為小鼠CDR之鹼基序列，可設計成彼此重疊。接著，使以人類抗體基因為模板而合成之產物之重疊的CDR部分彼此黏合，進行互補鏈合成反應。利用該反應，人類FR經由小鼠CDR之序列而連結。

【0069】 最後，將連結有3個CDR與4個FR之V區基因，利用黏合在其5'末端與3'末端並附加有適當之限制酶認識序列的引子，將其全長放大。藉由將以上述方式獲得之DNA與編碼為人類抗體C區之DNA以於框架內融合之方式插入於表現載體中，藉此可製作人類型抗體表現用載體。將該重組載體導入寄主並樹立重組細胞後，培養該重組細胞，使編碼為該人類化抗體之DNA表現，藉此使該培養細胞之培養物中產生該人類化抗體(參照歐洲專利公開EP 239400、國際公開WO1996/002576)。

【0070】 以定性或定量測定以上述方式製作之人類化抗體對於抗原之結合活性並進行評價，可以理想地選擇當經由CDR連結時該CDR會形成良好之抗原結合部位的人類抗體之FR。視需要，可以將FR之胺基酸殘基取代，使再構成人類抗體之CDR能形成適當的抗原結合部位。例如，應用將小鼠CDR移植到人類FR時使用之PCR法，可對於FR導入胺基酸序列之突變。具體而言，可對於與FR黏合之引子導入部分的鹼基序列的突變。以如此的引子合成之FR，導入有鹼基序列之突變。以上述方法測定並評價將胺基酸取代過的突變型抗體對於抗原之結合活性，可以選擇具所望性質之突變FR序列(Sato, K.et al., Cancer Res, 1993, 53, 851-856)。

【0071】 又，可以將具有人類抗體基因所有曲目的基因轉殖動物(參照國際公開WO1993/012227、WO1992/003918、WO1994/002602、WO1994/025585、

WO1996/034096、WO1996/033735)當做免疫動物，以DNA免疫取得所望之人類抗體。

【0072】 再者，使用人類抗體庫以淘選取得人類抗體之技術亦為已知。例如，將人類抗體之V區以單鏈抗體(scFv)之形式，以噬菌體呈現法使表現在噬菌體之表面。可以選擇表現與抗原結合之scFv的噬菌體。藉由解析選擇之噬菌體之基因，可以決定編碼為與抗原結合之人類抗體之V區的DNA序列。決定與抗原結合之scFv之DNA序列後，將該V區序列與所望之人類抗體C區之序列於框架內融合後插入適當表現載體，可以製作表現載體。將該表現載體導入上述列舉之適當表現細胞中，並使編碼為該人類抗體之基因表現，可取得該人類抗體。該等方法已為公知(參照國際公開WO1992/001047、WO1992/020791、WO1993/006213、WO1993/011236、WO1993/019172、WO1995/001438、WO1995/015388)。

【0073】 含有具Glypican3(GPC3)結合活性之抗體可變區之域

本說明書中，「含有具Glypican3(GPC3)結合活性之抗體可變區之域」係指含和上述GPC3 蛋白質或其部分胜肽之一部分或全部專一性結合且互補之區而成之抗體之部分。含抗體可變區之域可由一或多數抗體之可變域提供。較佳為，含抗體可變區之域包含抗體輕鏈可變區(VL)與抗體重鏈可變區(VH)。如此之含抗體可變區之域，例如「scFv(single chain Fv)」、「單鏈抗體(single chain antibody)」、「Fv」、「scFv2(single chain Fv 2)」、「Fab」或「F(ab')₂」等。

【0074】 含有具T細胞受體複合體結合活性之抗體可變區之域

本說明書中，「含有具T細胞受體複合體結合活性之抗體可變區之域」係指含和T細胞受體複合體之一部分或全部專一性結合且互補之區而成之T細胞受體複合體抗體之部分。T細胞受體複合體可為T細胞受體自身，也可為和T細胞受體一起構成T細胞受體複合體之適配子(adaptor)分子。適配子宜為CD3。

【0075】 含具T細胞受體結合活性之抗體可變區之域

第 51 頁，共 122 頁(發明說明書)

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本說明書中，「含具T細胞受體結合活性之抗體可變區之域」，係指含和T細胞受體之一部分或全部專一性結合且互補之區而成之T細胞受體抗體之部分。

本發明之域所結合之T細胞受體之部分可以為可變區也可以為不變區，較佳為存在於不變區之抗原決定基。不變區之序列例如RefSeq註冊編號CAA26636.1之T細胞受體 α 鏈(序列編號：4)、RefSeq註冊編號C25777之T細胞受體 β 鏈(序列編號：5)、RefSeq註冊編號A26659之T細胞受體 γ 1鏈(序列編號：6)、RefSeq註冊編號AAB63312.1之T細胞受體 γ 2鏈(序列編號：7)、RefSeq註冊編號AAA61033.1之T細胞受體 δ 鏈(序列編號：8)之序列。

【0076】 含具CD3結合活性之抗體可變區之域

本說明書中，「含具CD3結合活性之抗體可變區之域」，係指含和CD3之一部分或全部專一性結合且互補之區而成之CD3抗體之部分。較佳為該域包括抗CD3抗體之輕鏈可變區(VL)與抗CD3抗體之重鏈可變區(VH)。如此之域，例如「scFv(single chain Fv)」、「單鏈抗體(single chain antibody)」、「Fv」、「scFv2(single chain Fv 2)」、「Fab」或「F(ab')₂」等。

【0077】 本發明之含具CD3結合活性之抗體可變區之域只要是結合於存在於構成人CD3之 γ 鏈、 δ 鏈或 ϵ 鏈序列之抗原決定基即可，可為結合於任一抗原決定基者。本發明中，較佳為使用含有結合於存在人CD3複合體之 ϵ 鏈之細胞外區之抗原決定基之抗CD3抗體之輕鏈可變區(VL)與抗CD3抗體之重鏈可變區(VH)之域。如此的域，除了實施例記載之抗CD3抗體之輕鏈可變區(VL)與抗CD3抗體之重鏈可變區(VH)以外，尚有OKT3抗體(Proc. Natl. Acad. Sci. USA (1980) 77, 4914-4917)、各種公知之含CD3抗體之輕鏈可變區(VL)與CD3抗體之重鏈可變區(VH)之CD3結合域可理想地使用。又，可適當使用藉由將構成人CD3之 γ 鏈、 δ 鏈或 ϵ 鏈依前述方法對於所望動物進行免疫而取得之以具所望性質之抗CD3抗體作為起源之含抗體可變區之域。成為含具CD3結合活性之抗體可變區之域之起

源之抗CD3抗體可適當使用如前述適當人化之抗體、人抗體。構成CD3之 γ 鏈、 δ 鏈或 ϵ 鏈之結構其多核苷酸序列記載於序列編號：9(NM_000073.2)、10(NM_000732.4)及11(NM_000733.3)，其多胜肽序列記載於序列編號：12(NP_000064.1)、13(NP_000723.1)及14(NP_000724.1)(括弧內代表RefSeq註冊編號)。

【0078】 本發明之抗原結合分子之含抗體可變區之域可結合於相同之抗原決定基。在此，相同之抗原決定基可存在於由序列編號：2或序列編號：14之胺基酸序列構成之蛋白質中。或本發明之抗原結合分子之含抗體可變區之域可結合於彼此不同的抗原決定基。在此，不同的抗原決定基可存在於由序列編號：2或序列編號：14之胺基酸序列構成之蛋白質中。

【0079】 專一性

專一性係指專一性結合之分子中其中之一的分子對於其一或多數之結合對象的分子以外之分子未顯示任何顯著結合之狀態。又，含抗體可變區之域也可用在對於某抗原中所含之多數抗原決定基當中特定抗原決定基為專一性的情形。又，含抗體可變區之域所結合之抗原決定基包含在多數不同抗原時，具該含抗體可變區之域之抗原結合分子可以與含該抗原決定基之各種抗原結合。

【0080】 抗原決定基

意指抗原中所存在之抗原決定基的抗原決定基，意指本說明書揭示之抗原結合分子中之含抗體可變區之域所結合之抗原上之部位。是以，例如抗原決定基可由其結構定義。又，也可利用認識該抗原決定基之抗原結合分子中對於抗原之結合活性將該抗原決定基定義。抗原為胜肽或多胜肽時，可以利用構成抗原決定基之胺基酸殘基指定抗原決定基。又，抗原決定基為糖鏈時，也可依特定之糖鏈構造指定抗原決定基。

【0081】 直線狀抗原決定基，係含有認識胺基酸一次序列之抗原決定基的

第 53 頁，共 122 頁(發明說明書)

14948AAAAAAPTWF

抗原決定基。直線狀抗原決定基典型上在固有序列含至少3個，且最普通為至少5個，例如約8～約10個、6～20個胺基酸。

【0082】 立體構造抗原決定基係與直線狀抗原決定基為對照，為含抗原決定基之胺基酸之一次序列並非所認識之抗原決定基之單一規定成分之抗原決定基(例如，胺基酸之一次序列不一定由規定抗原決定基之抗體所認識之抗原決定基)。立體構造抗原決定基可能包含相對於直線狀抗原決定基為增大之數目之胺基酸。關於立體構造抗原決定基之認識，抗體係認識胜肽或蛋白質之三維構造。例如當蛋白質分子折疊並形成三維構造時，形成立體構造抗原決定基之某胺基酸及/或多胜肽主鏈成為並排，且抗體可認識抗原決定基。決定抗原決定基之立體構造之方法，例如包含X射線結晶學、二維核磁共振分光學及部位專一性旋轉標定及電磁場磁性共振分光學，但不限於該等。例如，參照Epitope Mapping Protocols in Methods in Molecular Biology (1996)、第66卷、Morris(編)。

【0083】 以下例示確認含具有對於GPC3有結合活性之抗體可變區之域之待驗抗原結合分子對於抗原決定基之結合的確認方法，但是確認具有對於T細胞受體複合體有結合活性之含抗體可變區之域的待驗多胜肽聯合體其對於抗原決定基之結合之確認方法，也可依據下列例示適當實施。

【0084】 例如含具有對於GPC3有抗原活性之抗體可變區之域的待驗抗原結合分子，其認識GPC3分子中存在之線狀抗原決定基之情事，例如可以如下方式確認。為了上述目的，合成由構成GPC3之細胞外域的胺基酸序列構成線狀胜肽。該胜肽可以化學合成。或，利用GPC3之cDNA中編碼為相當於細胞外域的胺基酸序列的區域，以基因工程的方法獲得。其次，評價由構成細胞外域之胺基酸序列構成的線狀胜肽、及含具有對GPC3有結合活性之抗體可變區之域的待驗抗原結合分子之間的結合活性。例如，可藉由經固定化之線狀胜肽為抗原之ELISA，而評價該抗原結合分子對於該胜肽之結合活性。或，基於該抗原結合分

子對於GPC3表現細胞之結合中，由於線狀胜肽所致之抑制的水平，解明對於線狀胜肽之結合活性。由於該等試驗，可以解明該多抗原結合分子對於線狀胜肽之結合活性。

【0085】 又，含具有對於GPC3有抗原活性之抗體可變區之域的待驗抗原結合分子認識立體構造抗原決定基之情事，可如以下方式確認。為了上述目的，製備表現GPC3之細胞。例如具有含對於GPC3有抗原活性之抗體可變區之域的待驗抗原結合分子當接觸GPC3表現細胞時會強力結合於該細胞，另一方面，該抗原結合分子對於由構成經固定化之GPC3之細胞外域的胺基酸序列構成線狀胜肽實質上不結合時等。在此，實質上不結合，係指為對於人類GPC3表現細胞之結合活性之80%以下、通常50%以下、較佳為30%以下、尤佳為15%以下之結合活性。

【0086】 測定含針對GPC3之抗原結合域的待驗抗原結合分子對於GPC3表現細胞之結合活性之方法，例如Antibodies A Laboratory Manual記載之方法(Ed Harlow, David Lane, Cold Spring Harbor Laboratory (1988) 359-420)。亦即，可依照以GPC3表現細胞當做抗原之ELISA或FACS(fluorescence activated cell sorting)之原理評價。

【0087】 ELISA格式中，含對於GPC3之抗原結合域的待驗抗原結合分子對於GPC3表現細胞之結合活性，可藉由比較酵素反應所生成之信號水平而定量的評價。亦即於固定化有GPC3表現細胞之ELISA平板添加待驗抗原結合分子，並且利用認識待驗抗原結合分子之酵素標識抗體而檢測與細胞結合之待驗抗原結合分子。或者，於FACS，製作待驗抗原結合分子之稀釋系列，並藉由決定對於GPC3表現細胞之抗體結合力價(titer)，可比較待驗抗原結合分子對於GPC3表現細胞之結合活性。

【0088】 待驗抗原結合分子對於懸浮於緩衝液等之細胞表面上表現的抗

原的結合，可利用流式細胞計數儀檢測。流式細胞計數儀例如已知有以下裝置。

FACSCanto™ II

FACSAria™

FACSArray™

FACSVantage™ SE

FACSCalibur™ (均為BD Biosciences公司之商品名)

EPICS ALTRA HyPerSort

Cytomics FC 500

EPICS XL-MCL ADC EPICS XL ADC

Cell Lab Quanta / Cell Lab Quanta SC(均為Beckman Coulter公司之商品名)

【0089】 例如，就含對於GPC3之抗原結合域的待驗抗原結合分子對於抗原之結合活性之理想測定方法，例如以下方法。首先，以認識與表現GPC3之細胞反應之待驗抗原結合分子的經FITC標記的二次抗體染色。將待驗抗原結合分子以適當的緩衝液稀釋，將該抗原結合分子製備為所望濃度後使用。例如，可使用10μg/ml至10 ng/ml之間的任一濃度。其次，利用FACSCalibur(BD公司)測定螢光強度及細胞數。抗體對於該細胞之結合量，係反映在使用CELL QUEST Software(BD公司)解析而得之螢光強度，亦即幾何平均值(Geometric Mean)。亦即，由該幾何平均值，可測定由待驗抗原結合分子之結合量表示之待驗抗原結合分子之結合活性。

【0090】 含對於GPC3之抗原結合域的待驗抗原結合分子，與抗原結合分子共有抗原決定基之情事，可藉由兩者對於相同抗原決定基之彼此競爭而確認。抗原結合分子間之彼此競爭，可利用交叉阻斷試驗等檢測。例如彼此競爭ELISA分析係較佳的交叉阻斷試驗。

【0091】 具體而言，交叉阻斷試驗中，係在微滴定平板的井上塗覆的GPC3

蛋白質，於成為候選的彼此競爭抗原結合分子存在下、或不存在下預備溫育後，添加待驗抗原結合分子。與井中之GPC3蛋白質結合之待驗抗原結合分子之量，間接相關於與對於相同抗原決定基之結合成為彼此競爭的候選者的彼此競爭抗原結合分子之結合能力。亦即，若競爭抗原結合分子對於相同抗原決定基之親和性愈大，則待驗抗原結合分子對於塗覆有GPC3蛋白質之井之結合活性愈低。

【0092】 經由GPC3蛋白質而與井結合之待驗抗原結合分子之量，可藉由預先標記抗原結合分子而輕易測定。例如，經生物素標記的抗原結合分子，可利用抗生物素過氧化酶接合體以及適當基質而測定。利用過氧化酶等酵素標記之交叉阻斷試驗，特別稱為彼此競爭ELISA分析。抗原結合分子能以可檢測或測定之其他標記物質標記。具體而言，放射標記或螢光標記等為公知。

【0093】 與於候選的彼此競爭抗原結合分子不存在下實施之對照試驗所得之結合活性比較，彼此競爭抗原結合分子若能阻斷含對於GPC3之抗原結合域的待驗抗原結合分子之結合至少20%、較佳為至少20—50%、更佳為至少50%，則該待驗抗原結合分子與彼此競爭抗原結合分子係實質上結合於相同抗原決定基，或對於相同抗原決定基之結合為彼此競爭的抗原結合分子。

【0094】 含對於GPC3之抗原結合域的待驗抗原結合分子所結合之抗原決定基之構造在鑑定時，待驗多胜肽聯合體與對照抗原結合分子共有抗原決定基之情形，可藉由比較兩者之抗原結合分子對於在構成該抗原決定基之胜肽導入有胺基酸突變之胜肽的結合活性而評價。

【0095】 如此測定結合活性之方法，例如可藉由比較前述ELISA格式中，待驗抗原結合分子及對照抗原結合分子對於導入有突變的線狀胜肽的結合活性而測定。就ELISA以外之方法而言，也可藉由將對於結合於管柱之該突變胜肽的結合活性，以使待驗抗原結合分子與對照抗原結合分子流下該管柱後溶出到溶出液中之抗原結合分子進行定量而測定。使突變胜肽例如與GST之融合胜肽吸附

於管柱之方法為公知。

【0096】 又，當鑑定的抗原決定基為立體抗原決定基時，待驗抗原結合分子與對照抗原結合分子共有抗原決定基之情事，可藉由以下方法評價。首先，製備表現GPC3之細胞以及表現對於抗原決定基導入有突變之GPC3的細胞。對於該等細胞懸浮於PBS等適當緩衝液而成的細胞懸浮液添加待驗抗原結合分子與對照抗原結合分子。其次，對於經適當緩衝液洗滌的細胞懸浮液，添加能夠認識待驗抗原結合分子與對照抗原結合分子的經FITC標記的抗體。利用FACSCalibur(BD公司)測定標記抗體所染色之細胞之螢光強度及細胞數。將待驗抗原結合分子與對照抗原結合分子之濃度以適當緩衝液適當稀釋以製備為所望濃度後使用。例如可使用10 μ g/ml至10 ng/ml之間的任一濃度。標記抗體對於該細胞之結合量，反映於使用CELL QUEST Software(BD公司)解析所獲得之螢光強度，亦即幾何平均值。亦即藉由獲得該幾何平均值，可以測定以標記抗體之結合量所代表之待驗抗原結合分子與對照抗原結合分子之結合活性。

【0097】 本方法中，例如「實質上不結合於突變GPC3表現細胞」之情事，可藉由以下方法判斷。首先，將已對於表現突變GPC3之細胞結合之待驗抗原結合分子與對照抗原結合分子以標記抗體染色。接著，檢測細胞之螢光強度。螢光檢測使用FACSCalibur當做流式細胞計數儀時，獲得之螢光強度可以使用CELL QUEST Software解析。從抗原結合分子存在下及非存在下之幾何平均值，將其比較值(Δ 幾何平均)依下列計算式計算，可以求得抗原結合分子之結合所致之螢光強度之增加比例。

【0098】

$$\Delta \text{幾何平均值} = \text{幾何平均值 (抗原結合分子存在下)} / \text{幾何平均值 (抗原結合分子非存在下)}$$

【0099】 將由解析獲得之反映待驗抗原結合分子對於突變GPC3表現細胞

第 58 頁，共 122 頁(發明說明書)

14948AAAAAAPTWF

之結合量的幾何平均比較值(突變GPC3分子 Δ 幾何平均值)，與反映待驗抗原結合分子對於GPC3表現細胞之結合量的 Δ 幾何平均值比較值進行比較。於該情形，求取對於突變GPC3表現細胞及GPC3表現細胞之 Δ 幾何平均比較值時使用之待驗抗原結合分子之濃度調整為彼此相同或實質上為相同濃度尤佳。可利用預先確認認識GPC3中之抗原決定基的抗原結合分子當做對照抗原結合分子。

【0100】 待驗抗原結合分子對於突變GPC3表現細胞之 Δ 幾何平均比較值，若比起待驗抗原結合分子對於GPC3表現細胞之 Δ 幾何平均比較值之至少80%、較佳為50%、更佳為30%、尤佳為15%還小，則判定為「實質上不結合於突變GPC3表現細胞」。求取幾何平均值(Geometric Mean)之計算式，記載於CELL QUEST Software User's Guide(BD biosciences公司)。若比較比較值而其實質上可視為相同之程度，則可評價待驗抗原結合分子與對照抗原結合分子之抗原決定基為相同。

【0101】 Fv(可變片段(variable fragment))

本說明書中，稱為「Fv(variable fragment)」的用語，係指由抗體之輕鏈可變區(VL(light chain variable region))與抗體之重鏈可變區(VH(heavy chain variable region))的配對構成的抗體而來的抗原結合域的最小單位。1988年Skerra與Pluckthun發現藉由在細菌的信號序列的下游插入有抗體之基因的大腸菌中誘導該基因表現，可以於均勻且保持活性的狀態從大腸菌之胞外質區分製備(Science (1988) 240 (4855), 1038-1041)。從胞外質區分製備的Fv，係VH與VL以對於抗原具結合之態樣組合。

【0102】 本說明書中，Fv例如以下之包含(1)二價之抗原結合域、(2)構成IgG1、IgG2a、IgG3或IgG4之Fc區之胺基酸當中含不具對於Fc γ 受體之結合活性之Fc區的域、及(3)至少一價之CD3結合域之抗原結合分子中，輕鏈Fv片段及重鏈Fv片段含以具對於抗原CD3之結合的態樣組合並且構成CD3結合域之一組Fv

亦為較佳；

二價之scFv當中，一價之scFv以中間為構成CD3結合域之重鏈Fv片段而連結於構成Fc區之其中一個多胜肽，另一個一價之scFv以中間為構成CD3結合域之輕鏈Fv片段而連結於構成Fc區之另一多胜肽而成的二價之抗原結合域為二價之scFv。

【0103】 scFv、單鏈抗體、或sc(Fv)2

本說明書中，「scFv」、「單鏈抗體」、或「sc(Fv)2」的用語係指在單一多胜肽鏈內，包含來自於重鏈及輕鏈兩者的可變區但是欠缺恆定區之抗體片段。一般而言，單鏈抗體更包含可形成能進行抗原結合的所望之構造的VH域與VL域之間的多胜肽連結子。單鏈抗體於The Pharmacology of Monoclonal Antibodies, 113卷, Rosenberg、及、Moore編, Springer-Verlag, New York, 269～315(1994)中，由Pluckthun詳細考察。同樣地，參照國際專利申請案公開WO1988/001649及美國專利第4,946,778號及美國專利第5,260,203號。特定態樣中，單鏈抗體也可為雙專一性、及/或人類化。

【0104】 scFv係構成Fv之VH與VL以胜肽連結子連結成的抗原結合域(Proc. Natl. Acad. Sci. U.S.A. (1988) 85 (16), 5879-5883)。利用該胜肽連結子，VH與VL可以保持在接近的狀態。

【0105】 sc(Fv)2係二個VL與二個VH之4個可變區以胜肽連結子等連結子連結成構成單鏈的單鏈抗體(J Immunol. Methods (1999) 231 (1-2), 177-189)。該二個VH與VL也可來自不同的單株抗體。例如Journal of Immunology (1994) 152 (11), 5368-5374揭示在相同抗原中存在認識二種抗原決定基之雙專一性(bispecific sc(Fv)2)。sc(Fv)2可以利用該技術領域人士公知之方法製作。例如，可藉由將scFv以胜肽連結子等連結子連結而製作。

【0106】 本說明書中，構成sc(Fv)2之抗原結合域之構成，例如二個VH及

第 60 頁，共 122 頁(發明說明書)

14948AAAAAAPTWF

二個VL以單鏈多胜肽之N末端側為基點，而依VH、VL、VH、VL([VH]連結子[VL]連結子[VH]連結子[VL])之順序排列為特徵的抗體，但二個VH與2個VL之順序不特別限於上述構成，可以任意順序排列。例如以下順序之構成。

- [VL]連結子[VH]連結子[VH]連結子[VL]
- [VH]連結子[VL]連結子[VL]連結子[VH]
- [VH]連結子[VH]連結子[VL]連結子[VL]
- [VL]連結子[VL]連結子[VH]連結子[VH]
- [VL]連結子[VH]連結子[VL]連結子[VH]

【0107】 針對sc(Fv)2之分子形態，在WO2006/132352已有詳細記載，該技術領域之人士可依據此等記載製作用於製作本說明書揭示之抗原結合分子用的適當所望之sc(Fv)2。

【0108】 又，本發明之抗原結合分子也可接合PEG等擔體高分子或抗癌劑等有機化合物。又，可以插入糖鏈附加序列並且適當附加使糖鏈獲得所望之效果。

【0109】 結合抗體可變區之連結子，可使用能以基因工程導入之任意胜肽連結子、或合成化合物連結子(例如參照Protein Engineering, 9 (3), 299-305, 1996)揭示之連結子等，但本發明中以胜肽連結子較佳。胜肽連結子之長度不特別限定，可以視目的由該技術領域之人士適當選擇，但較佳長度為5個胺基酸以上(上限不特別限定，但通常為30個胺基酸以下，較佳為20個胺基酸以下)，尤佳為15個胺基酸。sc(Fv)2含有3個胜肽連結子時，可全部使用同長度之胜肽連結子，也可使用不同長度之胜肽連結子。

【0110】 例如為胜肽連結子時：

Ser
Gly · Ser

- Gly · Gly · Ser
- Ser · Gly · Gly
- Gly · Gly · Gly · Ser(序列編號：15)
- Ser · Gly · Gly · Gly(序列編號：16)
- Gly · Gly · Gly · Gly · Ser(序列編號：17)
- Ser · Gly · Gly · Gly · Gly(序列編號：18)
- Gly · Gly · Gly · Gly · Gly · Ser(序列編號：19)
- Ser · Gly · Gly · Gly · Gly · Gly(序列編號：20)
- Gly · Gly · Gly · Gly · Gly · Gly · Ser(序列編號：21)
- Ser · Gly · Gly · Gly · Gly · Gly · Gly(序列編號：22)
- (Gly · Gly · Gly · Gly · Ser(序列編號：17))n
- (Ser · Gly · Gly · Gly · Gly(序列編號：18))n

[n為1以上之整數]等。惟，該技術領域之人士可因應目的適當選擇胜肽連結子之長度或序列。

【0111】 合成化學物連結子(化學交聯劑)為胜肽交聯通常可用之交聯劑，例如N-羥基琥珀醯亞胺(NHS)、二琥珀醯亞胺基辛二酸酯(DSS)、雙(磺基琥珀醯亞胺基)辛二酸酯(BS3)、二硫代雙(琥珀醯亞胺基丙酸酯)(DSP)、二硫代雙(磺基琥珀醯亞胺基丙酸酯)(DTSSP)、乙二醇雙(琥珀醯亞胺基琥珀酸酯)(EGS)、乙二醇雙(磺基琥珀醯亞胺基琥珀酸酯)(磺基－EGS)、二琥珀醯亞胺基酒石酸鹽(DST)、二磺基琥珀醯亞胺基酒石酸鹽(磺基－DST)、雙[2-(琥珀醯亞胺氧基羰氧基)乙基]砒(BSO-COES)、雙[2-(磺基琥珀醯亞胺氧基羰氧基)乙基]砒(磺基－BSO-COES)等，該等交聯劑有市售。

【0112】 結合4個抗體可變區時，通常需要3個連結子，但可全部使用相同連結子也可使用不同的連結子。

【0113】 Fab、F(ab')₂、或Fab'

「Fab」由一條輕鏈、及一條重鏈之CH1區域及可變區構成。Fab分子之重鏈無法與其他重鏈分子形成雙硫鍵。

【0114】 「F(ab')₂」及「Fab'」，係指將免疫球蛋白(單株抗體)以蛋白質分解酵素胃蛋白酶或木瓜酶等處理以製造，在鉸鏈區中之2條H鏈間存在之雙硫鍵的前後消化而生成之抗體片段。例如可製造將IgG以木瓜酶處理，將鉸鏈區中之2條H鏈間存在之雙硫鍵之上游切斷而由VL(L鏈可變區)與CL(L鏈恆定區)構成的L鏈、及由VH(H鏈可變區)與CH₁(H鏈恆定區中之 γ 1區)構成之H鏈片段在C末端區以雙硫鍵結合之相同的2個抗體片段。該等2個相同的抗體片段分別稱為Fab'。

【0115】 「F(ab')₂」包含二條輕鏈、及鏈間之雙硫鍵以形成於2條重鏈間之方式含有CH1域及CH2域之一部分恆定區之二條重鏈。構成本說明書揭示之抗原結合分子之F(ab')₂，可藉由將具所望之抗原結合域的全長單株抗體等以胃蛋白酶等蛋白質分解酵素予以部分消化後，使Fc片段吸附於PROTEIN A管柱而去除以理想地取得。該蛋白質分解酵素只要是藉由適當設定pH等酵素之反應條件而消化全長抗體以限制地產生F(ab')₂者即不特別限定，例如胃蛋白酶或無花果蛋白酶(ficin)等。

【0116】 Fc區

構成本說明書揭示之抗原結合分子的Fc區，當將單株抗體等抗體以胃蛋白酶等蛋白質分解酵素予以部分消化後，使片段吸附於PROTEIN A管柱、或PROTEIN G管柱後，以適當溶出緩衝液等使溶出可以理想地取得。該蛋白質分解酵素只要是藉由適當設定pH等酵素之反應條件而能消化單株抗體等抗體者即不特別限定，例如胃蛋白酶或無花果蛋白酶(ficin)等。

【0117】 本說明書記載之抗原結合分子中，包含構成IgG1、IgG2、IgG3

第 63 頁，共 122 頁(發明說明書)

14948AAAAAAPTWF

或IgG4之Fc區的胺基酸當中對於Fc γ 受體之結合活性降低的Fc區。

【0118】 抗體同種型係由恆定區之構造決定。IgG1、IgG2、IgG3、IgG4之各同種型之恆定區，各稱為C γ 1、C γ 2、C γ 3、C γ 4。構成人類C γ 1、C γ 2、C γ 3、C γ 4之Fc區的多胜肽的胺基酸序列例如序列編號：23、24、25、26。構成各胺基酸序列之胺基酸殘基、與kabat之EU編號(本說明書也稱為EU INDEX)之間的關係如第12圖所示。

【0119】 Fc區，係指包含二條輕鏈及以鏈間之雙硫鍵形成在2條重鏈間之方式包含CH1域及CH2域間之恆定區之一部分的二條重鏈的F(ab')₂以外的區。構成本說明書揭示之抗原結合分子之Fc區，可藉由將IgG1、IgG2、IgG3、IgG4單株抗體等以胃蛋白酶等蛋白質分解酵素部分消化後，使吸附於PROTEIN A管柱之區分再溶出而理想地取得。該蛋白質分解酵素只要是藉由適當設定pH等酵素之反應條件而消化全長抗體以限制地產生F(ab')₂者即不特別限定，例如胃蛋白酶或無花果蛋白酶(ficin)等。

【0120】 Fc γ 受體

Fc γ 受體係指能結合於IgG1、IgG2、IgG3、IgG4單株抗體之Fc區的受體，也意指實質上由Fc γ 受體基因所編碼之蛋白質之家族各成員。人類中，該家族包含：含同功型(isoform)Fc γ RIa、Fc γ RIb及Fc γ RIc之Fc γ RI(CD64)；同功型Fc γ RIIa(含同種異型(allotype)H131及R131)、Fc γ RIIb(含Fc γ RIIb-1及Fc γ RIIb-2)及含Fc γ RIIc之Fc γ RII(CD32)；及含同功型Fc γ RIIIa(含同種異型V158及F158)及Fc γ RIIIb(含同種異型Fc γ RIIIb-NA1及Fc γ RIIIb-NA2)之Fc γ RIII(CD16)，及各種未發現的人類Fc γ R類或Fc γ R同功型或同種異型，但不限於該等。Fc γ R包含人類、小鼠、大鼠、兔及猴來源，但不限於該等，可為各種生物來源。小鼠Fc γ R類，包含Fc γ RI(CD64)、Fc γ RII(CD32)、Fc γ RIII(CD16)及Fc γ RIII-2(CD16-2)、及各種未發現的小鼠Fc γ R類或Fc γ R同功型或同種異型，但不限於該等。如此的Fc γ 受體，較

佳例有人類FcγRI(CD64)、FcγRIIA(CD32)、FcγRIIB(CD32)、FcγRIIIA(CD16)及/或FcγRIIIB(CD16)。FcγRI之多核苷酸序列及胺基酸序列各記載於序列編號：27(NM_000566.3)及28(NP_000557.1)，FcγRIIA之多核苷酸序列及胺基酸序列各記載於序列編號：29(BC020823.1)及30(AAH20823.1)，FcγRIIB之多核苷酸序列及胺基酸序列各記載於序列編號：31(BC146678.1)及32(AAI46679.1)，FcγRIIIA之多核苷酸序列及胺基酸序列各記載於序列編號：33(BC033678.1)及34(AAH33678.1)，FcγRIIIB之多核苷酸序列及胺基酸序列各記載於序列編號：35(BC128562.1)及36(AAI28563.1) (括弧內代表RefSeq註冊編號)。Fcγ受體是否對於IgG1、IgG2、IgG3、IgG4單株抗體之Fc區具結合活性，除了上述記載之FACS或ELISA格式以外，可利用ALPHA篩選 (Amplified Luminescent Proximity Homogeneous Assay)或利用表面等離子共振(SPR)現象之BIAcore法等確認(Proc.Natl.Acad.Sci.USA (2006) 103 (11), 4005-4010)。

【0121】 又，「Fc配體」或「效應子配體」係指與抗體之Fc區結合而形成Fc/Fc配體複合體之任意生物來源的分子，較佳為多肽。Fc配體對於Fc之結合，較佳為誘發1或更多的效應子機能。Fc配體包含Fc受體、FcγR、FcαR、FcεR、FcRn、C1q、C3、甘露聚糖結合凝集素、甘露糖受體、葡萄球菌之PROTEIN A、葡萄球菌之蛋白質G及病毒之FcγR，但不限於該等。Fc配體也包含與FcγR相同之Fc受體之家族Fc受體相同體(FcRH)(Davis et al.,(2002)Immunological Reviews 190, 123-136)。Fc配體也包含與Fc結合之未曾發現的分子。

【0122】 對於Fcγ受體之結合活性

Fc區對於FcγI、FcγIIA、FcγIIB、FcγIIIA及/或FcγIIIB中任一Fcγ受體之結合活性降低之情事，除可藉由上述記載之FACS或ELISA格式，也可利用ALPHA篩選 (Amplified Luminescent Proximity Homogeneous Assay)或利用表面等離子共振(SPR)現象之BIAcore法等確認(Proc.Natl.Acad.Sci.USA (2006) 103 (11),

4005-4010)。

【0123】 ALPHA篩選，係使用捐出者與接受者2個珠粒的ALPHA技術，依據下列原理實施。結合於捐出者珠粒的分子，會與結合於接受者珠粒之分子於生物學上交互作用，僅有2個珠粒於接近狀態時，檢測到發光信號。由雷射激發之捐出者珠粒內的光敏化劑，會將周邊的氧變換為激發狀態之單線態氧(singlet)。單線態氧會往捐出者珠粒周邊擴散，當到達接近的接受者珠粒時，會引起珠粒內之化學發光反應，最終發出光。當結合於捐出者珠粒之分子與結合於接受者珠粒之分子無交互作用時，捐出者珠粒產生之單線態氧不會到達接受者珠粒，故不會引起化學發光反應。

【0124】 例如，經生物素標記之抗原結合分子結合於捐出者珠粒，且於接受者珠粒有以谷胱甘肽S轉移酶(GST)標籤化之Fc γ 受體結合。於不存在彼此競爭之具突變Fc區之抗原結合分子時，具野生型Fc區之抗原結合分子會與Fc γ 受體交互作用，產生520-620 nm之信號。具未經標籤化之突變Fc區的抗原結合分子，會與具野生型Fc區之抗原結合分子彼此競爭Fc γ 受體間之交互作用。彼此競爭之結果，可藉由定量表現的螢光減少而決定相對的結合親和性。抗體等抗原結合分子使用Sulfo-NHS-生物素等予以生物素化之方法為公知。就將Fc γ 受體以GST標籤化之方法，可適當採用將編碼為Fc γ 受體之多核苷酸與編碼為GST之多核苷酸於框架內融合成的融合基因保持於可表現之載體之細胞等中表現，並使用谷胱甘肽管柱精製之方法等。獲得之信號例如可使用GRAPHPAD PRISM(GraphPad公司、San Diego)等軟體，利用非線形迴歸解析，並擬合於單部位彼此競爭(one-site competition)模型而適當解析。

【0125】 若將觀察交互作用之物質的其中之一(配體)固定在感應晶片的金薄膜上，並從感應晶片的背側照光使在金薄膜與玻璃的境界面發生全反射，則一部分反射光會形成反射強度降低的部分(SPR信號)。若觀察交互作用之物質

的其中另一者(分析物)流到感應晶片之表面並且配體與分析物結合，則經固定化的配體分子的質量會增加，且感應晶片表面之溶媒之折射率會改變。由於該折射率之改變，SPR信號之位置會偏移(反之，若結合解離，會回到信號的位置)。Biacore系統取上述偏移量，亦即在感應晶片表面之質量變化為縱軸，表示質量之時間變化當做測定數據(傳感圖)。從傳感圖的曲線可以求取動力學：結合速度常數(k_a)與解離速度常數(k_d)，從該常數之比可求取親和性(KD)。BIACORE法也可適用抑制測定法。抑制測定法例如記載於Proc.Natl.Acad.Sci.USA (2006) 103 (11), 4005-4010。

【0126】 本說明書中，對於Fc γ 受體之結合活性降低，係例如基於上述解析方法，比起當為對照之抗原結合分子之彼此競爭活性，待驗抗原結合分子之彼此競爭活性顯示50%以下、較佳為45%以下、40%以下、35%以下、30%以下、20%以下、15%以下、尤佳為10%以下、9%以下、8%以下、7%以下、6%以下、5%以下、4%以下、3%以下、2%以下、1%以下之結合活性。

【0127】 當做對照之抗原結合分子，可以適當使用具IgG1、IgG2、IgG3或IgG4單株抗體之Fc區的多胜肽聯合體。該Fc區之構造，記載於序列編號：37 (RefSeq註冊編號AAC82527.1之N末端加成A)、38 (RefSeq註冊編號AAB59393.1之N末端加成A)、25 (RefSeq註冊編號CAA27268.1之N加成A)、39 (RefSeq註冊編號AAB59394.1之N末端加成A)。又，當使用具某特定同種型之抗體之Fc區之突變體的抗原結合分子當做待驗物質時，藉由以具該特定同種型之抗體之Fc區的抗原結合分子當做對照，可以驗證該突變體具有之突變對於Fc γ 受體之結合活性的效果。如上述，可以適當製作已驗證對於Fc γ 受體之結合活性降低之具Fc區之突變體之抗原結合分子。

【0128】 如此的突變體，例如依EU編號於特定胺基酸231A-238S缺失(WO 2009/011941)、C226S、C229S、P238S、(C220S)(J.Rheumatol (2007) 34, 11)、

C226S、C229S(Hum.Antibod.Hybridomas (1990) 1(1), 47-54)、C226S、C229S、E233P、L234V、L235A(Blood (2007) 109, 1185-1192)等突變體為公知。

【0129】 亦即，構成特定同種型之抗體之Fc區的胺基酸，依EU編號指定之下列任一胺基酸；220位、226位、229位、231位、232位、233位、234位、235位、236位、237位、238位、239位、240位、264位、265位、266位、267位、269位、270位、295位、296位、297位、298位、299位、300位、325位、327位、328位、329位、330位、331位、332位經取代之具Fc區之抗原結合分子為理想。Fc區之起源抗體之同種型不特別限定，可以適當利用以IgG1、IgG2、IgG3或IgG4單株抗體為起源之Fc區，但較佳為使用以IgG1抗體為起源之Fc區。

【0130】 例如，構成IgG1抗體之Fc區的胺基酸當中，具施有依EU編號指定之下列任一取代(數字代表依EU編號指定之胺基酸殘基之位置，位於數字前之單字母胺基酸記號代表取代前之胺基酸殘基，位於數字後之單字母胺基酸記號代表取代前之胺基酸殘基)；

- (a)L234F、L235E、P331S、
- (b)C226S、C229S、P238S、
- (c)C226S、C229S、
- (d)C226S、C229S、E233P、L234V、L235A
- (e)L234A、L235A或L235R、N297A
- (f)L235A或L235R、S239K、N297A

之Fc區、或具231位至238位之胺基酸序列缺失之Fc區的抗原結合分子也可適當使用。

【0131】 又，構成IgG2抗體之Fc區之胺基酸當中，施以依EU編號指定之下列任一取代(數字代表依EU編號指定之胺基酸殘基之位置，位於數字前之單字母胺基酸記號代表取代前之胺基酸殘基，位於數字後之單字母胺基酸記號代表

取代前之胺基酸殘基)；

(g)H268Q、V309L、A330S、P331S

(h)V234A

(i)G237A

(j)V234A、G237A

(k)A235E、G237A

(l)V234A、A235E、G237A

之具有Fc區的抗原結合分子也可適當使用。

【0132】 又，如下的抗原結合分子也可適當使用，構成IgG3抗體之Fc區之胺基酸當中，施有依EU編號指定下列任一取代(數字代表依EU編號指定之胺基酸殘基之位置，位於數字前之單字母胺基酸記號代表取代前之胺基酸殘基，位於數字後之單字母胺基酸記號代表取代前之胺基酸殘基)；

(m)F241A

(n)D265A

(o)V264A

。

【0133】 又，構成IgG4抗體之Fc區之胺基酸當中，施有依EU編號指定下列任一取代(數字代表依EU編號指定之胺基酸殘基之位置，位於數字前之單字母胺基酸記號代表取代前之胺基酸殘基，位於數字後之單字母胺基酸記號代表取代前之胺基酸殘基)；

(p)L235A、G237A、E318A

(q)L235E

(r)F234A、L235A的具Fc區的抗原結合分子也可適當使用。

【0134】 其他較佳例，例如構成IgG1抗體之Fc區之胺基酸當中，依EU編

號指定之下列任一胺基酸；233位、234位、235位、236位、237位、327位、330位、331位取代為對應的IgG2或IgG4中其EU編號所對應之胺基酸的具Fc區的抗原結合分子。

【0135】 作為其他理想例，構成IgG1抗體之Fc區之胺基酸中，依EU編號指定之下列任一或更多之胺基酸；234位、235位、297位取代成其他胺基酸之具Fc區之抗原結合分子。取代後存在之胺基酸之種類不特別限定，宜為234位、235位、297位中之任一或更多胺基酸取代為丙胺酸之具Fc區之抗原結合分子尤佳。

【0136】 作為其他理想例，例如構成IgG1抗體之Fc區之胺基酸中，依EU編號指定之下列任一胺基酸；265位取代成其他胺基酸之具Fc區之抗原結合分子。取代後存在之胺基酸種類不特別限定，265位之胺基酸取代為丙胺酸之具Fc區之抗原結合分子尤佳。

【0137】 多專一性抗原結合分子

本發明之「多專一性抗原結合分子」之理想態樣之一可列舉多專一性抗體。當使用針對Fc γ 受體之結合活性降低之Fc區作為多專一性抗體之Fc區時，也可以適當使用將多專一性抗體作為起源之Fc區。本發明之多專一性抗體尤佳為雙專一性抗體。在此，雙專一性抗體係指有2種不同之專一性之抗體。IgG型之雙專一性抗體可藉由使將2種產生IgG抗體之融合瘤予以融合而生成的混成融合瘤(hybrid hybridoma(quadroma))分泌(Milstein C et al.Nature (1983) 305, 537-540)。

【0138】 又，IgG型雙專一性抗體係藉由將構成目的之二種IgG之L鏈及H鏈的基因共計四種基因導入細胞並使其共表現而分泌。但該等方法產生之IgG之H鏈與L鏈之組合理論上有10種。從10種IgG精製出由目的組合之H鏈L鏈構成的IgG有困難。再者，目的組合者的分泌量在理論上顯著降低，故需要大規模培養，製造上成本會更增加。

【0139】 所以，本發明之多專一性抗原結合分子可適用促進目的組合之H

鏈間及L鏈H鏈間之聯合之技術。

例如:多專一性抗體之聯合化可採用對於抗體H鏈之第2不變區(CH2)或H鏈之第3不變區(CH3)之界面導入電荷性排斥而抑制非目的之H鏈彼此聯合之技術(WO2006/106905)。

於CH2或CH3之界面導入電荷性排斥而抑制非意圖之H鏈彼此聯合之技術中，在H鏈之另一不變區之界面接觸之胺基酸殘基，例如CH3區之EU編號356號殘基、EU編號439號殘基、EU編號357號殘基、EU編號370號殘基、EU編號399號殘基、EU編號409號殘基對應之區域。

更具體而言例如:可為含有2種H鏈CH3區之抗體，第1H鏈CH3區之以下之(1)~(3)所示之胺基酸殘基之群組選出之1組至3組胺基酸殘基有同種電荷之抗體；(1)為H鏈CH3區所含之胺基酸殘基且EU編號356位及439位之胺基酸殘基、(2)H鏈CH3區所含之胺基酸殘基且EU編號357位及370位之胺基酸殘基、(3)H鏈CH3區所含之胺基酸殘基且EU編號399位及409位之胺基酸殘基。

又，可製作從和上述第1H鏈CH3區為不同之第2H鏈CH3區之前述(1)~(3)所示之胺基酸殘基之群組選出之胺基酸殘基之群組且和前述第1H鏈CH3區有同種電荷之前述(1)~(3)所示之胺基酸殘基之群組所對應之1組至3組胺基酸殘基，具有和前述第1H鏈CH3區之對應之胺基酸殘基有相反電荷之抗體。

上述(1)~(3)記載之各胺基酸殘基於聯合時彼此接近。若為該技術領域中有通常知識者可針對所望之H鏈CH3區或H鏈不變區，利用使用市售軟體之同源性模擬等找到上述(1)~(3)之胺基酸殘基所對應的部位，能適當地將該部位之胺基酸殘基供改變。

【0140】 上述抗體之「具有電荷之胺基酸殘基」宜從例如:以下(a)或(b)中任一群所含之胺基酸殘基選擇較佳；

(a)麩胺酸(E)、天冬胺酸(D)、

第 71 頁，共 122 頁(發明說明書)

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(b)離胺酸(K)、精胺酸(R)、組胺酸(H)。

上述抗體中，「有同種電荷」，係指例如:2個以上之胺基酸殘基均具上述(a)或(b)中任一群所含之胺基酸殘基。「有相反電荷」，係指例如:2個以上之胺基酸殘基中之至少1個胺基酸殘基具有上述(a)或(b)中任一群所含之胺基酸殘基時，其餘的胺基酸殘基具有不同群所含之胺基酸殘基。

於理想態樣，上述抗體也可第1H鏈CH3區與第2H鏈CH3區利用雙硫鍵交聯。

【0141】 本發明中供改變的胺基酸殘基不限於上述抗體之可變區或抗體之不變區之胺基酸殘基。若為該技術領域中有通常知識者，可針對多胜肽變異體或異種多聚體，利用使用市售軟體的同源性模擬等，找出形成界面之胺基酸殘基，並以控制聯合之方式將該部位之胺基酸殘基供改變。

【0142】 本發明之多專一性抗體之聯合化可以更適用其他公知技術。藉由將存在於抗體之其中一H鏈之Fc區之胺基酸側鏈取代成較大側鏈(knob; 突起)並將存在於另一H鏈之相對之Fc區之胺基酸側鏈取代成較小側鏈(hole; 空隙)，以突起能配置於空隙內的方式，能有效率地使具Fc區之有不同胺基酸之多胜肽彼此之聯合化 (WO1996/027011、Ridgway JB et al., Protein Engineering (1996) 9, 617-621、Merchant AM et al. Nature Biotechnology (1998) 16, 677-681、US20130336973)。

【0143】 此外，本發明之多專一性抗體之形成可更使用其他公知技術。藉由使用抗體之其中一H鏈之CH3之一部分為來自此部分所對應之IgA之序列，另一H鏈之CH3之互補部分導入了來自和此部分對應之IgA之序列而成的strand-exchange engineered domain CH3，能利用CH3的互補的聯合化有效率地引起有不同序列之多胜肽之聯合化(Protein Engineering Design & Selection, 23; 195-202, 2010)。使用此公知技術也能有效率地形成目的之多專一性抗體。

【0144】 此外，多專一性抗體之形成也可利用以下技術:WO2011/028952、

第 72 頁，共 122 頁(發明說明書)

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WO2014/018572、Nat Biotechnol. 2014 Feb;32(2):191-8.記載之利用抗體之CH1與CL之聯合化、VH、VL之聯合化之抗體製作技術、WO2008/119353、WO2011/131746記載之使用各別製備之單株抗體彼此而製作雙專一性抗體之技術(Fab Arm Exchange)、WO2012/058768、WO2013/063702記載之控制抗體重鏈之CH3間之聯合之技術、WO2012/023053記載之製作由2種輕鏈與1種重鏈構成之雙專一性抗體之技術、Christoph等(Nature Biotechnology Vol. 31, p 753-758 (2013))記載之利用分別表現由1條H鏈與1條L鏈構成之抗體之一條鏈之2個細菌細胞株之製作雙專一性抗體之技術等。

【0145】 又，即使無法有效率地形成目的之多專一性抗體，利用從產生之抗體之中將目的之多專一性抗體予以分離、精製，也可獲得本發明之多專一性抗體。例如有人報告以下方法:藉由於2種H鏈之可變區導入胺基酸取代而賦予等電點(pI)之差異，可以將2種同體與目的之異體抗體以離子交換層析精製(WO2007114325)。又，作為精製異體之方法，至今已有人報告以下方法:使用Protein A 精製由結合於Protein A之小鼠IgG2a之H鏈與不結合於Protein A之大鼠IgG2b之H鏈構成之異二聚化抗體(WO98050431、WO95033844)。又，藉由使用將為IgG與ProteinA之結合部位之EU編號435號及436號之胺基酸殘基取代成Tyr、His等向ProteinA之結合力不同之胺基酸而成的H鏈，或藉由使用依參考實施例5記載之方法取得之向ProteinA之結合力不同的H鏈，使各H鏈與Protein A之交互作用變化，並使用Protein A管柱，也可有效率地只精製異二聚化抗體。

【0146】 又，也可取得能給予不同之多數H鏈結合能力之共通L鏈並當作多專一性抗體之共通L鏈使用。藉由將如此之共通L鏈與不同之多數H鏈基因導入到細胞以使IgG表現，能為良好效率之多專一性IgG之表現(Nature Biotechnology (1998) 16, 677-681)。選擇共通H鏈時，也可利用選擇對應於任意不同之H鏈且顯示高結合能力之共通L鏈之方法(WO2004/065611)。

【0147】 又，作為本發明之Fc區，可適當使用Fc區之C末端之異質性經改善之Fc區。更具體而言，可提供構成IgG1、IgG2、IgG3或IgG4為起源之Fc區之二條多胜肽之胺基酸序列之中，依EU編號指定之446位之甘胺酸、及447位之離胺酸缺失之Fc區。

【0148】 該等技術也可組合多數，例如組合2個以上使用。又，該等技術可以對欲使其聯合之2個H鏈適當地分別適用。再者，該等技術也可對於針對上述Fc γ 受體之結合活性降低之Fc區組合使用。又，本發明之抗原結合分子也可為將已施加上述改變者作為基礎，分別製作有同一胺基酸序列之抗原結合分子。

【0149】 本發明之多專一性抗原結合分子如前述，只要包括如下的域即可，其結構不限定：

- (1)含有具Glypican3結合活性之抗體可變區之域、
- (2)含有具T細胞受體複合體結合活性之抗體可變區之域、及、
- (3)含有針對Fc γ 受體之結合活性降低之Fc區之域。

本發明中，上述各域可利用胜肽鍵直接連結。例如：使用F(ab')₂作為(1)及(2)之含抗體可變區之域，使用該等Fc區作為(3)含有針對Fc γ 受體之結合活性降低之Fc區之域時，當將(1)及(2)記載之含抗體可變區之域與(3)記載之含Fc區之域以胜肽鍵連結時，已連結之多胜肽形成抗體之結構。為了製作如此的抗體，除了從前述融合瘤之培養液精製以外，也可從安定地保持編碼為構成該抗體之多胜肽之多核苷酸的所望寄主細胞之培養液將該抗體精製。

【0150】 本發明之理想的具Glypican3結合活性之抗體可變區所含之抗體H鏈可變區，例如：表1記載之抗體H鏈可變區、或CDR1、CDR2及CDR3之胺基酸序列和表1記載之抗體H鏈可變區擁有之CDR1、CDR2及CDR3之胺基酸序列有相同CDR序列之抗體H鏈可變區、或與該可變區為機能上同等的抗體H鏈可變區。

【0151】 [表1]

序列名	序列編號	序列名	序列編號
H0000	40	GCH042	193
GCH003	170	GCH043	194
GCH005	171	GCH045	195
GCH006	172	GCH053	196
GCH007	173	GCH054	197
GCH008	174	GCH055	198
GCH010	175	GCH056	199
GCH012	176	GCH057	200
GCH013	177	GCH059	201
GCH014	178	GCH060	202
GCH015	179	GCH061	203
GCH016	180	GCH062	204
GCH019	181	GCH064	205
GCH022	182	GCH065	206
GCH023	183	GCH066	207
GCH025	184	GCH067	208
GCH026	185	GCH068	209
GCH027	186	GCH073	210
GCH029	187	GCH094	211
GCH032	188	GCH098	212
GCH034	189	GCH099	213
GCH035	190	GCH100	214
GCH039	191	H0610	215
GCH040	192		

【0152】 又，本發明之理想之具T細胞受體複合體結合活性之抗體可變區可以列舉對於T細胞受體有結合活性之抗體可變區。T細胞受體之中CD3較理想，尤其CD3ε較佳。如此之抗體可變區所含之抗體H鏈可變區，例如:表2記載之抗體H鏈可變區、或CDR1、CDR2及CDR3之胺基酸序列和表2記載之抗體H鏈可變區擁有之CDR1、CDR2及CDR3之胺基酸序列具有相同CDR序列之抗體H鏈可變區、或與該可變區為機能上同等之抗體H鏈可變區。

【0153】 [表2]

序列名	序列編號	序列名	序列編號	序列名	序列編號
hCE115HA	52	TR01H036	99	TR01H074	135
CE115HA177	64	TR01H037	100	TR01H075	136
CE115HA178	65	TR01H038	101	TR01H076	137
CE115HA179	66	TR01H039	102	TR01H077	138
CE115HA180	67	TR01H040	103	TR01H079	139
hCE115HAa	68	TR01H041	104	TR01H080	140
TR01H006	69	TR01H042	105	TR01H081	141
TR01H007	70	TR01H043	106	TR01H082	142
TR01H008	71	TR01H044	107	TR01H083	143
TR01H009	72	TR01H045	108	TR01H084	144
TR01H010	73	TR01H046	109	TR01H090	145
TR01H011	74	TR01H047	110	TR01H091	146
TR01H012	75	TR01H048	111	TR01H092	147
TR01H013	76	TR01H049	112	TR01H093	148
TR01H014	77	TR01H050	113	TR01H094	149
TR01H015	78	TR01H051	114	TR01H095	150
TR01H016	79	TR01H052	115	TR01H096	151
TR01H017	80	TR01H053	116	TR01H097	152
TR01H018	81	TR01H054	117	TR01H098	153
TR01H019	82	TR01H055	118	TR01H099	154
TR01H020	83	TR01H056	119	TR01H100	155
TR01H021	84	TR01H057	120	TR01H101	156
TR01H022	85	TR01H058	121	TR01H102	157
TR01H023	86	TR01H061	122	TR01H103	158
TR01H024	87	TR01H062	123	TR01H104	159
TR01H025	88	TR01H063	124	TR01H105	160
TR01H026	89	TR01H064	125	TR01H106	161
TR01H027	90	TR01H065	126	TR01H107	162
TR01H028	91	TR01H066	127	TR01H108	163
TR01H029	92	TR01H067	128	TR01H109	164
TR01H030	93	TR01H068	129	TR01H110	165
TR01H031	94	TR01H069	130	TR01H111	166
TR01H032	95	TR01H070	131	TR01H112	167
TR01H033	96	TR01H071	132	TR01H113	168
TR01H034	97	TR01H072	133	TR01H114	169
TR01H035	98	TR01H073	134	TR01H001	420
				TR01H002	421
				TR01H003	422
				TR01H004	423
				rCE115H	424
				CE115HA121	425
				CE115HA122	426
				CE115HA124	427
				CE115HA192	428
				CE115HA236	429
				CE115HA251	430
				CE115HA252	431

【0154】 針對構成抗體H鏈胺基酸序列之胺基酸殘基之CDR區與kabat編號之關係，列舉於第13圖。

本發明之具Glypican3結合活性之抗體可變區與具T細胞受體複合體結合活性之抗體可變區所含之抗體L鏈可變區，宜取得能給予對於Glypican3有結合活性之H鏈與對於T細胞受體複合體有結合活性之H鏈兩者之結合能力的共通L鏈，並將其作為多專一性抗原結合分子之共通L鏈可變區較佳。

本發明使用之共通之L鏈可變區可列舉：表3記載之L鏈可變區、或CDR1、CDR2及CDR3之胺基酸序列和表3記載之抗體L鏈可變區擁有之CDR1、CDR2及CDR3之胺基酸序列有相同CDR序列之抗體L鏈可變區、或與該可變區為機能上同等之抗體L可變區。

【0155】 [表3]

序列名	序列編號	序列名	序列編號	序列名	序列編號
L0000	53	L0125	264	L0214	312
L0002	217	L0126	265	L0215	313
L0003	218	L0127	266	L0216	314
L0006	219	L0129	267	L0217	315
L0007	220	L0132	268	L0218	316
L0008	221	L0134	269	L0219	317
L0009	222	L0136	270	L0220	318
L0011	223	L0137	271	L0222	319
L0012	224	L0138	272	L0223	320
L0013	225	L0139	273	L0224	321
L0014	226	L0140	274	L0226	322
L0015	227	L0141	275	L0227	323
L0016	228	L0143	276	L0228	324
L0032	229	L0144	277	L0229	325
L0038	230	L0145	278	L0230	326
L0039	231	L0147	279	L0231	327
L0041	232	L0148	280	L0232	328
L0042	233	L0149	281	L0233	329
L0043	234	L0151	282	L0234	330
L0044	235	L0152	283	L0235	331
L0045	236	L0154	284	L0236	332
L0046	237	L0155	285	L0237	333
L0047	238	L0157	286	L0238	334
L0062	239	L0160	287	L0239	335
L0063	240	L0161	288	L0240	336
L0064	241	L0163	289	L0241	337
L0065	242	L0167	290	L0242	338
L0066	243	L0168	291	L0243	339
L0069	244	L0173	292	L0246	340
L0075	245	L0175	293	L0247	341
L0079	246	L0180	294	L0248	342
L0082	247	L0181	295	L0249	343
L0085	248	L0186	296	L0250	344
L0089	249	L0187	297	L0258	345
L0090	250	L0200	298	L0259	346
L0091	251	L0201	299	L0260	347
L0093	252	L0202	300	L0261	348
L0104	253	L0203	301	L0262	349
L0106	254	L0204	302	L0263	350
L0107	255	L0205	303	L0264	351
L0109	256	L0206	304	L0265	352
L0113	257	L0207	305	L0266	353
L0115	258	L0208	306	L0267	354
L0117	259	L0209	307	L0268	355
L0120	260	L0210	308	L0269	356
L0122	261	L0211	309	L0270	357
L0123	262	L0212	310	L0271	358
L0124	263	L0213	311	L0272	359

【0156】 構成抗體L鏈胺基酸序列之胺基酸殘基之CDR區與kabat編號之關係列舉於第14圖。

【0157】 在此，本發明中，「機能上同等」係指:針對抗原之結合親和性為同等、或作為多專一性抗原結合分子使用時，對於表現Glypican3之細胞或含該細胞之組織之細胞傷害活性為同等。結合親和性及細胞傷害活性可基於本說明書之記載測定。測定細胞傷害活性之細胞可使用表現GPC3之所望之細胞或含該細胞之所望組織，例如可使用表現GPC3之人癌細胞株PC-10或NCI-H446。又，可為抗體不變區對Fc γ 受體之結合活性之降低為同等。

【0158】 例如:和本說明書記載之抗體H鏈可變區(原本之H鏈可變區)為機能上同等之抗體H鏈可變區，係指當和本說明書記載之抗體L鏈可變區組合成原本之H鏈之配對時，結合親和性為同等，或作為多專一性抗原結合分子使用時，對於表現Glypican3之細胞或含該細胞之組織之細胞傷害活性為同等。又，和本說明書記載之抗體L鏈可變區(原本之L鏈可變區)為機能上同等之抗體L鏈可變區，係指當和本說明書記載之抗體H鏈可變區組合作為原本L鏈之配對時，結合親和性同等，或作為多專一性抗原結合分子使用時，對於表現Glypican3之細胞或含該細胞之組織之細胞傷害活性為同等。

【0159】 又，「同等」不一定須為同程度之活性，也可活性增強。具體而言，可列舉:針對抗原之結合親和性之情形，和成為對照之抗體可變區之結合親和性(親KD值)比較之值(KD值/親KD值)為1.5以下的情形。KD值/親KD值之值較佳為1.3以下，更佳為1.2以下、1.1以下、1.0以下、0.9以下、0.8以下、0.7以下、0.6以下、或0.5以下。下限無限制，例如 10^{-1} 、 10^{-2} 、 10^{-3} 、 10^{-4} 、 10^{-5} 、或 10^{-6} 亦可。具體而言，本發明之KD值/親代KD值之值宜為 10^{-6} ~ 1.5×10^{-0} ，更佳為 10^{-6} ~ 10^{-1} ，再更佳為 10^{-6} ~ 10^{-2} ，又更佳為 10^{-6} ~ 10^{-3} 。細胞傷害活性之情形，可列舉和成為對照之多專一性抗原結合分子之細胞增殖抑制率(親代細胞增殖抑制

率)比較之值(細胞增殖抑制率/親代細胞增殖抑制率)為0.7以上的情形。添加之多專一性抗原結合分子之濃度可適當決定，較佳為例如於0.01nM、0.05nM、0.1nM、0.5nM、或1nM，較佳為0.05nM或0.1nM測定。細胞增殖抑制率/親代細胞增殖抑制率之值較佳為0.8以上，更佳為0.9以上、1.0以上、1.2以上、1.5以上、2以上、3以上、5以上、10以上、或20以上。上限無限制，可為例如10、 10^2 、 10^3 、 10^4 、 10^5 、或 10^6 。

【0160】 又，細胞傷害活性之情形，可列舉和相對於原本之多專一性抗原結合分子之細胞之50%增殖抑制濃度(親代細胞50%增殖抑制濃度)比較之值(細胞50%增殖抑制濃度/親代細胞50%增殖抑制濃度)為1.5以下的情形。50%增殖抑制濃度係指:和未添加多專一性抗原結合分子的情形相比，使細胞增殖率減半所須之多專一性抗原結合分子之濃度。「細胞50%增殖抑制濃度/親代細胞50%增殖抑制濃度」之值較佳為1.3以下，更佳為1.2以下、1.1以下、1.0以下、0.9以下、0.8以下、0.7以下、0.6以下、或0.5以下。下限無限制，例如 10^{-1} 、 10^{-2} 、 10^{-3} 、 10^{-4} 、 10^{-5} 、或 10^{-6} 亦可。具體而言 10^{-6} ~ 1.5×10^{-0} 較理想，更佳為 10^{-6} ~ 10^{-1} ，又更佳為 10^{-6} ~ 10^{-2} ，再更佳為 10^{-6} ~ 10^{-3} 。

【0161】 又，針對含具有GPC3結合活性之抗體可變區之域，針對GPC3(例如人GPC3)之KD值例如可為 5×10^{-9} M 以下，較佳為 4×10^{-9} M 以下，例如 3×10^{-9} M 以下、 2×10^{-9} M 以下、 1×10^{-9} M 以下、 8×10^{-10} M 以下、 5×10^{-10} M 以下、 4×10^{-10} M 以下、 3×10^{-10} M 以下、 2×10^{-10} M 以下、 1×10^{-10} M 以下、 8×10^{-11} M 以下、 5×10^{-11} M 以下、 4×10^{-11} M 以下、 3×10^{-11} M 以下、 2×10^{-11} M 以下、 1×10^{-11} M 以下、 8×10^{-12} M 以下、 5×10^{-12} M 以下、 4×10^{-12} M 以下、 3×10^{-12} M 以下、 2×10^{-12} M 以下、 1×10^{-12} M 以下、 8×10^{-13} M 以下、 5×10^{-13} M 以下、 4×10^{-13} M 以下、 3×10^{-13} M 以下、 2×10^{-13} M 以下、或 1×10^{-13} M 以下。

【0162】 又，針對含有具T細胞受體複合體結合活性之抗體可變區之域，

針對人T細胞受體複合體，例如人T細胞受體，更具體而言例如人CD3ε鏈之KD值，可為例如 2×10^{-7} M 以下，較佳為 1.5×10^{-7} M 以下，例如 1.4×10^{-7} M以下、 1.3×10^{-7} M以下、 1.2×10^{-7} M以下、 1×10^{-7} M以下、 3×10^{-8} M以下、 2×10^{-8} M以下、 1×10^{-8} M以下、 8×10^{-9} M以下、 5×10^{-9} M以下、 4×10^{-9} M以下、 3×10^{-9} M以下、 2×10^{-9} M以下、 1×10^{-9} M以下、 8×10^{-10} M以下、 5×10^{-10} M以下、 4×10^{-10} M以下、 3×10^{-10} M以下、 2×10^{-10} M以下、 1×10^{-10} M以下、 8×10^{-11} M以下、 5×10^{-11} M以下、 4×10^{-11} M以下、 3×10^{-11} M以下、 2×10^{-11} M以下、 1×10^{-11} M以下、 8×10^{-12} M以下、 5×10^{-12} M以下、 4×10^{-12} M以下、 3×10^{-12} M以下、 2×10^{-12} M以下、或 1×10^{-12} M以下。

【0163】 本發明之多專一性抗原結合分子較佳為針對人GPC3及人T細胞受體複合體(例如人CD3ε鏈)之KD值各為 5×10^{-9} M 以下及 2×10^{-7} M 以下，更佳為各為 1×10^{-9} M 以下及 5×10^{-8} M 以下。

【0164】 本發明之「機能上同等」之抗體可變區只要是符合上述條件之抗體H鏈可變區及/或抗體L鏈可變區即可，無特殊限定。如此的抗體可變區，例如：可於上述表1~3之可變區之胺基酸序列有1或多數胺基酸(例如1、2、3、4、5或10胺基酸)取代、缺失、附加及/或插入。為了在胺基酸序列將1或多數胺基酸取代、缺失、附加及/或插入之對於該技術領域中有通常知識者周知的方法已知有對於蛋白質導入變異之方法。例如：若為該技術領域中有通常知識者，可藉由使用部位專一性變異誘發法 (Hashimoto-Gotoh, T, Mizuno, T, Ogasahara, Y, and Nakagawa, M. (1995) An oligodeoxyribonucleotide- directed dual amber method for site-directed mutagenesis. Gene 152, 271-275、Zoller, MJ, and Smith, M.(1983) Oligonucleotide-directed mutagenesis of DNA fragments cloned into M13 vectors.Methods Enzymol. 100, 468-500、Kramer,W, Drutsa,V, Jansen,HW, Kramer,B, Pflugfelder,M, and Fritz,HJ(1984) The gapped duplex DNA approach to oligonucleotide-directed mutation construction. Nucleic Acids Res. 12, 9441-9456、

Kramer W, and Fritz HJ(1987) Oligonucleotide-directed construction of mutations via gapped duplex DNA Methods. Enzymol. 154, 350-367、Kunkel,TA(1985) Rapid and efficient site-specific mutagenesis without phenotypic selection.Proc Natl Acad Sci U S A. 82, 488-492)等於胺基酸序列導入適當變異，以製備和有上述機能之抗體可變區為機能上同等之可變區。

【0165】 改變胺基酸殘基時，希望是變異成保守胺基酸側鏈之性質之另一胺基酸。例如胺基酸側鏈之性質可以列舉:疏水性胺基酸(A、I、L、M、F、P、W、Y、V)、親水性胺基酸(R、D、N、C、E、Q、G、H、K、S、T)、有脂肪族側鏈之胺基酸(G、A、V、L、I、P)、有含羥基之側鏈之胺基酸(S、T、Y)、有含硫原子之側鏈之胺基酸(C、M)、有含羧酸及醯胺之側鏈之胺基酸(D、N、E、Q)、有含鹼之側鏈之胺基酸(R、K、H)、及有含芳香族之側鏈之胺基酸(H、F、Y、W) (括弧內均表示胺基酸之單字母標記)。該等各群內之胺基酸之取代稱為保守性取代。已知具有藉由對於某胺基酸序列利用1或多個胺基酸殘基之缺失、附加及/或取代為其他胺基酸所為之修飾而得之胺基酸序列之多胜肽會維持其生物學活性(Mark, D. F. et al., Proc.Natl.Acad.Sci.USA (1984)81:5662-6; Zoller, M. J. and Smith, M., Nucleic Acids Res.(1982)10:6487-500; Wang, A. et al., Science(1984)224:1431-3; Dalbadie-McFarland, G. et al., Proc.Natl.Acad.Sci.USA (1982)79:6409-13)。含如此之胺基酸改變之本發明之可變區，和改變前之可變區之CDR序列、FR序列或可變區全體之胺基酸序列有至少70%，更佳為至少75%，更佳為至少80%，更佳為至少85%，又更佳為至少90%，最佳為至少95%之胺基酸序列同一性。本說明書之序列同一性，係定義為:以序列同一性成為最大的方式將序列排列，導入適當間隙(gap)後，和原本H鏈可變區或L鏈可變區之胺基酸序列之殘基為相同之殘基之比例。胺基酸序列之同一性可以依後述方法決定。

【0166】 又，「機能上同等之抗體可變區」，可由例如對於由編碼為上述

第 82 頁，共 122 頁(發明說明書)

14948AAAAAAPTWF

表1~3記載之可變區之胺基酸序列之鹼基序列構成之核酸於嚴格條件下雜交的核酸獲得。為了將在嚴格條件下和由編碼為可變區之胺基酸序列之鹼基序列構成之核酸雜交的核酸予以單離，嚴格的雜交條件可列舉:6 M尿素、0.4% SDS、0.5 x SSC、37°C之條件或與其同等嚴格的雜交條件。若使用更嚴格的條件，例如:6 M尿素、0.4% SDS、0.1 x SSC、42°C之條件，能期待單離相同性更高之核酸。雜交後之洗滌條件例如0.5xSSC(1xSSC係0.15 M NaCL、0.015M 檸檬酸鈉、pH7.0)、及0.1% SDS、60°C之洗滌，更佳為 0.2xSSC、及0.1% SDS、60°C之洗滌，再更佳為 0.2xSSC、及0.1% SDS、62°C之洗滌，又更佳為 0.2xSSC、及0.1% SDS、65°C之洗滌，更佳為 0.1xSSC、及0.1% SDS、65°C之洗滌。已單離之核酸之定序可依後述公知之方法實施。單離之核酸之相同性，在鹼基序列全體至少有50%以上，更佳為70%以上，更佳為90%以上(例如:95%、96%、97%、98%、99%以上)之序列同一性。

也可將上述利用雜交技術之方法改為使用採用依據編碼為可變區之胺基酸序列之鹼基序列資訊合成之引子之基因放大法，例如:聚合酶連鎖反應(PCR)法，可將會和由編碼為可變區之胺基酸序列之鹼基序列構成之核酸於嚴格條件下雜交的核酸予以單離。

【0167】 鹼基序列及胺基酸序列之同一性可依Karlin與Altschul之演算法BLAST(Proc.Natl.Acad.Sci.USA(1993)90: 5873-7)決定。依此演算法，已開發出稱為BLASTN、BLASTX之程式(Altschul et al.,J.Mol.Biol.(1990)215:403-10)。當依據BLAST以BLASTN解析鹼基序列時，參數設為例如score = 100、wordlength = 12。又，依據BLAST利用BLASTX解析胺基酸序列時，參數設為例如score = 50、wordlength = 3。使用BLAST與Gapped BLAST程式時，使用各程式的預設參數。該等解析方法之具體手法為公知(NCBI (參照National Center for Biotechnology Information) 之 BLAST(Basic Local Alignment Search Tool) 之 網 站 ；

<http://www.ncbi.nlm.nih.gov>)。

【0168】 本發明之多專一性抗原結合分子所含之有Glypican3結合活性之抗體可變區與有T細胞受體複合體結合活性之抗體可變區之組合，只要有上述活性即不特別限定，本發明中宜為多專一性抗原結合分子之細胞傷害活性和實施例3記載之雙專一性抗體GPC3_ERY22_rCE115為同等或更高之抗原結合分子較佳。在此，「同等」，如上述，不一定要是同程度之活性，活性也可增強。和GPC3_ERY22_rCE115比較為同等，可舉和GPC3_ERY22_rCE115之細胞增殖抑制率(細胞增殖抑制率(GPC3_ERY22_rCE115))比較而得之值(細胞增殖抑制率/細胞增殖抑制率(GPC3_ERY22_rCE115))為0.7以上，較佳為0.8以上、0.9以上、1.0以上、1.2以上、1.5以上、2以上、3以上、5以上、10以上、或20以上的情形。上限不限制，例如可為10、 10^2 、 10^3 、 10^4 、 10^5 、或 10^6 。添加之多專一性抗原結合分子之濃度可適當決定，較佳為於例如0.01nM、0.05nM、0.1nM、0.5nM、或1nM，較佳為0.05nM或0.1nM測定。

【0169】 又，可舉和針對GPC3_ERY22_rCE115之細胞之50%增殖抑制濃度(50%增殖抑制濃度(GPC3_ERY22_rCE115))比較而得之值(細胞50%增殖抑制濃度/細胞50%增殖抑制濃度(GPC3_ERY22_rCE115))為1.5以下的情形。「細胞50%增殖抑制濃度/細胞50%增殖抑制濃度(GPC3_ERY22_rCE115)」之值較佳為1.3以下，更佳為1.2以下、1.1以下、1.0以下、0.9以下、0.8以下、0.7以下、0.6以下、或0.5以下。下限不限制，可以為例如 10^{-1} 、 10^{-2} 、 10^{-3} 、 10^{-4} 、 10^{-5} 、或 10^{-6} 。具體而言，宜為 10^{-6} ~ 1.5×10^{-0} ，更佳為 10^{-6} ~ 10^{-1} ，更佳為 10^{-6} ~ 10^{-2} ，又更佳為 10^{-6} ~ 10^{-3} 。

又，針對人GPC3及人T細胞受體複合體(例如人CD3ε鏈)之理想之具體KD值亦如上述。又，細胞可使用表現GPC3之所望之細胞或含該細胞之所望組織，例如可使用表現GPC3之人癌細胞株PC-10或NCI-H446。

【0170】 如此之有Glypican3結合活性之抗體可變區與有T細胞受體複合體結合活性之抗體可變區之組合，例如:表4記載之抗體H鏈可變區之組合、或CDR1、CDR2及CDR3之胺基酸序列和表4記載之抗體H鏈可變區擁有之CDR1、CDR2及CDR3之胺基酸序列具同一CDR序列之抗體H鏈可變區之組合、或與該可變區為機能上同等之抗體H鏈可變區之組合。在此，「機能上同等」如上述記載。

【0171】 [表4]

GPC3 側/T 細胞受體複合體側	序列編號
H0000/hCE115HA	40/52
H0000/CE115HA251	40/500
H0000/CE115HA236	40/429
H0000/TR01H002	40/421
H0000/CE115HA122	40/426
H0610/rCE115H	215/424
H0610/TR01H040	215/103
H0610/TR01H061	215/122
H0610/TR01H068	215/129
H0610/TR01H071	215/132
GCH054/TR01H067	197/128
GCH094/TR01H082	211/142
GCH094/TR01H084	211/144
GCH065/TR01H084	206/144
GCH065/TR01H082	206/142
GCH094/TR01H109	211/164
GCH065/TR01H109	206/164
GCH094/TR01H113	211/168
GCH065/TR01H113	206/168

【0172】 對於如此之有Glypican3結合活性之抗體可變區與有T細胞受體複合體結合活性之抗體可變區之組合為理想之共通L鏈，例如:L0000、L0011、L0201、L0203、L0204、L0206、L0208、L0209、L0211、L0212、L0222、或共通L鏈之CDR1、CDR2及CDR3之胺基酸序列和此等共通L鏈之CDR1、CDR2及CDR3之胺基酸序列有同一CDR序列之共通L鏈。具體組合，例如:表5記載之抗體H鏈可變區及共通L鏈之組合、或CDR1、CDR2及CDR3之胺基酸序列和表5記載之抗體可變區及共通L鏈擁有之CDR1、CDR2及CDR3之胺基酸序列有同一

CDR序列之抗體可變區之組合、或與該可變區為機能上同等之抗體H鏈可變區及
共通L鏈之組合。在此「機能上同等」如上述記載。

【0173】 [表5]

GPC3 側/T 細胞受體複合體側/共通 L 鏈	序列編號
H0610/rCE115H/L0000	215/424/53
H0610/TR01H040/L0000	215/103/53
H0610/TR01H040/L0201	215/103/299
H0610/TR01H040/L0203	215/103/301
H0610/TR01H040/L0204	215/103/302
H0610/TR01H040/L0206	215/103/304
H0610/TR01H040/L0208	215/103/306
H0610/TR01H040/L0209	215/103/307
H0610/TR01H040/L0211	215/103/309
H0610/TR01H061/L0000	215/122/53
H0610/TR01H068/L0000	215/129/53
H0610/TR01H071/L0000	215/132/53
GCH054/TR01H067/L0201	197/128/299
GCH054/TR01H067/L0212	197/128/310
GCH054/TR01H067/L0222	197/128/319
GCH054/TR01H067/L0000	197/128/53
GCH094/TR01H082/L0201	211/142/299
GCH094/TR01H082/L0011	211/142/223
GCH094/TR01H084/L0011	211/144/223
GCH065/TR01H084/L0011	206/144/223
GCH065/TR01H082/L0011	206/142/223
GCH094/TR01H109/L0011	211/164/223
GCH065/TR01H109/L0011	206/164/223
GCH094/TR01H113/L0011	211/168/223
GCH065/TR01H113/L0011	206/168/223

【0174】 本發明之多專一性抗原結合分子所含之Fc區只要是對於Fcγ受體
之結合活性降低之Fc區即無特殊限制，本發明之理想Fc區，例如:E22Hh之Fc區
部分與E22Hk之Fc區部分之組合、E2702GsKsc之Fc區部分與E2704sEpsc之Fc區
部分之組合、E2702sKsc之Fc區部分與E2704sEpsc之Fc區部分之組合。

【0175】 本發明之理想多專一性抗原結合分子可列舉包括對於Glypican3
有結合活性之抗體可變區與對於CD3ε有結合活性之抗體可變區之雙專一性抗

體。和雙專一性抗體GPC3_ERY22_rCE115相比較，細胞傷害活性為同等或更高較佳。如此的雙專一性抗體，例如:具表13記載之H鏈及L鏈之雙專一性抗體，或結合於和該抗體所結合之抗原決定基重複之抗原決定基且具有對於上述Fc γ 受體之結合活性降低之Fc區之雙專一性抗體。

【0176】 在此，某抗體是否認識和其他抗體重複之抗原決定基可利用兩者對於抗原決定基之競爭以確認。抗體間之競爭可利用競爭結合分析評價，就其方式可列舉酵素連結免疫吸附檢定法(ELISA)、螢光能量轉移測定法(FRET)、螢光微量測定技術(FMAT(註冊商標))等。和抗原結合之該抗體之量，與和對於重複之抗原決定基之結合競爭之候選競爭抗體(待驗抗體)之結合能力間接相關。亦即，待驗抗體對於重複之抗原決定基之量、親和性愈大，則該抗體向抗原之結合量愈低，待驗抗體向抗原之結合量愈增加。具體而言，同時對於抗原添加經適當標記之該抗體與待評價之抗體，利用標記檢測已結合之該抗體。和抗原結合之該抗體量可藉由預先標記該抗體而輕易測定。此標記無特殊限制，可選擇因應手法之標記方法。標記方法，具體而言可列舉螢光標記、放射標記、酵素標記等。

例如:對於已固定GPC3或CD3 ϵ 之珠粒同時添加經螢光標記之該抗體及未標記之該抗體或待驗抗體，以螢光微量測定技術檢測經標記的該抗體。

【0177】 在此所指「和重複之抗原決定基結合之抗體」，係指就對於經標記之該抗體之結合量因為未標記之該抗體之結合減少50%之濃度(IC₅₀)而言，待驗抗體能於未標記之該抗體之IC₅₀之通常、100倍，較佳為80倍，更佳為50倍，更佳為30倍，更佳為10倍高之濃度使標識該抗體之結合量減少至少50%之抗體。

具有和上述抗體所結合之抗原決定基為重複之抗原決定基結合之抗體之抗原結合部位的多專一性抗原結合分子可獲優良的細胞傷害活性。

【0178】 本發明之多專一性抗原結合分子可依和前述重組抗體之製造方

法為相同手法製作。

【0179】 又，本發明係關於編碼為本發明之抗原結合分子之多核苷酸。本發明之抗原結合分子可以納入任意的表現載體。於表現載體將適當寄主轉形，可製成抗原結合分子之表現細胞。培養抗原結合分子之表現細胞，並從培養上清液回收表現產物，則可與得該多核苷酸所編碼之抗原結合分子。即本發明係關於含編碼為本發明之抗原結合分子之多核苷酸的載體、保持該載體之細胞、及包含培養該細胞並從培養上清液回收抗原結合分子之步驟的抗原結合分子之製造方法。該等可以依照與例如前述重組抗體為同樣的手法獲得。

【0180】 醫藥組合物

於另一觀點，本發明提供一種將包含含有如下域之多專一性抗原結合分子作為有效成分之醫藥組合物：(1)含有具Glypican3結合活性之抗體可變區之域、(2)含有具T細胞受體複合體結合活性之抗體可變區之域、及(3)含有針對Fc γ 受體之結合活性降低之Fc區之域。又，本發明係關於含有該抗原結合分子作為有效成分之誘導細胞傷害之醫藥組合物。本發明之醫藥組合物會誘導該細胞傷害，尤其T細胞依存性細胞傷害，且宜對於罹有對該活性為預防或治療所必要之疾病之對象或有再發可能性之對象較佳。

【0181】 又，本發明之將含有以下域之多專一性抗原結合分子作為有效成分之細胞傷害誘導劑及細胞增殖抑制劑，可使用在包括對於對象投予該抗原結合分子之步驟之誘導細胞傷害之方法，或在製造細胞傷害誘導劑及細胞增殖抑制劑時使用及表現該抗原結合分子。

- (1)含有具Glypican3結合活性之抗體可變區之域、
- (2)含有具T細胞受體複合體結合活性之抗體可變區之域、及
- (3)含有針對Fc γ 受體之結合活性降低之Fc區之域。

【0182】 本發明中「包含含有(1)含有具Glypican3結合活性之抗體可變區

第 88 頁，共 122 頁(發明說明書)

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之域、(2)含有具T細胞受體複合體結合活性之抗體可變區之域、及、(3)含有針對Fc γ 受體之結合活性降低之Fc區之域之多專一性抗原結合分子作為有效成分」，係指含有該抗原結合分子作為主要活性成分，該抗原結合分子之含有率不限制。

【0183】 又，視需要可將本發明之多專一性抗原結合分子包封入微膠囊(經基甲基纖維素、明膠、聚[甲基甲基丙烯酸]等微膠囊)、膠體藥劑運送系(微脂體、白蛋白微球體、微乳劑、奈米粒子及奈米膠囊等)(參照"Remington's Pharmaceutical Science 16th edition", Oslo Ed. (1980)等)。再者，藥劑製成緩釋性藥劑之方法亦為公知，該方法可適用在本發明之多專一性抗原結合分子(J.Biomed.Mater.Res. (1981) 15, 267-277、Chemtech. (1982) 12, 98-105、美國專利第3773719號、歐洲專利公開公報EP58481號、EP133988號、Biopolymers (1983) 22, 547-556)。

【0184】 本發明之醫藥組合物、或細胞傷害誘導劑及細胞增殖抑制劑，可經口、非經口投予任一者對於患者投予。較佳為非經口投予。該投予方法具體而言例如注射投予、經鼻投予、經肺投予、經皮投予等。注射投予例如靜脈內注射、肌肉內注射、腹腔內注射、皮下注射等。例如以注射投予可將本發明之醫藥組合物、或細胞傷害誘導劑及細胞增殖抑制劑全身或局部投予。又，可依患者年紀、症狀選擇適當投予方法。投予量例如一次投予體重每1 kg可從0.0001 mg至1000 mg之範圍選擇投予量。或，可從例如每位患者在0.001 mg/體重至100000 mg/體重的範圍選擇投予量。但是本發明之醫藥組合物、或細胞傷害誘導劑及細胞增殖抑制劑不限於該等投予量。

【0185】 本發明之醫藥組合物、或細胞傷害誘導劑及細胞增殖抑制劑可依常法製劑化(例如 Remington's Pharmaceutical Science, latest edition, Mark Publishing Company, Easton, U.S.A)，也可同時含有醫藥上可容許之擔體或添加

物。例如界面活性劑、賦形劑、著色料、著香料、保存料、安定劑、緩衝劑、懸浮劑、等張化劑、黏結劑、崩散劑、潤滑劑、流動性促進劑、矯味劑等。又，不限於該等，可適當使用其他常用的擔體。具體而言，例如：輕質矽酸酐、乳糖、結晶纖維素、甘露醇、澱粉、羧甲纖維素鈣、羧甲纖維素鈉、羥基丙基纖維素、羥基丙基甲基纖維素、聚乙烯縮醛二乙基胺基乙酸酯、聚乙烯吡咯烷酮、明膠、中鏈脂肪酸三甘油酯、聚氧乙烯硬化蓖麻子油60、白糖、羧甲纖維素、玉米澱粉、無機鹽類等可當做擔體。

【0186】 又，本發明提供藉由使表現Glypican3抗原之細胞和會與該抗原結合之本發明之多專一性抗原結合分子接觸以傷害表現該抗原之細胞、或含該表現細胞之腫瘤組織之方法、或抑制該細胞或腫瘤組織之增殖之方法。會和該抗原結合之多專一性抗原結合分子作為在本發明之細胞傷害誘導劑及細胞增殖抑制劑含有之會和該抗原結合之本發明之抗原結合分子，如上述。會和該抗原結合之本發明之多專一性抗原結合分子所結合之細胞只要是表現該抗原之細胞即可，無特殊限定。

【0187】 本發明中，「接觸」係藉由在例如試驗管內培養之GPC3抗原表現細胞之培養液中添加該與癌抗原結合之本發明之多專一性抗原結合分子而實行。於該情形，添加之抗原結合分子之形狀，可適當使用溶液或由冷凍乾燥等獲得之固體等形狀。以水溶液添加時，可為純粹僅含本發明之多專一性抗原結合分子之水溶液，也可為含例如上述記載之界面活性劑、賦形劑、著色料、著香料、保存料、安定劑、緩衝劑、懸浮劑、等張化劑、黏結劑、崩散劑、潤滑劑、流動性促進劑、矯味劑等之溶液。添加濃度不特別限定，就培養液中之最終濃度而言，較佳為1 pg/ml至1 g/ml之範圍，更佳為1 ng/ml至1 mg/ml，又更佳為於1μg/ml至1 mg/ml。

【0188】 又，本發明中，「接觸」在另一態樣中，也可藉由對於將GPC3

抗原現細胞移植到體內之非人類動物，或內在具表現該抗原之細胞的動物投予而實行。投予方法可以利用經口、非經口投予任一者實施。特佳為非經口投予的投予方法，該投予方法具體而言，例如注射投予、經鼻投予、經肺投予、經皮投予等。注射投予如靜脈內注射、肌肉內注射、腹腔內注射、皮下注射等。例如利用注射投予可將本發明之醫藥組合物、或細胞傷害誘導劑及細胞增殖抑制劑對全身或局部投予。又，可由待驗動物年紀、症狀選擇適當投予方法。以水溶液投予時，可為純粹僅含本發明之多專一性抗原結合分子之水溶液，也可為含有例如上述記載之界面活性劑、賦形劑、著色料、著香料、保存料、安定劑、緩衝劑、懸浮劑、等張化劑、黏結劑、崩散劑、潤滑劑、流動性促進劑、矯味劑等之溶液。投予量例如一次投予體重每1 kg可從0.0001 mg至1000 mg之範圍選擇投予量。或，可從例如每位患者在0.001 mg/體重至100000 mg/體重的範圍選擇投予量。但是本發明之多專一性抗原結合分子不限於該等投予量。

【0189】 由於本發明之多專一性抗原結合分子之接觸引起表現構成該抗原結合分子之具有有Glypican3結合活性之抗體可變區之域所結合之表現Glypican3抗原之細胞中的細胞傷害的評價或測定方法，可適當使用以下方法。就於試管內評價或測定該細胞傷害活性之方法而言，例如細胞傷害性T細胞活性等測定法。本發明之多專一性抗原結合分子是否具T細胞性傷害活性，可以利用公知方法測定(例如Current protocols in Immunology, Chapter 7. Immunologic studies in humans, Editor, John E, Coligan et al., John Wiley & Sons, Inc.,(1993)等)。活性測定時，使用Glypican3為不同之抗原且與試驗使用之細胞未表現之抗原結合之抗原結合分子，與本發明之多專一性抗原結合分子同樣當做對照，藉由本發明之多專一性抗原結合分子比起當做對照使用之抗原結合分子顯示較強細胞傷害活性，可以判定活性。

【0190】 又，為了於活體內評價或測定細胞傷害活性，例如將表現

Glypican3抗原的細胞，移植到非人類待驗動物之皮內或皮下後，於當日或次日起每日或數日間隔將待驗抗原結合分子對於靜脈或腹腔內投予。藉由經日測定腫瘤大小，可以將該腫瘤大小的變化的差異規定為細胞傷害活性。與試管內的評價同樣投予成為對照之抗原結合分子，本發明之抗原結合分子之投予群中，腫瘤大小比起對照抗原結合分子之投予群中之腫瘤大小顯著為小時，可判定具細胞傷害活性。

【0191】 對於表現Glypican3抗原的細胞增殖的抑制效果其評價或測定方法，可理想地使用經放射線同位素標定的胸腺嘧啶攝入細胞之測定或MTT法。又，就評價或測定於活體內之細胞增殖抑制活性的方法而言，可以理想地使用與上述記載於活體內評價或測定細胞傷害活性之方法為相同之方法。

【0192】 又，本發明提供用於在本發明之方法使用的套組，其包含本發明之多專一性抗原結合分子或依照本發明之製造方法製造之多專一性抗原結合分子。該套組中可以更包裝有藥學上可容許之擔體、介質、記載使用方法之指示書等。

又，本發明係關於本發明之方法使用之本發明之多專一性抗原結合分子或依照本發明之製造方法所製造之多專一性抗原結合分子。

【0193】 又，本發明係關於具有GPC3結合活性之分子，包括本發明之多專一性抗原結合分子之具GPC3結合活性之含抗體可變區之域。又，本發明係關於具GPC3結合活性之分子，包括含有該分子所含之H鏈及L鏈各3個CDR(合計6個CDR)之H鏈及L鏈抗體可變區。又，本發明係關於具有T細胞受體複合體結合活性之分子，包括本發明之多專一性抗原結合分子之含有具T細胞受體複合體結合活性之抗體可變區之域。又，本發明係關於具T細胞受體複合體結合活性之分子，包括該分子所含之H鏈及L鏈之各3個CDR(合計6個CDR)之各H鏈及L鏈之抗體可變區。該等分子可為抗體也可為含有抗體之抗原結合片段之多胜肽。本發

明係關於結合於和該等分子重複或競爭之抗原決定基之抗體或含其抗原結合片段之多胜肽。作為含有抗體之抗原結合片段之多胜肽可適當列舉scFv、單鏈抗體(single chain antibody)、Fv、scFv2(single chain Fv 2)、Fab及F(ab')₂等。又，該等分子也可為非多專一性(雙專一性)，也可只結合在GPC3或T細胞受體複合體(例如CD3ε鏈)中的某一者。

【0194】 該等分子包括:本說明書之實施例具體例示之包含多專一性抗原結合分子之具GPC3結合活性之含抗體可變區之域(包括具GPC3結合活性之H鏈可變區及共通L鏈可變區)之分子、本說明書實施例例示之包含多專一性抗原結合分子之含有具T細胞受體複合體結合活性之抗體可變區之域(包括具T細胞受體複合體結合活性之H鏈可變區及共通L鏈可變區)之分子，此外包括此等分子所含之H鏈及L鏈之各3個CDR(合計6個CDR)且具有和相同抗原蛋白質(GPC3或T細胞受體複合體)結合之活性的分子。

【0195】 該等分子因為和本發明之多專一性抗原結合分子的CDR共通，故可期待和本發明之多專一性抗原結合分子為重複之抗原決定基結合。因此該等分子藉由和本發明之多專一性抗原結合分子共存，能和本發明之多專一性抗原結合分子競爭。藉此，例如可作為用以抑制本發明之多專一性抗原結合分子之活性(抗原結合活性、細胞傷害活性、抗腫瘤活性等)的調節劑使用。又，藉由預先使此分子和目標蛋白質(GPC3或T細胞受體複合體)結合，檢測添加本發明之多專一性抗原結合分子時因為競爭而游離出來的分子，作為用以檢測本發明之多專一性抗原結合分子已結合於目標蛋白質之檢測劑為有用。此時該等分子也可適當地以螢光物質等標記。或該等分子也可以用於篩選結合於和本發明之多專一性抗原結合分子為重複之抗原決定基的新抗體。如上述，若預先使此分子和目標蛋白質(GPC3或T細胞受體複合體)結合，並添加待驗抗體，使已結合之分子游離出來，則此待驗抗體會成為和本發明之多專一性抗原結合分子重複之抗原

決定基的抗體的候選者。藉此，能有效率地篩選新的多專一性抗原結合分子。

【0196】 該等分子之H鏈可變區及L鏈可變區之CDR之具體組合直接作為本發明之多專一性抗原結合分子之各CDR之組合而使用在本說明書列舉者。該等分子之抗原親和性(KD值)較佳為就本發明之多專一性抗原結合分子之KD值在本說明書例示之值，但不限定於此。

【0197】 又，本發明也關於編碼為該等分子之核酸、已導入該核酸之載體、含該核酸或該載體之細胞、藉由培養該細胞以製造該分子之方法、及以該方法製得之分子。

【0198】 又，本說明書引用之全部先前技術文獻納入本說明書作為參考。

[實施例]

【0199】 以下依實施例對於本發明更詳細說明，但該等實施例不限制本發明之範圍。

【0200】 [實施例1]GPC3_ERY22_rCE115之製作與細胞傷害活性之測定
(1-1)GPC3_ERY22_rCE115之製作

將針對癌抗原(GPC3)之IgG作為基本骨架，製作其中一Fab置換成針對CD3 epsilon之結合域之形式之分子。此時，作為基本骨架之IgG之Fc係使用向FcγR(Fcγ受體)之結合性減弱之靜默型Fc。作為針對GPC3之結合域，使用抗GPC3抗體H0000(序列編號：40)/GL4(序列編號：41)。又，作為針對CD3之結合域，使用抗CD3抗體rCE115H/rCE115L(序列編號：42 / 序列編號：43)。

作為抗體H鏈不變區，使用已去除IgG1之C末端之Gly及Lys的G1d，並將其和H0000/GL4及rCE115H/rCE115L組合使用。又，令抗體H鏈不變區之名稱H1時，可變區帶有H0000之抗體之H鏈所對應的序列示如H0000-H1。在此，顯示胺基酸之改變時，係以D356K之方式表示。開頭的字母(D356K之D)代表改變前之胺基酸殘基以單字母表記表示時之字母，接續的數字(D356K之356)係指此改變

處之EU編號，最後的字母(D356K之K)係指改變後之胺基酸殘基以單字母表示時之字母。依參考實施例1之方法製備IgG1之C末端之Gly及Lys已除去之G1dh(序列編號：44)、於G1dh導入了L234A/L235A/Y349C/T366W之變異之ERY22_Hk(序列編號：45)、於G1dh導入了L234A/L235A/D356C/T366S/L368A/Y407V之變異之ERY22_Hh(序列編號：46)。於各自之H鏈導入的L234A及L235A之變異會減弱向FcγR(Fcγ受體)之結合性，且Y349C/T366W 及D356C/T366S/L368A/Y407V 之變異係為了使產生由2個H鏈構成之異二聚化抗體時能有效率地使各H鏈之異體形成而導入。

【0201】 依參考實施例1製作針對GPC3之Fab之VH域與VL域經置換之異二聚化抗體GPC3_ERY22_rCE115(第1圖a)。

亦即，依照使用和上述方法同樣之附加適當序列之引子的PCR法等該技術領域中有通常知識者公知之方法，製作分別插入了編碼為GL4-ERY22_Hk(序列編號：47)、H0000-ERY22_L(序列編號：48)、rCE115H-ERY22_Hh(序列編號：49)、rCE115L-k0(序列編號：50)之多核苷酸的一系列表現載體。

【0202】 將以下所示組合之表現載體導入到FreeStyle293-F細胞，使目的分子暫時性表現。

目的分子：GPC3_ERY22_rCE115

由已插入到表現載體之多核苷酸編碼之多胜肽： GL4-ERY22_Hk、H0000-ERY22_L、rCE115H-ERY22_Hh、rCE115L-k0

【0203】 (1-2)GPC3_ERY22_rCE115之精製

將獲得之培養上清添加到Anti FLAG M2管柱(Sigma公司)，實施管柱洗滌後實施使用0.1 mg/mL FLAG胜肽(Sigma公司)所為之溶出。將含有目的分子之級分添加到HisTrap HP管柱(GE Healthcare公司)，該管柱洗滌後，實施利用咪唑之濃度梯度進行溶出。將含有目的分子之級分利用超過濃縮後，將該級分添加到

Superdex 200管柱(GE Healthcare公司)，只回收溶出液之單體級分，藉此獲得經精製之各目的分子。

【0204】 (1-3)使用人末梢血單核球之GPC3_ERY22_rCE115之細胞傷害活性之測定

針對GPC3_ERY22_rCE115檢查活體外(in vitro)之細胞傷害活性。

(1-3-1)人末梢血單核球(PBMC)溶液之製備

使用預先將1,000單位/mL之肝素溶液(Novo・heparin注5千單位，Novonordic公司)100 μ L注入的注射器，從健康人自願者(成人)抽取末梢血50 mL。將以PBS(-)稀釋2倍後進行4等分而得之末梢血加到預先注入15 mL之Ficoll-Paque PLUS並實施離心操作之Leucosep淋巴球分離管(Cat. No. 227290、Greiner bio-one公司)中。將該分離管離心分離(2,150 rpm、10分鐘、室溫)後分取單核球級分層。以含有10%FBS之Dulbecco's Modified Eagle's Medium(SIGMA公司、以下10%FBS/D-MEM)洗滌單核球級分之細胞1次後，將該細胞使用10%FBS/D-MEM製備成細胞密度為 4×10^6 /mL。將以此方式製備之細胞溶液作為人PBMC溶液供以後之試驗。

【0205】 (1-3-2)細胞傷害活性之測定

細胞傷害活性係以使用xCELLigence即時細胞分析儀(Roche Diagnostics公司)之細胞增殖抑制率評價。目標細胞使用表現人GPC3之NCI-H446人癌細胞株或PC-10人癌細胞株。將NCI-H446或PC-10從培養皿剝離，以成為 1×10^4 cells/well之方式以100 μ L/well接種在E-Plate 96(Roche Diagnostics公司)板，並使用xCELLigence即時細胞分析儀開始測定活細胞之測定。次日，從xCELLigence即時細胞分析儀取出板，於該板添加製備成各濃度(0.004、0.04、0.4、4、40 nM)之各抗體50 μ L。於室溫使其反應15分鐘後加入(1-2)製備之人PBMC溶液50 μ L(2×10^5 cells/well)，將該板再設置於xCELLigence即時細胞分析儀以開使活細

胞之測定。反應於5%二氧化碳氣體、37°C之條件下實施，從人PBMC添加72小時後之細胞索引值依下式求出細胞增殖抑制率(%)。計算使用之細胞索引值係使用標準化成即將添加抗體時之細胞索引值為1後之數值。

【0206】

細胞增殖抑制率(%) = $(A-B) \times 100 / (A-1)$

【0207】 A代表未添加抗體之井之細胞索引值之平均值(只有目標細胞與人PBMC)，B代表各井之細胞索引值之平均值。試驗重複三次。

【0208】 將由人血液製備之PBMC(Peripheral Blood Mononuclear Cell)作為效應子細胞，測定GPC3_ERY22_rCE115之細胞傷害活性，結果認為有極強的活性(第2圖)。

【0209】 [實施例2] 抗CD3抗體rCE115之H鏈之人化、及共通L鏈化

(2-1)rCE115人化H鏈可變區hCE115HA之設計

實施抗CD3抗體rCE115之H鏈可變區(序列編號：42)之人化。CDR、FR之決定係依照Kabat之定義(Kabat編號)。

【0210】 首先比較資料庫上之人抗體可變區序列與rCE115大鼠可變區序列以選擇人FR序列。資料庫係利用IMGT Database (<http://www.imgt.org/>)及NCBI GenBank(<http://www.ncbi.nlm.nih.gov/genbank/>)。藉由將rCE115可變區之H鏈之CDR序列和選擇之人FR序列連結，設計人化H鏈可變區序列。命其為人化H鏈可變區序列hCE115HL(序列編號：51)。

【0211】 於選擇之人H鏈FR3之序列，Kabat編號表示之93號胺基酸殘基為Ala，但rCE115可變區序列之胺基酸殘基為Arg。從大鼠及人之生殖腺序列之資料庫IMGT Database(<http://www.imgt.org/>)確認該部位含有Arg之序列少。又，據報告Kabat編號表示之94號胺基酸殘基會形成上核(upper core)而有助於抗體結構之安定化(Ewert等人(Methods. 2004 Oct;34(2):184-99))。由該等資訊，重新設計H

鏈FR3之Kabat 93號、94號胺基酸殘基取代為在rCE115可變區序列存在之殘基而得的人化H鏈可變區序列。命其為人化H鏈可變區序列hCE115HA(序列編號：52)。

【0212】 (2-2)抗CD3抗體rCE115與抗GPC3抗體之共通L鏈L0000之設計實施抗CD3抗體rCE115之L鏈可變區rCE115L(序列編號：43)與抗GPC3抗體之L鏈可變區GL4(序列編號：41)之FR/CDR曳步(shuffling)。

【0213】 選擇GL4之FR序列作為L鏈FR序列。L鏈CDR2在rCE115L與GL4為相同。L鏈CDR1從GL4，L鏈CDR3從rCE115L之CDR序列分別選擇。再者，重新設計將選擇之L鏈CDR3之Kabat 94號胺基酸殘基Asp取代成於GL4存在之殘基Val而得的L鏈CDR3。

【0214】 藉由將上述選擇之FR與CDR予以連結，設計人化L鏈可變區序列。命其為人化L鏈可變區序列L0000(序列編號：53)。

【0215】 (2-3)針對人GPC3之親和性之評價
評價使用GL4(序列編號：41)與L0000(序列編號：53)作為L鏈可變區時之針對人GPC3之結合活性。分子型係以利用knobs-into-hole而異化之人IgG1之Fc區帶有1個Fab之單臂抗體實施。抗GPC3抗體之H鏈可變區使用H0000(序列編號：40)。

【0216】 抗GPC3抗體對抗原之親和性與結合速度常數使用利用Biacore™-T200(GEHealthcare Japan)所為之表面電漿共振分析之multi-cycle kinetics法測定。運行緩衝液使用HBS-EP+ (GEHealthcare Japan)，並使用胺偶聯套組(GEHealthcare Japan)使Protein A/G共價鍵結於CM5晶片(羧基甲基葡聚糖被覆晶片)。各抗GPC3抗體係製備成在Protein A/G 捕捉約 100 RU。作為分析物使用之人GPC3係使用 HBS-EP+，製備成8、16、32、64、128 nM。測定先使抗體溶液捕捉於Protein A/G，再以流速30μL/min注射人GPC3溶液3 min以使其反應，之後切換成 HBS-EP+，測定解離相15 min。解離相之測定結束後，以10 mM Gly-HCl, pH1.5洗滌，將傳感晶片再生。濃度0之測定係同樣使抗體溶液捕捉於

Protein A/G，注射HBS-EP+3 min使其反應，之後切換成HBS-EP+，測定解離相15 min。解離相之測定結束後以10 mM Gly-HCl, pH 1.5洗滌，將傳感晶片再生。從獲得之傳感圖使用Biacore 專用之數據解析軟體Biacore T200 Evaluation Software Version 1.0 實施速度論的解析，並算出結合速度常數(ka)、解離速度常數(kd)及速度常數比。結果示於表6。

【0217】 [表6]

可變區		針對人 GPC3 之親和性		
H 鏈可變區	L 鏈可變區	KD (M)	ka (1/Ms)	kd (1/s)
H0000	GL4	4.2x10 ⁻⁹	4.3x10 ⁵	1.8x10 ⁻³
H0000	L0000	3.6x10 ⁻⁸	3.0x10 ⁵	1.1x10 ⁻²

【0218】 (2-4)針對人CD3之親和性之評價

評價使用hCE115HA(序列編號：52)作為H鏈可變區，使用L0000(序列編號：53)作為L鏈可變區時針對人CD3之結合活性。分子型係以利用knobs-into-hole異化之人IgG1之Fc區帶有1個Fab之單臂抗體實施。

【0219】 抗CD3抗體對抗原之親和性與結合速度常數使用利用Biacore™-T200(GEHealthcare Japan)所為之表面電漿共振分析之single-cycle kinetics法測定。運行緩衝液使用HBS-EP+ (GEHealthcare Japan)，並使用胺偶聯套組(GEHealthcare Japan)使人CD3共價鍵結於CM4晶片(羧基甲基葡聚糖被覆晶片)。作為分析物使用之抗CD3抗體係使用 HBS-EP+，製備成5、20μg/mL。測定先使抗體溶液捕捉於Protein A/G，再以流速20μL/min連續注射5、20μg/mL之抗CD3抗體溶液各3 min以使其反應，之後切換成 HBS-EP+，測定解離相3 min。解離相之測定結束後，以10 mM Gly-HCl, pH1.5洗滌，將傳感晶片再生。濃度0之測定係連續各注射 HBS-EP+ 各3 min進行2次使其反應，之後切換成HBS-EP+，測定解離相3 min。解離相之測定結束後以10 mM Gly-HCl, pH 1.5洗滌，將傳感晶片再生。從獲得之傳感圖使用Biacore 專用之數據解析軟體Biacore

T200 Evaluation Software Version 1.0 實施速度論的解析，並算出結合速度常數 (ka)、解離速度常數(kd)及速度常數比。結果示於表7。

【0220】 [表7]

可變區		針對人 CD3 之親和性		
H 鏈可變區	L 鏈可變區	KD (M)	ka (1/Ms)	kd (1/s)
rCE115H	rCE115L	1.0x10 ⁻⁷	5.9x10 ⁴	6.0x10 ⁻³
hCE115HA	L0000	1.2x10 ⁻⁷	1.9x10 ⁵	2.3x10 ⁻²

【0221】 (2-5)GPC3_ERY27_hCE115之製作

將針對癌抗原(GPC3)之IgG4作為基本骨架，將其中一Fab之H鏈可變區替換為針對CD3 epsilon之結合域，製作L鏈於兩者的Fab為共通形式的ERY27分子(第1圖b)。此時，作為基本骨架之IgG4之Fc係使用向FcγR(Fcγ受體)之結合性減弱之靜默型Fc。針對GPC3之結合域之H鏈可變區使用H0000(序列編號：40)，針對CD3之結合域之H鏈可變區使用hCE115HA(序列編號：52)。又，L鏈可變區使用L0000(序列編號：53)。對於各H鏈導入之D356K及K439E之變異，係為了於產生由2個H鏈構成之異二聚化抗體時，能有效率地形成各H鏈之異體而導入(WO2006/106905)。H435R係妨礙向Protein A之結合之改變，係為了能以良好效率地將異體與同體分離而導入(WO/2011/078332)。

【0222】 依公知方法，製作插入了分別編碼為H0000-ERY27_HK(序列編號：54)、hCE115HA-ERY27_HE(序列編號：55)、L0000-k0(序列編號：56)之多核苷酸之一系列表現載體。

【0223】 將以下所示組合之表現載體導入到FreeStyle293-F細胞，使各目的分子暫時性表現。

【0224】 目的分子：GPC3_ERY27_hCE115

由插入於表現載體之多核苷酸編碼之多胜肽： H0000-ERY27_HK、hCE115HA-ERY27_HE、L0000-k0

【0225】 (2-6)GPC3_ERY27_hCE115之精製

依實施例1-2記載之方法精製各目的分子。

【0226】 (2-7)使用人末梢血單核球之細胞傷害活性之測定

(2-7-1)人末梢血單核球(PBMC：Peripheral Blood Mononuclear Cell)溶液之製備

以實施例1-3-1記載之方法製備。

【0227】 (2-7-2)細胞傷害活性之測定

以實施例1-3-2記載之方法測定。

【0228】 將從人血液製備之PBMC作為效應子細胞，測定GPC3_ERY27_hCE115之細胞傷害活性，結果：認為因rCE115之H鏈之人化、及共通L鏈化導致活性降低(第2圖)。

【0229】 [實施例3]為了各種性質之改善之人化雙專一性抗體改變體之製作與評價

實施例2獲得之人化抗人CD3 ϵ 鏈及抗人GPC3雙專一性抗體GPC3_ERY27_hCE115(序列編號54、55、56)之T細胞依存的細胞傷害活性比起GPC3_ERY22_rCE115(序列編號47、48、49、50)之T細胞依存的細胞傷害活性還低。此據認為係：因為人化及L鏈共通化導致向GPC3及CD3 ϵ 鏈之親和性減弱。至今並無針對帶有獨立序列之GPC3及CD3 ϵ 鏈抗原使用共通抗體L鏈使針對兩抗原之親和性提高，並使T細胞依存的細胞傷害活性增強之人化雙專一性抗體之報告。故，以前認為：取得顯示和GPC3_ERY22_rCE115有同等或更高藥效之人化抗體雙專一性係為困難。

【0230】 在如此的狀況中，本案申請人藉由依該技術領域中有通常知識者公知之方法，即製作針對人GPC3及人CD3 ϵ 鏈兩抗原之抗體基因之胺基酸殘基之網羅的取代體，並實施各種篩選評價，藉此製作針對人GPC3及人CD3 ϵ 鏈之親和

性有所改變之人化雙專一性改造抗體。又，依同樣手法，製作物理化學性質改變之人化雙專一性改造抗體。再者，藉由取得為了使親和性及物理化學性質變化之有效果的胺基酸殘基取代，製作和人化前之GPC3_ERY22_rCE115之T細胞依存的細胞傷害活性帶有同等或更高之TDCC活性之最適化雙專一性抗體。

【0231】 人化雙專一性抗體最適化之點突變導入、抗體表現精製、抗原親和性測定、T細胞依存的細胞傷害活性測定，係以和實施例1、2同樣的方法實施CDR、FR之決定依照Kabat之定義(Kabat編號)。

【0232】 又，因應目的，使用下者作為抗體H鏈不變區(編號為EU編號)。使用針對人IgG1導入了L234A/L235A/N297A/D356C/T366S/L368A/Y407V/G446缺損/K447缺損變異之E22Hh(序列編號57)、針對人IgG1導入了L234A/L235A/N297A/Y349C/T366W/G446缺損/K447缺損變異及在緊鄰118之前導入了Ser-Ser插入變異之E22Hk(序列編號58)、針對人IgG1導入了D356C/T366S/L368A/Y407V/G446缺損/K447缺損變異之G1dh、針對人IgG1導入了118-215缺損變異及C220S/Y349C/T366W/H435R變異之none-Hi-Kn010G3、針對人IgG4導入了L235R/S239K/N297A/E356K/R409K/H435R/L445P/G446缺損/K447缺損變異之E2702GsKsc(序列編號60)、針對人IgG4導入了K196Q/L235R/S239K/N297A/R409K/K439E/L445P/G446缺損/K447缺損變異之E2704sEpsc(序列編號61)、針對人IgG4導入了L235R/S239K/N297A/E356K/R409K/L445P/G446缺損/K447缺損變異之E2702sKsc(序列編號62)。又，作為抗體L鏈不變區，使用人κ鏈之k0(序列編號63)、針對人κ鏈導入了R108A/T109S變異之E22L(序列編號432)。

【0233】 EU編號356號Asp取代為Cys之變異、及EU編號366號The取代為Ser之變異、及EU編號368號Leu取代為Ala之變異、及EU編號407號Tyr取代為Val之變異、及EU編號349號Tyr取代為Cys之變異、及EU編號366號Thr取代為Trp之變異、及在緊鄰118號前插入Ser-Ser之變異係為了於產生異抗體時能有效率地使

各H鏈之異分子形成者。同樣，EU編號356號Glu取代為Lys之變異及EU編號439號Lys取代為Glu之變異係為了使產生異抗體時各H鏈之異分子能有效率地形成者。藉此，可期待雙專一性抗體之生成效率改善。

【0234】 EU編號234號Leu取代為Ala之變異、及EU編號235號Leu取代為Ala或Arg之變異、及EU編號239號Ser取代為Lys之變異、及EU編號297號Asn取代為Ala之變異係為了使針對Fc γ 受體及補體(C1q)之親和性減弱之變異。藉此，可期待:抑制Fab所為之CD3結合與Fc所為之和Fc γ 受體或補體之交聯，能避免因非專一效應子作用增強伴隨細胞介素釋出症狀。

【0235】 已導入EU編號118-215號缺損變異之H鏈藉由和帶有全長序列之H鏈組合，能製作只有1個Fab之抗體(一價抗體)，對於評價親和性有用。

【0236】 EU編號409號Arg取代為Lys之變異、及EU編號435號His取代為Arg之變異，各係為了接近人IgG1、及人IgG3之性質之變異。

【0237】 (3-1)利用點突變所為之人化抗CD3抗體之親和性改變

首先，針對實施例2製作之人化抗人CD3 ϵ 鏈抗體序列hCE115HA-ERY27_HE (序列編號：55)，於FR1、FR2、FR3、CDR1、CDR2、CDR3導入點突變，製備改造抗體。然後，測定該等改造抗體針對可溶性人CD3 ϵ 鏈之親和性。藉由組合有親和性提高效果之部位，獲得表8所示帶有親和性之改造抗體。

【0238】 [表8]

抗體名	KD (人 CD3)
hCE115HA-E22Hh/-HI-Kn010G3/L0000-k0	1.43E-07
TR01H083-E22Hh/none-HI-Kn010G3/L0212-k0	5.86E-11
TR01H040-E22Hh/none-HI-Kn010G3/L0240-k0	2.17E-09
TR01H002-E22Hh/GLS3108-k0/GL4-E22Hh/H0610-E22L	2.04E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0212-k0	2.17E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0235-k0	2.81E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0238-k0	2.91E-08
TR01H040-E22Hh/none-HI-Kn010G3/TR01L015-k0	2.52E-08
TR01H083-E22Hh/none-HI-Kn010G3/L0262-k0	2.45E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0207-k0	2.60E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0241-k0	3.48E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0242-k0	3.68E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0205-k0	2.90E-09
TR01H040-E22Hh/none-HI-Kn010G3/TR01L019-k0	3.20E-09
TR01H060-E22Hh/none-HI-Kn010G3/L0000-k0	3.25E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0211-k0	3.22E-09
TR01H002-E22Hh/-HI-Kn010G3/GLC3108-k0	4.81E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0208-k0	4.25E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0208-k0	4.15E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0224-k0	5.08E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0238-k0	5.84E-09
TR01H083-E22Hh/none-HI-Kn010G3/L0201-k0	4.42E-09
TR01H084-E2702GsKsc/none-HI-E2704sE/L0011-k0	4.14E-08
TR01H040-E22Hh/none-HI-Kn010G3/L0210-k0	5.05E-09
TR01H114-E2702GsKsc/none-HI-E2704sE/L0011-k0	4.22E-09
CE115HA236-E22Hh/GLS3108-k0/GL4-E22Hh/H0610-E22L	6.08E-09
TR01H077-E22Hh/none-HI-Kn010G3/L0200-k0	6.12E-09
TR01H071-E22Hh/none-HI-Kn010G3/L0200-k0	6.13E-09
TR01H111-E2702GsKsc/none-HI-E2704sE/L0011-k0	4.91E-09
TR01H081-E22Hh/none-HI-Kn010G3/L0262-k0	5.76E-09
TR01H001-E22Hh/-HI-Kn010G3/GLC3105-k0	8.22E-09
CE115HA179-G1dh/-HI-Kn010G3/L0000-k0	8.35E-09
TR01H112-E2702GsKsc/none-HI-E2704sE/L0011-k0	5.12E-09
TR01H113-E2702GsKsc/none-HI-E2704sE/L0011-k0	5.14E-09
TR01H082-E22Hh/none-HI-Kn010G3/L0212-k0	4.75E-09
CE115HA236-E22Hh/-HI-Kn010G3/GLC3108-k0	9.10E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0231-k0	7.75E-09
TR01H037-E22Hh/none-HI-Kn010G3/L0000-k0	6.93E-09
CE115HA252-E22Hh/-HI-Kn010G3/L0000-k0	8.48E-09
TR01H083-E22Hh/none-HI-Kn010G3/L0011-k0	6.70E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0223-k0	8.15E-09
TR01H083-E22Hh/none-HI-Kn010G3/L0000-k0	6.83E-09
TR01H071-E22Hh/none-HI-Kn010G3/L0000-k0	8.85E-09
TR01H067-E22Hh/none-HI-Kn010G3/L0212-k0	6.88E-09
CE115HA178-G1dh/-HI-Kn010G3/L0000-k0	1.09E-08
TR01H040-E22Hh/none-HI-Kn010G3/L0237-k0	1.02E-08
TR01H083-E22Hh/none-HI-Kn010G3/L0222-k0	9.42E-09
TR01H084-E22Hh/none-HI-Kn010G3/L0262-k0	8.51E-09
TR01H071-E22Hh/none-HI-Kn010G3/L0215-k0	9.51E-09
TR01H040-E22Hh/none-HI-Kn010G3/L0218-k0	8.20E-09
TR01H081-E22Hh/none-HI-Kn010G3/L0201-k0	9.46E-09
TR01H071-E22Hh/none-HI-Kn010G3/L0222-k0	1.04E-08
TR01H040-E22Hh/none-HI-Kn010G3/L0220-k0	9.15E-09
TR01H087-E22Hh/none-HI-Kn010G3/TR01L016-k0	1.09E-08
TR01H002-E22Hh/GLS3108-k0/GL4-E22Hh/H0000-E22L	4.78E-09
TR01H087-E22Hh/none-HI-Kn010G3/TR01L019-k0	1.21E-08
TR01H038-E22Hh/none-HI-Kn010G3/L0000-k0	1.24E-08
TR01H081-E22Hh/none-HI-Kn010G3/L0200-k0	1.27E-08
TR01H082-E2702GsKsc/none-HI-E2704sE/L0011-k0	1.01E-08
CE115HA180-G1dh/-HI-Kn010G3/L0000-k0	1.68E-08
CE115HA251-E22Hh/L0000-k0/GL4-E22Hh/H0610-E22L	1.37E-08
TR01H100-E2702GsKsc/none-HI-E2704sE/L0011-k0	1.11E-08
TR01H040-E22Hh/none-HI-Kn010G3/L0228-k0	1.60E-08
TR01H081-E22Hh/none-HI-Kn010G3/L0011-k0	1.35E-08
TR01H081-E22Hh/none-HI-Kn010G3/L0215-k0	1.54E-08
TR01H110-E2702GsKsc/none-HI-E2704sE/L0011-k0	1.26E-08
TR01H043-E22Hh/none-HI-Kn010G3/L0000-k0	1.52E-08
TR01H081-E22Hh/none-HI-Kn010G3/L0000-k0	1.56E-08
CE115HA251-E22Hh/-HI-Kn010G3/L0000-k0	2.23E-08
TR01H081-E2702GsKsc/none-HI-E2704sE/L0011-k0	1.39E-08
CE115HA236-E22Hh/GLS3108-k0/GL4-E22Hh/H0000-E22L	6.95E-09
TR01H084-E22Hh/none-HI-Kn010G3/L0201-k0	1.55E-08
TR01H072-E22Hh/none-HI-Kn010G3/L0000-k0	2.03E-08
TR01H088-E2702GsKsc/none-HI-E2704sE/L0011-k0	1.48E-08
TR01H081-E22Hh/none-HI-Kn010G3/L0222-k0	1.88E-08
TR01H040-E22Hh/none-HI-Kn010G3/L0239-k0	2.31E-08
TR01H040-E22Hh/none-HI-Kn010G3/L0262-k0	1.81E-08
TR01H040-E22Hh/none-HI-Kn010G3/L0234-k0	2.40E-08
TR01H012-E22Hh/none-HI-Kn010G3/L0000-k0	7.94E-09
TR01H081-E22Hh/none-HI-Kn010G3/L0000-k0	1.71E-08
TR01H040-E22Hh/none-HI-Kn010G3/L0243-k0	2.46E-08
TR01H109-E2702GsKsc/none-HI-E2704sE/L0011-k0	1.84E-08
TR01H047-E22Hh/none-HI-Kn010G3/L0000-k0	2.04E-08
TR01H082-E22Hh/none-HI-Kn010G3/L0267-k0	2.29E-08
TR01H082-E22Hh/none-HI-Kn010G3/L0268-k0	2.29E-08
TR01H084-E22Hh/none-HI-Kn010G3/L0011-k0	1.96E-08
TR01H040-E22Hh/none-HI-Kn010G3/L0250-k0	2.15E-08
TR01H040-E22Hh/none-HI-Kn010G3/L0204-k0	2.21E-08
TR01H084-E22Hh/none-HI-Kn010G3/L0000-k0	2.13E-08
TR01H040-E22Hh/none-HI-Kn010G3/L0213-k0	2.01E-08

抗體名	KD (人 CD3)
hCE115HA-E22Hh/-Hi-Kn010G3/L0000-k0	1.43E-07
TR01H040-E22Hh/none-Hi-Kn010G3/L0214-k0	2.02E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0217-k0	2.07E-08
TR01H071-E22Hh/none-Hi-Kn010G3/L0226-k0	2.51E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0200-k0	2.87E-08
TR01H074-E22Hh/none-Hi-Kn010G3/L0000-k0	2.91E-08
TR01H039-E22Hh/none-Hi-Kn010G3/L0000-k0	2.61E-08
CE115HA177-G1dh/-Hi-Kn010G3/L0000-k0	3.55E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0201-k0	2.81E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0263-k0	3.09E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0000-k0	3.60E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0216-k0	2.53E-08
TR01H051-E22Hh/none-Hi-Kn010G3/L0000-k0	2.91E-08
TR01H003-E22Hh/-Hi-Kn010G3/L0000-k0	4.03E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0264-k0	3.44E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0232-k0	3.86E-08
TR01H041-E22Hh/none-Hi-Kn010G3/L0000-k0	3.16E-08
CE115HA122-E22Hh/-Hi-Kn010G3/L0000-k0	4.28E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0233-k0	4.01E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0215-k0	3.37E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0203-k0	3.24E-08
TR01H015-E2702GstKsc/GCH019-E2704sEpsc/L0000-k0	2.96E-08
TR01H040-E22Hh/none-Hi-Kn010G3/TR01L008-k0	2.93E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0205-k0	3.42E-08
TR01H015-E22Hh/L0000-k0/GL4-E22Hh/H0610-E22L	3.57E-08
TR01H084-E22Hh/none-Hi-Kn010G3/L0000-k0	3.07E-08
TR01H044-E22Hh/none-Hi-Kn010G3/L0000-k0	3.52E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0262-k0	3.98E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0000-k0	3.13E-08
CE115HA251-E22Hh/L0000-k0/GL4-E22Hh/H0000-E22L	1.48E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0011-k0	3.48E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0222-k0	4.65E-08
CE115HA192-E22Hh/-Hi-Kn010G3/L0000-k0	5.05E-08
TR01H040-E22Hh/none-Hi-Kn010G3/TR01L010-k0	3.28E-08
TR01H025-E22Hh/none-Hi-Kn010G3/L0000-k0	3.86E-08
TR01H082-E22Hh/none-Hi-Kn010G3/TR01L023-k0	4.25E-08
TR01H040-E22Hh/none-Hi-Kn010G3/TR01L015-k0	3.95E-08
TR01H055-E22Hh/none-Hi-Kn010G3/L0000-k0	3.88E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0260-k0	4.53E-08
TR01H040-E22Hh/none-Hi-Kn010G3/TR01L009-k0	3.56E-08
TR01H040-E22Hh/none-Hi-Kn010G3/TR01L011-k0	3.57E-08
TR01H017-E22Hh/none-Hi-Kn010G3/L0000-k0	3.60E-08
CE115HA122-E22Hh/L0000-k0/GL4-E22Hh/H0000-E22L	1.69E-08
TR01H076-E22Hh/none-Hi-Kn010G3/L0000-k0	4.78E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0258-k0	4.70E-08
TR01H046-E22Hh/none-Hi-Kn010G3/L0000-k0	4.23E-08
rCE115H-G1dh/-Hi-Kn010G3/L0000-k0	5.76E-08
TR01H082-E22Hh/none-Hi-Kn010G3/TR01L024-k0	4.78E-08
TR01H016-E22Hh/none-Hi-Kn010G3/L0000-k0	3.69E-08
TR01H040-E22Hh/none-Hi-Kn010G3/TR01L018-k0	4.51E-08
TR01H084-E22Hh/none-Hi-Kn010G3/L0271-k0	2.76E-08
TR01H084-E22Hh/none-Hi-Kn010G3/L0270-k0	2.76E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0000-k1-k0	4.69E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0219-k0	3.94E-08
TR01H014-E22Hh/none-Hi-Kn010G3/L0000-k0	3.67E-08
TR01H061-E22Hh/none-Hi-Kn010G3/L0226-k0	4.71E-08
TR01H048-E22Hh/none-Hi-Kn010G3/L0000-k0	4.52E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0259-k0	5.07E-08
TR01H028-E22Hh/none-Hi-Kn010G3/L0000-k0	4.80E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0201-k0	4.49E-08
TR01H040-E22Hh/none-Hi-Kn010G3/TR01L013-k0	4.15E-08
TR01H033-E22Hh/none-Hi-Kn010G3/L0000-k0	4.66E-08
hCE115HA-G1dh/-Hi-Kn010G3/L0000-k0	6.50E-08
TR01H040-E22Hh/none-Hi-Kn010G3/TR01L012-k0	4.22E-08
TR01H065-E22Hh/none-Hi-Kn010G3/L0000-k0	4.31E-08
TR01H079-E22Hh/none-Hi-Kn010G3/L0000-k0	5.05E-08
TR01H042-E22Hh/none-Hi-Kn010G3/L0000-k0	4.48E-08
TR01H063-E22Hh/none-Hi-Kn010G3/L0000-k0	4.35E-08
TR01H084-E22Hh/none-Hi-Kn010G3/L0272-k0	3.10E-08
CE115HA121-E22Hh/-Hi-Kn010G3/L0000-k0	6.76E-08
TR01H026-E22Hh/none-Hi-Kn010G3/L0000-k0	5.12E-08
TR01H067-E22Hh/none-Hi-Kn010G3/L0262-k0	4.92E-08
TR01H073-E22Hh/none-Hi-Kn010G3/L0000-k0	5.97E-08
TR01H045-E22Hh/none-Hi-Kn010G3/L0000-k0	5.22E-08
TR01H007-E22Hh/none-Hi-Kn010G3/L0000-k0	2.17E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0203-k0	4.07E-08
TR01H032-E22Hh/none-Hi-Kn010G3/L0000-k0	5.73E-08
TR01H008-E22Hh/none-Hi-Kn010G3/L0000-k0	2.30E-08
TR01H013-E22Hh/none-Hi-Kn010G3/L0000-k0	4.94E-08
TR01H050-E22Hh/none-Hi-Kn010G3/L0000-k0	5.78E-08
TR01H067-E22Hh/none-Hi-Kn010G3/L0200-k0	6.03E-08
TR01H015-E22Hh/none-Hi-Kn010G3/L0000-k0	6.13E-08
hCE115HA-E22Hh/L0000-k0/GL4-E22Hh/H0000-E22L	6.18E-08
hCE115HA-E22stHh/none-Hi-Kn010G3/L0000-k0	5.17E-08
TR01H069-E22Hh/none-Hi-Kn010G3/L0000-k0	7.11E-08
TR01H015-E22Hh/none-Hi-Kn010G3/TR01L003-k0	6.34E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0202-k0	6.19E-08
TR01H067-E22Hh/none-Hi-Kn010G3/L0201-k0	6.93E-08
TR01H020-E22Hh/none-Hi-Kn010G3/L0000-k0	6.49E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0011-k0	5.95E-08

抗體名	KD (人 CD3)
hCE115HA-E22Hh//Hi-Kn010G3/L0000-k0	1.43E-07
TR01H082-E22Hh/none-Hi-Kn010G3/TR01L018-k0	4.72E-08
TR01H015-E22Hh/none-Hi-Kn010G3/TR01L005-k0	6.53E-08
TR01H052-E22Hh/none-Hi-Kn010G3/L0000-k0	6.27E-08
TR01H038-E22Hh/none-Hi-Kn010G3/L0000-k0	6.50E-08
TR01H067-E22Hh/none-Hi-Kn010G3/L0203-k0	4.79E-08
TR01H030-E22Hh/none-Hi-Kn010G3/L0000-k0	6.54E-08
TR01H015-E22Hh/none-Hi-Kn010G3/TR01L001-k0	6.56E-08
TR01H100-E22Hh/none-Hi-Kn010G3/L0011-k0	6.25E-09
TR01H029-E22Hh/none-Hi-Kn010G3/L0000-k0	6.70E-09
TR01H019-E22Hh/none-Hi-Kn010G3/L0000-k0	6.85E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0000-k0	7.37E-08
TR01H018-E22Hh/none-Hi-Kn010G3/L0000-k0	6.93E-08
TR01H027-E22Hh/none-Hi-Kn010G3/L0000-k0	6.95E-08
TR01H049-E22Hh/none-Hi-Kn010G3/L0000-k0	6.79E-08
TR01H066-E22Hh/none-Hi-Kn010G3/L0000-k0	6.02E-08
TR01H081-E22Hh/none-Hi-Kn010G3/L0011-k0	6.67E-08
rCE115H-E22Hh/none-Hi-Kn010G3/L0000-k0	8.00E-08
TR01H015-E22Hh/none-Hi-Kn010G3/TR01L002-k0	7.14E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0226-k0	8.01E-08
TR01H067-E22Hh/none-Hi-Kn010G3/TR01L018-k0	5.26E-08
TR01H093-E22Hh/none-Hi-Kn010G3/L0011-k0	6.80E-08
TR01H067-E22Hh/none-Hi-Kn010G3/L0215-k0	7.41E-08
TR01H015-E22Hh/none-Hi-Kn010G3/TR01L004-k0	7.34E-08
TR01H107-E22Hh/none-Hi-Kn010G3/L0011-k0	6.91E-08
TR01H105-E22Hh/none-Hi-Kn010G3/L0011-k0	6.95E-08
TR01H090-E22Hh/none-Hi-Kn010G3/L0011-k0	6.95E-08
TR01H108-E22Hh/none-Hi-Kn010G3/L0011-k0	6.95E-08
TR01H094-E22Hh/none-Hi-Kn010G3/L0011-k0	7.00E-08
TR01H109-E22Hh/none-Hi-Kn010G3/L0011-k0	7.06E-08
TR01H056-E22Hh/none-Hi-Kn010G3/L0000-k0	7.32E-08
TR01H031-E22Hh/none-Hi-Kn010G3/L0000-k0	7.55E-08
TR01H022-E22Hh/none-Hi-Kn010G3/L0000-k0	7.58E-08
TR01H092-E22Hh/none-Hi-Kn010G3/L0011-k0	7.21E-08
TR01H067-E22Hh/none-Hi-Kn010G3/L0000-k0	7.15E-08
TR01H067-E22Hh/none-Hi-Kn010G3/L0011-k0	7.18E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0248-k0	7.89E-08
TR01H009-E22Hh/none-Hi-Kn010G3/L0000-k0	3.15E-08
TR01H023-E22Hh/none-Hi-Kn010G3/L0000-k0	7.94E-08
TR01H096-E22Hh/none-Hi-Kn010G3/L0011-k0	7.47E-08
TR01H040-E22Hh/none-Hi-Kn010G3/TR01L007-k0	6.82E-08
TR01H054-E22Hh/none-Hi-Kn010G3/L0000-k0	7.79E-08
TR01H021-E22Hh/none-Hi-Kn010G3/L0000-k0	8.05E-08
TR01H103-E22Hh/none-Hi-Kn010G3/L0011-k0	7.72E-08
TR01H089-E22Hh/none-Hi-Kn010G3/L0011-k0	7.74E-08
rCE115H-E22Hh/none-Hi-Kn010G3/L0000vk1-k0	8.52E-08
TR01H101-E22Hh/none-Hi-Kn010G3/L0011-k0	7.87E-08
TR01H053-E22Hh/none-Hi-Kn010G3/L0000-k0	8.23E-08
TR01H035-E22Hh/none-Hi-Kn010G3/L0000-k0	8.49E-08
TR01H087-E22Hh/none-Hi-Kn010G3/TR01L015-k0	8.64E-08
TR01H104-E22Hh/none-Hi-Kn010G3/L0011-k0	8.26E-08
TR01H075-E22Hh/none-Hi-Kn010G3/L0000-k0	9.88E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0227-k0	1.01E-07
TR01H102-E22Hh/none-Hi-Kn010G3/L0011-k0	8.54E-08
TR01H034-E22Hh/none-Hi-Kn010G3/L0000-k0	9.11E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0222-k0	1.01E-07
rCE115H-E22Hh/rCE115L-k0/GL4-E22Hh/L0000-E22L	9.37E-08
TR01H016-E22Hh/none-Hi-Kn010G3/TR01L006-k0	9.30E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0246-k0	9.28E-08
TR01H097-E22Hh/none-Hi-Kn010G3/L0011-k0	8.76E-08
TR01H011-E22Hh/none-Hi-Kn010G3/L0000-k0	3.71E-08
TR01H010-E22Hh/none-Hi-Kn010G3/L0000-k0	3.73E-08
TR01H095-E22Hh/none-Hi-Kn010G3/L0011-k0	9.08E-08
TR01H082-E22Hh/none-Hi-Kn010G3/TR01L020-k0	1.06E-07
TR01H096-E22Hh/none-Hi-Kn010G3/L0011-k0	9.14E-08
TR01H082-E22Hh/none-Hi-Kn010G3/TR01L017-k0	1.09E-07
TR01H040-E22Hh/none-Hi-Kn010G3/L0247-k0	1.00E-07
rCE115H-E22Hh/none-Hi-Kn010G3/rCE115L-k0	1.24E-07
TR01H004-E22Hh//Hi-Kn010G3/L0000-k0	1.35E-07
TR01H067-E22Hh/none-Hi-Kn010G3/L0222-k0	7.63E-08
rCE115H-E22Hh//Hi-Kn010G3/rCE115L-k0	1.38E-07
TR01H008-E22Hh/none-Hi-Kn010G3/L0000-k0	4.22E-08
TR01H070-E22Hh/none-Hi-Kn010G3/L0000-k0	1.20E-07
TR01H106-E22Hh/none-Hi-Kn010G3/L0011-k0	1.00E-07
TR01H024-E22Hh/none-Hi-Kn010G3/L0000-k0	1.08E-07
CE115HA124-E22Hh//Hi-Kn010G3/L0000-k0	1.43E-07
TR01H040-E22Hh/none-Hi-Kn010G3/L0249-k0	1.11E-07
TR01H082-E22Hh/none-Hi-Kn010G3/L0271-k0	6.82E-08
TR01H057-E22Hh/none-Hi-Kn010G3/L0000-k0	1.12E-07
TR01H058-E22Hh/none-Hi-Kn010G3/L0000-k0	1.15E-07
TR01H068-E22Hh/none-Hi-Kn010G3/L0000-k0	1.01E-07
TR01H082-E22Hh/none-Hi-Kn010G3/L0270-k0	7.42E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0272-k0	7.44E-08
hCE115HA-E22Hh/none-Hi-Kn010G3/L0000-k0	1.24E-07
TR01H082-E22Hh/none-Hi-Kn010G3/L0268-k0	1.36E-07
hCE115HAa-E22Hh/none-Hi-Kn010G3/L0000-k0	1.08E-07
TR01H067-E22Hh/none-Hi-Kn010G3/L0226-k0	1.32E-07
TR01H067-E22Hh/none-Hi-Kn010G3/L0248-k0	1.39E-07

【0239】 (3-2)人化抗GPC3抗體之親和性改變

首先，針對實施例2製作之抗人GPC3雙專一性抗體序列H0000-ERY27_HK (序列編號：54)，於CDR1、CDR2、CDR3導入點突變並製備改造抗體。然後，測定該等改造抗體針對可溶性人GPC3之親和性。藉由將有親和性提高效果之部位予以組合，獲得表9所示之帶有親和性之改造抗體。

【0240】 [表9]

抗體名	KD (人 GPC3)
H0610-G1dh/none-Hi-Kn010G3/L0003-k0	3.97E-09
H0610-G1dh/none-Hi-Kn010G3/L0222-k0	1.40E-13
H0610-G1dh/none-Hi-Kn010G3/L0259-k0	3.52E-13
GCH054-G1dh/none-Hi-Kn010G3/L0262-k0	5.25E-13
GCH060-G1dh/none-Hi-Kn010G3/L0222-k0	6.42E-13
H0610-G1dh/none-Hi-Kn010G3/L0246-k0	1.21E-12
GCH057-G1dh/none-Hi-Kn010G3/L0222-k0	1.85E-12
GCH054-G1dh/none-Hi-Kn010G3/L0249-k0	3.61E-12
GCH055-G1dh/none-Hi-Kn010G3/L0222-k0	3.90E-12
GCH094-G1dh/none-Hi-Kn010G3/L0246-k0	4.12E-12
H0610-G1dh/none-Hi-Kn010G3/L0249-k0	6.86E-12
H0610-G1dh/none-Hi-Kn010G3/TR01L017-k0	8.27E-12
H0610-G1dh/none-Hi-Kn010G3/L0265-k0	8.70E-12
H0610-G1dh/none-Hi-Kn010G3/L0261-k0	1.07E-11
GCH055-G1dh/none-Hi-Kn010G3/L0262-k0	1.18E-11
GCH056-G1dh/none-Hi-Kn010G3/L0262-k0	1.19E-11
H0610-G1dh/none-Hi-Kn010G3/L0268-k0	1.69E-11
H0610-G1dh/none-Hi-Kn010G3/TR01L020-k0	2.24E-11
GCH054-G1dh/none-Hi-Kn010G3/L0246-k0	3.15E-11
GCH054-G1dh/none-Hi-Kn010G3/L0222-k0	3.15E-11
GCH073-G1dh/none-Hi-Kn010G3/L0201-k0	3.50E-11
H0610-G1dh/none-Hi-Kn010G3/L0246-k0	5.55E-11
GCH065-G1dh/none-Hi-Kn010G3/L0201-k0	7.74E-11
H0610-G1dh/none-Hi-Kn010G3/L0226-k0	9.30E-11
H0610-G1dh/none-Hi-Kn010G3/L0093-k0	1.06E-10
GCH098-G1dh/none-Hi-Kn010G3/L0201-k0	1.11E-10
H0610-G1dh/none-Hi-Kn010G3/L0267-k0	1.79E-10
H0610-G1dh/none-Hi-Kn010G3/L0228-k0	2.02E-10
H0610-G1dh/none-Hi-Kn010G3/L0262-k0	2.11E-10
H0610-G1dh/none-Hi-Kn010G3/L0266-k0	2.13E-10
H0610-G1dh/none-Hi-Kn010G3/L0264-k0	2.19E-10
H0610-G1dh/none-Hi-Kn010G3/L0224-k0	2.43E-10
H0610-G1dh/none-Hi-Kn010G3/L0167-k0	2.11E-10
CE115HA251-E22Hh/L0000-k0/GL4-E22Hh/H0610-E22L	2.39E-10
TR01H015-E22Hh/L0000-k0/GL4-E22Hh/H0610-E22L	2.63E-10
CE115HA236-E22Hh/GLS3108-k0/GL4-E22Hh/H0610-E22L	2.67E-10
H0610-G1dh/none-Hi-Kn010G3/L0259-k0	3.34E-10
H0610-G1dh/none-Hi-Kn010G3/L0227-k0	4.08E-10
GCH065-G1dh/none-Hi-Kn010G3/L0272-k0	3.93E-10
H0610-G1dh/none-Hi-Kn010G3/L0269-k0	4.58E-10
H0610-G1dh/none-Hi-Kn010G3/L0223-k0	4.75E-10
TR01H002-E22Hh/GLS3108-k0/GL4-E22Hh/H0610-E22L	4.76E-10
GCH054-G1dh/none-Hi-Kn010G3/L0212-k0	5.17E-10
H0610-G1dh/none-Hi-Kn010G3/L0208-k0	5.30E-10
H0610-G1dh/none-Hi-Kn010G3/L0263-k0	5.64E-10
H0610-G1dh/none-Hi-Kn010G3/L0231-k0	5.89E-10
H0610-G1dh/none-Hi-Kn010G3/L0143-k0	5.73E-10
GCH055-G1dh/none-Hi-Kn010G3/L0212-k0	6.14E-10
H0610-G1dh/none-Hi-Kn010G3/L0211-k0	6.47E-10
H0610-G1dh/none-Hi-Kn010G3/L0238-k0	6.37E-10
H0610-G1dh/none-Hi-Kn010G3/L0214-k0	6.57E-10
H0610-G1dh/none-Hi-Kn010G3/L0243-k0	6.49E-10
GCH025-G1dh/none-Hi-Kn010G3/L0204-k0	6.70E-10
GCH054-G1dh/none-Hi-Kn010G3/TR01L016-k0	7.63E-10
H0610-G1dh/none-Hi-Kn010G3/L0168-k0	6.99E-10
GCH094-G1dh/none-Hi-Kn010G3/L0271-k0	6.92E-10
GCH054-G1dh/none-Hi-Kn010G3/TR01L019-k0	8.71E-10
H0610-G1dh/none-Hi-Kn010G3/L0234-k0	7.79E-10
GCH098-G1dh/none-Hi-Kn010G3/L0011-k0	8.02E-10
H0610-G1dh/none-Hi-Kn010G3/L0204-k0	7.27E-10
H0610-G1dh/none-Hi-Kn010G3/L0240-k0	8.48E-10
H0610-G1dh/none-Hi-Kn010G3/L0239-k0	8.74E-10
H0610-G1dh/none-Hi-Kn010G3/L0212-k0	9.94E-10
GCH065-G1dh/none-Hi-Kn010G3/L0011-k0	8.84E-10
H0610-G1dh/none-Hi-Kn010G3/L0200-k0	1.04E-09
H0610-G1dh/none-Hi-Kn010G3/L0124-k0	9.72E-10
GCH073-G1dh/none-Hi-Kn010G3/L0011-k0	9.10E-10
H0610-G1dh/none-Hi-Kn010G3/TR01L016-k0	1.08E-09
GCH054-G1dh/none-Hi-Kn010G3/L0201-k0	1.08E-09
H0610-G1dh/none-Hi-Kn010G3/L0090-k0	1.12E-09
H0610-G1dh/none-Hi-Kn010G3/L0209-k0	1.12E-09
H0610-G1dh/none-Hi-Kn010G3/L0201-k0	1.13E-09
H0610-G1dh/none-Hi-Kn010G3/L0161-k0	9.73E-10
H0610-G1dh/none-Hi-Kn010G3/L0206-k0	8.65E-10
H0610-G1dh/none-Hi-Kn010G3/L0186-k0	1.08E-09
H0610-G1dh/none-Hi-Kn010G3/TR01L019-k0	1.15E-09
H0610-G1dh/none-Hi-Kn010G3/L0095-k0	1.17E-09
GCH055-G1dh/none-Hi-Kn010G3/L0200-k0	1.13E-09
H0610-G1dh/none-Hi-Kn010G3/L0154-k0	1.01E-09
H0610-G1dh/none-Hi-Kn010G3/L0229-k0	1.20E-09
GCH054-G1dh/none-Hi-Kn010G3/L0200-k0	1.18E-09
GCH094-G1dh/none-Hi-Kn010G3/L0201-k0	1.17E-09

抗體名	KD (人 GPC3)
H0610-G1dh/none-Hi-Kn010G3/L0000-k0	3.97E-09
H0610-G1dh/none-Hi-Kn010G3/L0205-k0	1.01E-09
GCH099-G1dh/none-Hi-Kn010G3/L0201-k0	1.29E-09
H0610-G1dh/none-Hi-Kn010G3/L0242-k0	1.19E-09
GCH056-G1dh/none-Hi-Kn010G3/L0201-k0	1.16E-09
H0610-G1dh/none-Hi-Kn010G3/L0213-k0	1.25E-09
GCH060-G1dh/none-Hi-Kn010G3/L0200-k0	1.34E-09
GCH065-G1dh/none-Hi-Kn010G3/L0000-k0	1.41E-09
GCH100-G1dh/none-Hi-Kn010G3/L0201-k0	1.37E-09
H0610-G1dh/none-Hi-Kn010G3/L0015-k0	1.31E-09
H0610-G1dh/none-Hi-Kn010G3/L0151-k0	1.26E-09
H0610-G1dh/none-Hi-Kn010G3/L0237-k0	1.31E-09
H0610-G1dh/none-Hi-Kn010G3/L0220-k0	1.36E-09
H0610-G1dh/none-Hi-Kn010G3/L0155-k0	1.28E-09
GCH055-G1dh/none-Hi-Kn010G3/L0215-k0	1.52E-09
H0610-G1dh/none-Hi-Kn010G3/L0202-k0	1.22E-09
GCH056-G1dh/none-Hi-Kn010G3/L0215-k0	1.59E-09
H0610-G1dh/none-Hi-Kn010G3/L0012-k0	1.55E-09
GCH064-G1dh/none-Hi-Kn010G3/L0215-k0	1.62E-09
H0610-G1dh/none-Hi-Kn010G3/L0215-k0	1.64E-09
GCH098-G1dh/none-Hi-Kn010G3/L0000-k0	1.77E-09
H0610-G1dh/none-Hi-Kn010G3/L0125-k0	1.71E-09
GCH057-G1dh/none-Hi-Kn010G3/L0215-k0	1.83E-09
H0610-G1dh/none-Hi-Kn010G3/L0217-k0	1.79E-09
H0610-G1dh/none-Hi-Kn010G3/L0014-k0	1.82E-09
H0610-G1dh/none-Hi-Kn010G3/L0216-k0	1.86E-09
TR01H015-E2702GsKsc/GCH019-E2704sEpsc/L0000-k0	1.64E-09
H0610-G1dh/none-Hi-Kn010G3/TR01L015-k0	2.16E-09
H0610-G1dh/none-Hi-Kn010G3/TR01L016-k0	2.17E-09
H0610-G1dh/none-Hi-Kn010G3/L0216-k0	1.99E-09
H0610-G1dh/none-Hi-Kn010G3/L0000vk1-k0	2.16E-09
H0610-G1dh/none-Hi-Kn010G3/L0160-k0	2.12E-09
H0610-G1dh/none-Hi-Kn010G3/L0047-k0	2.23E-09
GCH073-G1dh/none-Hi-Kn010G3/L0000-k0	2.00E-09
GCH054-G1dh/none-Hi-Kn010G3/TR01L015-k0	2.45E-09
H0610-G1dh/none-Hi-Kn010G3/L0219-k0	2.28E-09
GCH094-G1dh/none-Hi-Kn010G3/L0272-k0	2.10E-09
H0610-G1dh/none-Hi-Kn010G3/L0149-k0	2.16E-09
GCH054-G1dh/none-Hi-Kn010G3/TR01L018-k0	2.59E-09
GCH054-G1dh/none-Hi-Kn010G3/L0203-k0	2.48E-09
H0610-G1dh/none-Hi-Kn010G3/L0122-k0	2.42E-09
H0610-G1dh/none-Hi-Kn010G3/L0134-k0	2.53E-09
H0610-G1dh/none-Hi-Kn010G3/L0152-k0	2.36E-09
H0610-G1dh/none-Hi-Kn010G3/L0203-k0	2.11E-09
H0610-G1dh/none-Hi-Kn010G3/L0075-k0	2.85E-09
H0610-G1dh/none-Hi-Kn010G3/L0038-k0	2.75E-09
H0610-G1dh/none-Hi-Kn010G3/L0011-k0	2.76E-09
H0610-G1dh/none-Hi-Kn010G3/L0157-k0	2.80E-09
H0610-G1dh/none-Hi-Kn010G3/L0145-k0	2.68E-09
H0610-G1dh/none-Hi-Kn010G3/TR01L010-k0	2.92E-09
H0610-G1dh/none-Hi-Kn010G3/L0009-k0	2.99E-09
GCH099-G1dh/none-Hi-Kn010G3/L0011-k0	2.78E-09
H0610-G1dh/none-Hi-Kn010G3/L0006-k0	3.04E-09
H0610-G1dh/none-Hi-Kn010G3/L0173-k0	2.83E-09
H0610-G1dh/none-Hi-Kn010G3/L0127-k0	3.12E-09
H0610-G1dh/none-Hi-Kn010G3/L0082-k0	3.43E-09
H0610-G1dh/none-Hi-Kn010G3/L0064-k0	3.37E-09
H0610-G1dh/none-Hi-Kn010G3/L0008-k0	3.30E-09
H0610-G1dh/none-Hi-Kn010G3/L0013-k0	3.35E-09
H0610-G1dh/none-Hi-Kn010G3/L0140-k0	3.38E-09
H0610-G1dh/none-Hi-Kn010G3/L0039-k0	3.41E-09
GCH043-G1dh/none-Hi-Kn010G3/L0000-k0	3.74E-09
H0610-G1dh/none-Hi-Kn010G3/TR01L008-k0	3.46E-09
H0610-G1dh/none-Hi-Kn010G3/L0148-k0	3.26E-09
GCH062-G1dh/none-Hi-Kn010G3/L0000-k0	3.73E-09
H0610-G1dh/none-Hi-Kn010G3/L0163-k0	3.38E-09
H0610-G1dh/none-Hi-Kn010G3/L0233-k0	3.55E-09
H0610-G1dh/none-Hi-Kn010G3/L0230-k0	4.00E-09
GCH006-G1dh/none-Hi-Kn010G3/L0000-k0	4.06E-09
H0610-G1dh/none-Hi-Kn010G3/L0032-k0	3.72E-09
H0610-G1dh/none-Hi-Kn010G3/L0181-k0	3.51E-09
H0610-G1dh/none-Hi-Kn010G3/TR01L009-k0	3.81E-09
H0610-G1dh/none-Hi-Kn010G3/L0141-k0	3.86E-09
H0610-G1dh/none-Hi-Kn010G3/L0079-k0	4.23E-09
GCH094-G1dh/none-Hi-Kn010G3/L0270-k0	3.60E-09
GCH066-G1dh/none-Hi-Kn010G3/L0000-k0	4.29E-09
GCH064-G1dh/none-Hi-Kn010G3/L0000-k0	4.14E-09
H0610-G1dh/none-Hi-Kn010G3/L0066-k0	4.20E-09
GCH027-G1dh/none-Hi-Kn010G3/L0000-k0	3.83E-09
H0610-G1dh/none-Hi-Kn010G3/L0003-k0	4.01E-09
H0610-G1dh/none-Hi-Kn010G3/L0042-k0	4.27E-09
H0610-G1dh/none-Hi-Kn010G3/TR01L011-k0	4.02E-09

抗體名	KD (入 GPC3)
H0610-G1dh/none-Hi-Kn010G3/L0000-k0	3.97E-09
GCH015-G1dh/none-Hi-Kn010G3/L0000-k0	4.14E-09
H0610-G1dh/none-Hi-Kn010G3/L0175-k0	3.84E-09
GCH100-G1dh/none-Hi-Kn010G3/L0011-k0	3.81E-09
GCH014-G1dh/none-Hi-Kn010G3/L0000-k0	4.20E-09
GCH053-G1dh/none-Hi-Kn010G3/L0000-k0	4.05E-09
hCE115HA-E22Hh/L0000-k0/GL4-E22Hh/H0000-E22L	4.28E-09
GCH094-G1dh/none-Hi-Kn010G3/L0011-k0	3.88E-09
GCH045-G1dh/none-Hi-Kn010G3/L0000-k0	4.63E-09
H0610-G1dh/none-Hi-Kn010G3/TR01L012-k0	4.25E-09
H0610-G1dh/none-Hi-Kn010G3/L0115-k0	4.34E-09
H0610-G1dh/none-Hi-Kn010G3/L0044-k0	4.57E-09
H0610-G1dh/none-Hi-Kn010G3/L0107-k0	4.38E-09
H0610-G1dh/none-Hi-Kn010G3/L0007-k0	4.39E-09
GCH013-G1dh/none-Hi-Kn010G3/L0000-k0	4.44E-09
H0610-G1dh/none-Hi-Kn010G3/L0045-k0	4.66E-09
GCH010-G1dh/none-Hi-Kn010G3/L0000-k0	4.12E-09
GCH040-G1dh/none-Hi-Kn010G3/L0000-k0	4.80E-09
H0610-G1dh/none-Hi-Kn010G3/L0002-k0	4.43E-09
H0610-G1dh/none-Hi-Kn010G3/L0016-k0	4.44E-09
GCH007-G1dh/none-Hi-Kn010G3/L0000-k0	4.93E-09
GCH042-G1dh/none-Hi-Kn010G3/L0000-k0	4.88E-09
rCE115H-E22Hh/rCE115L-k0/GL4-E22Hh/H0000-E22L	4.57E-09
H0610-G1dh/none-Hi-Kn010G3/L0120-k0	4.54E-09
H0610-G1dh/none-Hi-Kn010G3/L0065-k0	4.79E-09
GCH018-G1dh/none-Hi-Kn010G3/L0000-k0	4.59E-09
GCH035-G1dh/none-Hi-Kn010G3/L0000-k0	4.94E-09
GCH039-G1dh/none-Hi-Kn010G3/L0000-k0	4.85E-09
GCH099-G1dh/none-Hi-Kn010G3/L0000-k0	4.24E-09
H0610-G1dh/none-Hi-Kn010G3/L0041-k0	4.85E-09
GCH019-G1dh/none-Hi-Kn010G3/L0000-k0	4.36E-09
GCH029-G1dh/none-Hi-Kn010G3/L0000-k0	5.01E-09
GCH058-G1dh/none-Hi-Kn010G3/L0011-k0	4.31E-09
H0610-G1dh/none-Hi-Kn010G3/L0147-k0	4.38E-09
GCH034-G1dh/none-Hi-Kn010G3/L0000-k0	5.09E-09
GCH003-G1dh/none-Hi-Kn010G3/L0000-k0	5.20E-09
H0610-G1dh/none-Hi-Kn010G3/L0139-k0	4.78E-09
H0610-G1dh/none-Hi-Kn010G3/L0089-k0	5.24E-09
H0610-G1dh/none-Hi-Kn010G3/L0113-k0	4.82E-09
H0610-G1dh/none-Hi-Kn010G3/L0180-k0	4.48E-09
GCH005-G1dh/none-Hi-Kn010G3/L0000-k0	5.32E-09
GCH067-G1dh/none-Hi-Kn010G3/L0000-k0	5.24E-09
H0610-G1dh/none-Hi-Kn010G3/L0187-k0	4.92E-09
H0610-G1dh/none-Hi-Kn010G3/L0043-k0	5.14E-09
H0610-G1dh/none-Hi-Kn010G3/L0117-k0	4.92E-09
GCH061-G1dh/none-Hi-Kn010G3/L0000-k0	5.13E-09
GCH022-G1dh/none-Hi-Kn010G3/L0000-k0	4.92E-09
H0610-G1dh/none-Hi-Kn010G3/L0091-k0	5.43E-09
GCH023-G1dh/none-Hi-Kn010G3/L0000-k0	4.94E-09
H0610-G1dh/none-Hi-Kn010G3/L0062-k0	5.28E-09
H0610-G1dh/none-Hi-Kn010G3/L0136-k0	5.04E-09
H0610-G1dh/none-Hi-Kn010G3/TR01L003-k0	5.08E-09
H0610-G1dh/none-Hi-Kn010G3/L0069-k0	5.32E-09
H0610-G1dh/none-Hi-Kn010G3/L0123-k0	5.08E-09
GCH025-G1dh/none-Hi-Kn010G3/L0000-k0	5.05E-09
GCH100-G1dh/none-Hi-Kn010G3/L0000-k0	5.39E-09
H0610-G1dh/none-Hi-Kn010G3/L0046-k0	5.45E-09
H0610-G1dh/none-Hi-Kn010G3/L0144-k0	4.84E-09
GCH026-G1dh/none-Hi-Kn010G3/L0000-k0	5.17E-09
H0610-G1dh/none-Hi-Kn010G3/L0138-k0	5.24E-09
GCH056-G1dh/none-Hi-Kn010G3/L0000-k0	5.03E-09
H0610-G1dh/none-Hi-Kn010G3/L0129-k0	5.28E-09
GCH032-G1dh/none-Hi-Kn010G3/L0000-k0	5.74E-09
H0610-G1dh/none-Hi-Kn010G3/TR01L005-k0	5.37E-09
GCH012-G1dh/none-Hi-Kn010G3/L0000-k0	5.40E-09
GCH055-G1dh/none-Hi-Kn010G3/L0000-k0	5.60E-09
H0610-G1dh/none-Hi-Kn010G3/L0104-k0	5.90E-09
GCH059-G1dh/none-Hi-Kn010G3/L0000-k0	5.70E-09
GCH054-G1dh/none-Hi-Kn010G3/L0000-k0	5.30E-09
GCH008-G1dh/none-Hi-Kn010G3/L0000-k0	5.55E-09
H0610-G1dh/none-Hi-Kn010G3/L0232-k0	5.38E-09
H0610-G1dh/none-Hi-Kn010G3/L0126-k0	5.62E-09
GCH094-G1dh/none-Hi-Kn010G3/L0000-k0	5.89E-09
H0610-G1dh/none-Hi-Kn010G3/L0132-k0	5.65E-09
H0610-G1dh/none-Hi-Kn010G3/L0106-k0	5.66E-09
GCH054-G1dh/none-Hi-Kn010G3/L0011-k0	5.25E-09
H0610-G1dh/none-Hi-Kn010G3/L0109-k0	5.70E-09
H0610-G1dh/none-Hi-Kn010G3/L0063-k0	6.03E-09
GCH068-G1dh/none-Hi-Kn010G3/L0000-k0	6.23E-09
GCH067-G1dh/none-Hi-Kn010G3/L0000-k0	5.61E-09
H0610-G1dh/none-Hi-Kn010G3/L0137-k0	5.87E-09

【0241】 (3-3) 利用點突變所為之pI改變

雙專一性抗體之商用生產須要高度精製。使用離子交換層析時，據報告改變分子之等電點(pI)係為有效(PLoS One. 2013;8(2):e57479)。所以，針對實施例2製作之人化抗人GPC3抗體序列H0000-ERY27_HK(序列編號：54)，考慮於CDR1、CDR2、CDR3導入已考慮pI改變之點突變，製備改造抗體。然後，測定該等改造抗體針對可溶性人GPC3之親和性。

其結果就維持針對人GPC3之親和性且能使pI降低之可能胺基酸改變而言，找到Kabat編號19位、43位、53位、61位之胺基酸。

藉由將維持針對人GPC3之親和性且有pI降低效果之部位予以組合，獲得表10所示之維持親和性與pI之抗體。

【0242】 [表10]

抗體名 (同抗體)	pI 計算值 (同抗體)	抗體名 (單臂抗體)	人 GPC3 KD (單臂抗體)	以 H0610-E2704sEpsc 作為基礎之變異部位
H0610-E2704sEpsc/L0000-k0	7.8	H0610-G1dh/none-Hi-Kn010G3/L0000-k0	4.18E-09	-
GCH054-E2704sEpsc/L0011-k0	6.2	GCH054-G1dh/none-Hi-Kn010G3/L0011-k0	5.25E-09	K19T/Q43E/P52aG/K53E/G55P/Q61E
GCH065-E2704sEpsc/L0011-k0	6.4	GCH065-G1dh/none-Hi-Kn010G3/L0011-k0	8.84E-10	K19T/Q43E/P52aG/K53P/G55P/Q61E
GCH094-E2704sEpsc/L0011-k0	6.2	GCH094-G1dh/none-Hi-Kn010G3/L0011-k0	4.54E-09	K19T/I37V/P40A/Q43E/M48M/P52aG/K53E/G55P/Q61E

【0243】 (3-4)點突變所致細胞外基質結合能力改變

據報告向細胞外基質(ECM)等之非專一性結合可能會影響藥物動態(MAbs. 2012 Nov-Dec;4(6):753-60)。所以針對本實施例獲得之改造抗體，依參考實施例4記載之方法實施針對ECM之結合能力。其結果，確認人化抗人CD3ε鏈及抗人GPC3雙專一性抗體GPC3_ERY27_hCE115(序列編號54、55、56)之ECM結合能力高。所以，使用關於實施例3-1、3-2、3-3研究之針對人化抗人CD3ε鏈抗體序列hCE115HA-ERY27_HE(序列編號：55)之任意點突變，研究使ECM結合能力減低之組合。其結果，發現Kabat編號11位、16位、52a位、53位、98位及100位之胺基酸維持針對CD3ε之親和性且對於ECM結合能力降低有影響，獲得了比起人化抗人CD3ε鏈及抗人GPC3雙專一性抗體GPC3_ERY27_hCE115改造抗體，ECM

結合能力更為減低的抗體(表11)。

【0244】 [表11]

抗體名	ECM結合比 (標準=1)
GPC3_ERY22_CE115 (rCE115H-E22Hh/rCE115L-k0/GL4-E22Hk/H0000-E22L)	4.0
GPC3_ERY27 (hCE115HA-E22Hh/L0000-k0/GL4-E22Hk/H0000-E22L)	50.9
CE115HA236-E22Hh/GLS3108-k0/GL4-E22Hk/H0610-E22L	429.9
CE115HA236-E22Hh/GLS3108-k0/GL4-E22Hk/H0000-E22L	414.8
CE115HA251-E22Hh/L0000-k0/GL4-E22Hk/H0000-E22L	346.9
CE115HA251-E22Hh/L0000-k0/GL4-E22Hk/H0610-E22L	334.4
TR01H002-E22Hh/GLS3108-k0/GL4-E22Hk/H0610-E22L	301.1
TR01H002-E22Hh/GLS3108-k0/GL4-E22Hk/H0000-E22L	216.9
TR01H015-E22Hh/L0000-k0/GL4-E22Hk/H0610-E22L	185.7
TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0208-k0	50.4
CE115HA122-E22Hh/L0000-k0/GL4-E22Hk/H0000-E22L	47.0
TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0211-k0	15.5
TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0206-k0	15.4
TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0209-k0	7.4
rCE115H-E22Hh/rCE115L-k0/GL4-E22Hk/H0610-E22L	4.6
TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0204-k0	4.4
TR01H067-E2702GsKsc/GCH054-E2704sEpsc/L0212-k0	3.3
TR01H113-E2702GsKsc/GCH065-E2704sEpsc/L0011-k0	2.5
TR01H082-E2702GsKsc/GCH065-E2704sEpsc/L0011-k0	1.7
TR01H113-E2702GsKsc/GCH094-E2704sEpsc/L0011-k0	1.6
rCE115H-E22Hh/rCE115L-k0/L0000-E22Hk/H0610-E22L	1.4
TR01H084-E2702GsKsc/GCH065-E2704sEpsc/L0011-k0	1.3
TR01H084-E2702GsKsc/GCH094-E2704sEpsc/L0011-k0	1.2
TR01H082-E2702GsKsc/GCH094-E2704sEpsc/L0201-k0	1.1
TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0000-k0	0.8
TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0201-k0	0.8
TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0203-k0	0.8
TR01H082-E2702GsKsc/GCH094-E2704sEpsc/L0011-k0	0.7
TR01H109-E2702GsKsc/GCH065-E2704sEpsc/L0011-k0	0.7
TR01H067-E2702GsKsc/GCH054-E2704sEpsc/L0222-k0	0.6
TR01H067-E2702GsKsc/GCH054-E2704sEpsc/L0201-k0	0.5
TR01H109-E2702GsKsc/GCH094-E2704sEpsc/L0011-k0	0.4
TR01H113-E2702sKsc/GCH065-E2704sEpsc/L0011-k0	0.3
MRAH-G1d/MRAL-k0 (標準)	1

【0245】 (3-5)利用點突變所為之對於SuRe™ 配體之結合能力改變

已知有依存抗體之可變區序列(VH3)而結合於Protein A之例 (J Biomol Tech. 2011 Jul;22(2):50-2)。於人化抗人CD3ε鏈及抗人GPC3雙專一性抗體之Protein A精製，去除抗CD3抗體同抗體對於抑制介由CD3之非專一性反應方面係為重要。故，據認為宜抑制抗CD3抗體同抗體之Protein A結合。係假設商用生產時使用SuRe™ 配體，故於人化抗CD3抗體H鏈改變體TR01H082-E2702GsKsc及

TR01H084-E2702GsKsc(序列編號398及399)之CDR2導入考慮了SuRe™ 配體結合之點突變並製備改造抗體。該等改造抗體對於SuRe™ 配體之結合能力依參考實施例5記載之方法實施。其結果，發現Kabat編號19位、57位、59位之胺基酸維持對於CD3ε之親和性且影響對於Sure™ 配體之結合能力，獲得了相對於TR01H082-E2702GsKsc/L0011-k0(序列編號398及410)、及TR01H084-E2702GsKsc/L0011-k0(序列編號399及410)，對於SuRe™ 配體之結合能力減低的抗體(表12)。

【0246】 [表12]

抗體名	SuRe™ 結合 (RU)	將 CE115HA000 作為基礎之變異部位
TR01H084-E2702GsKsc/L0011-k0	5065.8	R16G/A52aD/N53Q/D72A/L78I/G98A/Y100G/A102I
TR01H082-E2702GsKsc/L0011-k0	4469.2	V11L/A52aD/N53Q/G98A/Y100G
TR01H090-E2702GsKsc/L0011-k0	3606.3	V11L/R16G/A52aD/N53Q/G98A/Y100G
TR01H093-E2702GsKsc/L0011-k0	2459.7	V11L/A52aD/N53Q/K64Q/G98A/Y100G
TR01H094-E2702GsKsc/L0011-k0	2351.9	V11L/A52aD/N53Q/K64S/G98A/Y100G
TR01H114-E2702GsKsc/L0011-k0	1485.5	R16G/A52aD/N53Q/T57S/D72A/L78I/G98A/Y100G/A102I
TR01H092-E2702GsKsc/L0011-k0	1159.5	V11L/A52aD/N53Q/K64A/G98A/Y100G
TR01H100-E2702GsKsc/L0011-k0	383.0	V11L/A52aD/N53Q/T57S/G98A/Y100G
TR01H111-E2702GsKsc/L0011-k0	50.7	R16G/R19K/A52aD/N53Q/D72A/L78I/G98A/Y100G/A102I
TR01H110-E2702GsKsc/L0011-k0	29.5	R19K/A52aD/N53Q/G98A/Y100G
TR01H091-E2702GsKsc/L0011-k0	27.5	V11L/R19K/A52aD/N53Q/G98A/Y100G
TR01H091-E2702GsKsc/L0011-k0	15.0	V11L/R19K/A52aD/N53Q/G98A/Y100G
TR01H112-E2702GsKsc/L0011-k0	8.8	R16G/A52aD/N53Q/T57Q/D72A/L78I/G98A/Y100G/A102I
TR01H113-E2702GsKsc/L0011-k0	7.0	R16G/A52aD/N53Q/Y59V/D72A/L78I/G98A/Y100G/A102I
TR01H096-E2702GsKsc/L0011-k0	2.7	V11L/A52aD/N53Q/T57G/G98A/Y100G
TR01H109-E2702GsKsc/L0011-k0	2.2	V11L/A52aD/N53Q/Y59V/G98A/Y100G
TR01H098-E2702GsKsc/L0011-k0	1.6	V11L/A52aD/N53Q/T57P/G98A/Y100G
TR01H107-E2702GsKsc/L0011-k0	1.4	V11L/A52aD/N53Q/Y59Q/G98A/Y100G
TR01H103-E2702GsKsc/L0011-k0	1.4	V11L/A52aD/N53Q/Y59G/G98A/Y100G
TR01H104-E2702GsKsc/L0011-k0	1.0	V11L/A52aD/N53Q/Y59I/G98A/Y100G
TR01H105-E2702GsKsc/L0011-k0	0.8	V11L/A52aD/N53Q/Y59L/G98A/Y100G
TR01H099-E2702GsKsc/L0011-k0	0.6	V11L/A52aD/N53Q/T57Q/G98A/Y100G
TR01H102-E2702GsKsc/L0011-k0	0.5	V11L/A52aD/N53Q/Y59F/G98A/Y100G
TR01H101-E2702GsKsc/L0011-k0	0.5	V11L/A52aD/N53Q/T57V/G98A/Y100G
TR01H108-E2702GsKsc/L0011-k0	0.4	V11L/A52aD/N53Q/Y59T/G98A/Y100G
TR01H097-E2702GsKsc/L0011-k0	0.1	V11L/A52aD/N53Q/T57L/G98A/Y100G
TR01H106-E2702GsKsc/L0011-k0	0.0	V11L/A52aD/N53Q/Y59P/G98A/Y100G
TR01H095-E2702GsKsc/L0011-k0	-0.2	V11L/A52aD/N53Q/T57F/G98A/Y100G

【0247】 (3-6)利用各種性質改善之點突變之組合以製作最適化雙專一性抗體

藉由將實施例3-1至3-5記載之各種性質有改善之點突變予以組合，可以製作最適化之改造抗體。如此之改造抗體，例如製作表13記載之抗體，使用和實施例1為同樣之方法，供T細胞依存性細胞傷害(TDCC)活性評價。其結果記載於第4~9圖。其結果，獲得顯示和人化前之GPC3_ERY22_rCE115顯示同等或更高之T

細胞依存的細胞傷害活性的活性的最適化人化抗人CD3ε鏈及抗人GPC3雙專一性抗體。

【0248】 [表13]

於 TDCC 分析中之 樣本編號	抗體名
1	GPC3_ERY22_CE115 (rCE115H-E22Hh/rCE115L-k0/GL4-E22Hk/H0000-E22L)
2	GPC3_ERY27 (hCE115HA-E22Hh/L0000-k0/GL4-E22Hk/H0000-E22L)
3	CE115HA251-E22Hh/L0000-k0/GL4-E22Hk/H0000-E22L
4	CE115HA236-E22Hh/GLS3108-k0/GL4-E22Hk/H0000-E22L
5	TR01H002-E22Hh/GLS3108-k0/GL4-E22Hk/H0000-E22L
6	CE115HA122-E22Hh/L0000-k0/GL4-E22Hk/H0000-E22L
7	rCE115H-E22Hh/rCE115L-k0/L0000-E22Hk/H0610-E22L
8	rCE115H-E22Hh/rCE115L-k0/GL4-E22Hk/H0610-E22L
13	TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0000-k0
14	TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0201-k0
15	TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0203-k0
16	TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0204-k0
17	TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0206-k0
18	TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0208-k0
19	TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0209-k0
20	TR01H040-E2702GsKsc/H0610-E2704sEpsc/L0211-k0
21	rCE115H-E2702GsKsc/H0610-E2704sEpsc/L0000-k0
22	TR01H061-E2702GsKsc/H0610-E2704sEpsc/L0000-k0
23	TR01H068-E2702GsKsc/H0610-E2704sEpsc/L0000-k0
24	TR01H071-E2702GsKsc/H0610-E2704sEpsc/L0000-k0
25	TR01H067-E2702GsKsc/GCH054-E2704sEpsc/L0201-k0
26	TR01H067-E2702GsKsc/GCH054-E2704sEpsc/L0212-k0
27	TR01H067-E2702GsKsc/GCH054-E2704sEpsc/L0222-k0
28	TR01H067-E2702GsKsc/ GCH054-E2704sEpsc/L0000-k0
29	TR01H082-E2702GsKsc/GCH094-E2704sEpsc/L0201-k0
30	TR01H082-E2702GsKsc/GCH094-E2704sEpsc/L0011-k0
31	TR01H084-E2702GsKsc/GCH094-E2704sEpsc/L0011-k0
32	TR01H084-E2702GsKsc/GCH065-E2704sEpsc/L0011-k0
33	TR01H082-E2702GsKsc/GCH065-E2704sEpsc/L0011-k0
34	TR01H109-E2702GsKsc/GCH094-E2704sEpsc/L0011-k0
35	TR01H109-E2702GsKsc/GCH065-E2704sEpsc/L0011-k0
36	TR01H113-E2702GsKsc/GCH094-E2704sEpsc/L0011-k0
37	TR01H113-E2702GsKsc/GCH065-E2704sEpsc/L0011-k0
38	TR01H113-E2702sKsc/GCH065-E2704sEpsc/L0011-k0

【0249】 由實施例3-1~3-6可知:對於維持和人化前之 GPC3_ERY22_rCE115之T細胞依存的細胞傷害活性有同等或更高活性之最適化抗人CD3ε鏈及抗人GPC3雙專一性抗體之性質方面，例如以下之胺基酸殘基係為重要。

抗人CD3ε鏈抗體中例如11位之Leu、16位之Gly、52a位之Asp、53位之Gln、72位之Ala、78位之Ile、98位之Ala、100位之Gly、102位之Ile。抗人GPC3抗體中例如:19位之Thr、43位之Glu、52a位之Gly、53位之Pro或Glu、55位之Pro、61

位之Glu。又，共通抗體L鏈中例如25位之Pro、27a位之Pro、27b位之Pro、33位之Ile、34位之Gln、56位之Arg或Trp、89位之Tyr。(均依Kabat編號)

【0250】 [實施例4]活體內(in vivo)藥效之評價

針對上述抗體之一部分，也就使用罹癌模式之活體內(in vivo)藥效進行評價。

以實施例3-6記載之試管內(in vitro)分析法，實施已認定為細胞傷害活性之表13所示中之代表抗體的活體內(in vivo)之藥效之評價。活體內之藥效評價係考慮腫瘤塊形成所致之微小環境差異可能帶來的結果，使用GPC3之表現量大約同等但是該抗體所致藥效感受性不同之2種人癌細胞株，亦即PC-10及NCI-H446。將該等細胞株移植到NOD scid小鼠，於已確認腫瘤形成之NOD scid小鼠移入於試管內(in vitro)培養人PBMC以使其增殖之T細胞。對該小鼠實施藉由投予最適化抗人CD3ε鏈及抗人GPC3雙專一性抗體所為之治療(稱為T細胞移入模式)。

【0251】 亦即，於最適化抗人CD3ε鏈及抗人GPC3雙專一性抗體之PC-10 T細胞移入模式所為之藥效試驗，實施如下列試驗。使用從健康人自願者抽取之血液分離出的PBMC及T cell activation/ expansion kit/ human(MACS Miltenyi biotec公司)，實施T細胞之擴大培養。將人癌細胞株PC-10 1×10^7 細胞與Matrigel基底膜基質(BD公司)混合，移植到NOD scid小鼠(Clea Japan、♀、6W)之鼠蹊部皮下。移植日定義為day 0。在移植前日對於以腹腔內小鼠投予Anti asialo抗體(和光純藥)0.2 mg/隻。移植後13日至15日依腫瘤尺寸與體重分群後，再度以0.2 mg/隻對於腹腔內投予Anti asialo GM1抗體。隔日將前述擴大培養所得之T細胞以 3×10^7 細胞/隻的量移植到腹腔內。T細胞移植約4小時後，將最適化抗人CD3ε鏈及抗人GPC3雙專一性抗體以1 mg/kg的量對於尾靜脈內投予。最適化抗人CD3ε鏈及抗人GPC3雙專一性抗體之投予只進行1次。

【0252】 其結果，最適化抗人CD3ε鏈及抗人GPC3雙專一性抗體投予群相

第 115 頁，共 122 頁(發明說明書)

14948AAAAAAPTWF

較於溶劑投予群認為有明顯的抗腫瘤作用(第10圖a, b)。

【0253】 最適化抗人CD3 ϵ 鏈及抗人GPC3雙專一性抗體之利用NCI-H446 T細胞移入模式所為之藥效試驗也以同樣方法實施。對於NCI-H446以5 mg/kg的量將最適化抗人CD3 ϵ 鏈及抗人GPC3雙專一性抗體對於尾靜脈內進行1次投予。

【0254】 其結果，認為最適化抗人CD3 ϵ 鏈及抗人GPC3雙專一性抗體投予群比起溶劑投予群有較明顯的抗腫瘤作用(第11圖a, b)。

【0255】 [參考實施例]

[參考實施例1]抗體之表現載體之製作及抗體之表現與精製

胺基酸取代之導入係使用 QuikChange Site-Directed Mutagenesis Kit (Stratagene)、PCR或In fusion Advantage PCR cloning kit (TAKARA)等依該技術領域中有通常知識者公知之方法實施，建構表現載體。獲得之表現載體之鹼基序列依該技術領域中有通常知識者公知之方法決定。將製作之質體對於來自人胎兒腎癌細胞之HEK293H株(Invitrogen)、或FreeStyle293細胞(Invitrogen公司)進行暫時性導入，並實施抗體表現。從獲得之培養上清使用rProtein A Sepharose™ Fast Flow(GE Health care)依該技術領域中有通常知識者公知之方法精製抗體。精製抗體濃度，係使用分光光度計測定於280 nm之吸光度，並從依獲得之值使用PACE法算出之吸光係數，計算出抗體濃度(Protein Science 1995 ; 4 : 2411-2423)。

【0256】 [參考實施例2]

使用人末梢血單核球作為效應子細胞之各待驗抗體之ADCC活性

針對各待驗抗體依以下方法測定ADCC活性。

使用人末梢血單核球(以下稱為人PBMC)作為效應子細胞，依以下方式測定各待驗抗體之ADCC活性。

【0257】 (1)人PBMC溶液之製備

使用已預先注入了200 μ l 之1000單位/ml之肝素溶液(Novo heparin注5千單

位，Novo nordisc)的注射器，從中外製藥(股)公司所屬之健常人自願者(成人男性)抽取末梢血50 ml。將使用PBS(-)稀釋成2倍之該末梢血分為4等分，加到已預先注入15 ml Ficoll-Paque PLUS並離心操作之Leucosep淋巴球分離管(Greiner bio-one)中。對於已分注該末梢血之分離管以2150 rpm的速度於室溫10分鐘實施離心分離之操作後，分取單核球級分層。利用含10%FBS之Dulbecco's Modified Eagle's Medium(SIGMA)(以下稱為10%FBS/D-MEM。)將該各分層所含之細胞洗滌1次後，將該細胞懸浮於10%FBS/D-MEM中使細胞密度成為 5×10^6 細胞/ml。在培養箱中於37°C培養1小時後，以10%FBS/D-MEM將細胞洗滌1次，使該細胞懸浮於10%FBS/D-MEM中使細胞密度成為 2×10^5 細胞/ml。將該細胞懸浮液作為目標細胞，供以後之實驗。

【0258】 (2)鉻游離試驗(ADCC活性)

ADCC活性以利用鉻釋出法之專一性鉻游離率評價。首先，將製備成各濃度(0、0.004、0.04、0.4、4、40 μ g/ml)之抗體溶液各添加50 μ l 到96井U底板之各井中。然後，接種目標細胞各50 μ l(1×10^4 細胞/井)，於室溫靜置15分鐘。將於各井中已加入(1)製備之人PBMC溶液各100 μ l(5×10^5 細胞/井)之該板，於5%二氧化碳氣體培養箱中於37°C靜置4小時後進行離心操作。該板之各井中之100 μ l之培養上清之放射活性使用蓋氏計數器測定。依下式求出專一性的鉻游離率：

$$\text{專一性的鉻游離率(\%)} = (A - C) \times 100 / (B - C)。$$

【0259】 於上式，A表示各井中之100 μ l之培養上清之放射活性(cpm)之平均值。又，B表示目標細胞添加了100 μ l之2% NP-40水溶液(Nonidet P-40、Nacalaitesque)及50 μ l之10% FBS/D-MEM培養基之井中之100 μ l之培養上清之放射活性(cpm)平均值。再者，C表示於目標細胞添加10% FBS/D-MEM培養基150 μ l之井中之100 μ l之培養上清之放射活性(cpm)之平均值。試驗重複三次，計算反映了各待驗抗體之ADCC活性之前述試驗之專一性的鉻游離率(%)的平均值及標準偏

差。

【0260】 [參考實施例3]

利用差示掃描型螢光定量法所為之改造抗體之T_m評價

本研究中，以使用Rotor-Gene Q(QIAGEN)之差示掃描型螢光定量法評價改造抗體之T_m(熱改性溫度)。又，本手法，已有人報告和就抗體之熱安定性評價法廣為人知的使用差示掃描型熱量計之T_m評價有良好的相關性(Journal of Pharmaceutical Science 2010; 4: 1707-1720)。

【0261】 將 5000 倍 濃 度 之 SYPRO™ orange(Molecular Probes) 以 PBS(Sigma)稀釋後，和抗體溶液混合以製備測定樣本。將各樣本各20μL安置於測定用管，以240℃ /hr的升溫速度使溫度從30℃升高到99℃。於470 nm(激發波長)/ 555 nm(螢光波長)檢測伴隨升溫之螢光變化。

數據係使用Rotor-Gene Q Series Software(QIAGEN)計算認為有螢光遷移之溫度，定義其值為T_m值。

【0262】 [參考實施例4]ECM結合能力測定

依WO2012093704 記載之方法實施。具體而言，以TBS(TaKaRa、#T903)將BD Matrigel(BD Biosciences、#356237)調整為2mg/mL，各於測定用96井板(Meso Scale Discovery、#L15XB-3(High Bind))分注5μL後，於冷處靜置一晚。然後於各井中加入150μL之ECL 阻斷緩衝液 (含有0.05% Tween20、0.5% BSA、0.01% 疊氮化鈉之PBS)，於室溫靜置2小時以上。

將山羊抗人 IgG(γ)(Invitrogen、#628400)依 MSD SULFO-TAG NHS Ester(Meso Scale Discovery、#R91AN-2)之操作說明書進行釘化。將其使用ECL稀釋緩衝液(含有0.01% Tween20、0.1% BSA、0.01% 疊氮化鈉之PBS)稀釋成終濃度2μg/mL。又，將標準抗體及待驗抗體以PBS-T(含有0.05% Tween20、0.01% 疊氮化鈉之PBS)稀釋成終濃度3μg/mL。

於反應用96井板(Thermo scientific、Nunc #145399)按順序添加10 μ L之ECL 稀釋緩衝液、20 μ L之標準抗體及待驗抗體(3 μ g/mL)、30 μ L之釐化抗體 (2 μ g/mL)，於遮光下，邊於室溫攪拌邊進行1小時反應。

從測定用96井板傾倒去除ECL 阻斷緩衝液，並從反應用96井板添加50 μ L之樣本溶液，於遮光於下室溫靜置1小時。之後從測定用96井板將樣本溶液傾倒除去，加入2x T緩衝液 (4x MSD Read Buffer T (Meso Scale Discovery) 以ECL稀釋緩衝液稀釋成二倍者) 150 μ L，立即實施ECL測定。測定使用SECTOR Imager 2400 (Meso Scale Discovery)。

解析係將待驗抗體之螢光強度值除以標準抗體之值，算出令標準抗體為1時之強度並進行比較。

【0263】 [參考實施例5]SuRe™ 配體結合能力測定

對於SuRe™ 配體之結合能力之測定係使用Biacore™-T200(GEHealthcare Japan)。運行緩衝液係使用HBS-EP+ (GEHealthcare Japan)，使用胺偶聯套組(GEHealthcare Japan)使Mab Select SuRe™ 配體(GEHealthcare Japan)共價鍵結於CM5晶片(羧基甲基葡聚糖被覆晶片)。當作分析物使用之抗體使用 HBS-EP+製備成5 μ g/mL。測定係先以流速10 μ L/min注入5 μ g/mL之抗體溶液3 min使其反應，之後切換成HBS-EP+，測定流過0.5 min後之回應(RU)。測定結束後，以10 mM Gly-HCl, pH 1.5洗滌，使傳感晶片再生。對照流式細胞，係在晶片上未共價鍵結配體，而實施同樣的實驗，取兩者之回應(RU)之差以解析對於SuRe™ 配體之結合能力。

【0264】 和本說明書中之序列編號對應之序列如下表所示。

[表14]

序列編號	名稱	序列編號	名稱	序列編號	名稱
1	GPC3 核苷酸序列 (NM_001164617.1)	81	TR01H018	154	TR01H099
2	GPC3 胺基酸序列 (NP_001158089.1)	82	TR01H019	155	TR01H100
3	信號序列	83	TR01H020	156	TR01H101
4	T 細胞受體 α 鏈肽 (CAA26635.1)	84	TR01H021	157	TR01H102
5	T 細胞受體 β 鏈肽 (C25777)	85	TR01H022	158	TR01H103
6	T 細胞受體 γ1 鏈肽 (A26659)	86	TR01H023	159	TR01H104
7	T 細胞受體 γ2 鏈肽 (AAB63312.1)	87	TR01H024	160	TR01H105
8	T 細胞受體 δ 鏈肽 (AAA61033.1)	88	TR01H025	161	TR01H106
9	CD3γ 鏈核甘酸 (NM_000073.2)	89	TR01H026	162	TR01H107
10	CD3δ 鏈核甘酸 (NM_000732.4)	90	TR01H027	163	TR01H108
11	CD3ε 鏈核甘酸 (NM_000733.3)	91	TR01H028	164	TR01H109
12	CD3γ 鏈肽 (NP_000064.1)	92	TR01H029	165	TR01H110
13	CD3δ 鏈肽 (NP_000723.1)	93	TR01H030	166	TR01H111
14	CD3ε 鏈肽 (NP_000724.1)	94	TR01H031	167	TR01H112
15~22	肽鏈連結子	95	TR01H032	168	TR01H113
23	人 Cy1	96	TR01H033	169	TR01H114
24	人 Cy2	97	TR01H034	170	GCH003
25	人 Cy3	98	TR01H035	171	GCH005
26	人 Cy4	99	TR01H036	172	GCH006
27	FcγRI 核苷酸 (NM_000566.3)	100	TR01H037	173	GCH007
28	FcγRI 肽 (NP_000557.1)	101	TR01H038	174	GCH008
29	FcγRIIA 核苷酸 (BC020823.1)	102	TR01H039	175	GCH010
30	FcγRIIA 肽 (AAH20823.1)	103	TR01H040	176	GCH012
31	FcγRIIB 核苷酸 (BC146678.1)	104	TR01H041	177	GCH013
32	FcγRIIB 肽 (AA146679.1)	105	TR01H042	178	GCH014
33	FcγRIIIA 核苷酸 (BC033678.1)	106	TR01H043	179	GCH015
34	FcγRIIIA 肽 (AAH33678.1)	107	TR01H044	180	GCH016
35	FcγRIIIB 核苷酸 (BC128562.1)	108	TR01H045	181	GCH019
36	FcγRIIIB 肽 (AA128563.1)	109	TR01H046	182	GCH022
37	Fc 區(RefSeq 註冊編號 AAC82527.1 之 N 末附加 A)	110	TR01H047	183	GCH023
38	Fc 區(RefSeq 註冊編號 AAB59393.1 之 N 末附加 A)	111	TR01H048	184	GCH025
39	Fc 區(RefSeq 註冊編號 AAB59394.1 之 N 末附加 A)	112	TR01H049	185	GCH026
40	H0000, GPC3 H 鏈可變區	113	TR01H050	186	GCH027
41	GL4, GPC3 L 鏈可變區	114	TR01H051	187	GCH029
42	rCE115H, CE115H 鏈可變區	115	TR01H052	188	GCH032
43	rCE115L, CE115L 鏈可變區	116	TR01H053	189	GCH034
44	G1dh	117	TR01H054	190	GCH035
45	ERY22_Hk	118	TR01H055	191	GCH039
46	ERY22_Hh	119	TR01H056	192	GCH040
47	GL4-ERY22_Hk	120	TR01H057	193	GCH042
48	H0000-ERY22_L	121	TR01H058	194	GCH043
49	rCE115H-ERY22_Hh	122	TR01H061	195	GCH045
50	rCE115L-k0	123	TR01H062	196	GCH053
51	hCE115HL(人化 CE115 之重鏈)	124	TR01H063	197	GCH054
52	hCE115HA(人化 CE115 之重鏈)	125	TR01H064	198	GCH055
53	L0000(人化 CE115 之輕鏈)	126	TR01H065	199	GCH056
54	H0000-ERY27_HK	127	TR01H066	200	GCH057
55	hCE115HA-ERY27_HE	128	TR01H067	201	GCH059
56	L0000-k0	129	TR01H068	202	GCH060
57	E22Hh	130	TR01H069	203	GCH061
58	E22Hk	131	TR01H070	204	GCH062
59	Hi-Kn010G3	132	TR01H071	205	GCH064
60	E2702GsKsc	133	TR01H072	206	GCH065
61	E2704sEpsc	134	TR01H073	207	GCH066
62	E2702sKsc	135	TR01H074	208	GCH067
63	k0	136	TR01H075	209	GCH068
64	CE115HA177	137	TR01H076	210	GCH073
65	CE115HA178	138	TR01H077	211	GCH094
66	CE115HA179	139	TR01H079	212	GCH098
67	CE115HA180	140	TR01H080	213	GCH099
68	hCE115HAa	141	TR01H081	214	GCH100
69	TR01H006	142	TR01H082	215	H0610
70	TR01H007	143	TR01H083	216	L0000vk1
71	TR01H008	144	TR01H084	217	L0002
72	TR01H009	145	TR01H090	218	L0003
73	TR01H010	146	TR01H091	219	L0006
74	TR01H011	147	TR01H092	220	L0007
75	TR01H012	148	TR01H093	221	L0008
76	TR01H013	149	TR01H094	222	L0009
77	TR01H014	150	TR01H095	223	L0011
78	TR01H015	151	TR01H096	224	L0012
79	TR01H016	152	TR01H097	225	L0013
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[產業利用性]

【0265】 依本發明可提供一種新的多專一性抗原結合分子，其維持BiTE帶有的強抗腫瘤活性、及不誘導癌抗原非依存性細胞介素風暴等之安全性上之優良性質，且血中半衰期長。含有本發明之抗原結合分子作為有效成分之細胞傷害誘導劑可以將Glypican3表現細胞、含該細胞之腫瘤組織作為目標而誘導細胞傷害。本發明之多專一性抗原結合分子當對於患者投予時，不只安全性高，對身體的負擔也少，便利性也高之理想治療。

【符號說明】

無。

序列表

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<141> 2024-02-21

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Val Ile Tyr Thr Gln Leu Met Asn Pro Gly Leu Pro Asp Ser Ala Leu
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Gly Lys Leu Cys Ala His Ser Gln Gln Arg Gln Tyr Arg Ser Ala Tyr
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Cys Ser His Ser Pro Val Ala Glu Asn Asp Thr Leu Cys Trp Asn Gly
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Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val Ala
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Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn Ser
65 70 75 80

Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys Asp
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Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn Phe
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Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln Pro Leu Lys
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Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser Ser Arg Leu
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Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His Phe Arg Cys
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Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala Trp Gly Arg
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Thr Asn Asp Thr Tyr Met Lys Phe Ser Trp Leu Thr Val Pro Glu Lys
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aaacaaggag aggccaccac ctgttcccaa cccagactat gagcccatcc ggaaaggcca	840
gcgggacctg tattctggcc tgaatcagag acgcatctga ccctctggag aacactgcct	900
cccgtggcc caggtctcct ctccagtcce cctgcgactc cctgtttcct gggctagtct	960
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<211> 182
<212> PRT
<213> Homo sapiens

<400> 12

Met Glu Gln Gly Lys Gly Leu Ala Val Leu Ile Leu Ala Ile Ile Leu
1 5 10 15

Leu Gln Gly Thr Leu Ala Gln Ser Ile Lys Gly Asn His Leu Val Lys
20 25 30

Val Tyr Asp Tyr Gln Glu Asp Gly Ser Val Leu Leu Thr Cys Asp Ala
35 40 45

Glu Ala Lys Asn Ile Thr Trp Phe Lys Asp Gly Lys Met Ile Gly Phe
50 55 60

Leu Thr Glu Asp Lys Lys Lys Trp Asn Leu Gly Ser Asn Ala Lys Asp
65 70 75 80

Pro Arg Gly Met Tyr Gln Cys Lys Gly Ser Gln Asn Lys Ser Lys Pro
85 90 95

Leu Gln Val Tyr Tyr Arg Met Cys Gln Asn Cys Ile Glu Leu Asn Ala

100 105 110

Ala Thr Ile Ser Gly Phe Leu Phe Ala Glu Ile Val Ser Ile Phe Val
115 120 125

Leu Ala Val Gly Val Tyr Phe Ile Ala Gly Gln Asp Gly Val Arg Gln
130 135 140

Ser Arg Ala Ser Asp Lys Gln Thr Leu Leu Pro Asn Asp Gln Leu Tyr
145 150 155 160

Gln Pro Leu Lys Asp Arg Glu Asp Asp Gln Tyr Ser His Leu Gln Gly
165 170 175

Asn Gln Leu Arg Arg Asn
180

<210> 13
<211> 171
<212> PRT
<213> Homo sapiens

<400> 13

Met Glu His Ser Thr Phe Leu Ser Gly Leu Val Leu Ala Thr Leu Leu
1 5 10 15

Ser Gln Val Ser Pro Phe Lys Ile Pro Ile Glu Glu Leu Glu Asp Arg
20 25 30

Val Phe Val Asn Cys Asn Thr Ser Ile Thr Trp Val Glu Gly Thr Val
35 40 45

Gly Thr Leu Leu Ser Asp Ile Thr Arg Leu Asp Leu Gly Lys Arg Ile
50 55 60

Leu Asp Pro Arg Gly Ile Tyr Arg Cys Asn Gly Thr Asp Ile Tyr Lys
65 70 75 80

Asp Lys Glu Ser Thr Val Gln Val His Tyr Arg Met Cys Gln Ser Cys
85 90 95

Val Glu Leu Asp Pro Ala Thr Val Ala Gly Ile Ile Val Thr Asp Val
100 105 110

Ile Ala Thr Leu Leu Leu Ala Leu Gly Val Phe Cys Phe Ala Gly His
115 120 125

Glu Thr Gly Arg Leu Ser Gly Ala Ala Asp Thr Gln Ala Leu Leu Arg
130 135 140

Asn Asp Gln Val Tyr Gln Pro Leu Arg Asp Arg Asp Asp Ala Gln Tyr
145 150 155 160

Ser His Leu Gly Gly Asn Trp Ala Arg Asn Lys
165 170

<210> 14
<211> 207
<212> PRT
<213> Homo sapiens

<400> 14

Met Gln Ser Gly Thr His Trp Arg Val Leu Gly Leu Cys Leu Leu Ser
1 5 10 15

Val Gly Val Trp Gly Gln Asp Gly Asn Glu Glu Met Gly Gly Ile Thr
20 25 30

Gln Thr Pro Tyr Lys Val Ser Ile Ser Gly Thr Thr Val Ile Leu Thr
35 40 45

Cys Pro Gln Tyr Pro Gly Ser Glu Ile Leu Trp Gln His Asn Asp Lys
50 55 60

Asn Ile Gly Gly Asp Glu Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp
65 70 75 80

His Leu Ser Leu Lys Glu Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr
85 90 95

Val Cys Tyr Pro Arg Gly Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu
100 105 110

Tyr Leu Arg Ala Arg Val Cys Glu Asn Cys Met Glu Met Asp Val Met
115 120 125

Ser Val Ala Thr Ile Val Ile Val Asp Ile Cys Ile Thr Gly Gly Leu
130 135 140

Leu Leu Leu Val Tyr Tyr Trp Ser Lys Asn Arg Lys Ala Lys Ala Lys
145 150 155 160

Pro Val Thr Arg Gly Ala Gly Ala Gly Gly Arg Gln Arg Gly Gln Asn
165 170 175

Lys Glu Arg Pro Pro Pro Val Pro Asn Pro Asp Tyr Glu Pro Ile Arg
180 185 190

Lys Gly Gln Arg Asp Leu Tyr Ser Gly Leu Asn Gln Arg Arg Ile
195 200 205

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- <211> 4
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 15

Gly Gly Gly Ser

1

<210> 16
<211> 4
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<400> 16

Ser Gly Gly Gly
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<210> 17
<211> 5
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<213> Artificial

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<400> 17

Gly Gly Gly Gly Ser
1 5

<210> 18
<211> 5
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<400> 18

Ser Gly Gly Gly Gly
1 5

<210> 19
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<400> 19

Gly Gly Gly Gly Gly Ser
1 5

<210> 20

<211> 6

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<223> An artificially generated sequence

<400> 20

Ser Gly Gly Gly Gly Gly
1 5

<210> 21

<211> 7

<212> PRT

<213> Artificial

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<223> An artificially generated sequence

<400> 21

Gly Gly Gly Gly Gly Gly Ser
1 5

<210> 22

<211> 7

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 22

Ser Gly Gly Gly Gly Gly Gly
1 5

<210> 23
<211> 330
<212> PRT
<213> Homo sapiens

<400> 23

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 24
<211> 326
<212> PRT
<213> Homo sapiens

<400> 24

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
100 105 110

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
130 135 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145 150 155 160

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn

165					170					175						
Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp	Trp	
180					185					190						
Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	
195					200					205						
Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	
210					215					220						
Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	
225					230					235					240	
Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	
245					250					255						
Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	
260					265					270						
Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	
275					280					285						
Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	
290					295					300						
Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	
305					310					315					320	
Ser	Leu	Ser	Pro	Gly	Lys											
325																

<210> 25
<211> 377
<212> PRT
<213> Homo sapiens

<400> 25

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Thr Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro
100 105 110

Arg Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg
115 120 125

Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys
130 135 140

Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
145 150 155 160

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
165 170 175

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
180 185 190

Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Lys	Trp	Tyr	
		195					200					205				
Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	
		210					215				220					
Gln	Tyr	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	
225						230				235					240	
Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	
				245					250					255		
Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	
			260					265					270			
Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	
		275					280					285				
Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	
		290					295				300					
Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Ser	Gly	Gln	Pro	Glu	Asn	Asn	
305					310					315					320	
Tyr	Asn	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	
				325					330					335		
Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Ile	
			340					345					350			
Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	Arg	Phe	Thr	Gln	
		355					360					365				
Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys								
		370				375										

<210> 26
<211> 327
<212> PRT
<213> Homo sapiens

<400> 26

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Leu Gly Lys
325

<210> 27
<211> 2268
<212> DNA

<213> Homo sapiens

<400> 27

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caacaacacc agaactgtgt gtctcatggt atgtaactct taaagcaaat aaatgaactg	1320
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aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa 2268

<210> 28
<211> 374
<212> PRT
<213> Homo sapiens

<400> 28

Met Trp Phe Leu Thr Thr Leu Leu Leu Trp Val Pro Val Asp Gly Gln
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Val Asp Thr Thr Lys Ala Val Ile Thr Leu Gln Pro Pro Trp Val Ser
20 25 30

Val Phe Gln Glu Glu Thr Val Thr Leu His Cys Glu Val Leu His Leu

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

225						230											240
Thr	Ser	Ser	Glu	Tyr	Gln	Ile	Leu	Thr	Ala	Arg	Arg	Glu	Asp	Ser	Gly		
				245					250					255			
Leu	Tyr	Trp	Cys	Glu	Ala	Ala	Thr	Glu	Asp	Gly	Asn	Val	Leu	Lys	Arg		
			260					265					270				
Ser	Pro	Glu	Leu	Glu	Leu	Gln	Val	Leu	Gly	Leu	Gln	Leu	Pro	Thr	Pro		
		275					280					285					
Val	Trp	Phe	His	Val	Leu	Phe	Tyr	Leu	Ala	Val	Gly	Ile	Met	Phe	Leu		
	290					295					300						
Val	Asn	Thr	Val	Leu	Trp	Val	Thr	Ile	Arg	Lys	Glu	Leu	Lys	Arg	Lys		
305					310					315					320		
Lys	Lys	Trp	Asp	Leu	Glu	Ile	Ser	Leu	Asp	Ser	Gly	His	Glu	Lys	Lys		
			325						330					335			
Val	Ile	Ser	Ser	Leu	Gln	Glu	Asp	Arg	His	Leu	Glu	Glu	Glu	Leu	Lys		
			340					345					350				
Cys	Gln	Glu	Gln	Lys	Glu	Glu	Gln	Leu	Gln	Glu	Gly	Val	His	Arg	Lys		
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Glu	Pro	Gln	Gly	Ala	Thr												
	370																

<210>	29																
<211>	1396																
<212>	DNA																
<213>	Homo sapiens																
<400>	29																
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caaccattga	cagttttgct	gctgctggct	tctgcagaca	gtcaagctgc	tccccaaag											120	

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gagtacacgt gccagactgg ccagaccagc ctcagegacc ctgtgcatct gactgtgctt	360
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cacagtgggtg attaccactg cacaggaaac ataggctaca cgctgttctc atccaagcct	600
gtgaccatca ctgtccaagt gcccagcatg ggcagctctt caccaatggg ggtcattgtg	660
gctgtgggtca ttgcgactgc tgtagcagcc attgttgctg ctgtagtggc cttgatctac	720
tgcaggaaaa agcggatttc agccaattcc actgatactg tgaaggctgc ccaatttgag	780
ccacctggac gtcaaatgat tgccatcaga aagagacaac ttgaagaaac caacaatgac	840
tatgaaacag ctgacggcgg ctacatgact ctgaacccca gggcacctac tgacgatgat	900
aaaaacatct acctgactct tcttcccaac gaccatgtca acagtaataa ctaaagagta	960
acgttatgcc atgtgggtcat actctcagct tgctgagtgg atgacaaaaa gaggggaatt	1020
gttaaaggaa aatttaaagt gagactggaa aaatcctgag caaacaaaac cacctggccc	1080
ttagaaatag cttaaacttt gcttaaacta caaacacaag caaaacttca cggggtcata	1140
ctacatacaa gcataagcaa aacttaactt ggatcatttc tggtaaatgc ttatgttaga	1200
aataagacaa ccccagccaa tcacaagcag cctactaaca tataattagg tgactaggga	1260
ctttctaaga agatacctac cccccaaaaa caattatgta attgaaaacc aaccgattgc	1320
ctttattttg ctccacatt ttcccaataa atacttgcct gtgactaaaa aaaaaaaaaa	1380
aaaaaaaaaa aaaaaa	1396

<210> 30
<211> 316

<212> PRT
<213> Homo sapiens

<400> 30

Met Thr Met Glu Thr Gln Met Ser Gln Asn Val Cys Pro Arg Asn Leu
1 5 10 15

Trp Leu Leu Gln Pro Leu Thr Val Leu Leu Leu Leu Ala Ser Ala Asp
20 25 30

Ser Gln Ala Ala Pro Pro Lys Ala Val Leu Lys Leu Glu Pro Pro Trp
35 40 45

Ile Asn Val Leu Gln Glu Asp Ser Val Thr Leu Thr Cys Gln Gly Ala
50 55 60

Arg Ser Pro Glu Ser Asp Ser Ile Gln Trp Phe His Asn Gly Asn Leu
65 70 75 80

Ile Pro Thr His Thr Gln Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn
85 90 95

Asp Ser Gly Glu Tyr Thr Cys Gln Thr Gly Gln Thr Ser Leu Ser Asp
100 105 110

Pro Val His Leu Thr Val Leu Ser Glu Trp Leu Val Leu Gln Thr Pro
115 120 125

His Leu Glu Phe Gln Glu Gly Glu Thr Ile Met Leu Arg Cys His Ser
130 135 140

Trp Lys Asp Lys Pro Leu Val Lys Val Thr Phe Phe Gln Asn Gly Lys
145 150 155 160

Ser Gln Lys Phe Ser His Leu Asp Pro Thr Phe Ser Ile Pro Gln Ala
165 170 175

Asn His Ser His Ser Gly Asp Tyr His Cys Thr Gly Asn Ile Gly Tyr
180 185 190

Thr Leu Phe Ser Ser Lys Pro Val Thr Ile Thr Val Gln Val Pro Ser
195 200 205

Met Gly Ser Ser Ser Pro Met Gly Val Ile Val Ala Val Val Ile Ala
210 215 220

Thr Ala Val Ala Ala Ile Val Ala Ala Val Val Ala Leu Ile Tyr Cys
225 230 235 240

Arg Lys Lys Arg Ile Ser Ala Asn Ser Thr Asp Pro Val Lys Ala Ala
245 250 255

Gln Phe Glu Pro Pro Gly Arg Gln Met Ile Ala Ile Arg Lys Arg Gln
260 265 270

Leu Glu Glu Thr Asn Asn Asp Tyr Glu Thr Ala Asp Gly Gly Tyr Met
275 280 285

Thr Leu Asn Pro Arg Ala Pro Thr Asp Asp Asp Lys Asn Ile Tyr Leu
290 295 300

Thr Leu Pro Pro Asn Asp His Val Asn Ser Asn Asn
305 310 315

<210> 31
<211> 1497
<212> DNA
<213> Homo sapiens

<400> 31
tgtgactgct gtgctctggg cgccagctcg ctccagggag tgatgggaat cctgtcattc 60
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catatgcttc tgtggacagc tgtgctattc ctggtcctg ttgctgggac acctgcagct 180

cccccaaagg ctgtgctgaa actcgagccc cagtggatca acgtgctcca ggaggactct	240
gtgactctga catgccgggg gactcacage cctgagagcg actccattca gtggttccac	300
aatgggaatc tcattcccac ccacacgcag cccagctaca ggttcaaggc caacaacaat	360
gacagcgggg agtacacgtg ccagactggc cagaccagcc tcagcgaccc tgtgcatctg	420
actgtgcttt ctgagtggct ggtgctccag acccctcacc tggagttcca ggagggagaa	480
accatcgtgc tgaggtgcca cagctggaag gacaagcctc tggtaaggt cacattcttc	540
cagaatggaa aatccaagaa attttccgt tcggatccca acttctccat cccacaagca	600
aaccacagtc acagtggatga ttaccactgc acaggaaaca taggctacac gctgtactca	660
tccaagcctg tgaccatcac tgtccaagct cccagctctt caccgatggg gatcattgtg	720
gctgtggatca ctgggattgc tgtageggcc attgttgctg ctgtagtggc cttgatctac	780
tgcaggaaaa agcggatttc agccaatccc actaatcctg atgaggctga caaagttggg	840
gctgagaaca caatcaccta ttcacttctc atgcaccgg atgctctgga agagcctgat	900
gaccagaacc gtathtagtc tccattgtct tgcattggga ttgagaaga aaatcagaga	960
gggaagatct ggtatttcc tgcctaaatt ccccttgggg aggacaggga gatgctgcag	1020
ttccaaaaga gaaggtttct tccagagtca tctacctgag tcctgaagct ccctgtcctg	1080
aaagccacag acaatatggt cccaaataac cgactgcacc ttctgtgctt cagctcttct	1140
tgacatcaag gctcttccgt tccacatcca cacagccaat ccaattaatc aaaccactgt	1200
tattaacaga taatagcaac ttgggaaatg cttatgttac aggttacgtg agaacaatca	1260
tgtaaatcta tatgatttca gaaatgttaa aatagactaa cctctaccag cacattaaaa	1320
gtgattgttt ctgggtgata aaattattga tgatttttat tttctttatt tttctataaa	1380
gatcatatat tacttttata ataaaacatt ataaaaacaa aaaaaaaaaa aaaaaaaaaa	1440
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa	1497

<210> 32
<211> 291

<212> PRT
<213> Homo sapiens

<400> 32

Met Gly Ile Leu Ser Phe Leu Pro Val Leu Ala Thr Glu Ser Asp Trp
1 5 10 15

Ala Asp Cys Lys Ser Pro Gln Pro Trp Gly His Met Leu Leu Trp Thr
20 25 30

Ala Val Leu Phe Leu Ala Pro Val Ala Gly Thr Pro Ala Ala Pro Pro
35 40 45

Lys Ala Val Leu Lys Leu Glu Pro Gln Trp Ile Asn Val Leu Gln Glu
50 55 60

Asp Ser Val Thr Leu Thr Cys Arg Gly Thr His Ser Pro Glu Ser Asp
65 70 75 80

Ser Ile Gln Trp Phe His Asn Gly Asn Leu Ile Pro Thr His Thr Gln
85 90 95

Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn Asp Ser Gly Glu Tyr Thr
100 105 110

Cys Gln Thr Gly Gln Thr Ser Leu Ser Asp Pro Val His Leu Thr Val
115 120 125

Leu Ser Glu Trp Leu Val Leu Gln Thr Pro His Leu Glu Phe Gln Glu
130 135 140

Gly Glu Thr Ile Val Leu Arg Cys His Ser Trp Lys Asp Lys Pro Leu
145 150 155 160

Val Lys Val Thr Phe Phe Gln Asn Gly Lys Ser Lys Lys Phe Ser Arg
165 170 175

Ser Asp Pro Asn Phe Ser Ile Pro Gln Ala Asn His Ser His Ser Gly
180 185 190

Asp Tyr His Cys Thr Gly Asn Ile Gly Tyr Thr Leu Tyr Ser Ser Lys
195 200 205

Pro Val Thr Ile Thr Val Gln Ala Pro Ser Ser Ser Pro Met Gly Ile
210 215 220

Ile Val Ala Val Val Thr Gly Ile Ala Val Ala Ala Ile Val Ala Ala
225 230 235 240

Val Val Ala Leu Ile Tyr Cys Arg Lys Lys Arg Ile Ser Ala Asn Pro
245 250 255

Thr Asn Pro Asp Glu Ala Asp Lys Val Gly Ala Glu Asn Thr Ile Thr
260 265 270

Tyr Ser Leu Leu Met His Pro Asp Ala Leu Glu Glu Pro Asp Asp Gln
275 280 285

Asn Arg Ile
290

<210> 33
<211> 2137
<212> DNA
<213> Homo sapiens

<400> 33
cttgtccact ccagtgtggc atcatgtggc agctgctcct cccaactgct ctgctacttc 60

tagtttcagc tggcatgcgg actgaagatc tcccaaaggc tgtggtgttc ctggagcctc 120

aatggtacag ggtgctcgag aaggacagtg tgactctgaa gtgccaggga gcctactccc 180

ctgaggacaa ttccacacag tggtttcaca atgagagcct catctcaagc caggcctcga 240

gctacttcat tgacgtgcc acagttgacg acagtggaga gtacaggtgc cagacaaacc 300

tctccaccct cagtgacccg gtgcagctag aagtccatat cggttggtg ttgctccagg	360
ccccctcggtg ggtgttcaag gaggaagacc ctattcacct gaggtgtcac agctggaaga	420
acactgctct gcataaggtc acatatttac agaatggcaa aggcaggaag tattttcatc	480
ataattctga cttctacatt ccaaaagcca cactcaaaga cagcggctcc tactttctgca	540
gggggcttgt tgggagtaaa aatgtgtctt cagagactgt gaacatcacc atcactcaag	600
gtttgtcagt gtcaaccatc tcatcattct ttccacctgg gtaccaagtc tctttctgct	660
tggatgatgg actccttttt gcagtggaca caggactata tttctctgtg aagacaaaca	720
ttcgaagctc aacaagagac tggaaggacc ataaatttaa atggagaaag gaccctcaag	780
acaaatgacc cccatcccat gggggtaata agagcagtag cagcagcatc tctgaacatt	840
tctctggatt tgcaacceca tcatcctcag gcctctctac aagcagcagg aaacatagaa	900
ctcagagcca gatcccttat ccaactctcg acttttcctt ggtctccagt ggaagggaaa	960
agcccatgat ctcaagcag ggaagcccca gtgagtagct gcattcctag aaattgaagt	1020
ttcagagcta caciaaact ttttctgtcc caaccgttcc ctcacagcaa agcaacaata	1080
caggctaggg atggtaatcc tttaaacata caaaaattgc tcgtgttata aattaccag	1140
tttagagggg aaaaaaaaaac aattattcct aaataaatgg ataagtagaa ttaatggttg	1200
aggcaggacc atacagagtg tgggaactgc tgggatcta gggaattcag tgggaccaat	1260
gaaagcatgg ctgagaaata gcaggtagtc caggatagtc taagggaggt gttcccatct	1320
gagcccagag ataagggtgt cttcctagaa cattagccgt agtggaatta acaggaaatc	1380
atgagggtga cgtagaattg agtcttccag gggactctat cagaactgga ccatctccaa	1440
gtatataacg atgagtcctc ttaatgctag gagtagaaaa tggtcctagg aaggggactg	1500
aggattgcgg tggggggtgg ggtggaaaag aaagtacaga acaaaccctg tgtcactgtc	1560
ccaagttgct aagtgaacag aactatctca gcatcagaat gagaaagcct gagaagaaag	1620
aaccaaccac aagcacacag gaaggaaagc gcaggaggtg aaaatgcttt cttggccagg	1680
gtagtaagaa ttagaggtta atgcaggac tgtaaaacca ctttttctgc ttcaatatct	1740

aattcctgtg tagctttgtt cattgcattt attaaacaaa tgttgtataa ccaataactaa 1800
atgtactact gagcttcgct gagttaagtt atgaaacttt caaatccttc atcatgtcag 1860
ttccaatgag gtgggggatgg agaagacaat tgttgcttat gaaagaaagc tttagctgtc 1920
tctgttttgt aagctttaag cgcaacattt cttggttcca ataaagcatt ttacaagatc 1980
ttgcatgcta ctcttagata gaagatggga aaaccatggt aataaaatat gaatgataaa 2040
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2100
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa 2137

<210> 34
<211> 254
<212> PRT
<213> Homo sapiens

<400> 34

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

Gly Met Arg Thr Glu Asp Leu Pro Lys Ala Val Val Phe Leu Glu Pro
20 25 30

Gln Trp Tyr Arg Val Leu Glu Lys Asp Ser Val Thr Leu Lys Cys Gln
35 40 45

Gly Ala Tyr Ser Pro Glu Asp Asn Ser Thr Gln Trp Phe His Asn Glu
50 55 60

Ser Leu Ile Ser Ser Gln Ala Ser Ser Tyr Phe Ile Asp Ala Ala Thr
65 70 75 80

Val Asp Asp Ser Gly Glu Tyr Arg Cys Gln Thr Asn Leu Ser Thr Leu
85 90 95

Ser Asp Pro Val Gln Leu Glu Val His Ile Gly Trp Leu Leu Leu Gln

202448941

110

Ala Pro Arg Trp Val Phe Lys Glu Glu Asp Pro Ile His Leu Arg Cys
115 120 125

His Ser Trp Lys Asn Thr Ala Leu His Lys Val Thr Tyr Leu Gln Asn
130 135 140

Gly Lys Gly Arg Lys Tyr Phe His His Asn Ser Asp Phe Tyr Ile Pro
145 150 155 160

Lys Ala Thr Leu Lys Asp Ser Gly Ser Tyr Phe Cys Arg Gly Leu Val
165 170 175

Gly Ser Lys Asn Val Ser Ser Glu Thr Val Asn Ile Thr Ile Thr Gln
180 185 190

Gly Leu Ser Val Ser Thr Ile Ser Ser Phe Phe Pro Pro Gly Tyr Gln
195 200 205

Val Ser Phe Cys Leu Val Met Val Leu Leu Phe Ala Val Asp Thr Gly
210 215 220

Leu Tyr Phe Ser Val Lys Thr Asn Ile Arg Ser Ser Thr Arg Asp Trp
225 230 235 240

Lys Asp His Lys Phe Lys Trp Arg Lys Asp Pro Gln Asp Lys
245 250

<210> 35
 <211> 820
 <212> DNA
 <213> Homo sapiens

 <400> 35
 cactccagtg tggcatcatg tggcagctgc tcttcccaac tgctctgcta cttctagttt 60

 cagctggcat gcggactgaa gatctcccaa aggctgtggt gttcctggag cctcaatggt 120

acagcgtgct tgagaaggac agtgtgactc tgaagtgcc a gggagcctac tcccctgagg 180
acaattccac acagtgggtt cacaatgaga gcctcatctc aagccaggcc tcgagctact 240
tcattgacgc tgccacagtc aacgacagtg gagagtacag gtgccagaca aacctctcca 300
ccctcagtga cccgggtgcag ctagaagtcc atatcggtg gctgttgctc caggccccctc 360
ggtgggtgtt caaggaggaa gaccctattc acctgaggtg tcacagctgg aagaacactg 420
ctctgcataa ggtcacatat ttacagaatg gcaaagacag gaagtatttt catcataatt 480
ctgacttcca cattccaaaa gccacactca aagatagcgg ctcttacttc tgcagggggc 540
ttgttgggag taaaaatgtg tcttcagaga ctgtgaacat caccatcact caaggtttgg 600
cagtgtaaac catctcatca ttctctccac ctgggtacca agtctctttc tgcttggtga 660
tggtactcct ttttgcagtg gacacaggac tatatttctc tgtgaagaca aacatttgaa 720
gctcaacaag agactggaag gaccataaac ttaaattggag aaaggaccct caagacaaat 780
gacccccatc ccatgggagt aataagagca gtggcagcag 820

<210> 36
<211> 233
<212> PRT
<213> Homo sapiens

<400> 36

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

Gly Met Arg Thr Glu Asp Leu Pro Lys Ala Val Val Phe Leu Glu Pro
20 25 30

Gln Trp Tyr Ser Val Leu Glu Lys Asp Ser Val Thr Leu Lys Cys Gln
35 40 45

Gly Ala Tyr Ser Pro Glu Asp Asn Ser Thr Gln Trp Phe His Asn Glu
50 55 60

Ser Leu Ile Ser Ser Gln Ala Ser Ser Tyr Phe Ile Asp Ala Ala Thr
65 70 75 80

Val Asn Asp Ser Gly Glu Tyr Arg Cys Gln Thr Asn Leu Ser Thr Leu
85 90 95

Ser Asp Pro Val Gln Leu Glu Val His Ile Gly Trp Leu Leu Leu Gln
100 105 110

Ala Pro Arg Trp Val Phe Lys Glu Glu Asp Pro Ile His Leu Arg Cys
115 120 125

His Ser Trp Lys Asn Thr Ala Leu His Lys Val Thr Tyr Leu Gln Asn
130 135 140

Gly Lys Asp Arg Lys Tyr Phe His His Asn Ser Asp Phe His Ile Pro
145 150 155 160

Lys Ala Thr Leu Lys Asp Ser Gly Ser Tyr Phe Cys Arg Gly Leu Val
165 170 175

Gly Ser Lys Asn Val Ser Ser Glu Thr Val Asn Ile Thr Ile Thr Gln
180 185 190

Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Ser Pro Pro Gly Tyr Gln
195 200 205

Val Ser Phe Cys Leu Val Met Val Leu Leu Phe Ala Val Asp Thr Gly
210 215 220

Leu Tyr Phe Ser Val Lys Thr Asn Ile
225 230

<210> 37
<211> 330
<212> PRT

<213> Homo sapiens

<400> 37

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 38
<211> 326
<212> PRT
<213> Homo sapiens

<400> 38

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg

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

195200205

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
210215220

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225230235240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
245250255

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
260265270

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
275280285

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
290295300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305310315320

Ser Leu Ser Pro Gly Lys
325

<210> 39
<211> 327
<212> PRT
<213> Homo sapiens

<400> 39

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
151015

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
202530

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

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Leu Gly Lys
325

- <210> 40
- <211> 115
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 40

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 41
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 41

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
85 90 95

Thr His Val Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 42
<211> 122
<212> PRT
<213> Rattus norvegicus

<400> 42

Glu Val Gln Leu Val Glu Thr Gly Gly Ser Leu Val Gln Pro Gly Lys
1 5 10 15

Ser Leu Lys Leu Thr Cys Ala Thr Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ser Pro Glu Lys Gln Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Asn
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 43
<211> 112
<212> PRT
<213> Rattus norvegicus

<400> 43

Asp Val Val Met Thr Gln Thr Pro Val Ser Met Ser Val Ser Leu Gly
1 5 10 15

Gly Gln Val Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Asn
20 25 30

Asn Gly Asn Thr Tyr Val Ser Trp Tyr Ile Gln Lys Pro Ser Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Ile Ser
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Pro Asp Asp Leu Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Asp Pro Tyr Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> 44
<211> 328
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 44

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Cys Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

- <210> 45
- <211> 338
- <212> PRT
- <213> Artificial

- <220>
- <223> An artificially generated sequence

<400> 45

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
1 5 10 15

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
20 25 30

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
35 40 45

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

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
65 70 75 80

Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
85 90 95

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
100 105 110

Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
115 120 125

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
130 135 140

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
145 150 155 160

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
165 170 175

Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr
180 185 190

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
195 200 205

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
210 215 220

Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg
225 230 235 240

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
245 250 255

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
260 265 270

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
275 280 285

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
290 295 300

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
305 310 315 320

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro His His His His His His
325 330 335

His His

- <210> 46
- <211> 336
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence

<400> 46

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Cys Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Asp Tyr Lys Asp Asp Asp Asp Lys
325 330 335

- <210> 47
- <211> 450
- <212> PRT
- <213> Artificial

- <220>
- <223> An artificially generated sequence

- <400> 47

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
85 90 95

Thr His Val Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
115 120 125

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
130 135 140

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
145 150 155 160

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
165 170 175

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
180 185 190

Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
195 200 205

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
210 215 220

Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
225 230 235 240

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
245 250 255

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
260 265 270

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
275 280 285

Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr
290 295 300

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305 310 315 320

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
325 330 335

Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg
340 345 350

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
355 360 365

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
370 375 380

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
385 390 395 400

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
405 410 415

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
420 425 430

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro His His His His His His
435 440 445

His His
450

- <210> 48
 - <211> 222
 - <212> PRT
 - <213> Artificial
- <220>
- <223> An artificially generated sequence

<400> 48

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser Ala Ser Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
115 120 125

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
130 135 140

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
145 150 155 160

Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
165 170 175

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
180 185 190

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
195 200 205

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

- <210> 49
- <211> 458
- <212> PRT
- <213> Artificial

- <220>
- <223> An artificially generated sequence

- <400> 49

Glu Val Gln Leu Val Glu Thr Gly Gly Ser Leu Val Gln Pro Gly Lys
1 5 10 15

Ser Leu Lys Leu Thr Cys Ala Thr Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ser Pro Glu Lys Gln Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Asn
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
210 215 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
290 295 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
340 345 350

Val Tyr Thr Leu Pro Pro Ser Arg Cys Glu Leu Thr Lys Asn Gln Val
355 360 365

Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385 390 395 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Asp Tyr Lys Asp Asp Asp Asp Lys
450 455

- <210> 50
 - <211> 219
 - <212> PRT
 - <213> Artificial
- <220>
- <223> An artificially generated sequence

<400> 50

Asp Val Val Met Thr Gln Thr Pro Val Ser Met Ser Val Ser Leu Gly
1 5 10 15

Gly Gln Val Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Asn
20 25 30

Asn Gly Asn Thr Tyr Val Ser Trp Tyr Ile Gln Lys Pro Ser Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Ile Ser
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Pro Asp Asp Leu Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Asp Pro Tyr Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

- <210> 51
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 51

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 52
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 52

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 53
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 53

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 54
<211> 448
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 54

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
115 120 125

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
130 135 140

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145 150 155 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
165 170 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
180 185 190

Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
195 200 205

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
210 215 220

Pro Ala Pro Glu Phe Arg Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
225 230 235 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
245 250 255

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
260 265 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
275 280 285

Glu Gln Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
290 295 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305 310 315 320

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
325 330 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Lys Glu
340 345 350

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
355 360 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
370 375 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385 390 395 400

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
405 410 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Tyr Thr
420 425 430

Gln Lys Ser Leu Ser Leu Ser Leu His His His His His His His His
435 440 445

- <210> 55
- <211> 455
- <212> PRT
- <213> Artificial

<220>

<223> An artificially generated sequence

<400> 55

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Arg Gly Gly Pro
225 230 235 240

Lys Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Glu Ser Leu Ser Leu Ser Leu Asp
435 440 445

Tyr Lys Asp Asp Asp Asp Lys
450 455

- <210> 56
- <211> 219
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 56

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

- <210> 57
- <211> 336
- <212> PRT
- <213> Artificial

- <220>

<223> An artificially generated sequence

<400> 57

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Cys Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Asp Tyr Lys Asp Asp Asp Asp Lys
325 330 335

- <210> 58
- <211> 338
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence

<400> 58

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
1 5 10 15

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
20 25 30

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
35 40 45

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

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
65 70 75 80

Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
85 90 95

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
100 105 110

Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
115 120 125

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
130 135 140

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
145 150 155 160

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
165 170 175

Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr
180 185 190

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
195 200 205

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
210 215 220

Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg
225 230 235 240

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
245 250 255

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
260 265 270

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
275 280 285

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
290 295 300

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
305 310 315 320

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro His His His His His His
325 330 335

His His

- <210> 59
- <211> 230
- <212> PRT
- <213> Artificial

<220>

<223> An artificially generated sequence

<400> 59

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
100 105 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125

Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
130 135 140

Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Tyr Thr Gln Lys
210 215 220

Ser Leu Ser Leu Ser Pro
225 230

<210> 60
<211> 325
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 60

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
100 105 110

Glu Phe Arg Gly Gly Pro Lys Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170 175

Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn Arg Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Pro
325

<210> 61
<211> 325
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 61

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
100 105 110

Glu Phe Arg Gly Gly Pro Lys Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170 175

Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Glu Ser
305 310 315 320

Leu Ser Leu Ser Pro
325

- <210> 62
- <211> 325
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 62

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

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

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
100 105 110

Glu Phe Arg Gly Gly Pro Lys Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170 175

Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Lys Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Pro
325

<210> 63
<211> 107
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 63

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

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

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 64
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 64

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 65
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 65

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Gln Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 66

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 66

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Gln Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 67
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 67

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Gln Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 68
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 68

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 69
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 69

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 70
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 70

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ser Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 71
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 71

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 72
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 72

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Pro
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 73
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 73

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Tyr Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 74

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 74

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 75
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 75

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Tyr Tyr Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 76
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 76

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 77
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 77

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Pro
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 78
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 78

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 79
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 79

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Tyr Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 80
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 80

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 81
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 81

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 82

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 82

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 83
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 83

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Pro
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 84
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 84

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 85
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 85

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Pro
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 86
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 86

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 87
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 87

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 88
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 88

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ser Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 89
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 89

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ser Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 90

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 90

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ser Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 91
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 91

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ser Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 92
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 92

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 93
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 93

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 94
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 94

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 95
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 95

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ser Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 96
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 96

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ser Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 97
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 97

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 98

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 98

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 99
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 99

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 100
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 100

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met Pro Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 101
- <211> 122
- <212> PRT
- <213> Artificial

- <220>
- <223> An artificially generated sequence

- <400> 101

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 102
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 102

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 103
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 103

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 104
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 104

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 105
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 105

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 106

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 106

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 107
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 107

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 108
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 108

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 109
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 109

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 110
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 110

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 111
- <211> 122
- <212> PRT
- <213> Artificial

<220>
<223> An artificially generated sequence

<400> 111

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 112
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 112

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 113
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 113

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 114

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 114

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 115
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 115

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 116
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 116

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 117
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 117

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 118
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 118

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 119
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 119

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 120
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 120

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 121
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 121

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 122

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 122

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 123
- <211> 122
- <212> PRT
- <213> Artificial

- <220>
- <223> An artificially generated sequence

<400> 123

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 124
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 124

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 125
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 125

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 126
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 126

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 127
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 127

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 128
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 128

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 129
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 129

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 130

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 130

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 131
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 131

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 132
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 132

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 133
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 133

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 134
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 134

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 135
- <211> 122
- <212> PRT
- <213> Artificial

<220>
<223> An artificially generated sequence

<400> 135

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 136
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 136

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 137
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 137

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 138

<211> 124

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 138

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ala Glu Met Val Arg Asp Asp
100 105 110

Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 139
- <211> 128
- <212> PRT
- <213> Artificial

- <220>
- <223> An artificially generated sequence

<400> 139

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ala Glu Met Val Arg Asp Ser
100 105 110

Tyr Gly Val Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 140
<211> 128
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 140

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Val Arg Arg Arg Leu Ser Ser
100 105 110

Tyr Gly Val Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 141
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 141

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 142
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 142

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 143
- <211> 122
- <212> PRT
- <213> Artificial

<220>
<223> An artificially generated sequence

<400> 143

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 144
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 144

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 145
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 145

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 146

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 146

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 147
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 147

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Ala Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 148
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 148

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Gln Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 149
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 149

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Ser Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 150
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 150

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Phe Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 151
- <211> 122
- <212> PRT
- <213> Artificial

<220>
<223> An artificially generated sequence

<400> 151

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Gly Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 152
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 152

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Leu Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 153
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 153

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Pro Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 154

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 154

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Gln Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 155
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 155

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Ser Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 156
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 156

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Val Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 157
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 157

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Phe Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 158
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 158

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Gly Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 159
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 159

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Ile Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 160
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 160

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Leu Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 161
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 161

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Pro Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 162

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 162

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Gln Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 163
- <211> 122
- <212> PRT
- <213> Artificial

- <220>
- <223> An artificially generated sequence

<400> 163

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Thr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 164
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 164

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Val Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 165
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 165

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 166
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 166

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 167
- <211> 122
- <212> PRT
- <213> Artificial

<220>
<223> An artificially generated sequence

<400> 167

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Gln Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 168
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 168

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Val Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 169
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 169

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Ser Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 170

<211> 115

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 170

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 171
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 171

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 172
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 172

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Lys Thr Pro Asp Thr Ala Tyr Glu Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 173
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 173

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Lys Thr Pro Asp Thr Ala Tyr Ser Asp Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 174
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 174

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 175
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 175

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Asp Thr Pro Asp Thr Ala Tyr Glu Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 176
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 176

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Lys Thr Pro Asp Thr Ala Glu Glu Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 177
<211> 115
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 177

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Lys Thr Pro Asp Thr Ala Tyr Glu Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 178

<211> 115

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 178

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Lys Thr Pro Asp Thr Ala Tyr Glu Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 179
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 179

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Lys Thr Pro Asp Thr Ala Tyr Glu Glu Ser Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 180
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 180

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Lys Thr Pro Asp Thr Ala Tyr Glu Gln Lys Phe
50 55 60

Gln Asp Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

- <210> 181
- <211> 115
- <212> PRT
- <213> Artificial

- <220>
- <223> An artificially generated sequence

<400> 181

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Lys Thr Pro Asp Thr Ala Tyr Glu Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 182
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 182

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 183
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 183

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 184
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 184

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 185
<211> 115
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 185

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Glu Ser Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 186

<211> 115

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 186

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Glu Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 187
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 187

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Glu Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 188
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 188

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Lys Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

- <210> 189
- <211> 115
- <212> PRT
- <213> Artificial

- <220>
- <223> An artificially generated sequence

<400> 189

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Glu Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

- <210> 190
- <211> 115
- <212> PRT
- <213> Artificial

- <220>
- <223> An artificially generated sequence

<400> 190

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Glu Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 191
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 191

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Glu Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 192
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 192

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Glu Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 193
<211> 115
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 193

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Glu Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 194

<211> 115

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 194

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Glu Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 195
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 195

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Glu Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 196
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 196

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Glu Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 197
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 197

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 198
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 198

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Asp Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 199
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 199

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Gln Lys Phe
50 55 60

Glu Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 200
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 200

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe
50 55 60

Glu Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 201
<211> 115
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 201

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Gln Lys Phe
50 55 60

Glu Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Glu Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 202

<211> 115

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 202

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Glu Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Gln Lys Phe
50 55 60

Glu Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Glu Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 203
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 203

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 204
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 204

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 205
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 205

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 206
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 206

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Pro Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 207
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 207

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Trp Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 208
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 208

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Tyr Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 209
<211> 115
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 209

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Lys Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 210

<211> 115

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 210

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

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

Glu Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 211
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 211

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Met
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 212
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 212

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Met
35 40 45

Gly Ala Ile Asp Gly Pro Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

- <210> 213
- <211> 115
- <212> PRT
- <213> Artificial

- <220>
- <223> An artificially generated sequence

<400> 213

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Met
35 40 45

Gly Ala Ile Asp Gly Trp Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 214
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 214

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Met
35 40 45

Gly Ala Ile Asp Gly Tyr Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 215
<211> 115
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 215

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 216
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 216

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
65 70 75 80

Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 217
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 217

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ala Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 218
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 218

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ile Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 219
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 219

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Pro Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 220
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 220

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Thr Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 221
<211> 112

<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 221

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Val Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 222
<211> 112

<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 222

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Pro Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 223
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 223

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 224
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 224

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Phe Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 225
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 225

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 226
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 226

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Met Val His Ser
 20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
 35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
 85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110

<210> 227
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 227

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 228
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 228

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Val Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 229
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 229

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Arg Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 230
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 230

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Phe
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 231
<211> 112
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 231

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His His
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 232

<211> 112

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 232

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Leu
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 233
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 233

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Met
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 234
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 234

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Asn
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 235
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 235

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Pro
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 236
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 236

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Gln
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 237

<211> 112

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 237

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Val
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 238
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 238

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Trp
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 239
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 239

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asp Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 240
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 240

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Glu Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 241
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 241

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Phe Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 242
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 242

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Gly Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 243
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 243

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg His Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 244
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 244

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Met Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 245
<211> 112

<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 245

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Trp Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 246
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 246

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 247
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 247

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 248
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 248

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu Glu Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 249
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 249

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu Leu Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 250
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 250

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu Met Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 251
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 251

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 252
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 252

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 253
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 253

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Phe Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 254
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 254

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser His Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 255
<211> 112
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 255

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Ile Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 256

<211> 112

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 256

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Met Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 257
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 257

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Thr Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 258
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 258

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Trp Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 259
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 259

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 260
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 260

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Gly Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 261

<211> 112

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 261

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Ile Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 262
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 262

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Lys Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 263
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 263

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 264
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 264

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Met Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 265
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 265

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Asn Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 266
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 266

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Pro Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 267
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 267

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Arg Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 268
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 268

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Val Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 269
<211> 112

<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 269

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Tyr Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 270
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 270

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Phe Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 271
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 271

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Gly Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 272
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 272

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe His Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 273
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 273

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ile Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 274
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 274

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
 20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
 35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Leu Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
 85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110

<210> 275
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 275

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Met Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 276
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 276

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Pro Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 277
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 277

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Gln Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 278
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 278

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 279
<211> 112
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 279

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Val Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 280

<211> 112

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 280

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Trp Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 281
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 281

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ala Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 282
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 282

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Glu Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 283
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 283

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 284
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 284

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ile Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 285

<211> 112

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 285

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Leu Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 286
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 286

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Asn Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 287
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 287

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Thr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 288
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 288

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Val Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 289
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 289

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 290
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 290

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Ser
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 291
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 291

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Thr
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 292
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 292

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Phe Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 293
<211> 112

<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 293

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln His Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 294
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 294

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Asn Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 295
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 295

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Pro Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 296
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 296

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 297
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 297

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 298
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 298

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Pro Ser Gln Ser Pro Val His Ser
 20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
 35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
 85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110

<210> 299
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 299

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 300
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 300

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Trp Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 301
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 301

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 302
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 302

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 303
<211> 112
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 303

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Trp Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 304

<211> 112

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 304

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 305
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 305

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 306
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 306

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Trp Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 307
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 307

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 308
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 308

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Trp Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 309

<211> 112

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 309

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 310
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 310

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Pro Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 311
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 311

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 312
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 312

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 313
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 313

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 314
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 314

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 315
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 315

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Pro Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 316
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 316

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 317
<211> 112

<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 317

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 318
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 318

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 319
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 319

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 320
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 320

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 321
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 321

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Pro Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 322
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 322

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ile Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 323
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 323

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Leu Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 324
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 324

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Val Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 325
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 325

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Ser
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 326
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 326

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Thr
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 327
<211> 112
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 327

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 328

<211> 112

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 328

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Glu Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 329
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 329

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Glu Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 330
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 330

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Glu Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 331
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 331

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Glu Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 332
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 332

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Glu Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Trp Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 333

<211> 112

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 333

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Glu Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 334
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 334

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Glu Pro Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 335
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 335

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Glu Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 336
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 336

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Glu Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 337
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 337

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Glu Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Trp Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 338
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 338

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Glu Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 339
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 339

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Glu Pro Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 340
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 340

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 341
<211> 112

<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 341

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ile Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 342
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 342

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Pro Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 343
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 343

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Pro Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 344
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 344

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Pro Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ile Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 345
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 345

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Thr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 346
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 346

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Thr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 347
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 347

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Pro Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Thr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 348
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 348

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Thr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 349
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 349

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ala Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 350
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 350

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ala Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 351
<211> 112
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 351

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Pro Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ala Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 352

<211> 112

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 352

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ala Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 353
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 353

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Val Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 354
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 354

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Pro Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Val Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 355
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 355

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Val Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 356
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 356

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 357

<211> 112

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 357

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Gln Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 358
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 358

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Pro Val His Ser
20 25 30

Asn Arg Gln Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 359
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 359

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Leu Val His Ser
20 25 30

Asn Arg Gln Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 360
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 360

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Gln Ala Ser Glu Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 361
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 361

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 362
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 362

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Glu
100 105 110

- <210> 363
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 363

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Gln Ala Ser Glu Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Glu
100 105 110

<210> 364
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 364

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Glu
100 105 110

<210> 365
<211> 112

<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 365

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Gln Ala Ser Glu Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Glu
100 105 110

<210> 366
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 366

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Gln Ala Ser Glu Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 367
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 367

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Gln Ala Ser Glu Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 368
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 368

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 369
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 369

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Glu
100 105 110

<210> 370
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 370

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Gln Ala Ser Glu Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Glu
100 105 110

<210> 371
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 371

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Glu
100 105 110

<210> 372
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 372

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Gln Ala Ser Glu Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Glu
100 105 110

- <210> 373
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 373

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 374
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 374

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 375
<211> 112
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 375

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 376

<211> 112

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 376

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Gln Ala Ser Glu Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 377
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 377

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Gln Ala Ser Glu Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

- <210> 378
- <211> 112
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 378

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Gln Ala Ser Glu Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 379
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 379

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Thr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 380
<211> 112
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 380

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Gln Ala Ser Glu Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Thr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 381

<211> 458

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 381

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
210 215 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
290 295 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
340 345 350

Val Tyr Thr Leu Pro Pro Ser Arg Cys Glu Leu Thr Lys Asn Gln Val
355 360 365

Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385 390 395 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Asp Tyr Lys Asp Asp Asp Asp Lys
450 455

- <210> 382
- <211> 458
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 382

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Tyr Ala Tyr Tyr Gly Val Gln Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
210 215 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
290 295 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
340 345 350

Val Tyr Thr Leu Pro Pro Ser Arg Cys Glu Leu Thr Lys Asn Gln Val
355 360 365

Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385 390 395 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Asp Tyr Lys Asp Asp Asp Asp Lys
450 455

- <210> 383
- <211> 458
- <212> PRT
- <213> Artificial

- <220>

<223> An artificially generated sequence

<400> 383

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Tyr Tyr Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
210 215 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
290 295 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
340 345 350

Val Tyr Thr Leu Pro Pro Ser Arg Cys Glu Leu Thr Lys Asn Gln Val
355 360 365

Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385 390 395 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Asp Tyr Lys Asp Asp Asp Asp Lys
450 455

<210> 384
<211> 440
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 384

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe
50 55 60

Lys	Gly	Arg	Val	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Thr	Arg	Phe	Tyr	Ser	Tyr	Thr	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr
			100					105					110		
Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro
			115				120					125			
Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val
			130			135					140				
Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala
145					150					155					160
Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly
				165					170					175	
Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly
			180					185					190		
Thr	Gln	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys
			195				200					205			
Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys
	210					215				220					
Pro	Ala	Pro	Glu	Phe	Arg	Gly	Gly	Pro	Lys	Val	Phe	Leu	Phe	Pro	Pro
225					230					235					240
Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys
				245					250					255	

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

<210> 385
<211> 440
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 385

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Gly Pro Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
115 120 125

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
130 135 140

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145 150 155 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
165 170 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
180 185 190

Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
195 200 205

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
210 215 220

Pro Ala Pro Glu Phe Arg Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
225 230 235 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
245 250 255

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
260 265 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
275 280 285

Glu Gln Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
290 295 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305 310 315 320

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
325 330 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
340 345 350

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
355 360 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
370 375 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385 390 395 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
405 410 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
420 425 430

Gln Glu Ser Leu Ser Leu Ser Pro
435 440

<210> 386
<211> 440
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 386

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Met
35 40 45

Gly	Ala	Ile	Asp	Gly	Glu	Thr	Pro	Asp	Thr	Ala	Tyr	Ser	Glu	Lys	Phe	
50						55					60					
Lys	Gly	Arg	Val	Thr	Leu	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr	
65					70				75						80	
Met	Glu	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
			85					90						95		
Thr	Arg	Phe	Tyr	Ser	Tyr	Thr	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	
			100					105					110			
Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	
		115					120					125				
Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	
	130					135					140					
Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	
145					150					155					160	
Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	
				165					170					175		
Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	
			180					185					190			
Thr	Gln	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	
		195					200					205				
Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys	
	210					215				220						
Pro	Ala	Pro	Glu	Phe	Arg	Gly	Gly	Pro	Lys	Val	Phe	Leu	Phe	Pro	Pro	
225					230					235				240		

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
245 250 255

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
260 265 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
275 280 285

Glu Gln Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
290 295 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305 310 315 320

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
325 330 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
340 345 350

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
355 360 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
370 375 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385 390 395 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
405 410 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
420 425 430

Gln Glu Ser Leu Ser Leu Ser Pro
435 440

<210> 387
<211> 440
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 387

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
115 120 125

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
130 135 140

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145 150 155 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
165 170 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
180 185 190

Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
195 200 205

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
210 215 220

Pro Ala Pro Glu Phe Arg Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
225 230 235 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
245 250 255

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
260 265 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
275 280 285

Glu Gln Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
290 295 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305 310 315 320

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
325 330 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
340 345 350

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
355 360 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
370 375 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385 390 395 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
405 410 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
420 425 430

Gln Glu Ser Leu Ser Leu Ser Pro
435 440

<210> 388
<211> 458
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 388

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

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

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
290 295 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
340 345 350

Val Tyr Thr Leu Pro Pro Ser Arg Cys Glu Leu Thr Lys Asn Gln Val
355 360 365

Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385 390 395 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Asp Tyr Lys Asp Asp Asp Asp Lys
450 455

- <210> 389
- <211> 458
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 389

Glu Val Gln Leu Val Glu Thr Gly Gly Ser Leu Val Gln Pro Gly Lys
1 5 10 15

Ser Leu Lys Leu Thr Cys Ala Thr Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ser Pro Glu Lys Gln Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Asn
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
210 215 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
290 295 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
340 345 350

Val Tyr Thr Leu Pro Pro Ser Arg Cys Glu Leu Thr Lys Asn Gln Val
355 360 365

Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385 390 395 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Asp Tyr Lys Asp Asp Asp Asp Lys
450 455

- <210> 390
- <211> 447
- <212> PRT
- <213> Artificial

<220>
<223> An artificially generated sequence

<400> 390

Glu Val Gln Leu Val Glu Thr Gly Gly Ser Leu Val Gln Pro Gly Lys
1 5 10 15

Ser Leu Lys Leu Thr Cys Ala Thr Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ser Pro Glu Lys Gln Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Asn
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Arg Gly Gly Pro
225 230 235 240

Lys Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

<210> 391
<211> 458
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 391

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Lys Lys Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Tyr Tyr Tyr Gly Val Gln Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
210 215 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
290 295 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
340 345 350

Val Tyr Thr Leu Pro Pro Ser Arg Cys Glu Leu Thr Lys Asn Gln Val
355 360 365

Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385 390 395 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Asp Tyr Lys Asp Asp Asp Asp Lys
450 455

<210> 392
<211> 458
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 392

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
210 215 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
290 295 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
340 345 350

Val Tyr Thr Leu Pro Pro Ser Arg Cys Glu Leu Thr Lys Asn Gln Val
355 360 365

Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385 390 395 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Asp Tyr Lys Asp Asp Asp Asp Lys
450 455

<210> 393
<211> 447
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 393

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Arg Gly Gly Pro
225 230 235 240

Lys Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

- <210> 394
- <211> 447
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 394

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Arg Gly Gly Pro
225 230 235 240

Lys Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

- <210> 395
- <211> 447
- <212> PRT
- <213> Artificial

- <220>
- <223> An artificially generated sequence

<400> 395

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

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Arg Gly Gly Pro
225 230 235 240

Lys Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

<210> 396
<211> 447
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 396

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr	Cys	Arg	Tyr	Val	His	Tyr	Ala	Ala	Ser	Tyr	Gly	Val	Asp	Ala	Trp
100			105			110									
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
115			120			125									
Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr
130			135			140									
Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
145			150			155			160						
Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
165			170			175									
Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
180			185			190									
Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp
195			200			205									
His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr
210			215			220									
Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Arg	Gly	Gly	Pro
225			230			235									
Lys	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
245			250			255									
Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp
260			265			270									
Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
275			280			285									

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

- <210> 397
- <211> 447
- <212> PRT
- <213> Artificial

- <220>

<223> An artificially generated sequence

<400> 397

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Ser Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Arg Gly Gly Pro
225 230 235 240

Lys Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

<210> 398
<211> 447
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 398

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Arg Gly Gly Pro
225 230 235 240

Lys Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

<210> 399
<211> 447

<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 399

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Arg Gly Gly Pro
225 230 235 240

Lys Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

<210> 400
<211> 447
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 400

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Val Ala Glu
50 55 60

Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Asn	Ser	
65					70					75					80	
Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	
				85					90					95		
Tyr	Cys	Arg	Tyr	Val	His	Tyr	Ala	Ala	Gly	Tyr	Gly	Val	Asp	Ala	Trp	
			100					105					110			
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	
		115					120					125				
Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	
	130					135					140					
Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	
145					150					155					160	
Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	
			165						170					175		
Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	
		180						185					190			
Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	
	195						200					205				
His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	
	210					215					220					
Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Arg	Gly	Gly	Pro	
225					230					235					240	
Lys	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	
			245						250					255		

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

<210> 401
<211> 447
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 401

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Val Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Arg Gly Gly Pro
225 230 235 240

Lys Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

<210> 402
<211> 447
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 402

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala	Gln	Ile	Lys	Asp	Lys	Ser	Gln	Asn	Tyr	Ala	Thr	Tyr	Val	Ala	Glu
50						55					60				
Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Ala	Asp	Ser	Lys	Asn	Ser
65					70					75					80
Ile	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr
			85						90					95	
Tyr	Cys	Arg	Tyr	Val	His	Tyr	Ala	Ala	Gly	Tyr	Gly	Val	Asp	Ile	Trp
		100						105					110		
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
	115						120					125			
Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr
	130					135					140				
Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
145					150					155					160
Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
			165						170					175	
Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
		180						185					190		
Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp
	195						200					205			
His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr
	210					215					220				
Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Arg	Gly	Gly	Pro
225					230					235					240

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

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

<210> 403
<211> 450
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 403

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
85 90 95

Thr His Val Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
115 120 125

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
130 135 140

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
145 150 155 160

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
165 170 175

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
180 185 190

Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
195 200 205

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
210 215 220

Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
225 230 235 240

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
245 250 255

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
260 265 270

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
275 280 285

Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr
290 295 300

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305 310 315 320

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
325 330 335

Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg
340 345 350

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
355 360 365

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
370 375 380

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
385 390 395 400

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
405 410 415

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
420 425 430

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro His His His His His His
435 440 445

His His
450

- <210> 404
- <211> 450
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 404

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

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

Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro
210						215					220				
Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe
225					230					235					240
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val
				245					250					255	
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe
			260					265					270		
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro
		275					280					285			
Arg	Glu	Glu	Gln	Tyr	Ala	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr
	290					295					300				
Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val
305					310					315					320
Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala
				325					330					335	
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Cys	Thr	Leu	Pro	Pro	Ser	Arg
			340					345						350	
Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Trp	Cys	Leu	Val	Lys	Gly
		355					360					365			
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro
	370					375					380				
Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser
385					390					395					400

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
405 410 415

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
420 425 430

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro His His His His His His
435 440 445

His His
450

<210> 405
<211> 222
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 405

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser Ala Ser Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
115 120 125

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
130 135 140

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
145 150 155 160

Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
165 170 175

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
180 185 190

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
195 200 205

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

<210> 406
<211> 222
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 406

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

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

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

<210> 407
<211> 219
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 407

Asp Val Val Met Thr Gln Thr Pro Val Ser Met Ser Val Ser Leu Gly
1 5 10 15

Gly Gln Val Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Asn
20 25 30

Asn Gly Asn Thr Tyr Val Ser Trp Tyr Ile Gln Lys Pro Ser Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Ile Ser
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Pro Asp Asp Leu Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Asp Pro Tyr Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 408
<211> 219
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 408

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

- <210> 409
- <211> 219
- <212> PRT
- <213> Artificial

- <220>

<223> An artificially generated sequence

<400> 409

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 410
<211> 219
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 410

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Leu Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 411
<211> 219
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 411

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 412
<211> 219
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 412

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 413
<211> 219
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 413

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Arg Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 414
<211> 219
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 414

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

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

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 415
<211> 219
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 415

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Trp Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 416
<211> 219
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 416

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

- <210> 417
- <211> 219
- <212> PRT
- <213> Artificial

- <220>

<223> An artificially generated sequence

<400> 417

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Pro Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

- <210> 418
- <211> 219
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 418

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Pro Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 419
<211> 219
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 419

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Pro Val His Ser
20 25 30

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
85 90 95

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 420
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 420

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Tyr Tyr Tyr Tyr Gly Val Gln Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 421
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 421

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Lys Lys Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Tyr Tyr Tyr Tyr Gly Val Gln Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 422

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 422

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Arg Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 423
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 423

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Arg Val His Tyr Tyr Tyr Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 424
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 424

Glu Val Gln Leu Val Glu Thr Gly Gly Ser Leu Val Gln Pro Gly Lys
1 5 10 15

Ser Leu Lys Leu Thr Cys Ala Thr Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ser Pro Glu Lys Gln Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Asn
65 70 75 80

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

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

- <210> 425
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 425

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 426
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 426

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 427
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 427

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Leu Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 428
<211> 122
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 428

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Tyr Ala Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 429
<211> 122
<212> PRT
<213> Artificial

<220>

<223> An artificially generated sequence

<400> 429

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Tyr Ala Tyr Tyr Gly Val Gln Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 430

<211> 122

<212> PRT

<213> Artificial

<220>

<223> An artificially generated sequence

<400> 430

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Tyr Tyr Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

- <210> 431
- <211> 122
- <212> PRT
- <213> Artificial
- <220>
- <223> An artificially generated sequence
- <400> 431

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Lys Lys Tyr Tyr Ala Glu
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Arg Tyr Val His Tyr Tyr Tyr Tyr Tyr Gly Val Asp Ala Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 432
<211> 107
<212> PRT
<213> Artificial

<220>
<223> An artificially generated sequence

<400> 432

Ala Ser Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

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

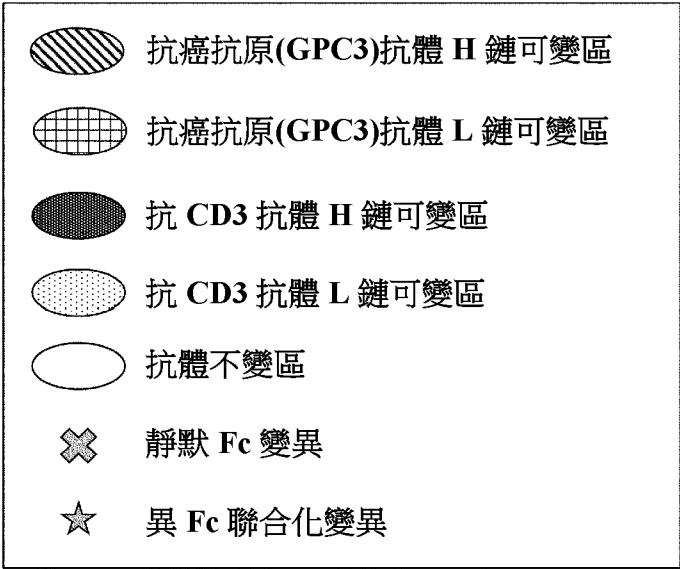
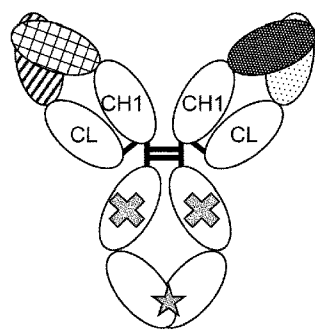
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

【發明申請專利範圍】

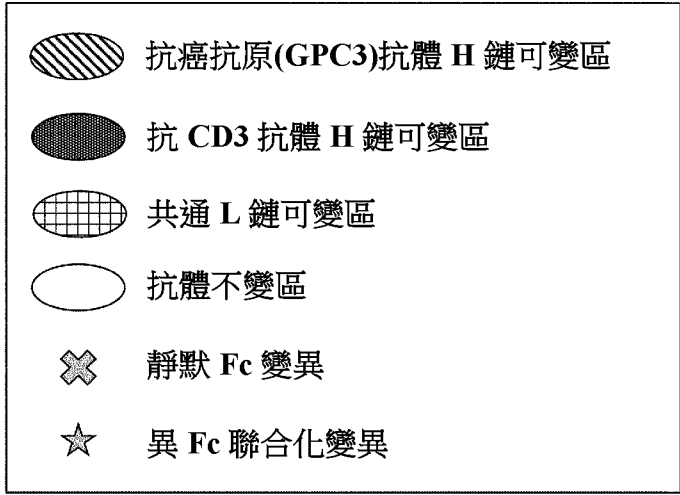
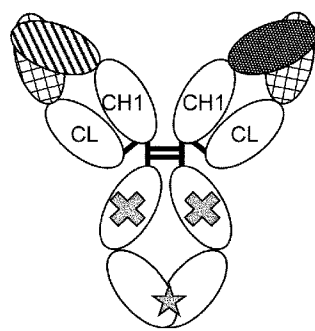
【請求項1】 一種如本說明書所記載之多專一性抗原結合分子。

【發明圖式】

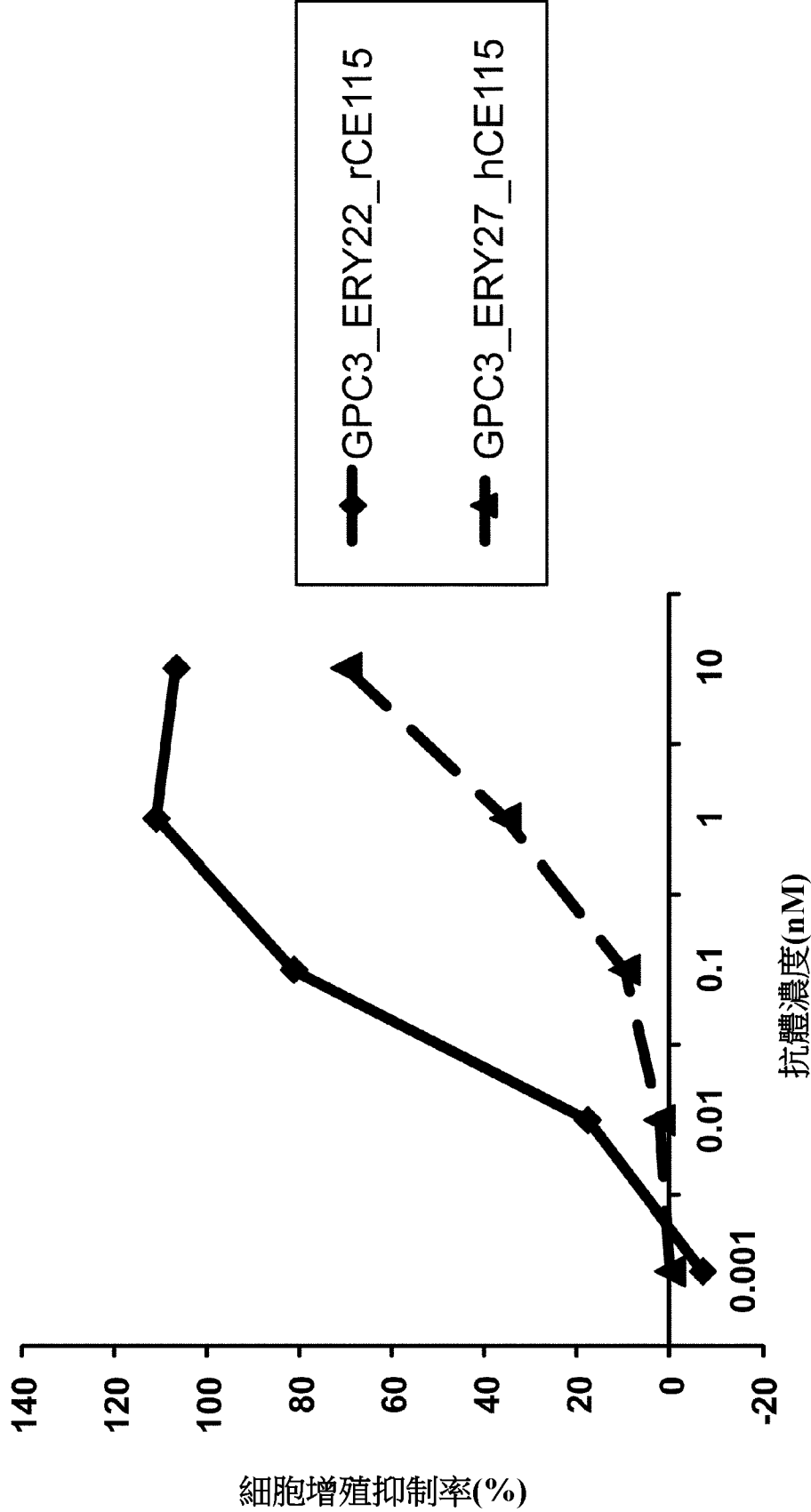
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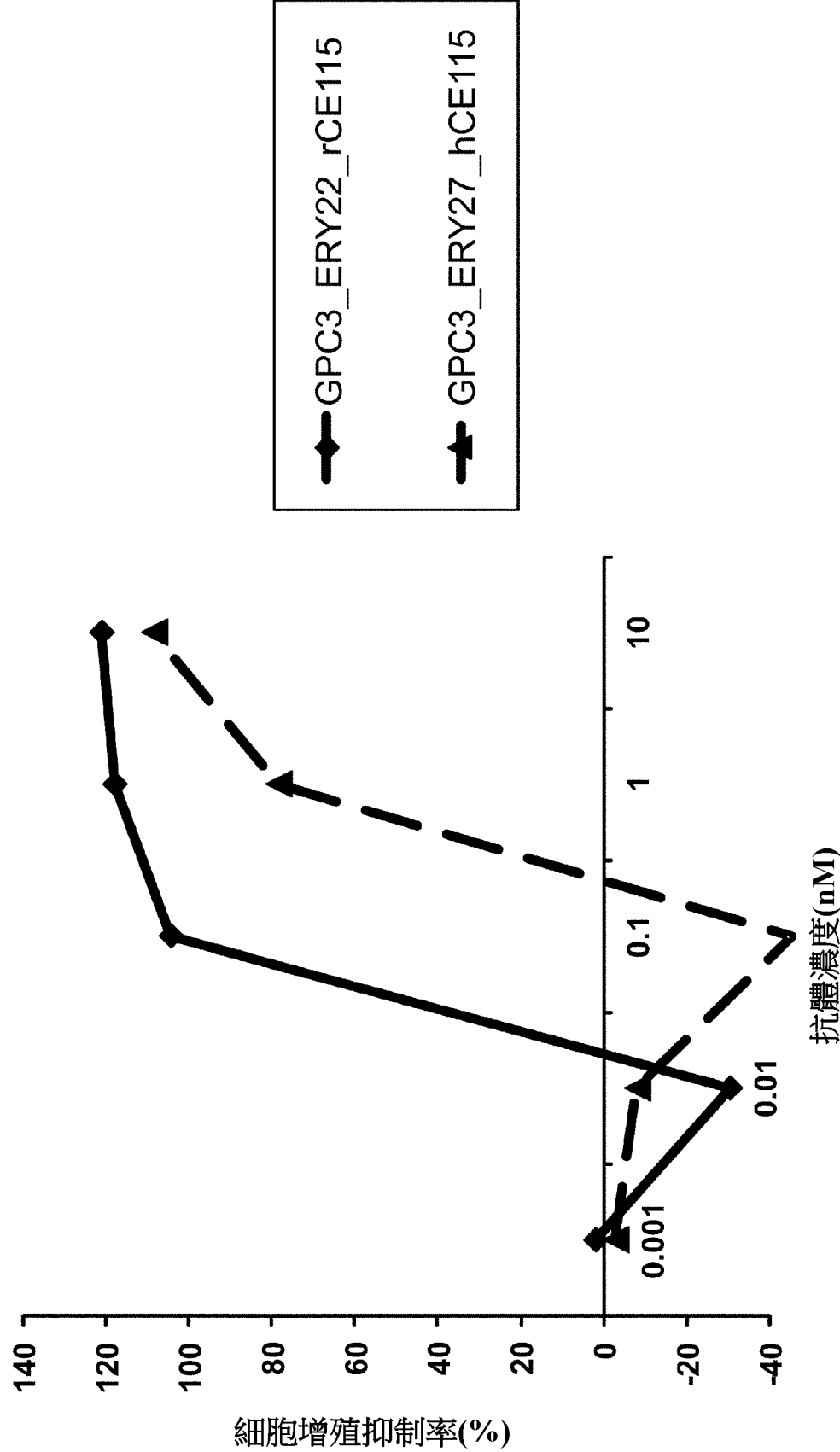
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第 1 圖

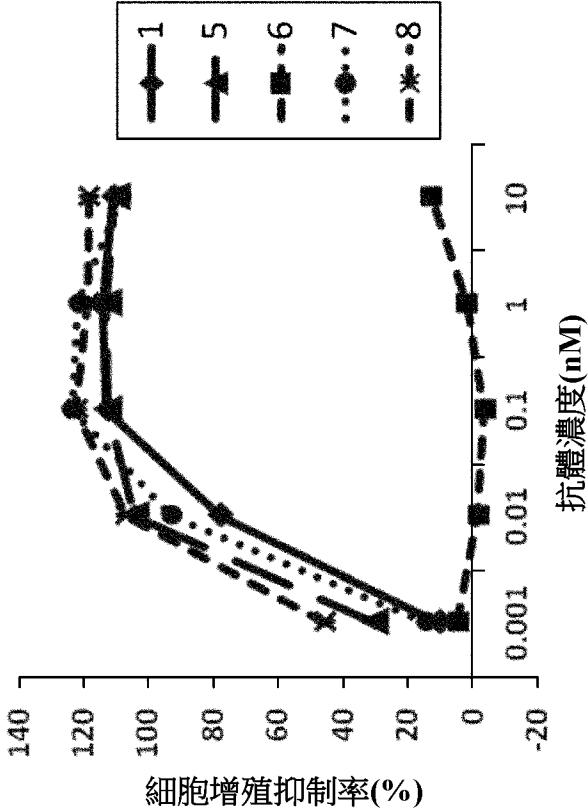


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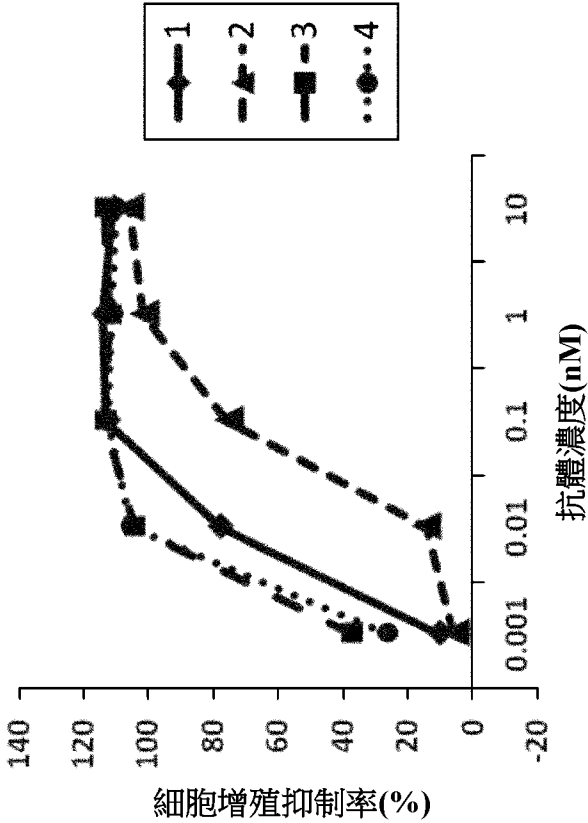


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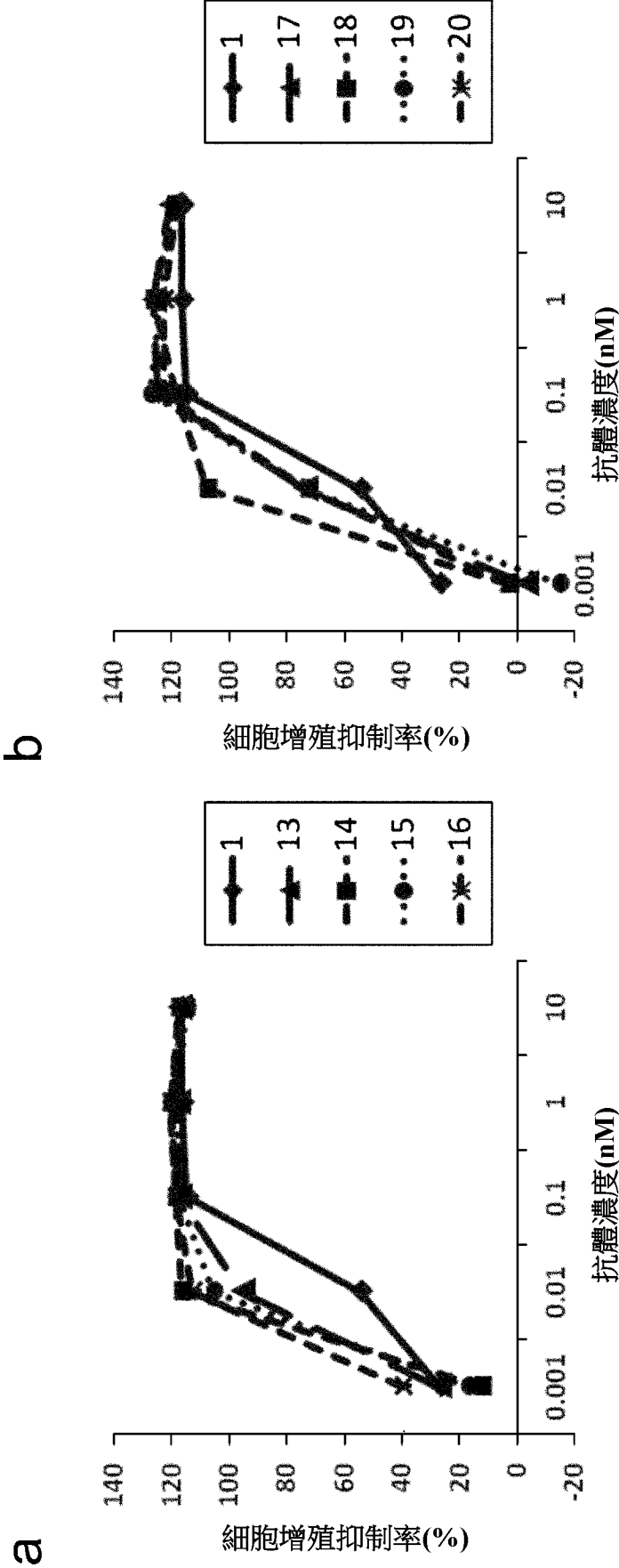
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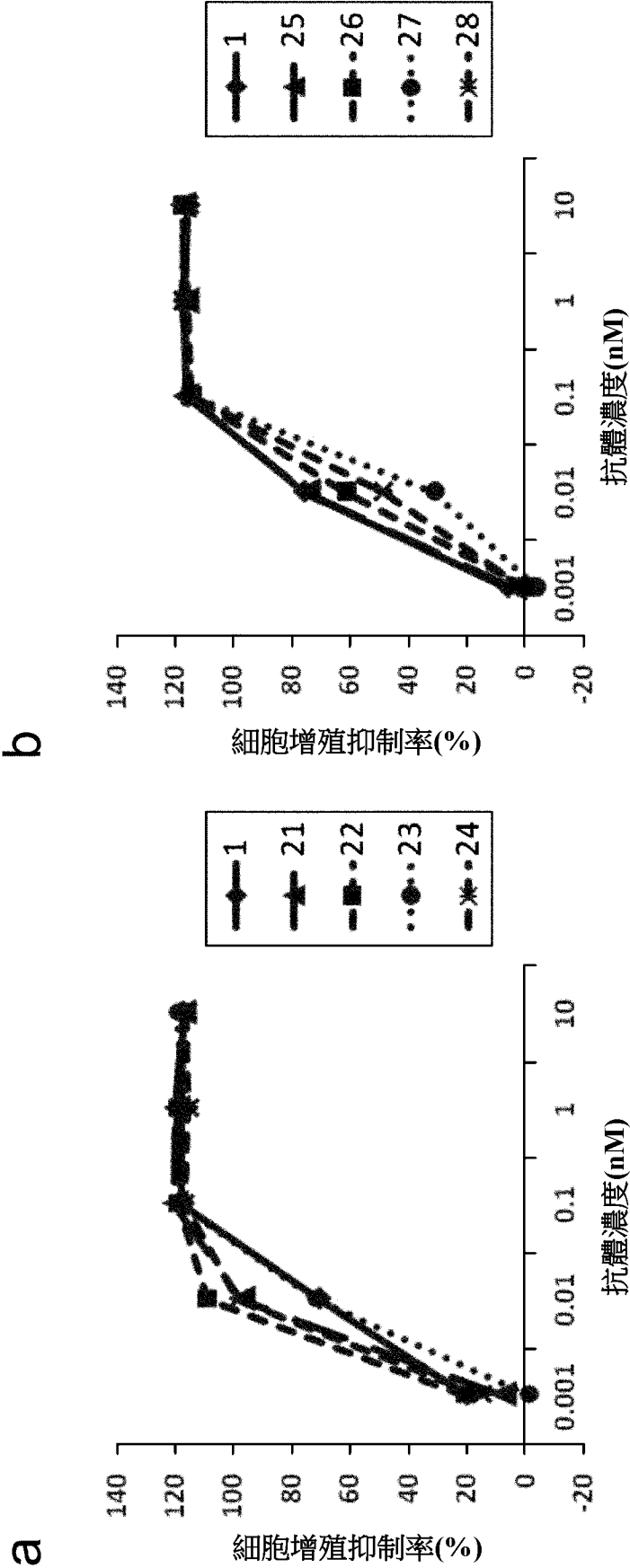
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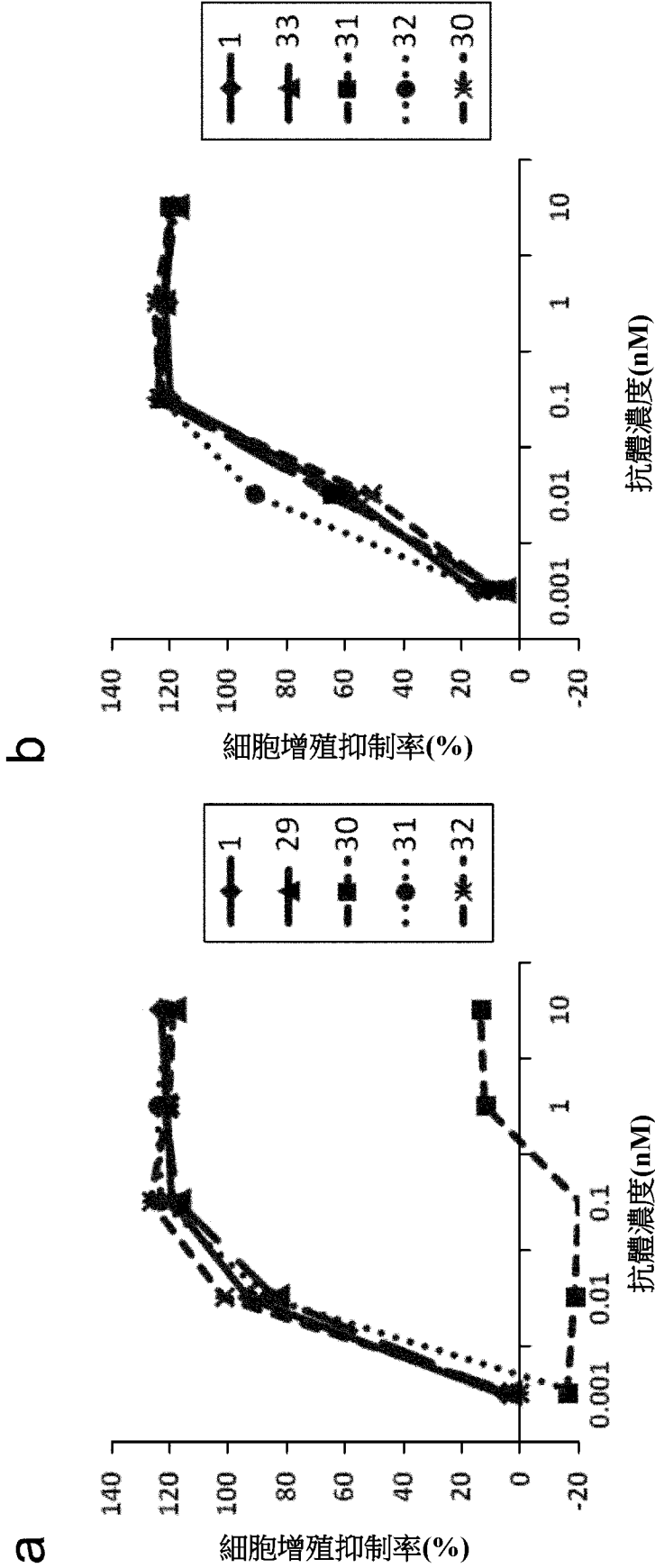
第4圖



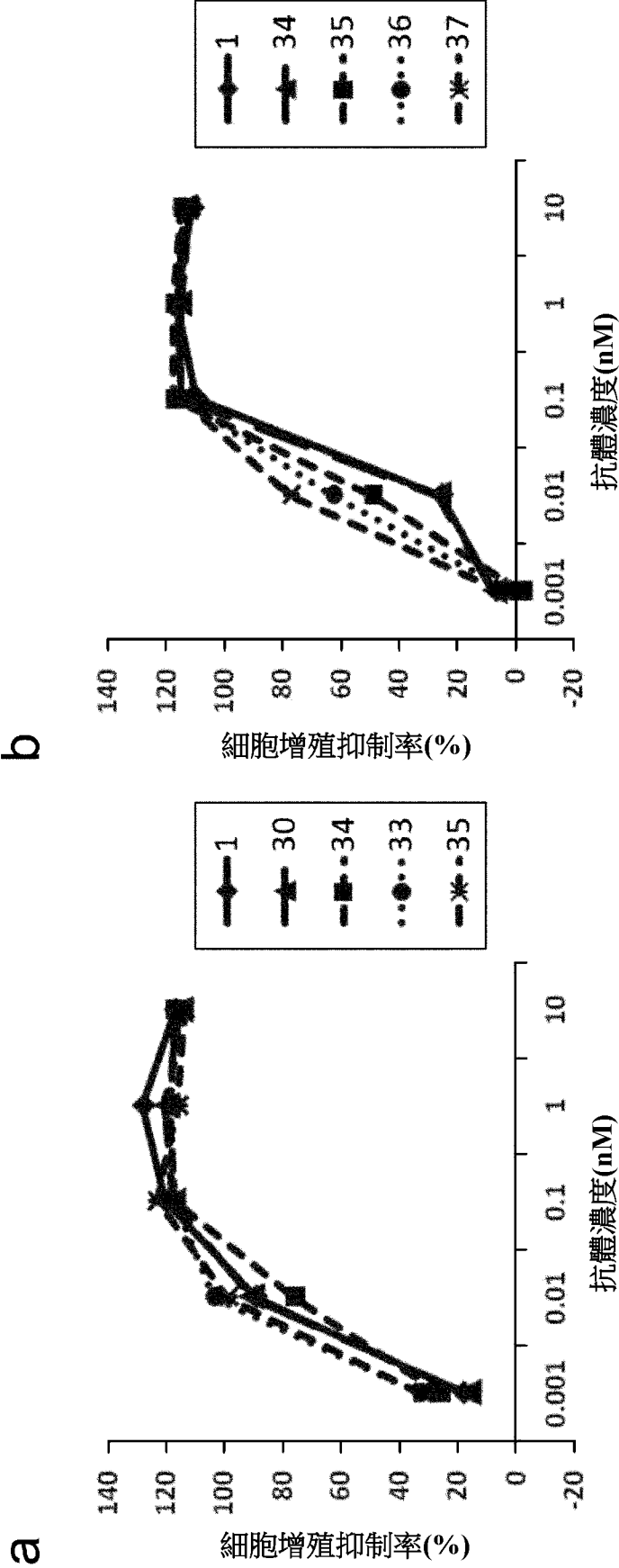
第 5 圖



第6圖

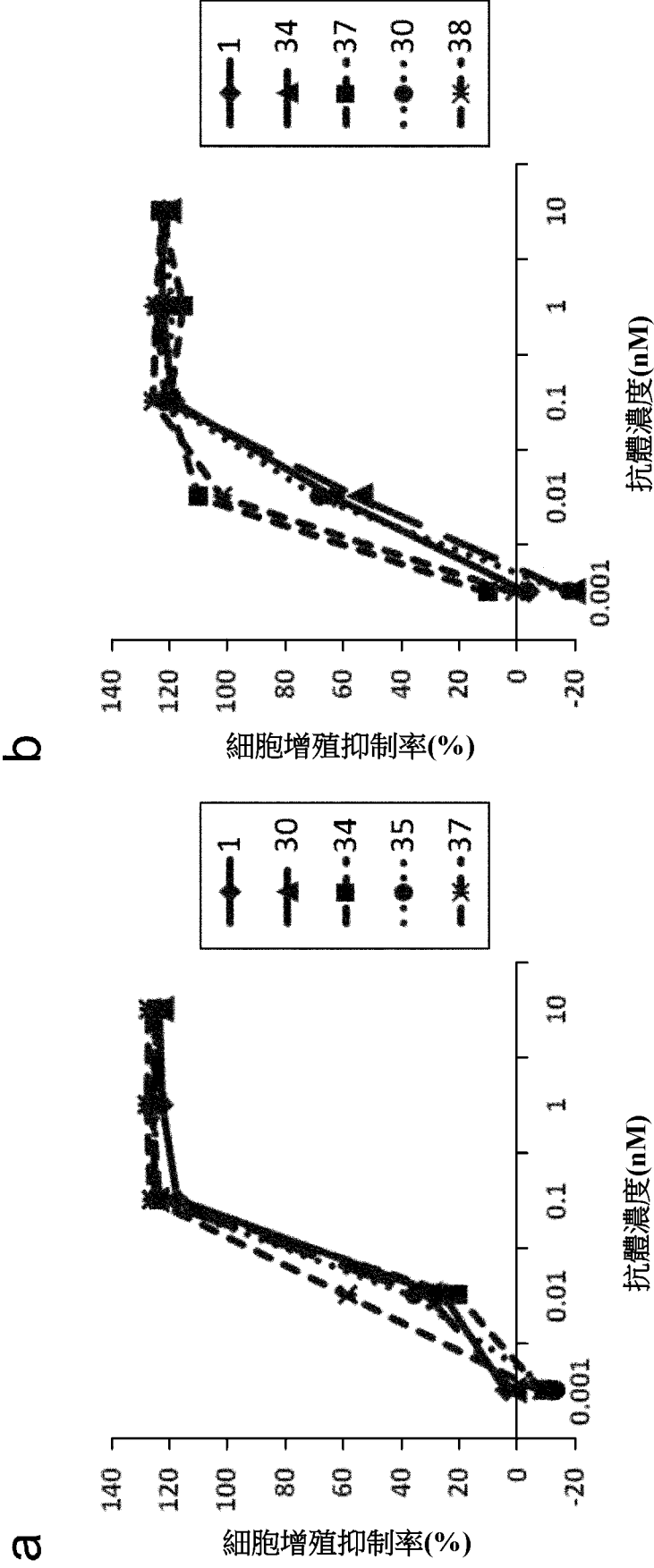


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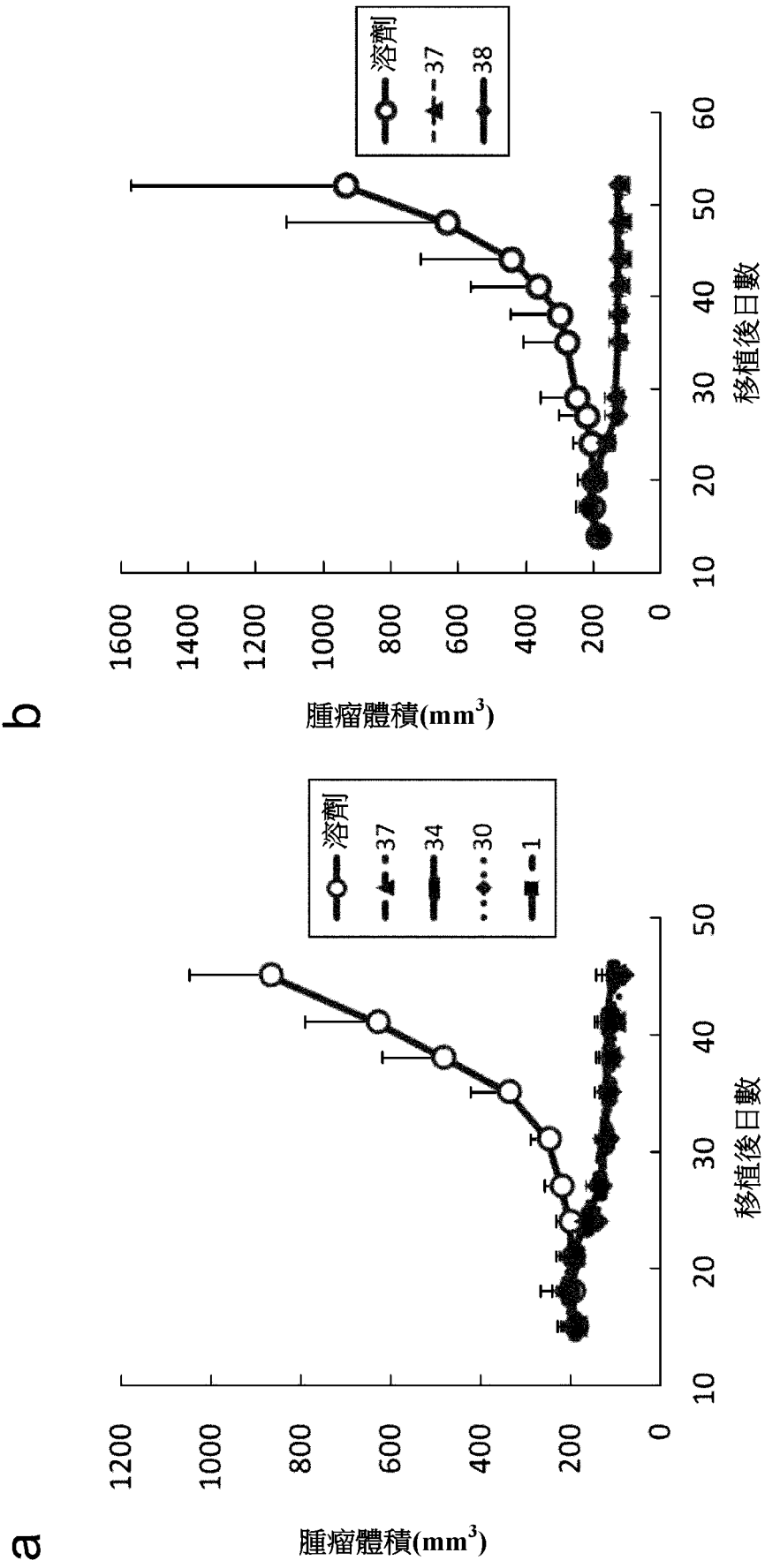


第 8 圖

第 8 圖

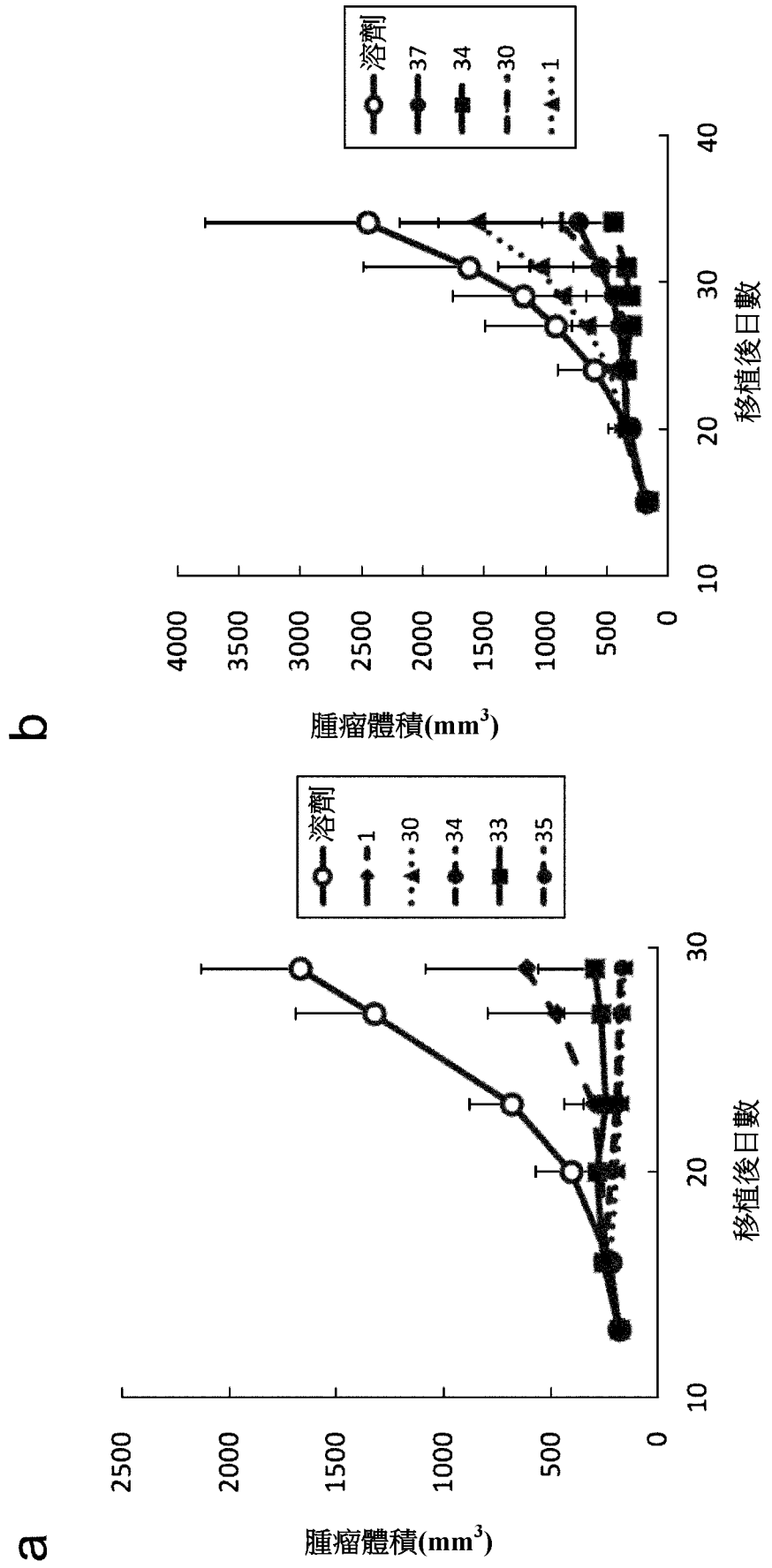


第9圖



第 10 圖

第 10 圖



第 11 圖

抗體名	Chothia CDR H1																														Kabat CDR H1											
	Contact CDR H1																																									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	35a	35b	36	37	38	39	40
CE115HA000	Q	V	Q	L	V	E	S	G	G	G	V	V	Q	P	G	R	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
TR01H040	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
TR01H071	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
TR01H082	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
TR01H084	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
TR01H109	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
TR01H113	Q	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	R	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	A	W	M	H	-	-	W	V	R	Q	A
H0000	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	E	M	H	-	-	W	I	R	Q	P
H0610	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	E	M	H	-	-	W	I	R	Q	P
GCH054	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	T	V	S	C	K	A	S	G	Y	T	F	T	D	Y	E	M	H	-	-	W	I	R	Q	P
GCH065	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	T	V	S	C	K	A	S	G	Y	T	F	T	D	Y	E	M	H	-	-	W	I	R	Q	P
GCH094	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	T	V	S	C	K	A	S	G	Y	T	F	T	D	Y	E	M	H	-	-	W	V	R	Q	A

抗體名	Chothia CDR H2																														Kabat CDR H2											
	Contact CDR H2																																									
	41	42	43	44	45	46	47	48	49	50	51	52	52a	52b	52c	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79
CE115HA000	P	G	K	G	L	E	W	V	A	Q	I	K	A	K	S	N	N	Y	A	T	Y	Y	A	E	S	V	K	G	R	F	T	I	S	R	D	S	K	N	S	L	Y	
TR01H040	P	G	K	G	L	E	W	V	A	Q	I	K	D	K	S	Q	N	Y	A	T	Y	Y	A	E	S	V	K	G	R	F	T	I	S	R	A	D	S	K	N	S	I	Y
TR01H071	P	G	K	G	L	E	W	V	A	Q	I	K	D	K	S	N	N	Y	A	T	Y	Y	A	E	S	V	K	G	R	F	T	I	S	R	A	D	S	K	N	S	I	Y
TR01H082	P	G	K	G	L	E	W	V	A	Q	I	K	D	K	S	Q	N	Y	A	T	Y	Y	A	E	S	V	K	G	R	F	T	I	S	R	D	S	K	N	S	L	Y	
TR01H084	P	G	K	G	L	E	W	V	A	Q	I	K	D	K	S	Q	N	Y	A	T	Y	Y	A	E	S	V	K	G	R	F	T	I	S	R	A	D	S	K	N	S	I	Y
TR01H109	P	G	K	G	L	E	W	V	A	Q	I	K	D	K	S	Q	N	Y	A	T	Y	V	A	E	S	V	K	G	R	F	T	I	S	R	D	S	K	N	S	L	Y	
TR01H113	P	G	K	G	L	E	W	V	A	Q	I	K	D	K	S	Q	N	Y	A	T	Y	V	A	E	S	V	K	G	R	F	T	I	S	R	A	D	S	K	N	S	I	Y
H0000	P	G	Q	G	L	E	W	I	G	A	I	D	P	-	-	K	T	G	D	T	A	Y	S	Q	K	F	K	G	R	V	T	L	T	A	D	K	S	T	S	T	A	Y
H0610	P	G	Q	G	L	E	W	I	G	A	I	D	G	-	-	K	T	P	D	T	A	Y	S	Q	K	F	K	G	R	V	T	L	T	A	D	K	S	T	S	T	A	Y
GCH054	P	G	E	G	L	E	W	I	G	A	I	D	G	-	-	E	T	P	D	T	A	Y	S	E	K	F	K	G	R	V	T	L	T	A	D	K	S	T	S	T	A	Y
GCH065	P	G	E	G	L	E	W	I	G	A	I	D	G	-	-	P	T	P	D	T	A	Y	S	E	K	F	K	G	R	V	T	L	T	A	D	K	S	T	S	T	A	Y
GCH094	P	G	E	G	L	E	W	M	G	A	I	D	G	-	-	E	T	P	D	T	A	Y	S	E	K	F	K	G	R	V	T	L	T	A	D	K	S	T	S	T	A	Y

第 13-1 圖

抗體名	Kabat CDR H3																																									
	Chothia CDR H3																																									
	Contact CDR H3																																									
	80	81	82	82a	82b	82c	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	100a	100b	100c	100d	100e	100f	100g	100h	100i	100j	100k	101	102	103	104	105	106	107
CE115HA000	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	Y	C	R	Y	V	H	Y	G	A	Y	Y	G	V	-	-	-	-	-	-	-	D	A	W	G	Q	G	T
TR01H040	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	Y	C	R	Y	V	H	Y	A	S	A	Y	G	V	-	-	-	-	-	-	-	D	I	W	G	Q	G	T
TR01H071	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	Y	C	R	Y	V	H	Y	A	A	S	Y	G	V	-	-	-	-	-	-	-	D	I	W	G	Q	G	T
TR01H082	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	Y	C	R	Y	V	H	Y	A	A	G	Y	G	V	-	-	-	-	-	-	-	D	I	W	G	Q	G	T
TR01H084	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	Y	C	R	Y	V	H	Y	A	A	G	Y	G	V	-	-	-	-	-	-	-	D	I	W	G	Q	G	T
TR01H109	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	Y	C	R	Y	V	H	Y	A	A	G	Y	G	V	-	-	-	-	-	-	-	D	A	W	G	Q	G	T
TR01H113	L	Q	M	N	S	L	K	T	E	D	T	A	V	Y	Y	Y	C	R	Y	V	H	Y	A	A	G	Y	G	V	-	-	-	-	-	-	-	D	I	W	G	Q	G	T
H0000	M	E	L	S	S	L	T	S	E	D	T	A	V	Y	Y	Y	C	T	R	F	Y	S	Y	-	-	-	-	-	-	-	-	-	-	-	-	T	Y	W	G	Q	G	T
H0610	M	E	L	S	S	L	T	S	E	D	T	A	V	Y	Y	Y	C	T	R	F	Y	S	Y	-	-	-	-	-	-	-	-	-	-	-	-	T	Y	W	G	Q	G	T
GCH054	M	E	L	S	S	L	T	S	E	D	T	A	V	Y	Y	Y	C	T	R	F	Y	S	Y	-	-	-	-	-	-	-	-	-	-	-	-	T	Y	W	G	Q	G	T
GCH065	M	E	L	S	S	L	T	S	E	D	T	A	V	Y	Y	Y	C	T	R	F	Y	S	Y	-	-	-	-	-	-	-	-	-	-	-	-	T	Y	W	G	Q	G	T
GCH094	M	E	L	S	S	L	T	S	E	D	T	A	V	Y	Y	Y	C	T	R	F	Y	S	Y	-	-	-	-	-	-	-	-	-	-	-	-	T	Y	W	G	Q	G	T

抗體名	108	109	110	111	112	113
CE115HA000	T	V	T	V	S	S
TR01H040	T	V	T	V	S	S
TR01H071	T	V	T	V	S	S
TR01H082	T	V	T	V	S	S
TR01H084	T	V	T	V	S	S
TR01H109	T	V	T	V	S	S
TR01H113	T	V	T	V	S	S
H0000	L	V	T	V	S	S
H0610	L	V	T	V	S	S
GCH054	L	V	T	V	S	S
GCH065	L	V	T	V	S	S
GCH094	L	V	T	V	S	S

第 13-2 圖

Kabab CDR L1																																												
Chothia CDR L1																																												
抗體名	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	27a	27b	27c	27e	27f	28	29	30	31	32	33	34	35	36			
L0000	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	S	Q	S	L	V	H	S	-	N	R	N	T	Y	L	H	W	Y	
L0011	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	S	Q	P	L	V	H	S	-	N	R	N	T	Y	L	H	W	Y	
L0201	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	S	Q	P	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y	
L0203	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	S	Q	S	P	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y
L0204	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	S	Q	S	P	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y
L0206	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	S	Q	S	P	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y
L0208	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	S	Q	S	P	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y
L0209	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	S	Q	P	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y	
L0211	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	S	Q	P	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y	
L0212	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	P	S	Q	S	P	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y	
L0222	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	S	Q	S	P	P	V	H	S	-	N	R	N	T	Y	L	H	W	Y
L0272	D	I	V	M	T	Q	S	P	L	S	L	P	V	T	P	G	E	P	A	S	I	S	C	R	S	S	S	Q	P	L	V	H	S	-	N	R	Q	T	Y	L	H	W	Y	

抗體名	Contact CDR L2												78																													
	37	38	39	40	41	42	43	44	45	46	47	48		49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77
L0000	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0011	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0201	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0203	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0204	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0206	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0208	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0209	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0211	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0212	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0222	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V
L0272	Q	Q	K	P	G	Q	A	P	R	L	L	I	Y	K	V	S	N	R	F	S	G	V	P	D	R	F	S	G	S	G	S	G	T	D	F	T	L	K	I	S	R	V

Kabab CDR L3																																				
Chothia CDR L3																																				
抗體名	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	95a	95b	95c	95d	95e	95f	96	97	98	99	100	101	102	103	104	105	106	107	
	L0000	E	A	E	D	V	G	V	Y	Y	C	G	Q	G	T	Q	V	P	-	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K
	L0011	E	A	E	D	V	G	V	Y	Y	C	G	Q	G	T	Q	V	P	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K	
	L0201	E	A	E	D	V	G	V	Y	Y	C	G	Q	G	T	Q	V	P	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K	
	L0203	E	A	E	D	V	G	V	Y	Y	C	G	Q	G	T	Q	V	P	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K	
	L0204	E	A	E	D	V	G	V	Y	Y	C	G	Q	G	T	Q	V	P	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K	
	L0206	E	A	E	D	V	G	V	Y	Y	C	Y	Q	G	T	Q	V	P	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K	
	L0208	E	A	E	D	V	G	V	Y	Y	C	Y	Q	G	T	Q	V	P	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K	
	L0209	E	A	E	D	V	G	V	Y	Y	C	Y	Q	G	T	Q	V	P	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K	
	L0211	E	A	E	D	V	G	V	Y	Y	C	Y	Q	G	T	Q	V	P	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K	
L0212	E	A	E	D	V	G	V	Y	Y	C	Y	Q	G	T	Q	V	P	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K		
L0222	E	A	E	D	V	G	V	Y	Y	C	Y	Q	G	T	Q	V	P	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K		
L0272	E	A	E	D	V	G	V	Y	Y	C	G	Q	G	T	Q	V	P	-	-	-	-	-	Y	T	F	G	Q	G	T	K	L	E	I	K		

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