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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。

發明專利說明書

(本說明書格式、順序，請勿任意更動)

【發明名稱】 (中文/英文)

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，尙已知會誘導 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】抗體爲了展現 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(Fc γ R)及各種補體成分結合。於人，就 Fc γ R 之蛋白質家族而言，有人報告了:Fc γ RIa、Fc γ RIIa、Fc γ RIIb、Fc γ RIIIa、Fc γ RIIIb 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，Fc γ RIa、Fc γ RIIa、Fc γ RIIIa 在細胞內域(domain)帶有稱爲 ITAM (Immunoreceptor Tyrosine-based Activation Motif) 之域，會傳達活化信號。另一方面，只有 Fc γ RIIb 在細胞內域帶有稱爲 ITIM (Immunoreceptor Tyrosine-based Inhibitory Motif) 之域，並抑制信號傳達。已知所有的 Fc γ R 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 Fc γ R 會成爲簇集，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 Fc γ R 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 Fc γ R、FcRn、Fc α R、Fc ϵ R 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 Fc γ R 和 FcRn 等不同， Fc γ R 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 CD3ε 鏈結合。Catumaxomab 藉由同時結合癌抗原與 CD3ε，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 FcγR，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 FcγR 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 CD3ε 與 FcγR，故即使於癌細胞不存在的環境仍會使表現 CD3ε 之 T 細胞與表現 FcγR 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 5μg/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 CD3ε 之兩者的抗原會同時結合於 FcγR，故在分子結構上不可能避免 FcγR 與第 2 抗原之 CD3ε 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 Fcγ 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。

爲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
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- 【非專利文獻 8】 J. Bio. Chem., (20001) 276, 16469-16477
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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：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害者，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】以下定義係爲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)爲較佳例。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爲公知。以下列舉製作和屬於 GPI 固定子(anchor)型受體家族之 Glypican3(以下也稱爲 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。爲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，爲了使 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。

- 可維持如 GPC3 之膜蛋白質之構造而提供免疫刺激
- 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(streptomine)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砷等輔助劑。

【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℃ 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。爲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(通常該足夠時間爲數日至數週)。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。爲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】爲了利用 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爲使 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爲對照，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。單株抗體爲小鼠來源時，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】爲了取得編碼爲可變區之基因，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 庫爲模板，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。此等引子爲依免疫球蛋白之次類而各不相同的鹼基序列。因此，次類理想爲預先使用 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，當目的爲取得例如編碼爲小鼠 IgG 之基因時，可利用將編碼爲當做重鏈之 $\gamma 1$ 、 $\gamma 2a$ 、 $\gamma 2b$ 、 $\gamma 3$ 、當做輕鏈之 κ 鏈與 λ 鏈的基因放大的引子。爲了放大 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，爲了將 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爲抗 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，若將編碼爲抗體恆定區(C 區)之基因、與編碼爲前述 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爲所望之抗體恆定區(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】爲了製造抗 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，例如包含增強子或啓動子。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 MGWSCIILFLVATATGVHS (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，可以取得表現編碼爲抗 GPC3 抗體之 DNA 的重組細胞。

【0059】爲了表現抗體基因，可將編碼爲抗體重鏈(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。或可將編碼爲 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爲公知。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爲公知。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爲公

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 與編碼爲人類抗體 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，使編碼爲該人類化抗體之 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

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 $\gamma 1$ 鏈(序列編號：6)、RefSeq 註冊編號 AAB63312.1 之 T 細胞受體 $\gamma 2$ 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 10 μ g/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(”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】

Δ 幾何平均值 = 幾何平均值 (抗原結合分子存在下) / 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 CH γ 1(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 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的各成員。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 Fc γ RI(CD64)、Fc γ RIIA(CD32)、Fc γ RIIB(CD32)、Fc γ RIIIA(CD16)及 / 或 Fc γ RIIIB(CD16)。Fc γ RI 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)，Fc γ RIIA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)，Fc γ RIIB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)，Fc γ RIIIA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)，Fc γ RIIIB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)。Fc γ 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，較佳為多胜肽。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、Fc γ R、Fc α R、Fc ϵ R、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 Fc γ R，但不限於該等。Fc 配體也包含與 Fc γ R 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 Fc γ 受體之結合活性

Fc 區對於 Fc γ I、Fc γ IIA、Fc γ IIB、Fc γ IIIA 及/或 Fc γ IIIB 中任一 Fc γ 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 $Fc\gamma$ 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 $\text{Fc}\gamma$ 受體之結合活性的效果。如上述，可以適當製作已驗證對於 $\text{Fc}\gamma$ 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)、

(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、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 CD3 ϵ 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 $Fc\gamma$ 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 $10^{-6} \sim 1.5 \times 10^{-0}$ ，更佳為 $10^{-6} \sim 10^{-1}$ ，再更佳為 $10^{-6} \sim 10^{-2}$ ，又更佳為 $10^{-6} \sim 10^{-3}$ 。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，細胞傷害活性的情形，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 $10^{-6} \sim 1.5 \times 10^{-0}$ 較理想，更佳為 $10^{-6} \sim 10^{-1}$ ，又更佳為 $10^{-6} \sim 10^{-2}$ ，再更佳為 $10^{-6} \sim 10^{-3}$ 。

【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 CD3 ϵ 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 CD3 ϵ 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℃ 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℃ 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℃ 之洗滌，更佳為 0.2xSSC、及 0.1% SDS、60℃ 之洗滌，再更佳為 0.2xSSC、及 0.1% SDS、62℃ 之洗滌，又更佳為 0.2xSSC、及 0.1% SDS、65℃ 之洗滌，更佳為 0.1xSSC、及 0.1% SDS、65℃ 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 $10^{-6}\sim 1.5\times 10^{-0}$ ，更佳為 $10^{-6}\sim 10^{-1}$ ，更佳為 $10^{-6}\sim 10^{-2}$ ，又更佳為 $10^{-6}\sim 10^{-3}$ 。

又，針對人 GPC3 及人 T 細胞受體複合體(例如人 CD3 ϵ 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 Fc γ 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 CD3 ϵ 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 $\text{Fc}\gamma$ 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 $\text{CD3}\epsilon$ 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(IC_{50})而言，待驗抗體能於未標記之該抗

體之 IC_{50} 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 $Fc\gamma$ 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(羥基甲基纖維素、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 1 μg/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，使用和 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 CD3 ϵ 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 鏈不變區之名稱為 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 之變異係爲了使產生由 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爲 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濾濃縮後，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，從健常人自願者 (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始活細胞之測定。反應於 5% 二氧化碳氣體、37 $^{\circ}$ 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】

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

【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 BiacoreTM-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 30 μ L/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(k_a)、解離速度常數(k_d)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)	k_a (1/Ms)	k_d (1/s)
H0000	GL4	4.2×10^{-9}	4.3×10^5	1.8×10^{-3}
H0000	L0000	3.6×10^{-8}	3.0×10^5	1.1×10^{-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 BiacoreTM-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、20 μ g/mL。測定先使抗體溶液捕捉於 Protein A/G，再以流速 20 μ L/min 連續注射 5、20 μ g/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(k_a)、解離速度常數(k_d)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)	k_a (1/Ms)	k_d (1/s)
rCE115H	rCE115L	1.0×10^{-7}	5.9×10^4	6.0×10^{-3}
hCE115HA	L0000	1.2×10^{-7}	1.9×10^5	2.3×10^{-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 Fc γ R(Fc γ 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，係爲了於產生由 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，係爲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爲 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)
NCE115HA-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-09
TR01H040-E22Hh/none-Hi-Kn010G3/TR01L016-k0	2.52E-09
TR01H083-E22Hh/none-Hi-Kn010G3/L0262-k0	2.45E-08
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	3.58E-09
TR01H040-E22Hh/none-Hi-Kn010G3/L0206-k0	2.90E-09
TR01H040-E22Hh/none-Hi-Kn010G3/TR01L019-k0	3.20E-09
TR01H080-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	4.61E-09
TR01H040-E22Hh/none-Hi-Kn010G3/L0209-k0	4.25E-09
TR01H040-E22Hh/none-Hi-Kn010G3/L0208-k0	4.16E-09
TR01H040-E22Hh/none-Hi-Kn010G3/L0224-k0	5.06E-09
TR01H040-E22Hh/none-Hi-Kn010G3/L0236-k0	5.64E-09
TR01H083-E22Hh/none-Hi-Kn010G3/L0201-k0	4.42E-09
TR01H084-E2702GsKsc/none-Hi-E2704sE/L0011-k0	4.14E-09
TR01H040-E22Hh/none-Hi-Kn010G3/L0210-k0	5.06E-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/GLC3108-k0	8.22E-09
CE115HA179-G1dh/-Hi-Kn010G3/L0000-k0	8.35E-08
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	9.48E-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	5.88E-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
TR01H067-E22Hh/none-Hi-Kn010G3/TR01L016-k0	1.09E-08
TR01H002-E22Hh/GLS3108-k0/GL4-E22Hh/H0000-E22L	4.78E-09
TR01H067-E22Hh/none-Hi-Kn010G3/TR01L019-k0	1.21E-08
TR01H038-E22Hh/none-Hi-Kn010G3/L0000-k0	1.24E-08
TR01H061-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
TR01H061-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
TR01H091-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	1.65E-08
TR01H072-E22Hh/none-Hi-Kn010G3/L0000-k0	2.03E-08
TR01H099-E2702GsKsc/none-Hi-E2704sE/L0011-k0	1.46E-08
TR01H061-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
TR01H061-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	1.64E-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/L0266-k0	2.29E-08
TR01H084-E22Hh/none-Hi-Kn010G3/L0011-k0	1.98E-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-E2702Gsk/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/H0810-E22L	3.57E-08
TR01H064-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
TR01H062-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	3.50E-08
CE115HA122-E22Hh/L0000-k0/GL4-E22Hh/H0000-E22L	1.69E-08
TR01H078-E22Hh/none-Hi-Kn010G3/L0000-k0	4.78E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0258-k0	4.70E-08
TR01H048-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	4.76E-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/L0000vk1-k0	4.69E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0219-k0	3.94E-08
TR01H014-E22Hh/none-Hi-Kn010G3/L0000-k0	3.87E-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	4.88E-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
TR01H006-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	5.76E-08
TR01H087-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	6.16E-08
hCE115HA-E22Hh/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	8.34E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0202-k0	6.19E-08
TR01H067-E22Hh/none-Hi-Kn010G3/L0201-k0	5.93E-08
TR01H020-E22Hh/none-Hi-Kn010G3/L0000-k0	6.48E-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
TR01H036-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-08
TR01H029-E22Hh/none-Hi-Kn010G3/L0000-k0	6.70E-08
TR01H019-E22Hh/none-Hi-Kn010G3/L0000-k0	6.85E-08
TR01H082-E22Hh/none-Hi-Kn010G3/L0000-k0	7.37E-08
TR01H016-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
TR01H091-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	6.98E-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
TR01H099-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
TR01H067-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/H0000-E22L	9.37E-08
TR01H015-E22Hh/none-Hi-Kn010G3/TR01L006-k0	9.30E-08
TR01H040-E22Hh/none-Hi-Kn010G3/L0248-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	9.09E-08
TR01H082-E22Hh/none-Hi-Kn010G3/TR01L020-k0	1.06E-07
TR01H098-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
hCE115HA-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/L0000-k0	3.97E-09
H0610-G1dh/none-Hi-Kn010G3/L0222-k0	1.40E-13
H0610-G1dh/none-Hi-Kn010G3/L0258-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
GCH065-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/L0248-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-E22Hk/H0610-E22L	2.36E-10
TR01H015-E22Hh/L0000-k0/GL4-E22Hk/H0610-E22L	2.63E-10
CE115HA236-E22Hh/GLS3108-k0/GL4-E22Hk/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	4.59E-10
H0610-G1dh/none-Hi-Kn010G3/L0223-k0	4.75E-10
TR01H002-E22Hh/GLS3108-k0/GL4-E22Hk/H0610-E22L	4.75E-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	7.78E-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/L0085-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	1.18E-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-08
H0610-G1dh/none-Hi-Kn010G3/L0151-k0	1.25E-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
GCH054-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/TR01L018-k0	2.17E-09
H0610-G1dh/none-Hi-Kn010G3/L0218-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	2.60E-09
H0610-G1dh/none-Hi-Kn010G3/L0145-k0	2.66E-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-08
GCH043-G1dh/none-Hi-Kn010G3/L0000-k0	3.74E-09
H0610-G1dh/none-Hi-Kn010G3/TR01L008-k0	3.48E-09
H0610-G1dh/none-Hi-Kn010G3/L0148-k0	3.28E-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
GCH008-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/L0068-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 (人 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	3.68E-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	4.89E-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
GCH016-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	4.95E-09
GCH089-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
GCH056-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
GCH057-G1dh/none-Hi-Kn010G3/L0000-k0	5.61E-09
H0610-G1dh/none-Hi-Kn010G3/L0137-k0	5.87E-09

【0241】(3-3) 利用點突變所爲之 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	4.16E-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/I48M/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 CD3 ϵ 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 SuReTM 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 CD3 ϵ 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 CD3 ϵ 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 CD3 ϵ 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 CD3 ϵ 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 CD3 ϵ 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 CD3 ϵ 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 CD3 ϵ 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 CD3 ϵ 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 CD3 ϵ 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 CD3 ϵ 鏈及抗人 GPC3 雙專一性抗體投予群相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、Nacalai tesque)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 SYPROTM 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 20 μ L 安置於測定用管，以 240 $^{\circ}$ C /hr 的升溫速度使溫度從 30 $^{\circ}$ C 升高到 99 $^{\circ}$ C。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 5 μ L 後，於冷處靜置一晚。然後於

各井中加入 150 μ L 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)之操作說明書進行鈎化。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 2 μ g/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 3 μ g/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 之鈎化抗體 (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]SuReTM 配體結合能力測定

對於 SuReTM 配體之結合能力之測定係使用 BiacoreTM-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 鏈勝肽 (CAA26636.1)	84	TR01H021	157	TR01H102
5	T 細胞受體 β 鏈勝肽 (C25777)	85	TR01H022	158	TR01H103
6	T 細胞受體 $\gamma 1$ 鏈勝肽 (A26659)	86	TR01H023	159	TR01H104
7	T 細胞受體 $\gamma 2$ 鏈勝肽 (AAB63312.1)	87	TR01H024	160	TR01H105
8	T 細胞受體 δ 鏈勝肽 (AAA61033.1)	88	TR01H025	161	TR01H106
9	CD3 γ 鏈核苷酸 (NM_000073.2)	89	TR01H026	162	TR01H107
10	CD3 δ 鏈核苷酸 (NM_000732.4)	90	TR01H027	163	TR01H108
11	CD3 ϵ 鏈核苷酸 (NM_000733.3)	91	TR01H028	164	TR01H109
12	CD3 γ 鏈勝肽 (NP_000064.1)	92	TR01H029	165	TR01H110
13	CD3 δ 鏈勝肽 (NP_000723.1)	93	TR01H030	166	TR01H111
14	CD3 ϵ 鏈勝肽 (NP_000724.1)	94	TR01H031	167	TR01H112
15~22	勝肽連結子	95	TR01H032	168	TR01H113
23	人 C $\gamma 1$	96	TR01H033	169	TR01H114
24	人 C $\gamma 2$	97	TR01H034	170	GCH003
25	人 C $\gamma 3$	98	TR01H035	171	GCH005
26	人 C $\gamma 4$	99	TR01H036	172	GCH006
27	Fc γ RI 核苷酸 (NM_000566.3)	100	TR01H037	173	GCH007
28	Fc γ RI 勝肽 (NP_000557.1)	101	TR01H038	174	GCH008
29	Fc γ RIIA 核苷酸 (BC020823.1)	102	TR01H039	175	GCH010
30	Fc γ RIIA 勝肽 (AAH20823.1)	103	TR01H040	176	GCH012
31	Fc γ RIIB 核苷酸 (BC146678.1)	104	TR01H041	177	GCH013
32	Fc γ RIIB 勝肽 (AAI46679.1)	105	TR01H042	178	GCH014
33	Fc γ RIIIA 核苷酸 (BC033678.1)	106	TR01H043	179	GCH015
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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

<110> 中外製藥股份有限公司(CHUGAI SEIYAKU KABUSHIKI KAISHA)

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<211> 771

<212> DNA

<213> Homo sapiens

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 <212> DNA
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<213> Homo sapiens

<400> 12

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Leu Gln Gly Thr Leu Ala Gln Ser Ile Lys Gly Asn His Leu Val Lys
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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

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Ser Gln Val Ser Pro Phe Lys Ile Pro Ile Glu Glu Leu Glu Asp Arg
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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
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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

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<213> Artificial

<220>

<223> An artificially generated sequence

<400> 15

Gly Gly Gly Ser

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<220>
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<400> 16

Ser Gly Gly Gly
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<210> 17
<211> 5
<212> PRT
<213> Artificial

<220>
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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
<211> 6
<212> PRT
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<223> An artificially generated sequence

<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

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<212> PRT

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<400> 21

Gly Gly Gly Gly Gly Gly Ser
1 5

<210> 22

<211> 7

<212> PRT

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<400> 22

Ser Gly Gly Gly Gly Gly Gly
1 5

<210> 23
 <211> 330
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 <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

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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
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
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
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Leu Ser Leu Ser Leu Gly Lys
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<210> 27

<211> 2268

<212> DNA

<213> Homo sapiens

<400> 27

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

<400> 28

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

Pro Gly Ser Ser Ser Thr Gln Trp Phe Leu Asn Gly Thr Ala Thr Gln
50 55 60

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

Gly Glu Tyr Arg Cys Gln Arg Gly Leu Ser Gly Arg Ser Asp Pro Ile
85 90 95

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

Val Phe Thr Glu Gly Glu Pro Leu Ala Leu Arg Cys His Ala Trp Lys
115 120 125

Asp Lys Leu Val Tyr Asn Val Leu Tyr Tyr Arg Asn Gly Lys Ala Phe
130 135 140

Lys Phe Phe His Trp Asn Ser Asn Leu Thr Ile Leu Lys Thr Asn Ile
145 150 155 160

Ser His Asn Gly Thr Tyr His Cys Ser Gly Met Gly Lys His Arg Tyr
165 170 175

Thr Ser Ala Gly Ile Ser Val Thr Val Lys Glu Leu Phe Pro Ala Pro
180 185 190

Val Leu Asn Ala Ser Val Thr Ser Pro Leu Leu Glu Gly Asn Leu Val
195 200 205

Thr Leu Ser Cys Glu Thr Lys Leu Leu Leu Gln Arg Pro Gly Leu Gln
210 215 220

Leu Tyr Phe Ser Phe Tyr Met Gly Ser Lys Thr Leu Arg Gly Arg Asn
225 230 235 240

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
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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
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<210> 29
<211> 1396
<212> DNA
<213> Homo sapiens

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ctgaggtgcc acagctggaa ggacaagcct ctggtcaagg tcacattctt ccagaatgga 480
aaatcccaga aatttccca tttggatccc accttctcca tcccacaagc aaaccacagt 540
cacagtgggtg attaccactg cacaggaaac ataggctaca cgctgttctc atccaagcct 600
gtgaccatca ctgtccaagt gccagcatg ggcagctctt caccaatggg ggtcattgtg 660
gctgtggtca ttgcgactgc tgtagcagcc attgttgctg ctgtagtggc cttgatctac 720
tgcaggaaaa agcggatttc agccaattcc actgatcctg tgaaggctgc ccaatttgag 780
ccacctggac gtcaaatgat tgccatcaga aagagacaac ttgaagaaac caacaatgac 840
tatgaaacag ctgacggcgg ctacatgact ctgaaccca gggcacctac tgacgatgat 900
aaaaacatct acctgactct tcctcccaac gaccatgtca acagtaataa ctaaagagta 960
acgttatgcc atgtgggtcat actctcagct tgctgagtgg atgacaaaaa gaggggaatt 1020
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ttagaaatag cttaaacttt gcttaaacta caaacacaag caaaacttca cggggtcata 1140
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ctttctaaga agatacctac ccccaaaaaa caattatgta attgaaaacc aaccgattgc 1320
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aaaaaaaaaa aaaaaa 1396

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<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
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ttacctgtcc ttgccactga gaggactgg gctgactgca agtcccccca gccttgggggt 120
catatgcttc tgtggacagc tgtgctattc ctggctcctg ttgctgggac acctgcagct 180
cccccaaagg ctgtgctgaa actcgagccc cagtggatca acgtgctcca ggaggactct 240

gtgactctga catgccgggg gactcacagc cctgagagcg actccattca gtggttccac 300
 aatgggaatc tcattcccac ccacacgcag cccagctaca ggttcaaggc caacaacaat 360
 gacagcgggg agtacacgtg ccagactggc cagaccagcc tcagcgaccc tgtgcatctg 420
 actgtgcttt ctgagtggct ggtgctccag acccctcacc tggagttcca ggaggagaa 480
 accatcgtgc tgaggtgcca cagctggaag gacaagcctc tggtaaggt cacattcttc 540
 cagaatggaa aatccaagaa attttccgt tcggatccca acttctccat cccacaagca 600
 aaccacagtc acagtgggta ttaccactgc acaggaaaca taggtacac gctgtactca 660
 tccaagcctg tgaccatcac tgtccaagct cccagctctt caccgatggg gatcattgtg 720
 gctgtggtea ctgggattgc tgtagcggcc attgttgctg ctgtagtggc cttgatctac 780
 tgcaggaaaa agcggatttc agccaatccc actaatcctg atgaggctga caaagttggg 840
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 gaccagaacc gtatttagtc tccattgtct tgcattggga ttgagaaga aaatcagaga 960
 gggaagatct ggtatttcct ggcctaaatt ccccttgggg aggacaggga gatgctgcag 1020
 ttccaaaaga gaaggtttct tccagagtea tctacctgag tctgaagct cctgtcctg 1080
 aaagccacag acaatatggc cccaaataac cgactgcacc ttctgtgctt cagctcttct 1140
 tgacatcaag gctcttccgt tccacatcca cacagccaat ccaattaatc aaaccactgt 1200
 tattaacaga taatagcaac ttgggaaatg cttatgttac aggttacgtg agaacaatca 1260
 tgtaaatacta 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 tgacgctgcc acagttgacg acagtggaga gtacaggtgc cagacaaacc 300
tctccaccct cagtgaccgg gtgcagctag aagtccatat cggctggctg ttgctccagg 360

cccctcgggtg ggtgttcaag gaggaagacc ctattcacct gaggtgtcac agctggaaga	420
acactgctct gcataaggtc acatatttac agaatggcaa aggcaggaag tattttcatc	480
ataattctga cttctacatt ccaaaagcca cactcaaaga cagcggctcc tacttctgca	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 tgcaacccca tcatcctcag gcctctctac aagcagcagg aaacatagaa	900
ctcagagcca gatecccttat ccaactctcg acttttcctt ggtctccagt ggaagggaaa	960
agcccatgat cttaagcag ggaagcccca gtgagtagct gcattcctag aaattgaagt	1020
ttcagagcta cacaaacact ttttctgtcc caaccgttcc ctcacagcaa agcaacaata	1080
caggctaggg atggtaatcc tttaaacata caaaaattgc tcgtgttata aattaccag	1140
tttagagggg aaaaaaaaaac aattattcct aaataaatgg ataagtagaa ttaatggttg	1200
aggcaggacc atacagagtg tgggaactgc tggggatcta gggaattcag tgggaccaat	1260
gaaagcatgg ctgagaaata gcaggtagtc caggatagtc taagggaggt gttcccatct	1320
gagcccagag ataagggtgt cttcctagaa cattagccgt agtggaatta acaggaaatc	1380
atgagggtga cgtagaattg agtcttcag gggactctat cagaactgga ccatctccaa	1440
gtatataacg atgagtcctc ttaatgctag gagtagaaaa tggtcctagg aaggggactg	1500
aggattgcgg tgggggggtgg ggtggaaaag aaagtacaga acaaaccctg tgtcactgtc	1560
ccaagttgct aagtgaacag aactatctca gcatcagaat gagaaagcct gagaagaaag	1620
aaccaaccac aagcacacag gaaggaaagc gcaggagggtg aaaatgcttt cttggccagg	1680
gtagtaagaa ttagaggtta atgcagggtg tgtaaaacca ctttttctgc ttcaatatct	1740
aattcctgtg tagctttgtt cattgcattt attaaacaaa tgttgtataa ccaatactaa	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
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 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 tcctcccaac tgctctgcta cttctagttt 60

cagctggcat gcggactgaa gatctcccaa aggctgtggt gttcctggag cctcaatggt 120

acagcgtgct tgagaaggac agtgtgactc tgaagtgccg gggagcctac tcccctgagg 180

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acaattccac acagtgggtt cacaatgaga gcctcatctc aagccaggcc tcgagctact   240
tcattgacgc tgccacagtc aacgacagtg gagagtacag gtgccagaca aacctctcca   300
ccctcagtga cccggtgcag ctagaagtcc atatcggtg gctgttgctc caggcccctc   360
ggtgggtgtt caaggaggaa gaccctattc acctgaggtg tcacagctgg aagaacactg   420
ctctgcataa ggtcacatat ttacagaatg gcaaagacag gaagtatitt catcataatt   480
ctgacttcca cattccaaaa gccacactca aagatagcgg ctctacttgc tgcagggggc   540
ttgttgggag taaaaatgtg tcttcagaga ctgtgaacat caccatcact caaggtttgg   600
cagtgtcaac catctcatca ttctctccac ctgggtacca agtctcttgc tgcttggtga   660
tggtactcct ttttcagtg gacacaggac tatatttctc tgtgaagaca aacatttgaa   720
gctcaacaag agactggaag gaccataaac tttaatggag aaaggaccct caagacaaat   780
gacccccatc ccatgggagt aataagagca gtggcagcag                        820

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

<400> 36

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Met Trp Gln Leu Leu Pro Thr Ala 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
 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> 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
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

245250255

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

260265270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser

275280285

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

290295300

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

305310315320

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

151015

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr

202530

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile

354045

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

65707580

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ser Gln Asn
859095

Thr His Val Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100105110

<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
151015

Ser Leu Lys Leu Thr Cys Ala Thr Ser Gly Phe Thr Phe Ser Asn Ala
202530

Trp Met His Trp Val Arg Gln Ser Pro Glu Lys Gln Leu Glu Trp Val
354045

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu
505560

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Asn
65707580

Ile Tyr Leu Gln Met Asn Ser Leu Lys Glu Glu Asp Thr Ala Val Tyr
859095

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Asp Ala Trp
100105110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115120

<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
210215220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Cys Glu
225230235240

Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr
245250255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260265270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275280285

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

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305310315320

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
151015

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

210215220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Cys Glu

225230235240

Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr

245250255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn

260265270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe

275280285

Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn

290295300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr

305310315320

Gln Lys Ser Leu Ser Leu Ser Pro Asp Tyr Lys Asp Asp Asp Asp Lys

325330335

<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

151015

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

65707580

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gly Gln Gly
859095

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100105110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115120125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130135140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145150155160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165170175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180185190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195200205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210215

<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
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
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			

195200205

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
210215220

Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg
225230235240

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
245250255

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
260265270

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
275280285

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
290295300

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
305310315320

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro His His His His His His
325330335

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
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
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

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu

505560

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser

65707580

Ile Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr

859095

Tyr Cys Arg Tyr Val His Tyr Gly Ala Tyr Tyr Gly Val Gln Ala Trp

100105110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser

115120

<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

151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

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

$\langle 210 \rangle$	69
$\langle 211 \rangle$	122
$\langle 212 \rangle$	PRT
$\langle 213 \rangle$	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

354045

Ala Gln Ile Lys Ala Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu

505560

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser

65707580

Ile Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr

859095

Tyr Cys Arg Tyr Val His Tyr Gly Ala Ser Tyr Gly Val Asp Ile Trp

100105110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser

115120

<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

151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

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	Tyr	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

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

$\langle 210 \rangle$	85
$\langle 211 \rangle$	122
$\langle 212 \rangle$	PRT
$\langle 213 \rangle$	Artificial

<220>
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<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

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

Ala Gln Ile Lys Ser Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu

505560

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser

65707580

Ile Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr

859095

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp

100105110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser

115120

<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

151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

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

859095

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp

100105110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser

115120

<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

151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

Ala Gln Ile Lys Gly Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu

505560

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser

65707580

Ile Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr

859095

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	Tyr	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														
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<213>	Artificial														
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<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

354045

Ala Gln Ile Lys Asp Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu

505560

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser

65707580

Ile Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr

859095

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp

100105110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser

115120

<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

151015

Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Asn Ala

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

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

859095

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ala Trp

100105110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser

115120

<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

151015

Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Asn Ala

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu

505560

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser

65707580

Ile Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr

859095

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

354045

Ala Gln Ile Lys Asp Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Glu

505560

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser

65707580

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr

859095

Tyr Cys Arg Tyr Val His Tyr Ser Ala Ser Tyr Gly Val Asp Ile Trp

100105110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser

115120

<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

151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

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	Tyr	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

65707580

Ile Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
859095

Tyr Cys Arg Tyr Val His Tyr Ala Ala Val Arg Arg Arg Leu Ser Ser
100105110

Tyr Gly Val Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115120125

<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
151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
354045

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu
505560

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Ala Asp Ser Lys Asn Ser
65707580

Ile Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
859095

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

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Tyr Ala Glu

505560

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser

65707580

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr

859095

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp

100105110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser

115120

<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

151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

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	Tyr	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

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Gln Tyr Tyr Ala Glu

505560

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser

65707580

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr

859095

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp

100105110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser

115120

<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

151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

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

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

Ala Gln Ile Lys Asp Lys Ser Gln Asn Tyr Ala Thr Tyr Gln Ala Glu

505560

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser

65707580

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr

859095

Tyr Cys Arg Tyr Val His Tyr Ala Ala Gly Tyr Gly Val Asp Ala Trp

100105110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser

115120

<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

151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala

202530

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

354045

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	Tyr	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

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

202530

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile

354045

Gly Ala Ile Asp Gly Lys Thr Pro Asp Thr Ala Tyr Ser Gln Lys Phe

505560

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

65707580

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys

859095

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr

100105110

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

151015

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Glu Asp Tyr

202530

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile

354045

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

354045

Gly Ala Ile Asp Gly Lys Thr Pro Asp Thr Ala Tyr Ser Gln Lys Phe

505560

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

65707580

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Glu Ala Val Tyr Tyr Cys

859095

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr

100105110

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

151015

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr

202530

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile

354045

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

859095

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr

100105110

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

151015

Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr

202530

Glu Met His Trp Ile Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile

354045

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Glu Lys Phe

505560

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

65707580

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys

859095

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

354045

Gly Ala Ile Asp Gly Glu Thr Pro Asp Thr Ala Tyr Ser Gln Lys Phe

505560

Glu Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

65707580

Met Glu Leu Ser Ser Leu Thr Glu Glu Asp Thr Ala Val Tyr Tyr Cys

859095

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr

100105110

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

151015

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr

202530

Glu Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile

354045

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

65707580

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
859095

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
100105110

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
151015

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
202530

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile
354045

Gly Ala Ile Asp Gly Lys Thr Pro Asp Thr Ala Tyr Ser Gln Lys Phe
505560

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65707580

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
859095

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

15

10

5

1

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

15

10

5

1

Asp

Ile

Val

Met

Thr

Gln

Ser

Pro

Leu

Ser

Leu

Pro

Val

Thr

Pro

Gly

20

25

30

Glu

Pro

Ala

Ser

Ile

Ser

Cys

Arg

Ser

Ser

Gln

Ser

Leu

Val

His

Ser

35

40

45

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

202530

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
354045

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
505560

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65707580

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Tyr Gln Gly
859095

Thr Gln Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100105110

<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
151015

Glu Pro Ala Ser Ile Ser Cys Arg Pro Ser Gln Ser Pro Val His Ser
202530

Asn Arg Asn Thr Tyr Ile Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
354045

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
505560

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

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 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				
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<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
 225 230 235 240

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>	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

420425430

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro His His His His His His

435440445

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

151015

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr

202530

Glu Met His Trp Ile Arg Gln Pro Pro Gly Gln Gly Leu Glu Trp Ile

354045

Gly Ala Ile Asp Pro Lys Thr Gly Asp Thr Ala Tyr Ser Gln Lys Phe

505560

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

65707580

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys

859095

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

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

$\langle 210 \rangle$	411
$\langle 211 \rangle$	219
$\langle 212 \rangle$	PRT
$\langle 213 \rangle$	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

I597290

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

發明摘要

※ 申請案號：104131736

※ 申請日：104/09/25

※IPC 分類： C07K 14/725 (2006.01)
C07K 16/28 (2006.01)
C12N 15/11 (2006.01)
C12N 15/63 (2006.01)
A61K 39/395 (2006.01)
A61P 35/00 (2006.01)

【發明名稱】（中文/英文）

細胞傷害誘導治療劑

【中文】

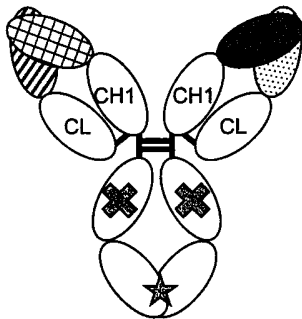
本發明找到一種新的多專一性抗原結合分子，其包含：含有具 Glypican3 結合活性之抗體可變區之域、及含有具 T 細胞受體複合體結合活性之抗體可變區之域，且維持優良的細胞傷害活性與高安全性。本發明之分子對於表現 Glypican3 之細胞、組織呈強細胞傷害性，故能製造用以治療或預防各種癌之新的醫藥組合物。

【英文】

無。

圖式

a ERY22



 抗癌抗原(GPC3)抗體 H 鏈可變區

 抗癌抗原(GPC3)抗體 L 鏈可變區

 抗 CD3 抗體 H 鏈可變區

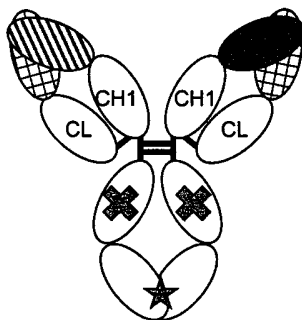
 抗 CD3 抗體 L 鏈可變區

 抗體不變區

 靜默 Fc 變異

 異 Fc 聯合化變異

b ERY27



 抗癌抗原(GPC3)抗體 H 鏈可變區

 抗 CD3 抗體 H 鏈可變區

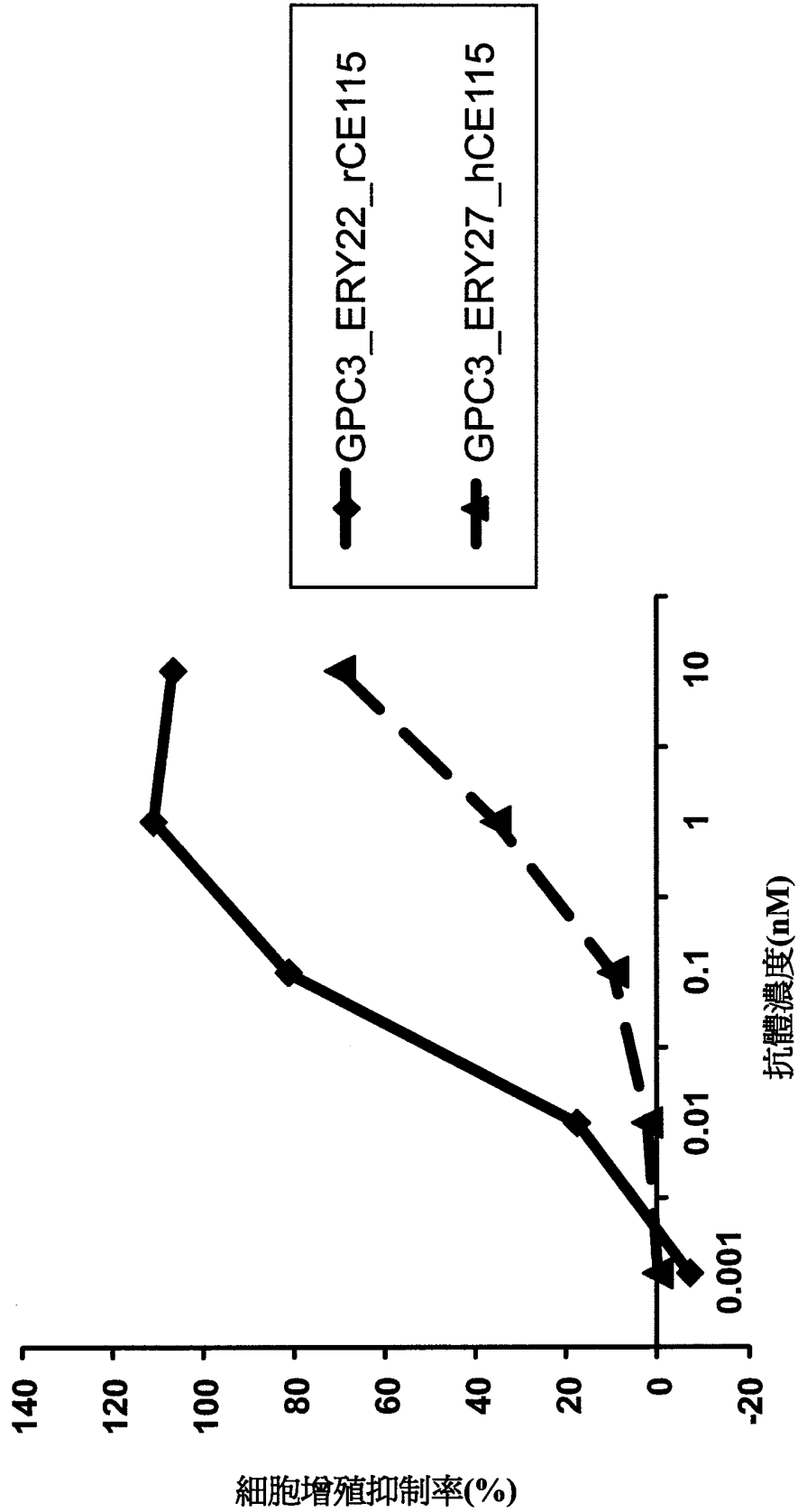
 共通 L 鏈可變區

 抗體不變區

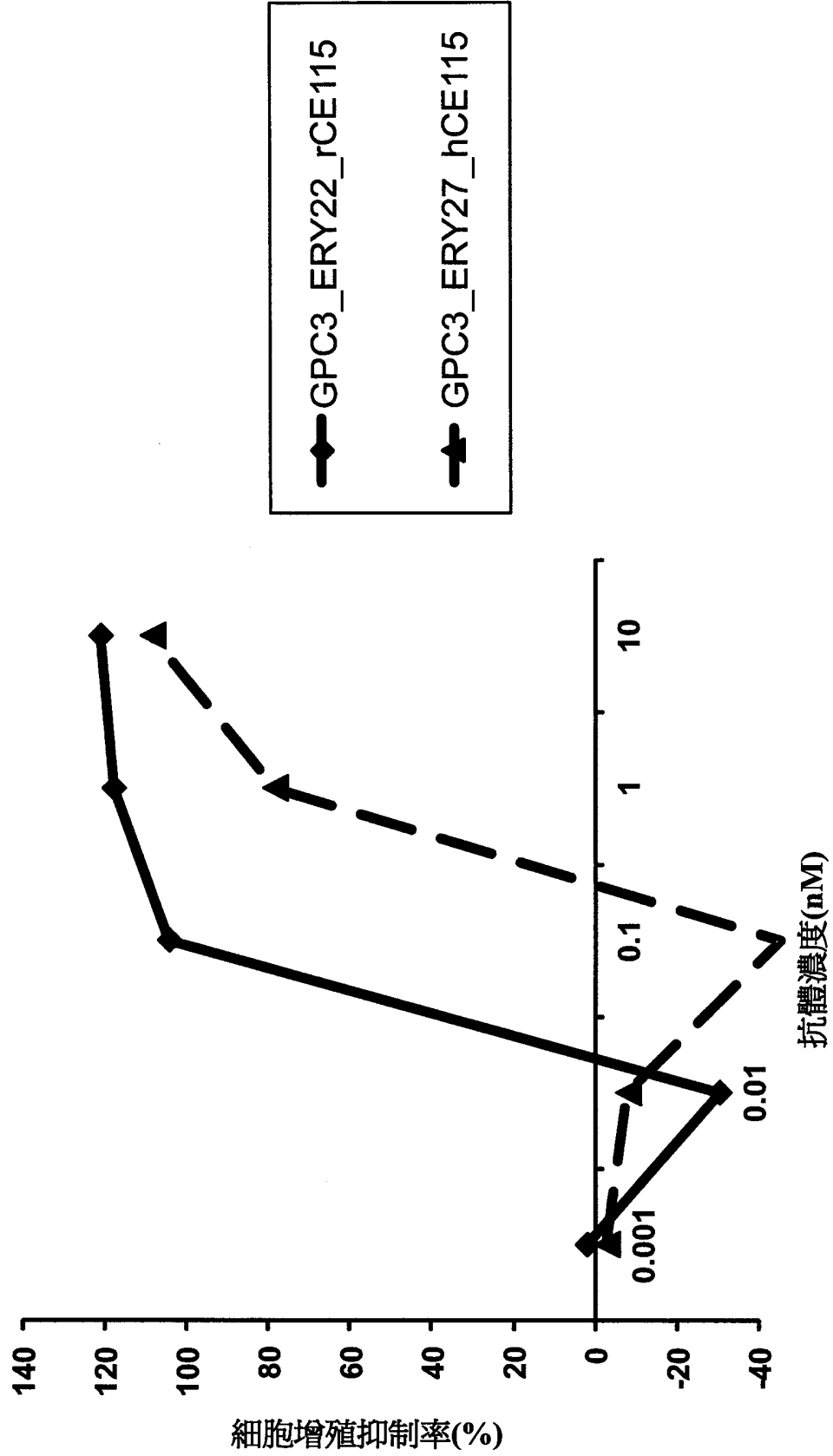
 靜默 Fc 變異

 異 Fc 聯合化變異

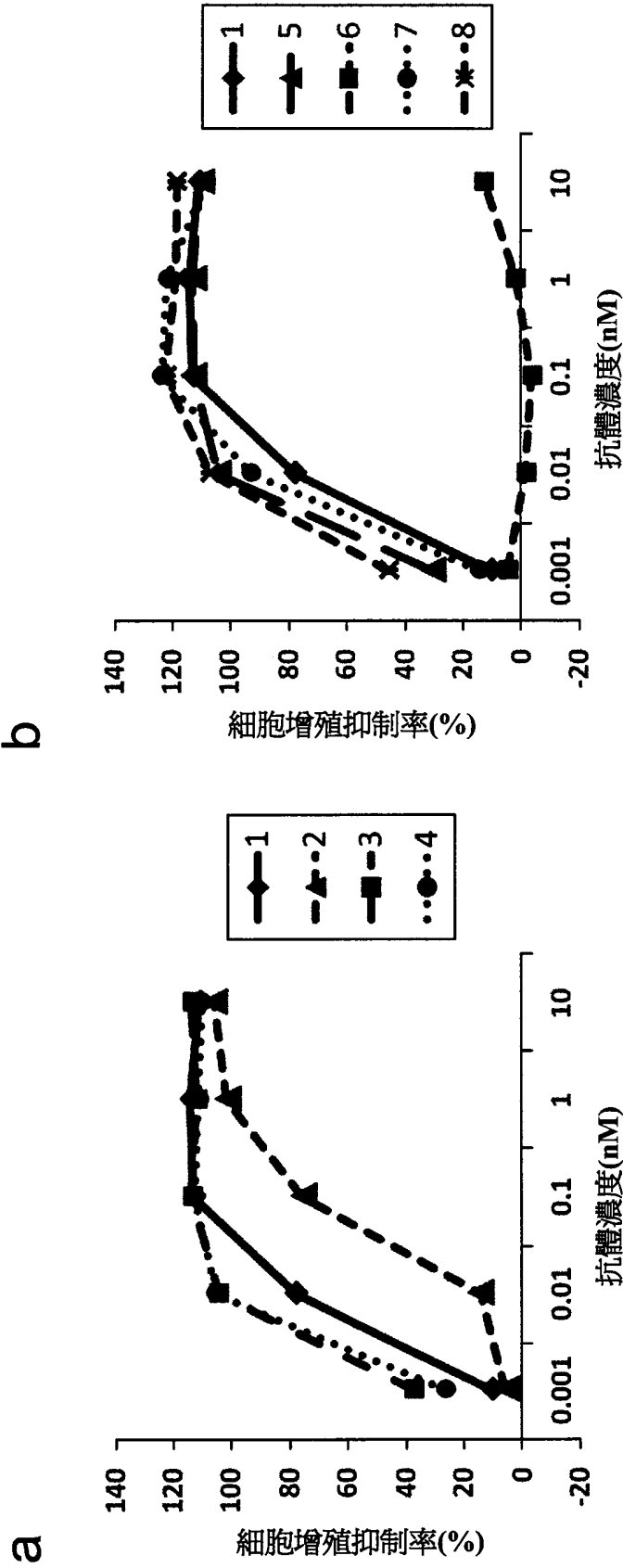
第 1 圖



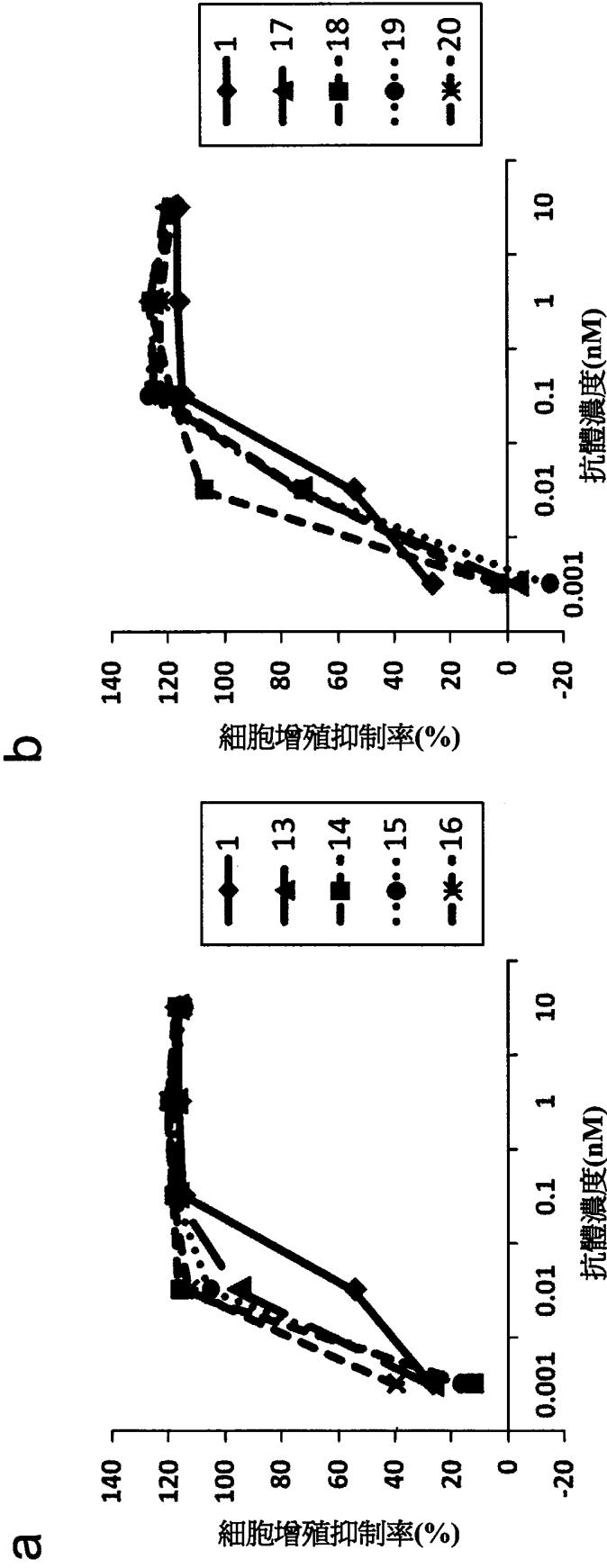
第 2 圖



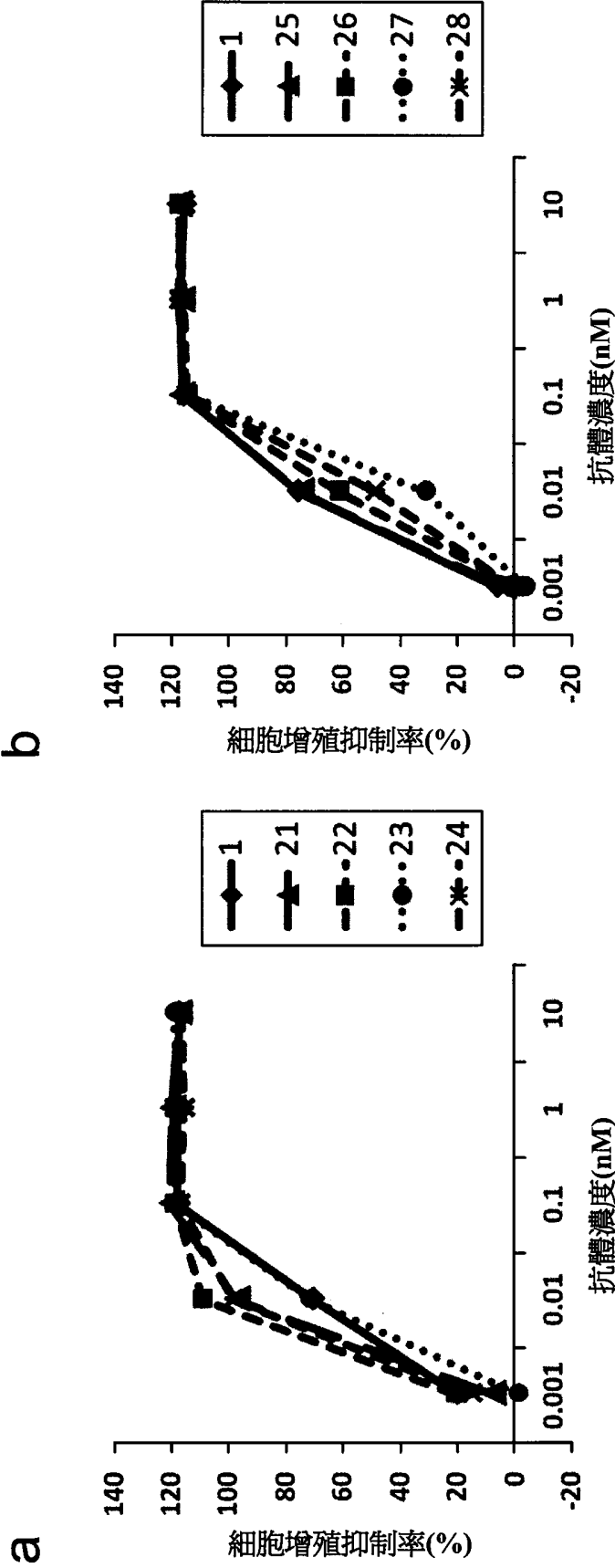
第 3 圖



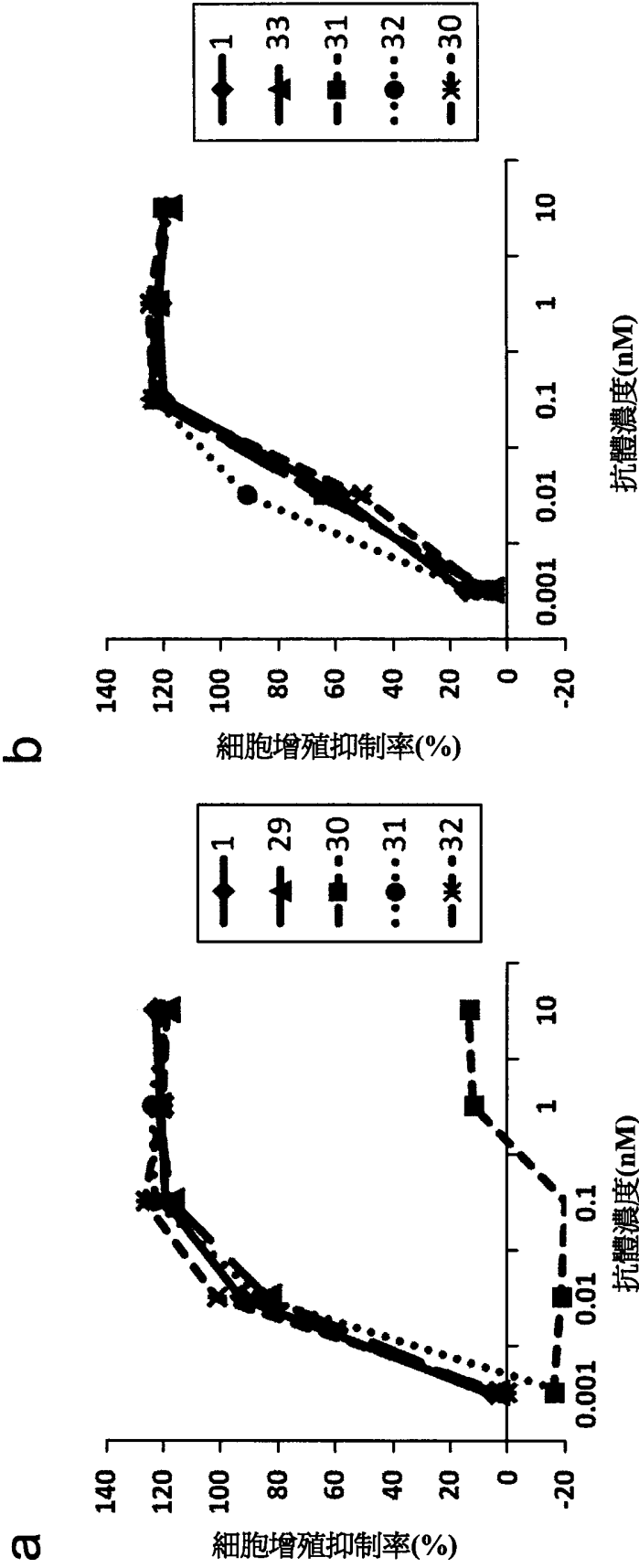
第 4 圖



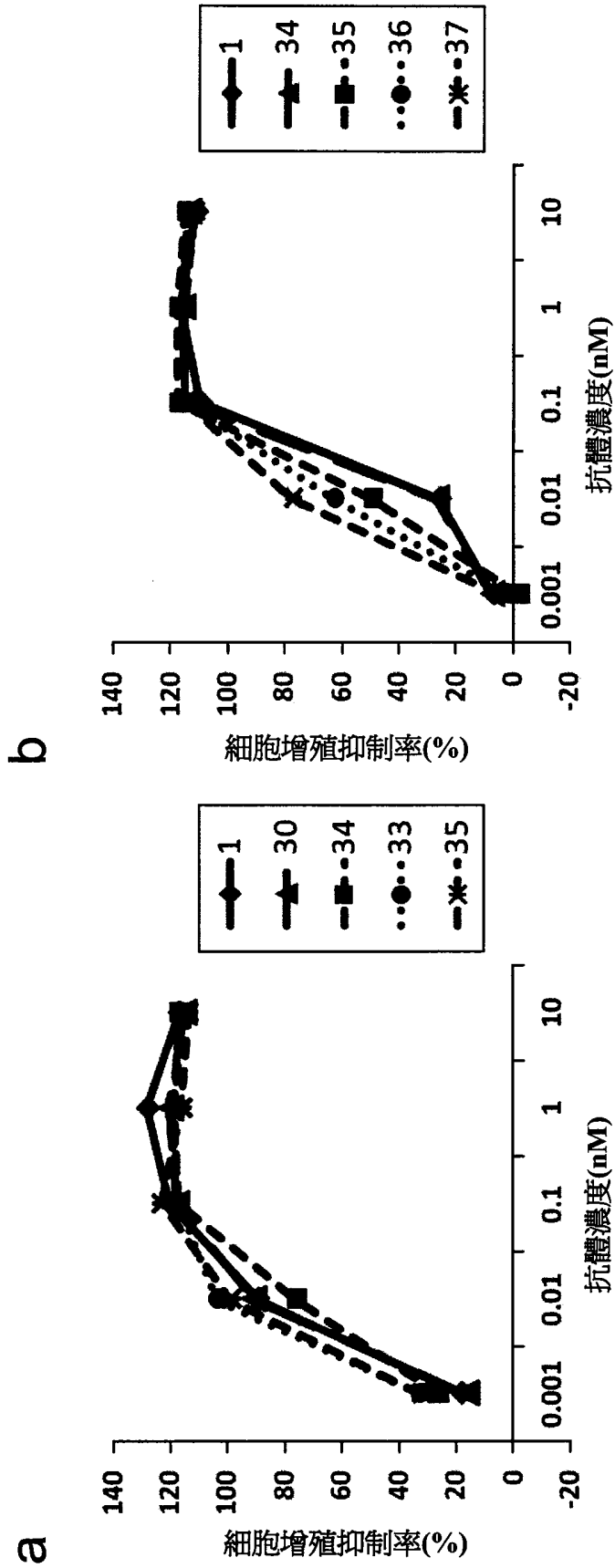
第 5 圖



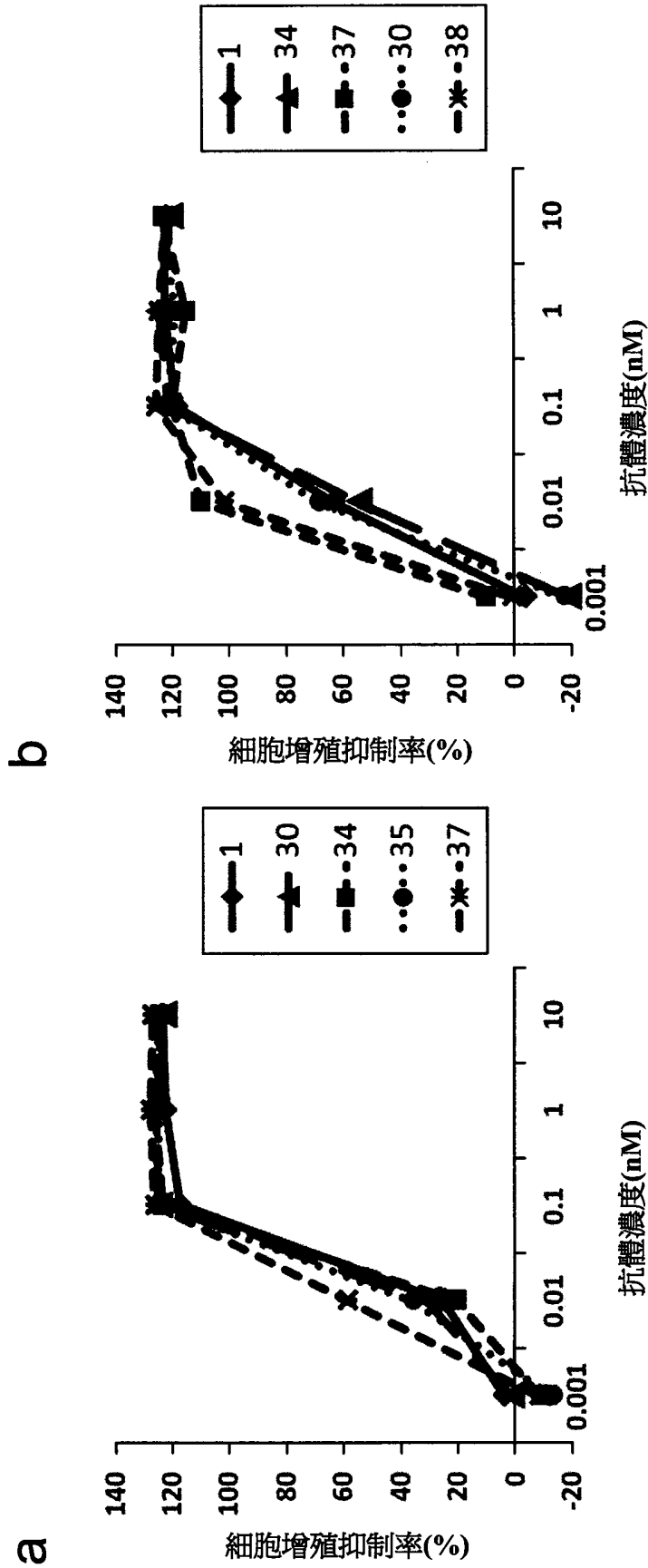
第 6 圖



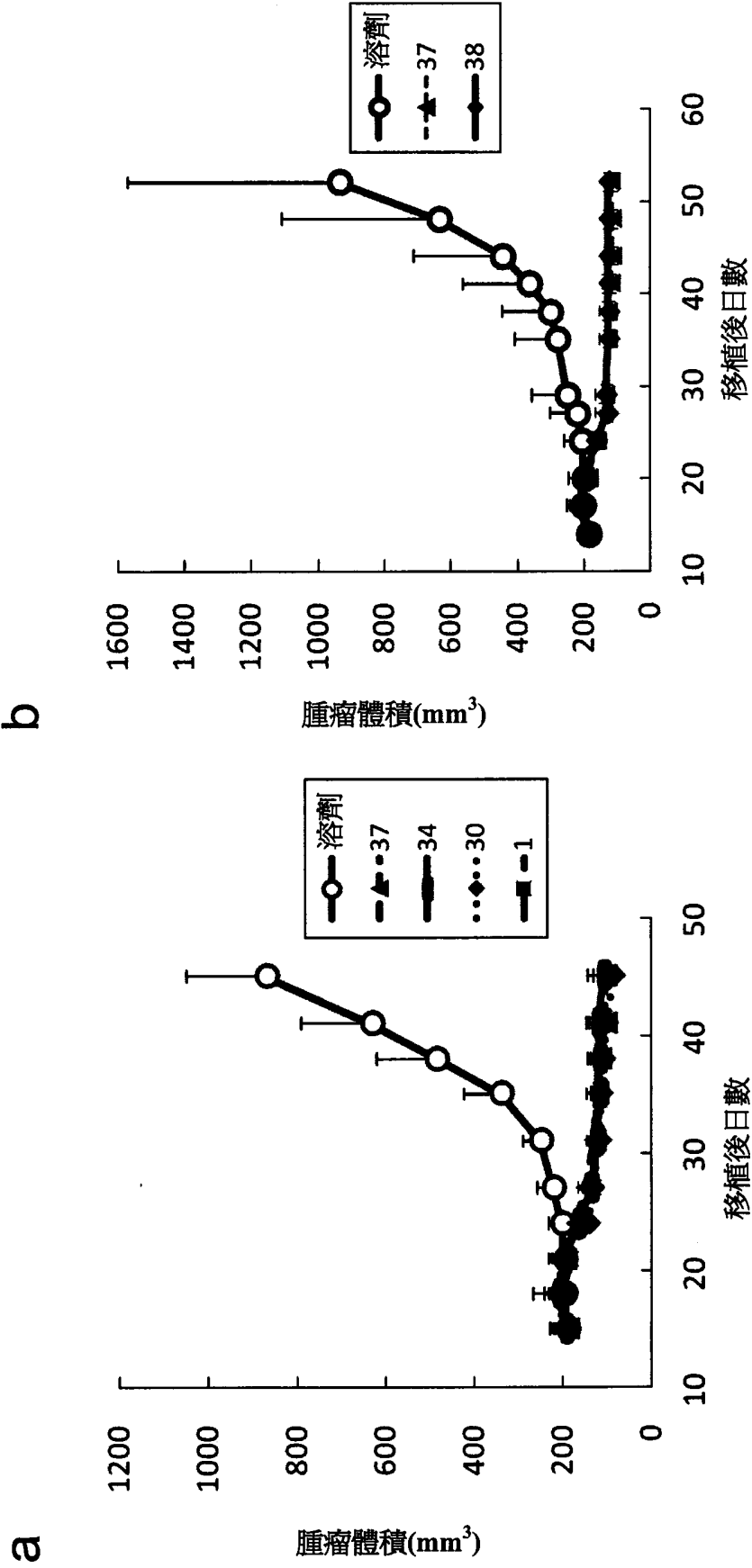
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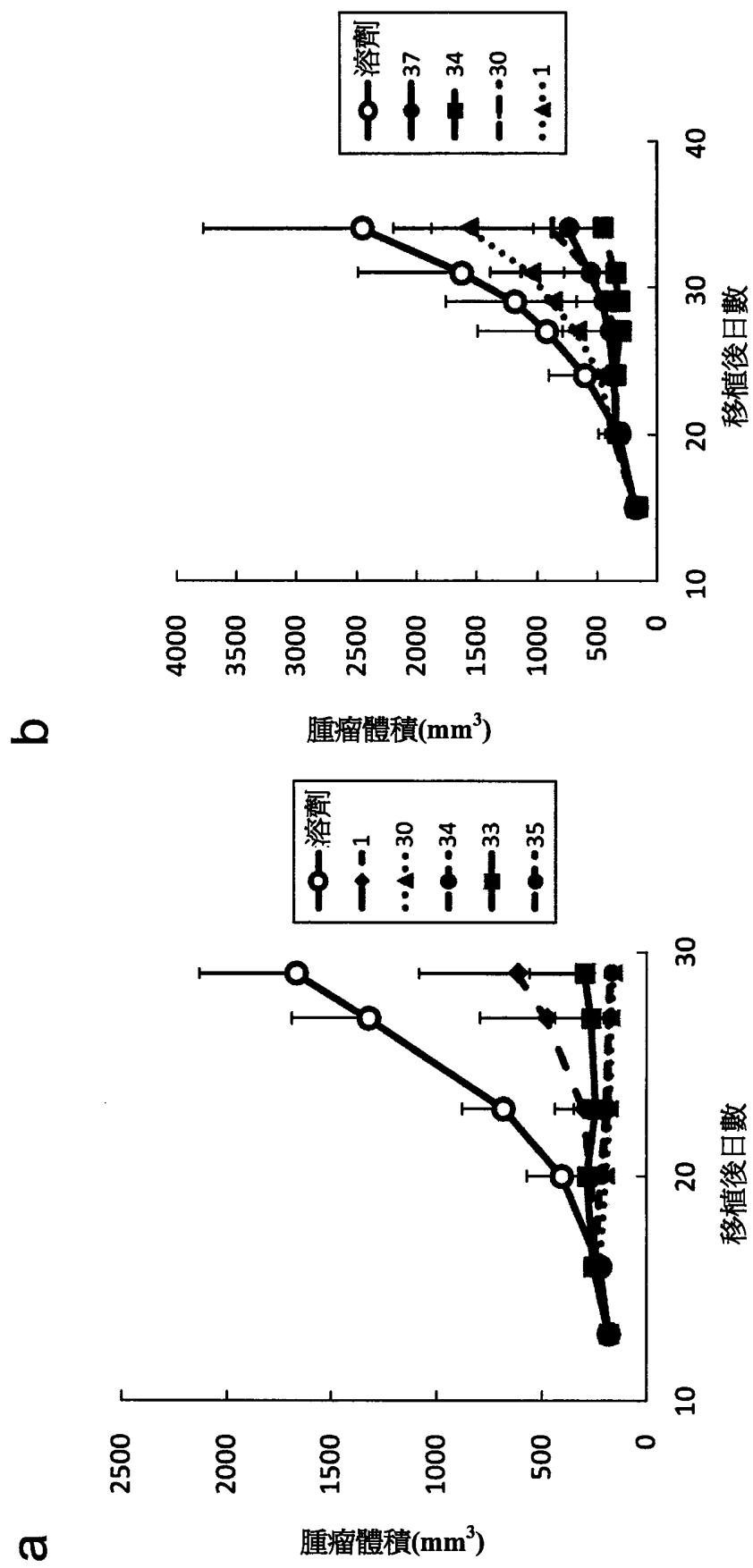
第 8 圖



第 9 圖



第 10 圖



第 11 圖

Kabat CDR H3																																											
Chothia CDR H3																																											
Contact CDR H3																																											
抗體名	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	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	G	V	-	-	-	-	-	-	-	-	-	-	-	D	A	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	G	V	-	-	-	-	-	-	-	-	-	-	D	A	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	G	V	-	-	-	-	-	-	-	-	-	-	D	A	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	G	V	-	-	-	-	-	-	-	-	-	-	D	A	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	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	G	V	-	-	-	-	-	-	-	-	-	-	D	A	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	
H0810	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	
GCH085	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
H0810	L	V	T	V	S	S
GCH054	L	V	T	V	S	S
GCH085	L	V	T	V	S	S
GCH094	L	V	T	V	S	S

【代表圖】

【本案指定代表圖】：無。

【本代表圖之符號簡單說明】：無。

【本案若有化學式時，請揭示最能顯示發明特徵的化學式】：
無。

申請專利範圍

1. 一種雙專一性抗體，係如以下(h1)~(h6)中任一者所記載：

(h1) 對於 Glypican3 有結合活性，並具有由具序列編號 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、及對於 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 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；

(h2) 對於 Glypican3 有結合活性，並具有由具序列編號 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、及對於 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 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；

(h3) 對於 Glypican3 有結合活性，並具有由具序列編號 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、及對於 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 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；

(h4) 對於 Glypican3 有結合活性，並具有由具序列編號 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、及對於 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 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；

(h5) 對於 Glypican3 有結合活性，並具有由具序列編號 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、及對於 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 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；

(h6) 對於 Glypican3 有結合活性，並具有由具序列編號 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、及對於 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 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。

2. 如申請專利範圍第 1 項之雙專一性抗體，更包含具有序列編號 63 之胺基酸序列之共通 L 鏈不變區。
3. 一種醫藥組合物，包含如申請專利範圍第 1 或 2 項之雙專一性抗體、及藥學上可容許之擔體。

4. 一種雙專一性抗體，其中具有對於 Glypican3 之結合活性之抗體可變區、具有對於 T 細胞受體複合體之結合活性之抗體可變區，及共通 L 鏈可變區係包括選自下列(a1)~(a5)中之任一 H 鏈 CDR1、CDR2 及 CDR3、以及 L 鏈 CDR1、CDR2 及 CDR3 之組合之抗體可變區，且該雙專一性抗體係包括 Fc 區，其中該 Fc 區係下列(b1)之胺基酸序列之組合，(a1) 具有對於 Glypican3 之結合活性之抗體可變區所含之 H 鏈 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，具有 T 細胞受體複合體結合活性之抗體可變區所含之 H 鏈 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，

(a2) 具有對於 Glypican3 之結合活性之抗體可變區所含之 H 鏈 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，具有 T 細胞受體複合體結合活性之抗體可變區所含之 H 鏈 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，

(a3) 具有對於 Glypican3 之結合活性之抗體可變區所含之 H 鏈 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，具有 T 細胞受體複合體結合活性之抗體可變區所含之 H 鏈 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，

(a4) 具有對於 Glypican3 之結合活性之抗體可變區所含之 H 鏈 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，具有 T 細胞受體複合體結合活性之抗體可變區所含之 H 鏈 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，

(a5) 具有對於 Glypican3 之結合活性之抗體可變區所含之 H 鏈 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，具有 T 細胞受體複合體結合活性之抗體可變區所含之 H 鏈 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，

(b1) 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。

5. 一種核酸，編碼為如申請專利範圍第 4 項之雙專一性抗體。
6. 一種載體，已導入如申請專利範圍第 5 項之核酸。
7. 一種細胞，包含如申請專利範圍第 6 項之載體。
8. 一種方法，係藉由培養如申請專利範圍第 7 項之細胞，以製造如申請專利範圍第 4 項之雙專一性抗體。
9. 一種醫藥組合物，包含如申請專利範圍第 4 項之雙專一性抗體、及藥學上可容許之擔體。