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(54)名稱

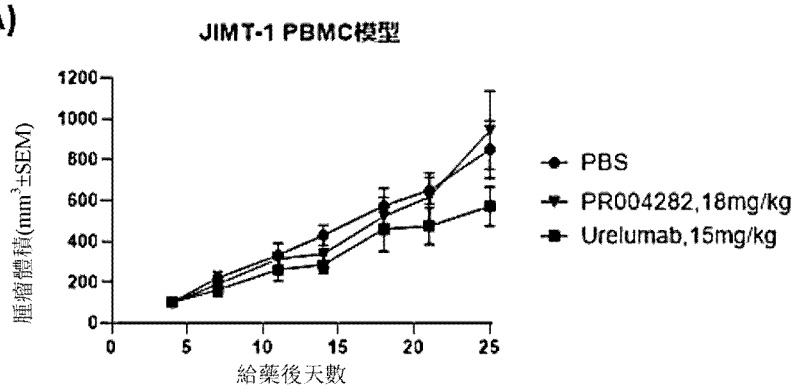
一種雙特異性抗體及其用途

(57)摘要

本發明揭示了一種雙特異性抗體及其用途。所述的雙特異性抗體包含標靶 B7-H4 的抗原結合結構域和標靶 4-1BB 的抗原結合結構域。本發明的雙特異性抗體具有一個或兩個或三個與 4-1BB 結合的位址，同時具有全新的全人 B7-H4 抗體；所述雙特異性抗體透過標靶 B7-H4 特異性結合腫瘤細胞，降低 4-1BB 活化引起的毒性；另外，本發明所述雙特異性抗體帶有人 Fc 片段，保留了 Fc 與 FcRn 的結合作用，具有較長的半衰期。

指定代表圖：

28-(A)


JIMT-1 PBMC模型
腫瘤體積(mm3±SEM)
給藥後天數
PBS
PR004282,18mg/kg
Urelumab,15mg/kg

28-(B)

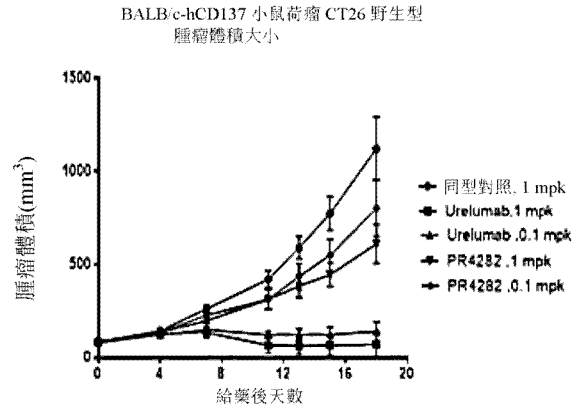

BALB/c-hCD137 小鼠荷瘤 CT26 野生型
腫瘤體積大小
腫瘤體積(mm3)
給藥後天數
同型對照, 1 mpk
Urelumab,1 mpk
Urelumab ,0.1 mpk
PR4282 ,1 mpk
PR4282 ,0.1 mpk

圖 28

公告本

I815136

【發明摘要】

【中文發明名稱】 一種雙特異性抗體及其用途

【中文】

本發明揭示了一種雙特異性抗體及其用途。所述的雙特異性抗體包含標靶B7-H4的抗原結合結構域和標靶4-1BB的抗原結合結構域。本發明的雙特異性抗體具有一個或兩個或三個與4-1BB結合的位址，同時具有全新的全人B7-H4抗體；所述雙特異性抗體透過標靶B7-H4特異性結合腫瘤細胞，降低4-1BB活化引起的毒性；另外，本發明所述雙特異性抗體帶有人Fc片段，保留了Fc與FcRn的結合作用，具有較長的半衰期。

【指定代表圖】 圖28A

【發明說明書】

【中文發明名稱】　一種雙特異性抗體及其用途

【技術領域】

【0001】　本申請要求申請日為2020/6/30的中國專利申請202010618149.1的優先權。本申請引用上述中國專利申請的全文。

【0002】　本發明涉及生物製藥領域，尤其涉及一種雙特異性抗體，特別是標靶B7-H4和4-1BB的雙特異性抗體及其用途。

【先前技術】

【0003】　B7-H4 (VTCN1, B7h.5, B7S1, B7x)是一種隸屬於B7/CD28超家族的跨膜蛋白。B7-H4蛋白表現於活化的T細胞和B細胞、單核細胞和樹突狀細胞，有可能負調控T細胞的免疫反應。

【0004】　儘管B7-H4 mRNA表現廣泛，B7-H4蛋白在大多數正常組織中無表現。但是，B7-H4過度表現於乳腺癌、卵巢癌、子宮內膜癌的腫瘤細胞表面。乳腺癌是全球範圍第二大的惡性腫瘤，且發病率逐漸上升。女性癌症患者中乳腺癌患者約占四分之一。美國乳腺癌患者2019年新增病例32萬，總人數約380萬，中國乳腺癌患者每年新增病例約30萬，預估2021年患者人數達250萬。卵巢癌、子宮內膜癌為女性生殖系統常見的惡性腫瘤。在中國，每年約5萬女性確診為卵巢癌，約2萬死於卵巢癌，卵巢癌的死亡率占婦科惡性腫

瘤之首。子宮內膜癌每年近20萬的新發病例，在導致死亡的婦科惡性腫瘤中排三位。

【0005】 B7-H4還過度表現於非小細胞肺癌和腎癌。肺癌為最常見的癌症之一，其中，非小細胞肺癌占肺癌的近80%。無論在全球還是在中國，肺癌的發病率和致死率都居首位。2018年全球肺癌新增病例約200萬，死亡人數176萬；中國每年新增病例約78萬，死亡人數約63萬。腎癌發病率較低，中國腎癌年發病患者約7萬。

【0006】 B7-H4作為這些腫瘤的一個新興標的，近年來受到關注。B7-H4抗體可以透過多種機制作用於腫瘤細胞，但是B7-H4抗體的研發方向主要集中在單株抗體和ADC上，目前尚無雙特異性抗體療法。

【0007】 4-1BB (TNFRSF9，CD137)是一種隸屬於TNF受體超家族的跨膜蛋白。4-1BB是在多種細胞上表現的共刺激分子，為免疫活性的多功能調節劑。其誘導表現於活化的T細胞、NK細胞和單核細胞、樹突狀細胞、巨噬細胞、腫瘤相關血管內皮細胞等。其配體為4-1BBL，主要表現在專職APC細胞(如單核巨噬細胞、DC細胞、B細胞)、活化的T細胞及一些腫瘤細胞上。抗4-1BB促效性抗體可抑制腫瘤，但是4-1BB抗體的研發方向主要集中在單株抗體以及同時標靶PD-L1和4-1BB的抗體。目前，尚無處於臨床開發階段的標靶B7-H4和4-1BB的雙特異性抗體。

【0008】 百時美施貴寶(BMS)公司的urelumab(BMS-663513)為抗4-1BB抗體的全人源IgG4抗體，是最早進入臨床試驗的抗4-1BB抗體。Urelumab最初的臨床結果發表於2008年，儘管有在部分患者上觀察到令人鼓舞的療效，但數據顯示Urelumab具有肝毒性，且與標的和劑量有關。嚴重的是，臨床試驗中有兩位患者因肝毒性死亡，導致Urelumab作為單藥的臨床試驗被終止。而標靶PD-L1和4-1BB的雙特異性抗體目前還在臨床一期階段，且在腫瘤細胞上PD-L1的表現與B7-H4的表現重疊很少。因此，急需研發更加安全有效的同時標靶人的B7-H4和4-1BB、並能結合食蟹猴的B7-H4和4-1BB的雙特異性抗體。

【發明內容】

【0009】 本發明所要解決的技術問題是為克服現有技術中缺乏安全有效的同時標靶人的B7-H4和4-1BB、並能結合食蟹猴的B7-H4和4-1BB的雙特異性抗體的缺陷，提供一種雙特異性抗體，特別是標靶B7-H4和4-1BB的雙特異性抗體及其應用。

【0010】 為解決上述技術問題，本發明提供以下技術方案。

【0011】 本發明的第一方面提供一種雙特異性抗體，其包括標靶B7-H4的抗原結合結構域和標靶4-1BB的抗原結合結構域。

【0012】 較佳地，所述的標靶B7-H4的抗原結合結構域含有序列如SEQ ID NO: 16所示的HCDR1、序列如SEQ ID NO: 46所示

的HCDR2以及序列如SEQ ID NO: 84所示的HCDR3；序列如SEQ ID NO: 23所示的HCDR1、序列如SEQ ID NO: 59所示的HCDR2以及序列如SEQ ID NO: 98所示的HCDR3；或者，序列如SEQ ID NO: 16所示的HCDR1、序列如SEQ ID NO: 60所示的HCDR2以及序列如SEQ ID NO: 84所示的HCDR3；優選包含序列如SEQ ID NO: 142所示、如SEQ ID NO: 159所示或者如SEQ ID NO: 160所示的VH；更優選包含序列如SEQ ID NO: 174所示、如SEQ ID NO: 191所示或者如SEQ ID NO: 192所示的重鏈；

更佳地，所述的標靶B7-H4的抗原結合結構域還含有LCDR1、LCDR2和LCDR3，所述的LCDR1的胺基酸序列如SEQ ID NO. 112或者113所示，所述的LCDR2的胺基酸序列如SEQ ID NO. 118所示，所述的LCDR3的胺基酸序列如SEQ ID NO. 131~133中任一個所示；

進一步更佳地，所述的標靶B7-H4的抗原結合結構域還含有序列如SEQ ID NO: 112所示的LCDR1、序列如SEQ ID NO: 118所示的LCDR2以及序列如SEQ ID NO: 131所示的LCDR3；序列如SEQ ID NO: 113所示的LCDR1、序列如SEQ ID NO: 118所示的LCDR2以及序列如SEQ ID NO: 132所示的LCDR3；或者序列如SEQ ID NO: 112所示的LCDR1、序列如SEQ ID NO: 118所示的LCDR2以及序列如SEQ ID NO: 133所示的LCDR3；優選還含有

序列如SEQ ID NO: 166~169任一個所示的VL；更優選還含有序列如SEQ ID NO: 198~201任一個所示的輕鏈。

【0013】 在如上所述的雙特異性抗體中：

所述的標靶B7-H4的抗原結合結構域較佳地含有序列如SEQ ID NO: 16所示的HCDR1、序列如SEQ ID NO: 46所示的HCDR2以及序列如SEQ ID NO: 84所示的HCDR3，序列如SEQ ID NO: 112所示的LCDR1、序列如SEQ ID NO: 118所示的LCDR2以及序列如SEQ ID NO: 131所示的LCDR3；序列如SEQ ID NO: 23所示的HCDR1、序列如SEQ ID NO: 59所示的HCDR2以及序列如SEQ ID NO: 98所示的HCDR3，序列如SEQ ID NO: 113所示的LCDR1、序列如SEQ ID NO: 118所示的LCDR2以及序列如SEQ ID NO: 132所示的LCDR3；或者，序列如SEQ ID NO: 16所示的HCDR1、序列如SEQ ID NO: 60所示的HCDR2以及序列如SEQ ID NO: 84所示的HCDR3，序列如SEQ ID NO: 112所示的LCDR1、序列如SEQ ID NO: 118所示的LCDR2以及序列如SEQ ID NO: 133所示的LCDR3。

【0014】 更佳地，所述的標靶B7-H4的抗原結合結構域含有序列如SEQ ID NO: 142所示的VH和序列如SEQ ID NO: 166所示的VL；序列如SEQ ID NO: 159所示的VH和序列如SEQ ID NO: 167所示的VL；序列如SEQ ID NO: 160所示的VH和序列如SEQ ID

NO: 168所示的VL；或者序列如SEQ ID NO: 159所示的VH和序列如SEQ ID NO: 169所示的VL。

【0015】 進一步更佳地，所述標靶B7-H4的抗原結合結構域含有序列如SEQ ID NO: 174所示的重鏈和序列如SEQ ID NO: 198所示的輕鏈；序列如SEQ ID NO: 191所示的重鏈和序列如SEQ ID NO: 199所示的輕鏈；序列如SEQ ID NO: 192所示的重鏈和序列如SEQ ID NO: 200所示的輕鏈；或者，序列如SEQ ID NO: 191所示的重鏈和序列如SEQ ID NO: 201所示的輕鏈。

【0016】 關於所述標靶B7-H4的抗原結合結構域，其形式優選單個VH、串聯VH、ScFv、Fab或者IgG的形式。其中，所述的串聯VH較佳地為2個以上VH串聯，如2個、3個或者4個。當為IgG形式時，其含有的恆定區較佳地來自含有突變L234A、L235A和P329G的人IgG1或者含有突變L234A和L235A的人IgG1。

【0017】 關於如上所述的標靶4-1BB的抗原結合結構域，其含有HCDR1、HCDR2和HCDR3，所述HCDR1、HCDR2和HCDR3優選如下所述：

所述的HCDR1的序列如SEQ ID NO: 19或其變體1、或者SEQ ID NO: 14所示，所述的HCDR2的序列如SEQ ID NO: 49或其變體2、SEQ ID NO: 51或者SEQ ID NO: 43所示，所述的HCDR3

的序列如SEQ ID NO: 86或其變體、SEQ ID NO: 96、SEQ ID NO: 89或者SEQ ID NO: 81所示；其中：

所述的變體1的突變包括T3I、S6N/R以及Y7F中的一個或多個；較佳地，所述變體1的序列優選如序列表中SEQ ID NO: 17~18以及SEQ ID NO: 20~22中任一個所示；

所述變體2的突變包括S1N/D、G2S/A、S3D/G、G5D/F/S/V以及S6T/N/D中的一個或多個；所述變體2的序列優選如序列表中SEQ ID NO: 47~48、SEQ ID NO: 50、SEQ ID NO: 52~58以及SEQ ID NO: 61中的任一個所示；

所述的變體3的突變包括G2R/D/A/K、S3A/T、S4G/N/A/T/H、E5T/V/M/G、T6A、D7G/S、H9Y/S、Y10H、Y11F、N12G/D以及V13I/M/T中的一個或多個；所述變體3的胺基酸序列優選如序列表中SEQ ID NO: 85、SEQ ID NO: 87~88以及SEQ ID NO: 90~95中的任一個所示。

【0018】 在具體實施方案中，所述的標靶4-1BB的抗原結合結構域含有：序列分別如SEQ ID NO: 17、47和85所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、48和86所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、49和87所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 19、50和88所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 20、51和89所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、52和90所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、49和90所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 21、53和91所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 21、54和92所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 19、55和93所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、49和86所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 19、49和94所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 22、56和86所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、57和95所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如 SEQ ID NO: 19、58和96所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、61和95所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 14、43和81所示的HCDR1、HCDR2和HCDR3；

較佳地，所述的標靶4-1BB的抗原結合結構域含有一個或者多個序列如SEQ ID NO: 143~157、139、284或者161所示的重鏈可變區。

【0019】 更佳地，所述的標靶4-1BB的抗原結合結構域包含序列如SEQ ID NO: 175~189、193、285或者171所示的重鏈。

【0020】 進一步更佳地，所述的標靶4-1BB的抗原結合結構域還包含序列分別如SEQ ID NO: 109、118和128所示的LCDR1、LCDR2和LCDR3；較佳地，包含序列如SEQ ID NO: 163所示的輕鏈可變區；更佳地，包含序列如SEQ ID NO: 195所示的輕鏈。

【0021】 本發明中如上所述的標靶4-1BB的抗原結合結構域可為本領域中的常規形式，例如：單個VH或者串聯VH的形式、HCAb的形式或者ScFv的形式；所述的串聯VH較佳地為2個以上VH串聯，如2個、3個或者4個。

【0022】 在本發明一具體實施方案中，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 109、118和128所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 14、43和81所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO:113、118和132所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 23、59和98所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 109、118和128所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 14、43和81所示的HCDR1、HCDR2和HCDR3；

所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分

別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 17、47和85所示的HCDR1、HCDR2和HCDR3；

所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、48和86所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、49和87所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 19、50和88所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3

和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 20、51和89所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、52和90所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 21、53和91所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 21、54和92所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3

和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 19、55和93所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、49和86所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 19、49和94所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 22、56和86所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3

和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、57和95所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和133所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、60和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 17、47和85所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和133所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、60和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、48和86所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和133所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、60和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、49和86所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和133所示的LCDR1、LCDR2和LCDR3

和序列分別如SEQ ID NO: 16、60和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 19、49和94所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和133所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、60和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、61和95所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 113、118和132所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 23、59和98所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、48和86所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 113、118和132所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 23、59和98所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 19、58和96所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 113、118和132所示的LCDR1、LCDR2和LCDR3

和序列分別如SEQ ID NO: 23、59和98所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、57和95所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 113、118和132所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 23、59和98所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、49和90所示的HCDR1、HCDR2和HCDR3。

【0023】 關於本發明所述的雙特異性抗體，在本發明的具體實施方案中：

所述標靶B7-H4的抗原結構域為IgG的形式，所述標靶4-1BB的抗原結合結構域為單個VH的形式；

或者，所述標靶B7-H4的抗原結構域為IgG的形式，所述標靶4-1BB的抗原結合結構域為ScFv的形式；

或者，所述標靶B7-H4的抗原結構域為IgG的形式，所述標靶4-1BB的抗原結合結構域為2個或者3個VH串聯的形式；

或者，所述標靶B7-H4的抗原結構域為Fab的形式，所述標靶4-1BB的抗原結合結構域為HCAb的形式或者為HCAb的形式和VH的形式(HCAb-VH形式)；

或者，所述標靶B7-H4的抗原結構域為Fab的形式，所述標靶4-1BB的抗原結合結構域為VH的形式，所述VH的形式優選單個VH、2個或者3個VH串聯的形式。

【0024】 更具體地：

所述的雙特異性抗體為如下形式：

(1) IgG的C端連接有ScFv，所述ScFv的VH連接於所述C端；較佳地，該形式的雙特異性抗體的多肽鏈1如式：VL_{B7-H4}-CL所示，多肽鏈2如式：VH_{B7-H4}-CH1-樞紐-CH2-CH3-連接子-VH_{4-1BB}-連接子-VL_{4-1BB}所示；

(2) IgG的C端連接有VH或者串聯VH；較佳地，該形式的雙特異性抗體的多肽鏈1如式：VL_{B7-H4}-CL所示，多肽鏈2如式：VH_{B7-H4}-CH1-樞紐-CH2-CH3-連接子-$(VH_{4-1BB})_n$-所示；

(3) HCAb的N端連接有Fab；較佳地，該形式的雙特異性抗體的多肽鏈1如式：VH_{B7-H4}-CH1所示，多肽鏈2如式：VL_{B7-H4}-CL-連接子-VH_{4-1BB}-連接子-CH2-CH3所示；

(4) HCAb的N端連接有Fab，所述Fab的C端連接有VH；較佳地，該形式的雙特異性抗體的多肽鏈1如式：VH_{B7-H4}-CH1所示，多肽鏈2如式：VL_{B7-H4}-CL-連接子-VH_{4-1BB}-連接子-CH2-CH3-VH_{4-1BB}所示；

或者，(5) Fc的2個CH2的N端分別連接有Fab，以及VH或者串聯VH；較佳地，該形式的雙特異性抗體含三條多肽鏈：

多肽鏈1如式：VL_{B7-H4}-CL所示；

多肽鏈2如式：VH_{B7-H4}-CH1-樞紐-CH2-CH3所示；

多肽鏈3如式：VH_{4-1BB}-連接子-CH2-CH3或者$(VH_{4-1BB})_n$-連接子-CH2-CH3所示；

其中，連接不同結構域的所述連接子序列相同或者不同。

【0025】 其中：所述IgG或者HCAb的Fc含有突變，優選含有如下突變之一：

1)為IgG1時，根據EU編號的L234A和L235A，可選地還含有P329G、YTE或者DHS；其中，YTE指的是M252Y/S254T/T256E，DHS指309位L突變為D，311位Q突變為H，434位N突變為S。

2)為IgG1時，根據EU編號的第233~235位的缺失；

3)為IgG1時，根據EU編號的L234A和G237A；

4)為IgG4時，根據EU編號的S228P和FALA；FALA指234位F突變位A，235位L突變為A；

5)為IgG1時，根據EU編號的N297A。

【0026】 如上所述的樞紐和所述的連接子可為本領域常規，較佳地：所述的連接子選自由SEQ ID NO: 241~261、282以及288~289構成的群組；其中：

形式(1)的連接子優選含有如SEQ ID NO: 245所示的序列；

形式(2)的連接子優選含有如SEQ ID NO: 243、245~247以及SEQ ID NO: 288~289任一所示的序列；

形式(3)的連接子優選含有如SEQ ID NO: 250所示的序列；

形式(4)的連接子優選含有如SEQ ID NO: 282所示的序列；

形式(5)的連接子優選含有如SEQ ID NO: 245所示的序列。

【0027】 在本發明一較佳實施例中，所述多肽鏈1的胺基酸序列如SEQ ID NO: 198所示，且所述多肽鏈2的胺基酸序列如SEQ ID NO: 202~215中任一個所示；

或者，所述多肽鏈1的胺基酸序列如SEQ ID NO: 201所示，且所述多肽鏈2的胺基酸序列如SEQ ID NO: 217、230、238、240、226、262或者239所示；

或者，所述多肽鏈1的胺基酸序列如SEQ ID NO: 200所示，且所述多肽鏈2的胺基酸序列如SEQ ID NO: 218~225、235~237、263~268、274~281、286以及287中任一個所示；

或者，所述多肽鏈1的胺基酸序列如SEQ ID NO: 201所示，所述多肽鏈2的胺基酸序列如SEQ ID NO: 227所示，且所述多肽鏈3的胺基酸序列如SEQ ID NO: 228、229、231或者232所示；

或者，所述多肽鏈1的胺基酸序列如SEQ ID NO: 233所示，且所述多肽鏈2的胺基酸序列如SEQ ID NO: 234、269~273中的任一個所示。

【0028】 本發明的第二方面提供一種分離的核酸，其編碼如上第一方面所述的雙特異性抗體。

【0029】 本發明的第三方面提供一種包含如第二方面所述的分離的核酸的表現載體。

【0030】 本發明的第四方面提供一種宿主細胞，其包含如第三方面所述的表現載體；優選地，所述宿主細胞為原核細胞或真核細胞。

【0031】 本發明的第五方面提供一種雙特異性抗體的製備方法，其包含培養如第四方面所述的宿主細胞，從培養物中獲得所述雙特異性抗體。

【0032】 本發明的第六方面提供一種藥物組成物，其包含如本發明第一方面所述的雙特異性抗體。

【0033】 本發明的第七方面提供如第一方面所述的雙特異性抗體、第六方面所述的藥物組成物在製備防治(預防和/或治療)4-1BB和/或B7-H4相關的疾病的藥物中的應用。

【0034】 其中所述的疾病優選癌症，所述的癌症優選乳腺癌、卵巢癌、子宮內膜癌、腎癌、黑色素瘤、肺癌、胃癌、肝癌、食道癌、子宮頸癌、頭頸部腫瘤、膽管癌、膽囊癌、膀胱癌、肉瘤或者結直腸癌。較佳地，所述的癌症優選乳腺癌、卵巢癌、子宮內膜癌、腎癌或膽管癌。更佳地，所述的癌症優選乳腺癌。

【0035】 本發明的第八方面提供一種嵌合抗原受體，其包含第一方面所述的雙特異性抗體。

【0036】 本發明的第九方面提供一種抗體藥物偶聯物，其包含細胞毒性劑，以及如第一方面所述的雙特異性抗體；優選地，所述細胞毒性劑為MMAF或MMAE。

【0037】 本發明的第十方面提供一種套組，其包括第一方面所述的雙特異性抗體、第八方面所述的嵌合抗原受體、第九方面所述的抗體藥物偶聯物和/或第六方面所述的藥物組成物；

優選地，所述套組還包括(i)施用抗體或其抗原結合片段或抗體藥物偶聯物或藥物組成物的裝置；和/或(ii)使用說明。

【0038】 本發明的第十一方面提供一種套裝藥盒，其包含藥盒A和藥盒B，其中：

所述藥盒A含有第一方面所述的雙特異性抗體、第八方面所述的嵌合抗原受體、第九方面所述的抗體藥物偶聯物和/或第六方面所述的藥物組成物；

所述藥盒B含有其他抗腫瘤抗體或者包含所述其他抗腫瘤抗體的藥物組成物，和/或由激素製劑、標靶小分子製劑、蛋白酶體抑制劑、成像劑、診斷劑、化療劑、溶瘤藥物、細胞毒性劑、細胞激素、共刺激分子的活化劑、抑制性分子的抑制劑以及疫苗組成的群組中的一種或多種。

【0039】 本發明的第十二方面涉及一種診斷、治療和/或預防4-1BB和/或B7-H4媒介的疾病或病症的方法，所述方法包括向有需要的患者施用治療有效量的如第一方面所述的雙特異性抗體、第八方面所述的嵌合抗原受體、第九方面所述的抗體藥物偶聯物和/或第六方面所述的藥物組成物，或者使用第十一方面所述的套裝藥盒治療有需要的患者。

【0040】 其中，所述的疾病或病症較佳地為腫瘤，優選乳腺癌、卵巢癌、子宮內膜癌、腎癌、黑色素瘤、肺癌、胃癌、肝癌、食道癌、子宮頸癌、頭頸部腫瘤、膽管癌、膽囊癌、膀胱癌、肉瘤或者結直腸癌；較佳地，所述的癌症優選乳腺癌、卵巢癌、子宮內膜癌、腎癌或膽管癌；更佳地，所述的癌症優選乳腺癌。

【0041】 本發明的第十三方面涉及一種免疫檢測或者測定4-1BB或者B7-H4的方法，其包括使用第一方面所述的雙特異性抗體、第八方面所述的嵌合抗原受體、第九方面所述的抗體藥物偶聯物和/或第六方面所述的藥物組成物檢測樣品；優選地，所述檢測為非診斷和/或治療目的的。

【0042】 本發明的第十四方面涉及一種聯合療法，其包括分別向有需要的患者施用第一方面所述的雙特異性抗體、第八方面所述的嵌合抗原受體、第九方面所述的抗體藥物偶聯物和/或第六方面所述的藥物組成物，和第二治療劑；所述第二治療劑較佳地包含其他抗腫瘤抗體或者包含所述其他抗腫瘤抗體的藥物組成物，和/或由激素製劑、標靶小分子製劑、蛋白酶體抑制劑、成像劑、診斷劑、化療劑、溶瘤藥物、細胞毒性劑、細胞激素、共刺激分子的活化劑、抑制性分子的抑制劑以及疫苗組成的群組中的一種或多種。

【0043】 需知：本發明中關於“變體1”、“變體2”和“變體3”中的數字沒有特殊含義，僅為區分相同術語。

【0044】 本發明的B7-H4×4-1BB雙特異性抗體是一種特有的B7-H4×4-1BB雙特異性抗體，具有一個或兩個或三個與4-1BB結合的位址；雙特異性抗體的兩個蛋白功能區均具有良好的結合食蟹猴的活性。

【0045】 本發明的積極進步效果在於：

1、本發明的4-1BB抗體是一種全新的僅含“重鏈”的全人抗體，具有與人4-1BB和食蟹猴4-1BB結合的活性。該4-1BB重鏈抗體的大小只有傳統IgG抗體的一半，由於不含輕鏈的這一特點，使得該抗體可以用於雙特異性抗體，並解決了輕鏈錯配和異源二聚化的問題。

2、本發明的B7-H4抗體是一種全新的全人抗體，具有與人B7-H4和食蟹猴B7-H4結合的活性。

3、本發明的雙特異性抗體具有一個或兩個或三個與4-1BB結合的位址，最適化了4-1BB端的活性。

4、本發明透過標靶B7-H4特異性結合腫瘤細胞，降低4-1BB活化引起的毒性。

5、本發明是一種帶有人Fc片段的雙特異性抗體結構，保留了Fc與FcRn的結合作用，從而具有較長的半衰期。

【圖式簡單說明】

【0046】

圖1中(A)為FACS檢測B7-H4單抗在高度表現B7-H4的SK-BR-3細胞株上的體外結合；(B)為FACS檢測B7-H4單抗在高度表現食蟹猴B7-H4的CHO-K1-食蟹猴B7-H4細胞株上的體外結合；(C)為FACS檢測B7-H4單抗在高度表現鼠B7-H4的CHO-K1-鼠B7-H4細胞株上的體外結合。

圖2-(A)-(I)為FACS檢測4-1BB單抗在高度表現人4-1BB的CHO-K1-人4-1BB細胞株上的體外結合。

圖3-(A)-(H)為FACS檢測4-1BB單抗在高度表現食蟹猴4-1BB的CHO-K1-食蟹猴4-1BB細胞株上的體外結合。

圖4-(A)-(E)為4-1BB單抗活化4-1BB途徑並誘導活化T細胞的功能。

圖5-(A)-(I)為B7-H4×4-1BB雙特異性分子的結構示意圖。

圖6-(A)-(L)為FACS檢測B7-H4×4-1BB雙特異性抗體在過度表現人4-1BB的CHO-K1細胞株上的體外結合。

圖7-(A)-(C)為FACS檢測B7-H4×4-1BB雙特異性抗體在過度表現食蟹猴4-1BB的CHO-K1細胞株上的體外結合。

圖8-(A)-(K)為FACS檢測B7-H4×4-1BB雙特異性抗體在高度表現B7-H4的SK-BR-3細胞株上的體外結合。

圖9-(A)-(E)為B7-H4×4-1BB雙特異性抗體在B7-H4高度表現細胞株SK-BR-3存在時的T細胞活化實驗以及細胞激素IFN-γ的釋放。

圖10-(A)-(N)為B7-H4×4-1BB雙特異性抗體在B7-H4高度表現細胞株SK-BR-3存在時的T細胞活化實驗以及細胞激素IL-2的釋放。

圖11-(A)-(B)為B7-H4×4-1BB雙特異性抗體對T細胞的活化不依賴FcγR的存在。

圖12-(A)-(B)為FACS檢測腫瘤細胞表面的B7-H4表現量。

圖13-(A)-(H)為B7-H4×4-1BB雙抗對T細胞活化特異性依賴B7-H4的表現。

圖14-(A)-(H)為B7-H4×4-1BB雙抗PR003334和PR003335及PR004282的血清穩定性。

圖15-(A)-(C)為B7-H4×4-1BB雙抗PR004282與人、猴及小鼠的4-1BB的體外結合。

圖16-(A)-(C)為B7-H4×4-1BB雙抗PR004282與人、猴及小鼠的B7H4的體外結合。

圖17為B7-H4×4-1BB雙抗PR004282與SK-BR-3及CHO-K1/4-1BB的體外同時結合。

圖18-(A)-(B)為B7-H4×4-1BB雙抗PR004282與體外活化的人、猴Pan T細胞的體外結合。

圖19-(A)-(B)為B7-H4×4-1BB雙抗PR004282與B7家族成員或TNFR家族其他成員的交叉反應結果。

圖20-(A)-(C)為B7-H4×4-1BB雙抗PR004282的ADCC效應結果。

圖21-(A)-(C)為B7-H4×4-1BB雙特異性抗體PR004282的非特異性細胞激素的釋放檢測結果。

圖22-(A)-(F)為B7-H4×4-1BB雙特異性抗體PR003334和PR003335及PR004282在野生型小鼠的藥代動力學數據。

圖23為B7-H4×4-1BB雙特異性抗體PR004282在正常猴體內的藥代動力學數據(單劑量)。

圖24-(A)-(B)為B7-H4×4-1BB雙特異性抗體PR003334在BALB/c-hCD137/CT26-B7-H4小鼠模型中的抗腫瘤藥效。

圖25-(A)-(B)為B7-H4×4-1BB 雙特異性抗體PR003338在MDA-MB-468 異種移植小鼠模型中的抗腫瘤藥效。

圖26-(A)-(B)為B7-H4×4-1BB雙特異性抗體PR004282在OVCAR3異種移植小鼠模型中的抗腫瘤藥效。

圖27-(A)-(I)為B7-H4×4-1BB雙特異性抗體PR004282在BALB/c-hCD137/CT26-B7-H4小鼠模型中的抗腫瘤藥效和記憶性免疫效應結果。

圖28-(A)-(B)為B7-H4×4-1BB雙特異性抗體PR004282的抗腫瘤藥效的特異性結果。

【實施方式】

具體實施方式

【0047】 下面透過實施例的方式進一步說明本發明，但並不因此將本發明限制在所述的實施例範圍之中。下列實施例中未註明具體條件的實驗方法，按照常規方法和條件，或按照商品說明書選擇。

【0048】 在本申請中，術語“抗體”通常是指包含結合抗原的部分的蛋白質，以及任選地允許結合抗原的部分採用促進抗體與抗原結合的構象的支架或骨架部分。可典型地包含抗體輕鏈可變區(VL)、抗體重鏈可變區(VH)或上述兩者。例如本申請中的“重鏈抗體”不含VL區，僅含VH區。VH或VL區可進一步被區分為稱為互補決定區(CDR)的高度變異區，它們散佈在稱為框架區(FR)的更保守的區域中。每個VH或VL可由三個CDR和四個FR區構成，它們從胺基端至羧基端可按以下順序排列：FR1、CDR1、FR2、CDR2、FR3、CDR3和FR4。重鏈和輕鏈的可變區含有與抗原相互作用的結合結構域。抗體的實例包括但不限於全長抗體、重鏈抗體(HCAb)、抗原結合片段(Fab，Fab’、$F(ab)_2$、Fv片段、$F(ab')_2$、scFv、di-scFv和/或dAb)、免疫綴合物、多特異性抗體(例如雙特異性抗體)、抗體片段、抗體衍生物、抗體類似物或融合蛋白等，只要它們顯示出所需的抗原結合活性即可。

【0049】 在本申請中，術語“可變”通常是指這樣的事實，即抗體的可變結構域的序列的某些部分變化強烈，它形成各種特定抗體對其特定抗原的結合和特異性。然而，變異性並非均勻地分佈在抗

體的整個可變區中。它集中在輕鏈和重鏈可變區中的三個區段，稱為CDR或高度變異區(HVR)，FR為可變域中更高度保守的部分。天然重鏈和輕鏈的可變結構域各自包含四個FR區，大部分採用β-摺疊構型，透過三個CDRs連接，形成環連接，並且在一些情況下形成β-摺疊結構的一部分。每條鏈中的CDRs透過FR區緊密靠近在一起，並與來自另一條鏈的CDR一起形成抗體的抗原結合位址，恆定區不直接參與抗體與抗原的結合，但是它們表現出不同的效應功能，例如參與抗體的依賴於抗體的細胞毒性。

【0050】 在本申請中，術語“全人源抗體”通常是指將人類編碼抗體的基因全部轉移至基因工程改造的抗體基因缺失動物中，使動物表現的抗體。抗體所有部分(包括抗體的可變區和恆定區)均由人類來源的基因所編碼。全人源抗體可以大大減少異源抗體對人體造成的免疫副反應。本領域獲得全人源抗體的方法可以有噬菌體展示技術、基因轉殖小鼠技術等。

【0051】 在本申請中，術語“核酸”是指DNA分子和RNA分子。其可以是單鏈或雙鏈的，但優選是雙鏈DNA。當將核酸與另一個核酸序列置於功能關係中時，核酸是“有效連接的”。例如，如果啟動子或增強子影響編碼序列的轉錄，那麼啟動子或增強子有效地連接至所述編碼序列。

【0052】 在本申請中，術語“特異性結合”通常是指抗體透過其抗原結合域與表位結合，並且該結合需要抗原結合域和表位之間的一些互補性。根據該定義，當抗體相比於其將結合隨機的，不相關的表位而言更容易透過其抗原結合域與表位結合時，抗體被稱為“特異性結合”該抗原。

【0053】 在本申請中，術語“Fab”通常指常規抗體(例如IgG)中與抗原結合的部分，包括抗體的重鏈可變區VH、輕鏈可變區VL和重鏈恆定區結構域CH1以及輕鏈恆定區CL。在常規抗體中，VH的C端與CH1的N端聯結形成重鏈Fd片段，VL的C端與CL的N端聯結形成輕鏈，CH1的C端又進一步與重鏈的樞紐區和其他恆定區結構域聯結形成重鏈。在一些實施例中，“Fab”也指Fab的變體結構。例如，在某些實施例中，VH的C端與CL的N端聯結形成一個多肽鏈，VL的C端與CH1的N端聯結形成另一個多肽鏈，形成Fab(cross VH/VL)的結構；在某些實施例中，Fab的CH1不與樞紐區聯結，而是CL的C端與重鏈的樞紐區聯結，形成Fab(cross Fd/LC)的結構。

【0054】 在本申請中，術語“VH”通常指抗體的重鏈可變區VH結構域，即可以是人或者其他動物的常規抗體(H2L2結構)的重鏈可變區VH，也可以是駱駝科等動物的重鏈抗體(HCAb結構)的重鏈可變區VHH，還可以是利用Harbour HCAb基因轉殖小鼠產生的全人源重鏈抗體(HCAb結構)的重鏈可變區VH。

【0055】 在本領域中，可以透過多種方法來定義抗體的CDR，例如基於序列可變性的Kabat定義規則(參見，Kabat等人，免疫學的蛋白質序列，第五版，美國國立衛生研究院，貝塞斯達，馬里蘭州(1991))和基於結構環區域位置的Chothia定義規則(參見，A1-Lazikani等人，J Mol Biol 273:927-48,1997)。本申請還可使用包含Kabat定義和Chothia定義的Combined定義規則確定可變結構域序列和全長抗體序列中的胺基酸殘基(表1)。在本發明中，根據Chothia定義確定各序列。

表1. 本申請抗體可用的CDR定義方法(可參見

http://bioinf.org.uk/abs/)

CDR區	Kabat定義	Chothia定義	Combined定義
LCDR1	L24--L34	L24--L34	L24--L34
LCDR2	L50--L56	L50--L56	L50--L56
LCDR3	L89--L97	L89--L97	L89--L97
HCDR1	H31--H35	H26--H32	H26--H35
HCDR2	H50--H65	H52--H56	H50--H65
HCDR3	H95--H102	H95--H102	H95--H102

【0056】 其中，Laa-Lbb可以指從抗體輕鏈的N端開始，第aa位(Chothia編碼規則)至第bb位(Chothia編碼規則)的胺基酸序列；Haa-Hbb可以指從抗體重鏈的N端開始，第aa位(Chothia編碼規則)至第bb位(Chothia編碼規則)的胺基酸序列。例如，L24-L34

可以指從抗體輕鏈N端開始，按照Chothia編碼規則的從第24位至第34位的胺基酸序列；H26-H32可以指從抗體重鏈N端開始，按照Chothia編碼規則的從第26位至第32位的胺基酸序列。本發明使用Chothia編碼規則來定義抗體的CDR。

【0057】 抗體Fc結構域媒介的效應子功能如ADCC和CDC也有非常重要的生物學功能，不同的IgG亞型有著不同的ADCC或CDC功能，例如IgG1和IgG3有較強的ADCC和CDC作用，而IgG2和IgG4的作用相對較弱。另外，透過胺基酸突變或者修飾來改變Fc與Fc受體的結合能力也可以調節Fc原有的效應子功能。例如，IgG1中的“LALA”雙突變體(L234A/L235A)能夠顯著降低與FcγRIIIA(CD16A)的親和力，進而降低ADCC作用。另外，P329G突變能夠顯著降低與多種Fcγ受體的結合(參見，Schlothauer T, Herter S, Koller CF, Grau-Richards S, Steinhart V, Spick C, Kubbies M, Klein C, Umaña P, Mössner E. Novel human IgG1 and IgG4 Fc-engineered antibodies with completely abolished immune effector functions. Protein EngDes Sel. 2016 Oct;29(10):457-466. doi: 10.1093/protein/gzw040. Epub 2016 Aug 29. PubMed PMID: 27578889)。在申請中，為了減少B7-H4×4-1BB雙特異性抗體與Fcγ受體的結合，這些抗體的Fc引入了“LALA”雙突變體(L234A/L235A)或者“LALAPG”三突變體(L234A/L235A/P329G)。

實施例1. 抗體的序列分析、表現純化、和理化性質特徵分析

1.1 抗體的序列分析和最適化

【0058】 抗體的重鏈可變結構域序列來源於染色體上重鏈基因群的胚系基因V、D、J基因片段的基因重排和體細胞超突變等事件；輕鏈可變結構域序列來源於輕鏈基因群的胚系基因V、J基因片段的基因重排和體細胞超突變等事件。基因重排和體細胞超突變是增加抗體多樣性的主要因素。來源於相同胚系V基因片段的抗體也可能產生不同的序列，但總體上相似性較高。利用一些演算法，例如IMGT/DomainGapAlign (http://imgt.org/3Dstructure-DB/cgi/DomainGapAlign.cgi)或者NCBI/IgBLAST (https://www.ncbi.nlm.nih.gov/igblast/)可以從抗體的可變結構域序列推測出其發生基因重排時可能的胚系基因片段。

【0059】 蛋白質或多肽胺基酸鏈在細胞中轉譯合成後有時會引入化學修飾，稱為轉譯後修飾(PTM)。對於抗體而言，一些PTM的位址是非常保守的，例如，在人的IgG1抗體的恆定結構域的第297位(EU編號)的保守的胺基酸天冬醯胺Asn通常會發生醣基化修飾形成糖鏈，而該醣鏈結構對於抗體結構和相關的效應功能是至關重要的。但是，如果在抗體的可變結構域尤其是抗原結合區域(如CDR)中存在PTM，那麼這些PTM的存在有可能會對抗原的結合有較大的

影響，也可能對抗體的物理化學性質帶來變化。例如，醣基化、脫醯胺、異構化、氧化等都可能增加抗體分子的不穩定性或異質性，從而增加抗體開發的難度和風險。因而避免一些潛在的PTM對於治療性抗體的開發是非常重要的。隨著經驗的積累，人們發現一些PTM是和胺基酸序列的組成尤其是相鄰胺基酸組成的“模式”是高度相關的，這樣使得可以從蛋白質的一級胺基酸序列預測出潛在的PTM。例如，N-x-S/T (第一位是天冬醯胺，第二位是非脯胺酸以外的任意胺基酸，第三位是絲胺酸或者蘇胺酸)的序列模式預測出N-連接醣基化位址。引起PTM的胺基酸序列模式有可能來源於胚系基因序列，例如人胚系基因片段IGHV3-33天然地在FR3區域存在醣基化模式NST；也可能來源於體細胞超突變。例如，NGS或NLT可能是醣基化位址，NS可能是脫醯胺位址，DG可能引起天冬胺酸的異構化。

【0060】 可以透過胺基酸突變來破壞PTM的胺基酸序列模式，從而降低或者去除特定PTM的形成。根據抗體序列和PTM序列模式的不同，有不同的突變設計方法。一種方法是將“熱點”胺基酸(如NS模式中的N或S)替換成物理化學性質相似的胺基酸(如把N突變為Q)。如果PTM序列模式來源於體細胞超突變，而並不存在於胚系基因序列中，那麼另一種方法可以是把該序列模式替換成對應的胚系基因序列。實際操作中，對同一個PTM序列模式可能採用多種突變設計方法。

1.2 抗體的表現和純化

【0061】 本實施例介紹了利用哺乳動物宿主細胞(例如，人胚腎細胞HEK293或中國倉鼠卵巢細胞CHO及其衍生細胞)、暫態轉染表現和親和捕捉分離等技術來製備抗體的一般方法。本方法適用於含有Fc區的目標抗體；目標抗體可以由一條或多條蛋白質多肽鏈組成；可以來源於一個或多個表現質體。

【0062】 將抗體多肽鏈的胺基酸序列透過密碼子最適化方法轉換成核苷酸序列；合成編碼的核苷酸序列並選殖到與宿主細胞相容的表現載體上。將編碼抗體多肽鏈的質體按照特定比例同時轉染哺乳動物宿主細胞，利用常規的重組蛋白表現和純化技術，可以得到具有正確摺疊和多肽鏈組裝的重組抗體。具體地，將FreeStyle™ 293-F細胞(Thermo, #R79007)在FreeStyle™ F17 Expression Medium培養基(Thermo, #A1383504)中擴大培養。暫態轉染開始之前，調節細胞濃度至6 - 8 $\times 10^5$細胞/ml，於37℃ 8% CO_2震盪培養箱中培養24小時，細胞濃度在1.2 $\times 10^6$細胞/ml。準備30 ml培養的細胞。將編碼抗體多肽鏈的質體按照一定比例混合共計30 μg質體(質體與細胞的比例為1 μg : 1 ml)溶解於1.5 ml Opti-MEM減血清培養基 (Thermo, #31985088)，並用0.22 μm濾膜過濾除菌。再取1.5 ml Opti-MEM溶入1 mg/ml PEI (Polysciences, #23966-2) 120 μl，靜置5分鐘。把PEI緩慢加入質體中，室溫培育

10分鐘，邊搖晃培養瓶邊緩慢滴入質體PEI混合溶液，於37℃ 8% CO_2震盪培養箱中培養5天。5天後觀測細胞存活率。收集培養物，以3300g轉速離心10分鐘後取上清；然後將上清高速離心去除雜質。用PBS pH7.4緩衝液平衡含有MabSelect™ (GE Healthcare, #71-5020-91)的重力管柱(Bio-Rad, #7311550)，2-5倍管柱體積沖洗。將上清樣品過管柱；用5-10倍管柱體積的PBS緩衝液沖洗管柱，再用pH3.5的0.1M甘胺酸洗提目標蛋白，隨後用pH 8.0的Tris-HCl調節至中性，最後用超濾管(Millipore, #UFC901024)濃縮換液至PBS緩衝液或者含有其他成分的緩衝液，得到純化的重組抗體溶液。最後用NanoDrop (Thermo, NanoDrop™ One)測定濃度，分裝、存儲備用。

1.3 利用SEC-HPLC分析蛋白純度和聚合體

【0063】 本實施例使用分析型分子粒徑篩析層析法(SEC)來分析蛋白樣品的純度和聚合體形式。將分析型層析管柱TSKgel G3000SWxl (Tosoh Bioscience, #08541, 5 μm, 7.8 mm × 30 cm)連接到高壓液相層析儀HPLC (Agilent Technologies, Agilent 1260 Infinity II)，用PBS緩衝液室溫下平衡至少1小時。適量蛋白樣品(至少10 μg)用0.22 μm濾膜過濾後注射入系統，並設定HPLC程式：用PBS緩衝液將樣品以1.0 ml/分鐘的流速流過層析

管柱，最長時間為25分鐘。HPLC將生成分析報告，報告出樣品內不同分子尺寸組份的滯留時間。

1.4 利用DSF測定蛋白分子的熱穩定性

【0064】 差示掃描螢光法(Differential Scanning Fluorimetry, DSF)是一種常用的高通量的測定蛋白質熱穩定性的方法。它使用即時螢光定量PCR儀器透過監測與去摺疊的蛋白分子結合的染料的螢光強度的變化，來反應蛋白質的變性的過程，從而反應出蛋白分子的熱穩定性。本實施例利用DSF方法來測定蛋白分子熱變性溫度(Tm)。10 μg蛋白加入96-孔PCR盤(Thermo, #AB-0700/W)，接著加入2 μl 100×稀釋的染料SYPROTM (Invitrogen, #2008138)，然後加入緩衝液使得終體積為40 μl每孔。將PCR盤密封，放置於即時螢光定量PCR儀器(Bio-Rad CFX96 PCR System)，先於25℃培育5分鐘，然後以0.2℃/0.2分鐘的梯度逐漸從25℃升溫至95℃，在測試結束時將溫度降至25℃。使用FRET掃描模式並使用Bio-Rad CFX Maestro軟體進行數據分析並計算出樣品的Tm。

實施例2. 抗B7-H4全人源抗體的獲得

【0065】 Harbour H2L2小鼠(Harbour Antibodies BV)是一種攜帶人免疫球蛋白免疫庫的基因轉殖小鼠，其產生的抗體具有完整的人的抗體可變結構域和大鼠恆定結構域。

【0066】 用可溶的重組人B7-H4-ECD-mFc融合蛋白(Sino Biological, #10738-H05H)對Harbour H2L2小鼠進行多輪免疫，或者用過度表現人B7-H4的CHO-K1細胞轉染mCD40L後，與免疫佐劑混合成免疫原試劑後對Harbour H2L2小鼠進行多輪免疫。

【0067】 當檢測小鼠血清中B7-H4特異的抗體效價達到一定的位準後，將小鼠的脾細胞取出。透過融合瘤融合技術，B細胞選殖技術和噬菌體庫技術進行篩選，對篩選獲得的單株抗體進行進一步的鑑定，根據其對人B7-H4的結合能力、食蟹猴B7-H4的結合能力等參數，選出2個選殖株80C8-2E9和1025_B-1H11。利用常規的定序手段獲得編碼抗體分子可變結構域的核苷酸序列以及對應的胺基酸序列。然後對候選抗體分子進行序列分析和最適化，得到數個變體序列。將抗體的VL和VH序列與相應的人的κ輕鏈恆定區和IgG1重鏈恆定區序列進行融合表現，得到重組全人源抗體分子。

【0068】 本實例中抗B7-H4的重組全人源IgG抗體列於表2。

表2. 抗B7-H4 H2L2抗體的序列編號(CDR都是按照Chothia規則定義)

抗體編號	備註	輕鏈	重鏈	VL	VH	LC DR1	LC DR2	LC DR3	HC DR1	HC DR2	HC DR3
PR001476	80C8-2E9選殖株	198	174	166	142	112	118	131	16	46	84
PR002037	1025_B-1H11選殖株	199	191	167	159	113	118	132	23	59	98
PR002408	PR001476	200	192	168	160	112	118	133	16	60	84

	變體										
PR002410	PR002037 變體	201	191	169	159	113	118	132	23	59	98

【0069】 另外根據專利查詢，(來自專利WO2016040724A1)，又稱1D11.v1.9varC2，設計了對照抗體1，在後續實驗中作為對照：

表3. B7-H4對照抗體的序列編號(SEQ ID NO:)

抗體名稱	抗體編號	輕鏈	重鏈	VL	VH	LCDR1	LCDR2	LCDR3	HCDR1	HCDR2	HCDR3
陽性對照1	PR000157	194	170	162	138	108	117	127	13	42	80

2.1 FACS檢測抗人B7-H4 H2L2單抗在細胞位準的結合能力

【0070】 本實施例是為了研究抗人B7-H4的H2L2單抗體外結合人/食蟹猴/小鼠B7-H4的活性。採用過度表現食蟹猴B7-H4的CHO-K1細胞株(CHO-K1/cyno B7-H4，和鉑自製)、過度表現小鼠B7-H4的CHO-K1細胞株(CHO-K1/m B7-H4，和鉑自製)和高度表現人B7-H4的細胞株SK-BR-3 (ATCC® HTB-30)進行細胞位準上的抗體結合實驗。簡言之，消化酶處理CHO-K1/cyno B7-H4細胞、CHO-K1/m B7-H4細胞或SK-BR-3細胞，並用含2% BSA的PBS重新懸浮。將細胞密度分別調整為1×10^6細胞/mL。以100 μL細胞/孔接種於96孔V底盤(Corning, #3894)，隨後加入100 μL/孔，2倍於終濃度的3倍濃度梯度稀釋的待測抗體。將細胞放置於4℃，避光培育2小時。之後，加入100 μL/孔預冷含2%BSA的PBS

漂洗細胞兩次，於500 g、4℃下離心5分鐘，棄上清。再加入100 μL/孔螢光二抗(Alexa Fluor 488-conjugated AffiniPure Goat Anti-Human IgG, Fcγ Fragment Specific, Jackson, #109-545-06, 1:500稀釋)，4℃，避光培育1小時。用100 μL /孔預冷含2% BSA的PBS洗滌細胞兩次，於500 g、4℃下離心5分鐘，棄上清。最後，200 μL/孔預冷含2% BSA的PBS重新懸浮細胞，使用ACEA Novocyte3000流式細胞儀讀取螢光發光訊號值。

【0071】 如圖1-(A)所示：B7-H4抗體在高度表現B7-H4的SK-BR-3細胞株上的體外結合；PR001476和PR002408與SK-BR-3細胞株結合活性優於對照抗體1。

【0072】 如圖1-(B)所示：B7-H4抗體在高度表現食蟹猴B7-H4的CHO-K1-食蟹猴B7-H4細胞株上的體外結合；PR001476和PR002408與CHO-K1-食蟹猴B7-H4細胞株結合活性優於對照抗體1。

【0073】 如圖1-(C)所示：B7-H4抗體在高度表現鼠B7-H4的CHO-K1-鼠B7-H4細胞株上的體外結合； PR002410與CHO-K1-鼠B7-H4細胞株結合活性與對照抗體1沒有顯著差異。

實施例3. 4-1BB全人源抗體的獲得

3.1 抗4-1BB全人源HCAb抗體的獲得

【0074】 Harbour HCAb小鼠(Harbour Antibodies BV，WO2010/109165A2)是一種攜帶人免疫球蛋白免疫庫的基因轉殖小鼠，能夠產生僅有重鏈的抗體，該抗體的大小只有傳統IgG抗體的一半。其產生的抗體僅具有人的抗體重鏈可變結構域和小鼠Fc恆定結構域。

【0075】 用可溶的重組人4-1BB-Fc融合蛋白(睿智化學)或者過度表現了人4-1BB的NIH-3T3細胞(睿智化學)對Harbour HCAb小鼠進行多輪免疫。當檢測小鼠血清中4-1BB特異的抗體效價達到一定的位準後，將小鼠的脾細胞取出分離B細胞，用BD FACS AriaII Cell Sorter分選CD138陽性的漿細胞和人4-1BB抗原陽性的B細胞群。用常規的分子生物學手段從漿細胞中擴增人VH基因，並將擴增的人VH基因片段建構到編碼人IgG1抗體重鏈Fc區域序列的哺乳動物細胞表現質體pCAG載體中。質體轉染哺乳動物宿主細胞 (如人胚腎細胞HEK293)進行表現，得到全人源HCAb抗體上清。用FACS測試HCAb抗體上清與高度表現人4-1BB的CHO-K1細胞CHO-K1/hu4-1BB的結合，鑑定出陽性HCAb抗體。對這些HCAb抗體進行進一步的鑑定，根據其對人4-1BB的結合能力、食蟹猴4-1BB的結合能力、T細胞活化能力等參數，優選出數個候選HCAb抗體分子。然後對候選HCAb抗體分子進行序列分析和最適化，得到數個變體序列。將HCAb抗體的VH序列和人的IgG1重鏈

Fc序列進行融合表現，得到全人源重組HCAb抗體分子。其中，PR004469是PR001838的PTM的變體，PR007381為PR004469的胚系化變體，具體突變位址見表5。

表4. 抗4-1BB的重組全人源HCAb抗體的序列表

抗體編號	重鏈	VH	HCDR1	HCDR2	HCDR3
PR001758	175	143	17	47	85
PR001760	176	144	18	48	86
PR001763	177	145	18	49	87
PR001764	178	146	19	50	88
PR001767	179	147	20	51	89
PR001768	180	148	18	52	90
PR001771	181	149	18	49	90
PR001774	182	150	21	53	91
PR001780	183	151	21	54	92
PR001781	184	152	19	55	93
PR001830	185	153	18	49	86
PR001833	186	154	19	49	94
PR001836	187	155	22	56	86
PR001838	188	156	18	57	95
PR001840	189	157	19	58	96
PR001842	190	158	19	49	97
PR004469	193	161	18	61	95
PR007381	285	284	18	61	95

表5. 4-1BB HCAb序列的突變位址設計

初始抗體	變體	可變區突變	重組抗體亞型
PR001838	PR004469	G53A	人 IgG1
PR001838	PR007381	F37V, P40A, E42G, T43K, K46E, G53A	人 IgG1

3.2 抗4-1BB全人源H2L2抗體的獲得

【0076】 Harbour H2L2小鼠(Harbour Antibodies BV)是一種攜帶人免疫球蛋白免疫庫的基因轉殖小鼠，其產生的抗體具有完整的人的抗體可變結構域和大鼠恆定結構域。用可溶的重組人4-1BB-Fc融合蛋白對Harbour H2L2小鼠進行多輪免疫。當檢測小鼠血清中4-1BB特異的抗體效價達到一定的位準後，將小鼠的脾細胞取出並與骨髓瘤細胞株融合得到融合瘤細胞；對融合瘤細胞經過多輪篩選和選殖之後，分離出表現抗-4-1BB單株抗體分子的融合瘤細胞株。利用常規的融合瘤定序手段獲得編碼抗體分子可變結構域的核苷酸序列以及對應的胺基酸序列。然後對候選抗體分子進行序列分析和最適化，得到數個變體序列。將抗體的VL和VH序列與相應的人的κ輕鏈恆定區和IgG1重鏈恆定區序列進行融合表現，得到重組全人源抗體分子。

表6. 抗4-1BB的重組全人源IgG抗體序列表

抗體編號	輕鏈	重鏈	VL	VH	LCDR1	LCDR2	LCDR3	HCDR1	HCDR2	HCDR3
PR000448	195	171	163	139	109	118	128	14	43	81

【0077】 另外根據專利查詢，設計了對照抗體，在後續實驗中作為對照：

表7. 對照抗體序列表

抗體名稱	抗體編號	輕鏈	重鏈	VL	VH	LCDR1	LCDR2	LCDR3	HCDR1	HCDR2	HCDR3
urelumab	PR000628	197	173	165	141	111	120	130	14	45	83

類似物											
utomilumab 類似物	PR000483	196	172	164	140	110	119	129	15	44	82

3.3 FACS檢測抗人4-1BB單抗在細胞位準的結合能力

【0078】 本實施例是為了研究抗人4-1BB的HCAb和H2L2單抗體外結合人和食蟹猴4-1BB的活性。採用過度表現人4-1BB的CHO-K1細胞株(CHO-K1-hu 4-1BB,Genescript)、過度表現食蟹猴4-1BB的CHO-K1細胞株(CHO-K1-cyno 4-1BB,Genescript)進行細胞位準上的抗體結合實驗。簡言之，消化酶處理細胞CHO-K1-hu 4-1BB和CHO-K1-cyno 4-1BB細胞，並用DMEM完全培養基重新懸浮，將細胞密度分別調整為1×10^6細胞/mL。以100 μL細胞/孔接種於96孔V底盤(Corning, #: 3894)，隨後加入100 μL/孔，2倍於終濃度的3倍濃度梯度稀釋的待測抗體。將細胞放置於4℃，避光培育1小時。之後，加入100 μL/孔預冷PBS 漂洗細胞兩次，於500 g、4℃下離心5分鐘，棄上清。再加入100 μL/孔螢光二抗(Alexa Fluor 488-conjugated AffiniPure Goat Anti-Human IgG, Fcγ Fragment Specific, Jackson, #:109-545-06, 1:500稀釋)，4℃，避光培育30分鐘。用100 μL/孔預冷PBS洗滌細胞兩次，於500 g、4℃下離心5分鐘，棄上清。最後，200 μL/孔預冷PBS重新懸浮細胞，使用BD FACS CANTOII讀取螢光發光訊號值。

【0079】 圖2-(A)-(I)：4-1BB抗體在高度表現人4-1BB的CHO-K1-人4-1BB細胞株上的體外結合；

【0080】 圖3-(A)-(H)：4-1BB抗體在高度表現食蟹猴4-1BB的CHO-K1-食蟹猴4-1BB細胞株上的體外結合。

【0081】 如圖2-(A)-(I)所示，本發明的抗4-1BB的抗體均能結合人4-1BB，且檢測到的抗體結合能力與抗體濃度成正相關關係遞增。與參照抗體(Urelumab和Utomilumab)相比，這些抗體能以較低的濃度更靈敏地結合人4-1BB，與參照抗體Utomilumab和Urelumab的EC50相當。

【0082】 如圖3-(A)-(H)所示，本發明的抗4-1BB的抗體均能結合猴4-1BB，且檢測到的抗體結合能力與抗體濃度成正相關關係遞增。與參照抗體Tab (Utomilumab)相比，這些抗體能以較低的濃度更靈敏地結合猴4-1BB，與參照抗體Utomilumab的EC50相當或更優。 而參照抗體Urelumab不具有與猴4-1BB交叉結合的活性。

3.4 抗原結合蛋白能在體外活化4-1BB途徑

【0083】 使用10 μg/ml的絲裂黴素(北京中生瑞泰科技，#10107409001)處理過度表現人CD32b的CHO-K1細胞(CHO-K1/CD32b,Genscript,# M00600)，30分鐘37℃。然後用含10% FBS的F-12K培養液，洗滌4次。把處理過的細胞放入96孔盤裡，每孔1.5×10^4個，37℃保溫箱培養過夜。第二天，使用MACS

套組(Miltenyi Biotec,#130-096-535)從人PBMC裡分離人CD3陽性T細胞。首先確定細胞數量，然後根據細胞數量加入相應量的MACS緩衝液和Pan-T細胞生物素抗體，混勻，4℃靜置5分鐘。然後加入相應量微磁珠，4℃靜置10分鐘。透過LS管柱的是CD3陽性的T細胞。將前一天96孔盤的培養液洗掉，加入純化的T細胞，每孔1×10^5個。然後加入相應濃度的4-1BB抗體或者是對照抗體，加入OKT3 (eBiosciences，#16-0037-85)並且使其最終濃度達到0.3μg/ml。37℃保溫箱培養72小時。72小時後，收取上清液，使用ELISA套組(Invitrogen，#88-7316-88)來檢測IFN-γ的含量。在96平底盤裡加入塗覆抗體，4℃過夜。第二天加入ELISA緩衝液，室溫1小時。加入收取的上清液，室溫培養2小時。洗盤2次，加入檢測抗體，室溫1小時。洗盤兩次，加入HRP-鏈黴親和素，室溫培育1小時。然後加入TMB基質，稍後加入ELISA終止液(BBI，#E661006-0200)。酵素標示讀取儀(PerkinElemer，# Enspire)讀取450 nm和570 nm吸光值(OD450-OD570)，計算IFN-γ濃度。

【0084】 結果如圖4-(A)-(E)：4-1BB抗體具有活化4-1BB途徑，並誘導活化T細胞的功能。PR001758，PR001760，PR001764，PR001771，PR001774，PR001780，PR001781，PR001830，PR001833，PR001836，PR001838，PR001840，PR000448活

化作用均比utomilumab更強，表現為IFN-γ的訊號高於utomilumab。

實施例4. B7-H4×4-1BB雙特異性抗體的製備

【0085】 自實施例2所選的抗B7-H4抗體和自實施例3所選的抗4-1BB抗體組合用於製備雙特異性抗體，可以同時結合兩個標的，其中一端可以辨識腫瘤細胞表面特異表現的B7-H4，而另一端可以結合T細胞上的4-1BB分子。當B7-H4×4-1BB雙抗分子結合到腫瘤細胞表面後，可以招募並活化腫瘤細胞附近的T細胞，從而殺死腫瘤細胞。

【0086】 本實施例製備的B7-H4×4-1BB雙特異性抗體包括多種分子結構：

圖5-(A)-(I)是本發明的雙特異性分子的結構示意圖。

4.1 建構IgG-scFv四價對稱結構的雙特異性抗體

【0087】 利用抗B7-H4的H2L2抗體和抗4-1BB的H2L2抗體建構IgG-scFv四價對稱結構的雙特異性抗體。IgG-scFv四價對稱結構(如圖5-(A)所示)的結合蛋白包含兩條多肽鏈：多肽鏈1，也稱短鏈，從胺基末端到羧基末端，其包含VL_A-CL；多肽鏈2，也稱長鏈，從胺基末端到羧基末端，其包含VH_A-CH1-h-CH2-CH3-L1-VH_B-L2-VL_B。h是IgG抗體的樞

紐區或衍生序列。多肽鏈2的連接胜肽L1和連接胜肽L2可以是表8中所列序列。

4.2 建構IgG-VH 四價對稱結構的雙特異性抗體

【0088】 利用抗B7-H4的H2L2抗體和抗4-1BB的HCAb抗體建構IgG-VH四價對稱結構的雙特異性抗體。IgG-VH四價對稱結構(如圖5-(B)所示)的結合蛋白包含兩條多肽鏈：多肽鏈1，也稱短鏈，從胺基末端到羧基末端，其包含VL_A-CL；多肽鏈2，也稱長鏈，從胺基末端到羧基末端，其包含VH_A-CH1-h-CH2-CH3-L-VH_B。h是IgG抗體的樞紐區或衍生序列。在一個實施方案中，多肽鏈2的CH3與VH_B直接融合聯結，即L的長度為0。在另一個實施方案中，多肽鏈2的CH3經由連接胜肽L聯結到VH_B；L可以是表8中所列序列。

4.3 建構IgG-VH-VH六價對稱結構的雙特異性抗體

【0089】 利用抗B7-H4的H2L2抗體和抗4-1BB的HCAb抗體建構IgG-VH-VH六價對稱結構的雙特異性抗體。IgG-VH-VH六價對稱結構(如圖5-(C)所示)的結合蛋白包含兩條多肽鏈：多肽鏈1，也稱短鏈，從胺基末端到羧基末端，其包含VL_A-CL；多肽鏈2，也稱長鏈，從胺基末端到羧基末端，其包含VH_A-CH1-h-CH2-CH3-L1-VH_B-L2-VH_B。h是IgG抗體的樞紐區或衍生序列。在一個實施方案中，多肽鏈2的CH3與VH_B直接

融合聯結，即L的長度為0。在另一個實施方案中，多肽鏈2的連接胜肽L1和L2可以是表8中所列序列。

4.4 建構Fab-HCAb結構的雙特異性抗體分子

【0090】 利用抗B7-H4的H2L2抗體和抗4-1BB的HCAb抗體建構Fab-HCAb對稱結構的雙特異性抗體，包含兩種不同的結構Fab(CL)-VH-Fc（如圖5-(D)所示）Fab(CH)-VH-Fc（如圖5-(E)所示)。Fab(CL)-VH-Fc的結合蛋白包含兩條多肽鏈，多肽鏈1，也稱短鏈，從胺基末端到羧基末端，其包含VH_A-CH1；多肽鏈2，也稱長鏈，從胺基末端到羧基末端，其包含VL_A-CL-L1-VH_B-L2-CH2-CH3。多肽鏈2的連接胜肽L1和L2可以是表8中所列序列。Fab(CH)-VH-Fc的結合蛋白包含兩條多肽鏈，多肽鏈1，也稱短鏈，從胺基末端到羧基末端，其包含VL_A-CL；多肽鏈2，也稱長鏈，從胺基末端到羧基末端，其包含VH_A-CH1-L1-VH_B-L2-CH2-CH3。多肽鏈2的連接胜肽L1和L2可以是表8中所列序列。

4.5 建構Fab-Fc-VH(n)非對稱結構

【0091】 利用抗B7-H4的H2L2抗體和抗4-1BB的HCAb抗體建構Fab-Fc-VH(n)非對稱結構的雙特異性抗體。Fab-Fc-VH(n)非對稱結構(如圖5-(F)(G)(H)所示)的結合蛋白包含三條多肽鏈，多肽鏈1，也稱短鏈，從胺基末端到羧基末端，其包含VL_A-CL；多

肽鏈2，也稱長鏈，從胺基末端到羧基末端，其包含VH_A-CH1-h-CH2-CH3；多肽鏈3，從胺基末端到羧基末端，其包含VH_B-h-CH2-CH3，或者多肽鏈3，從胺基末端到羧基末端，其包含VH_B-L-VH_B-h-CH2-CH3，或者多肽鏈3，從胺基末端到羧基末端，其包含VH_B-L1-VH_B-L2-VH_B-h-CH2-CH3。h是IgG抗體的樞紐區或衍生序列。多肽鏈3的連接胜肽L1和L2可以是表8中所列序列。

【0092】 為了將具有錯配的重鏈(例如抗4-1BB抗體的兩條重鏈或者抗B7-H4的兩條重鏈的錯配)的副產物形成最小化，使用了突變的異源二聚合體Fc區，其攜帶“knob-hole”突變和改造的二硫鍵，如WO2009080251和WO2009080252中所述。

4.6 建構Fab-VH-Fc-VH對稱結構

【0093】 利用抗B7-H4的H2L2抗體和抗4-1BB的HCAb抗體建構Fab-VH-Fc-VH對稱結構的雙特異性抗體。Fab-VH-Fc-VH對稱結構(如圖5-(I)所示)的結合蛋白包含兩條多肽鏈，多肽鏈1，也稱短鏈，從胺基末端到羧基末端，其包含VH_A-CH1；多肽鏈2，也稱長鏈，從胺基末端到羧基末端，其包含VL_A-CL-L1-VH_B-L2-CH2-CH3-L3-VH_B。多肽鏈2的連接胜肽L1、L2和L3可以是表8中所列序列。表11-(B)中的PR007379涉

及到的PR002408(H:gm)與PR002408的CDR相同，可變區VH的FR2有2個突變，分別為T69I，E101G。

表8. 連接胜肽序列表

連接胜肽名字	連接胜肽長度	連接胜肽序列	序列編號 SEQ ID NO:
GS_4	4	GSGS	241
GS_5	5	GGGGS	242
GS_6	6	GGSGGS	243
GS_7	7	GGGGSGS	244
GS_15	15	GGGGSGGGGSGGGGS	245
GS_20	20	GGGGSGGGGSGGGGSGGGGS	246
GS_25	25	GGGGSGGGGSGGGGSGGGGSGGGGS	247
人 IgG1 樞紐	15	EPKSCDKTHTCPPCP	248
人 IgG1 樞紐 (C220S)	15	EPKSSDKTHTCPPCP	249
H1_15	15	EPKSSDKTHTPPPPP	250
G5-LH	15	GGGGGDKTHTCPPCP	251
H1_15-RT	17	EPKSSDKTHTPPPPPRT	252
L-GS_15-RT	18	LGGGGSGGGGSGGGGSRT	253
L-H1_15-RT	18	LEPKSSDKTHTPPPPPRT	254
KL-H1_15-RT	19	KLEPKSSDKTHTPPPPPRT	255
KL-H1_15-AS	19	KLEPKSSDKTHTPPPPPAS	256
RT-GS_5-KL	9	RTGGGGSKL	257
RT-GS_15-KL	19	RTGGGGSGGGGSGGGGSKL	258
RT-GS_25-KL	29	RTGGGGSGGGGSGGGGSGGGGSGGGGSKL	259
EPKSSD	6	EPKSSD	260
AS-GS_15	17	ASGGGGSGGGGSGGGGS	261
H2_13	13	ERKCCVECPPCP	282
GS_2	2	GS	
(G2S)2	6	GGSGGS	288

(G4S)2	10	GGGGSGGGGS	289

【0094】 本發明所得雙抗分子的多肽鏈的胺基酸序列在序列表中如下所示。

表9. 本發明所得雙抗分子序列表

抗體編號	多肽鏈 1	多肽鏈 2	多肽鏈 3
PR002789	198	202	
PR002972	201	217	
PR002790	198	203	
PR002791	198	204	
PR002792	198	205	
PR002793	198	206	
PR002794	198	207	
PR002795	198	208	
PR002798	198	209	
PR002800	198	210	
PR002801	198	211	
PR002802	198	212	
PR002804	198	213	
PR002805	198	214	
PR002806	198	215	
PR002808	198	216	
PR003334	200	218	
PR003335	200	219	
PR003336	200	220	
PR003337	200	221	
PR003338	200	222	
PR004162	201	230	
PR004357	201	238	
PR004359	201	240	
PR004280	200	235	
PR004281	200	236	

PR004282	200	237	
PR003487	200	223	
PR003488	200	224	
PR003489	200	225	
PR004158	201	226	
PR004358	201	239	
PR004160	201	227	228
PR004161	201	227	229
PR004181	201	227	231
PR004182	201	227	232
PR004279	233	234	
PR004995	201	262	
PR005183	200	263	
PR005184	200	264	
PR005185	200	265	
PR005186	200	266	
PR005187	200	267	
PR005188	200	268	
PR005189	233	269	
PR005190	233	270	
PR005827	200	274	
PR005828	200	275	
PR005829	200	276	
PR005830	200	277	
PR005649	233	271	
PR005650	233	272	
PR005651	233	273	
PR005838	200	278	
PR005839	200	279	
PR005866	200	280	
PR007165	200	281	
PR007379	200	286	
PR007380	200	287	

【0095】 B7-H4×4-1BB雙特異性抗體為的抗原結構域的CDR序列編號如下表所示，表10中1#序號為結合B7-H4的抗原結構域，2#序號為結合4-1BB的抗原結構域。

表10. 雙抗的抗原結合結構域的CDR序列編號(SEQ ID NO:)

結構編號	抗體編號	抗原結合域序號	LCDR1	LCDR2	LCDR3	HCDR1	HCDR2	HCDR3
A	PR002789	#1	112	118	131	16	46	84
		#2	109	118	128	14	43	81
A	PR002972	#1	113	118	132	23	59	98
		#2	109	118	128	14	43	81
B	PR002790	#1	112	118	131	16	46	84
		#2				17	47	85
B	PR002791	#1	112	118	131	16	46	84
		#2				18	48	86
B	PR002792	#1	112	118	131	16	46	84
		#2				18	49	87
B	PR002793	#1	112	118	131	16	46	84
		#2				19	50	88
B	PR002794	#1	112	118	131	16	46	84
		#2				20	51	89
B	PR002795	#1	112	118	131	16	46	84
		#2				18	52	90
B	PR002798	#1	112	118	131	16	46	84
		#2				21	53	91
B	PR002800	#1	112	118	131	16	46	84
		#2				21	54	92
B	PR002801	#1	112	118	131	16	46	84
		#2				19	55	93
B	PR002802	#1	112	118	131	16	46	84
		#2				18	49	86
B	PR002804	#1	112	118	131	16	46	84
		#2				19	49	94
B	PR002805	#1	112	118	131	16	46	84
		#2				22	56	86
B	PR002806	#1	112	118	131	16	46	84
		#2				18	57	95
B	PR002808	#1	112	118	131	16	46	84
		#2				19	49	97
B	PR003334	#1	112	118	133	16	60	84

		#2				17	47	85
B	PR003335	#1	112	118	133	16	60	84
		#2				18	48	86
B	PR003336	#1	112	118	133	16	60	84
		#2				18	49	86
B	PR003337	#1	112	118	133	16	60	84
		#2				19	49	94
B	PR003338, PR004280, PR004281, PR004282, PR005183, PR005184, PR005185, PR005186, PR005187, PR005188, PR005827, PR005828, PR005829, PR005830, PR005838, PR005839, PR005866	#1	112	118	133	16	60	84
		#2				18	61	95
B	PR004162	#1	113	118	132	23	59	98
		#2				18	48	86
B	PR004357	#1	113	118	132	23	59	98
		#2				19	58	96
B	PR004359	#1	113	118	132	23	59	98
		#2				18	57	95
B	PR004995	#1	113	118	132	23	59	98
		#2				18	61	95
C	PR003487, PR003488, PR003489	#1	112	118	133	16	60	84
		#2				18	48	86
C	PR004158	#1	113	118	132	23	59	98
		#2				18	48	86
C	PR004358	#1	113	118	132	23	59	98
		#2				19	58	96
D	PR004279, PR005189, PR005649	#1	112	118	133	16	60	84
		#2				18	48	86
D	PR005190	#1	112	118	133	16	60	84
		#2				18	61	95
E	PR007165	#1	112	118	133	16	60	84
		#2				18	48	86
G	PR004160	#1	113	118	132	23	59	98
		#2				18	48	86
H	PR004161	#1	113	118	132	23	59	98

		#2				18	48	86
H	PR004181	#1	113	118	132	23	59	98
		#2				18	49	90
H	PR004182	#1	113	118	132	23	59	98
		#2				19	58	96
I	PR005650	#1	112	118	133	16	60	84
		#2				18	48	86
I	PR005651	#1	112	118	133	16	60	84
		#2				18	61	95

【0096】 表11-(A)-(F)是本發明的雙特異性抗體分子結構資訊。

表11-(A):具有IgG-scFv對稱結構的B7-H4 × 4-1BB雙抗分子

雙抗分子	B7-H4 抗體 (IgG)	4-1BB 抗體 (scFv)	scFv 端結構	第一連接胜肽 (Fc 和 scFv 之間)	第二連接胜肽 (VH_B 和 VL_B 之間)	Fc 類型(突變)	第一連接胜肽長度	第二連接胜肽長度
PR002789	PR001476	PR000448	VH-連接胜肽-VL	H1_15-RT	GS_15	人 IgG1 (L234A, L235A, P329G)	17	15
PR002972	PR002410	PR000448	VH-連接胜肽-VL	H1_15-RT	GS_15	人 IgG1 (L234A, L235A, P329G)	17	15

表11-(B):具有IgG-VH四價對稱結構的B7-H4 × 4-1BB雙抗分子

雙抗分子	B7-H4 抗體 (IgG)	4-1BB 抗體 (VH_B)	VH_B 相對 IgG 位置	連接胜肽 (VH_B 和 IgG 之間)	Fc 類型(突變)	連接胜肽長度
PR002790	PR001476	PR001758	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR002791	PR001476	PR001760	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR002792	PR001476	PR001763	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR002793	PR001476	PR001764	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17

PR002794	PR001476	PR001767	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR002795	PR001476	PR001768	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR002798	PR001476	PR001774	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR002800	PR001476	PR001780	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR002801	PR001476	PR001781	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR002802	PR001476	PR001830	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR002804	PR001476	PR001833	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR002805	PR001476	PR001836	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR002806	PR001476	PR001838	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR002808	PR001476	PR001842	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR003334	PR002408	PR001758	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A)	17
PR003335	PR002408	PR001760	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A)	17
PR003336	PR002408	PR001830	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A)	17
PR003337	PR002408	PR001833	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A)	17
PR003338	PR002408	PR004469	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A)	17
PR004162	PR002410	PR001760	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A)	17
PR004357	PR002410	PR001840	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A, P329G)	17
PR004359	PR002410	PR001838	重鏈 C 端	H1_15-RT	人 IgG1 (L234A, L235A)	17
PR004280	PR002408	PR004469	重鏈 C 端	EPKSSD	人 IgG1 (L234A, L235A)	6
PR004281	PR002408	PR004469	重鏈 C 端	無	人 IgG1 (L234A, L235A)	0
PR004282	PR002408	PR004469	重鏈 C 端	GS_6	人 IgG1 (L234A, L235A)	6
PR004995	PR002410	PR004469	重鏈 C 端	無	人 IgG1 (L234A, L235A)	0
PR005183	PR002408	PR004469	重鏈 C 端	無	人 IgG1 (L234A, L235A，P329G)	0
PR005184	PR002408	PR004469	重鏈 C 端	無	人 IgG1	0

					(del233-235)	
PR005185	PR002408	PR004469	重鏈 C 端	無	人 hIgG4(S228P,FALA)	0
PR005186	PR002408	PR004469	重鏈 C 端	無	人 IgG1 (L234A, G237A)	0
PR005187	PR002408	PR004469	重鏈 C 端	無	人 IgG1 (LALA,YTE)	0
PR005188	PR002408	PR004469	重鏈 C 端	無	人 IgG1 (LALA,DHS)	0
PR005827	PR002408	PR004469	重鏈 C 端	(G4S)2	人 IgG1 (L234A, L235A)	10
PR005828	PR002408	PR004469	重鏈 C 端	GS_15	人 IgG1 (L234A, L235A)	15
PR005829	PR002408	PR004469	重鏈 C 端	GS_20	人 IgG1 (L234A, L235A)	20
PR005830	PR002408	PR004469	重鏈 C 端	GS_25	人 IgG1 (L234A, L235A)	25
PR005838	PR002408	PR004469	重鏈 C 端	GS_6	人 IgG1 (L234A, , L235A ,G237A)	6
PR005839	PR002408	PR004469	重鏈 C 端	GS_6	人 IgG1 (L234A, G237A)	6
PR005866	PR002408	PR004469	重鏈 C 端	(G4S)2	人 IgG1 (N297A)	10
PR007379	PR002408 (H:gm)	PR004469 VH	重鏈 C 端	(G2S)2	人 IgG1 (L234A, L235A)	6
PR007380	PR002408 (H:gm)	PR004469 _ VH_gm	重鏈 C 端	(G2S)2	人 IgG1 (L234A, L235A)	6

表11-(C):具有IgG-VH-VH六價對稱結構的B7-H4 x 4-1BB雙抗分子

雙抗分子	B7-H4 抗體 (IgG)	4-1BB 抗體 (VH_B)	VH_B 相對 IgG 位置	第一連接胜肽 (VH_B 和 IgG 之間)	第二連接胜肽 (VH_B 和 VH_B 之間)	Fc 類型(突變)	第一連接胜肽長度	第二連接胜肽長度
PR003487	PR002408	PR001760	重鏈 C 端	H1_15-RT	無	人 IgG1 (L234A, L235A)	17	0
PR003488	PR002408	PR001760	重鏈 C 端	H1_15-RT	GS_5	人 IgG1 (L234A, L235A)	17	5

PR003489	PR002408	PR001760	重鏈 C 端	H1_15-RT	GS_15	人 IgG1 (L234A, L235A)	17	15
PR004158	PR002410	PR001760	重鏈 C 端	H1_15-RT	GS_5	人 IgG1 (L234A, L235A)	17	5
PR004358	PR002410	PR001840	重鏈 C 端	H1_15-RT	GS_5	人 IgG1 (L234A, L235A, P329G)	17	5

表11-(D):具有Fab-HCAb四價對稱結構的B7-H4 x 4-1BB雙抗分子

雙抗分子	B7-H4 抗體 (IgG)	4-1BB 抗體 (VH_B)	第一連接胜肽 (Fab 和 VH_B 之間)	第二連接胜肽 (VH_B 和 CH2 之間)	Fc 類型(突變)	第一連接胜肽長度	第二連接胜肽長度
PR004279	PR002408	PR001760	H1_15	人 IgG1 樞紐 (C220S)	人 IgG1 (L234A, L235A)	15	15
PR005189	PR002408	PR001760	無	人 IgG1 樞紐 (C220S)	人 IgG1 (L234A, L235A)	0	15
PR005190	PR002408	PR004469	H1_15	人 IgG1 樞紐 (C220S)	人 IgG1 (L234A, L235A)	15	15
PR005649	PR002408	PR001760	無	人 IgG1 樞紐 (C220S)	人 IgG1 (L234A, L235A)	0	15
PR007165	PR002408	PR001760	無	人 IgG1 樞紐 (C220S)	人 IgG1 (L234A, L235A)	0	15

表11-(E):具有Fab-Fc-VH(n)非對稱結構的B7-H4 x 4-1BB雙抗分子

雙抗分子	B7-H4 抗體 (IgG)	4-1BB 抗體 (VH_B)	VH_B 重複數 n	第一連接胜肽	第二連接胜肽	Fab 端的 Fc 類型 (突變)	VH_B 端的 Fc 類型(突變)	第一連接胜肽長度	第二連接胜肽長度
PR004160	PR002410	PR001760	2	GS_15	無	人 IgG1 (knob, LALA)	人 IgG1 (hole, LALA)	15	0

PR004161	PR002410	PR001760	3	GS_15	AS-GS_15	人 IgG1 (knob, LALA)	人 IgG1 (hole, LALA)	15	17
PR004181	PR002410	PR001771	3	GS_15	GS_15	人 IgG1 (knob, LALA)	人 IgG1 (hole, LALA)	15	15
PR004182	PR002410	PR001840	3	GS_15	GS_15	人 IgG1 (knob, LALA)	人 IgG1 (hole, LALA)	15	15

表11-(F):具有Fab-VH-Fc-VH結構的B7-H4 x 4-1BB雙抗分子

雙抗分子	B7-H4 抗體 (IgG)	4-1BB 抗體 (VH_B)	第一連接胜肽	第二連接胜肽	Fc 類型(突變)	第一連接胜肽長度	第二連接胜肽長度
PR005650	PR002408	PR001760	無	無	人 IgG1 (L234A, L235A)	0	0
PR005651	PR002408	PR004469	無	無	人 IgG1 (L234A, L235A)	0	0

【0097】 表12-(A)-(F)是本發明的雙特異性抗體的蛋白表現和物理化學性質。

表12-(A):IgG-scFv對稱結構的雙抗分子蛋白的表現和物理化學性質

雙抗分子	表現系統和體積	質體轉染比例 (短鏈：長鏈)	第一步純化後產量 (mg/L)	HPLC-SEC 純度 (%)	DSF Tm1 (°C)
PR002789	HEK293F (30ml)	3:2	23	59	51.4
PR002972	HEK293F (30ml)	3:2		59	50.6

表12-(B):IgG-VH對稱結構的雙抗分子蛋白的表現和物理化學性質

雙抗分子	表現系統和體積	質體轉染比例 (短鏈 ：長鏈)	第一步純化後產量 (mg/L)	HPLC-SEC 純度 (%)
PR002790	Expi293F (10ml)	3:2	74	95
PR002791	Expi293F (10ml)	3:2	60	95
PR002792	Expi293F (10ml)	3:2	52	92
PR002793	Expi293F (10ml)	3:2	49	92
PR002794	Expi293F (10ml)	3:2	47	94
PR002795	Expi293F (10ml)	3:2	69	93
PR002798	Expi293F (10ml)	3:2	67	94
PR002800	Expi293F (10ml)	3:2	73	85
PR002801	Expi293F (10ml)	3:2	57	89
PR002802	Expi293F (10ml)	3:2	33	76
PR002804	Expi293F (10ml)	3:2	26	83
PR002805	Expi293F (10ml)	3:2	3	83
PR002806	Expi293F (10ml)	3:2	20	88
PR002808	Expi293F (10ml)	3:2	16	71
PR003334	Expi-CHOs(200ml)	3:2	38.2	98
PR003335	Expi-CHOs(200ml)	3:2	68.9	99
PR003336	HEK293-F (30ml)	3:2	66.47	91
PR003337	HEK293-F (30ml)	3:2	91.41	93
PR003338	HEK293-F (30ml)	3:2	74.6	98
PR004162	HEK293-F (30ml)	3:2	57	44.81
PR004357	HEK293-F (30ml)	3:2	66	47.53
PR004359	HEK293-F (30ml)	3:2	81	96.82
PR004280	HEK293-F (30ml)	3:2	39.5	98.63
PR004281	HEK293-F (30ml)	3:2	28.5	98.73
PR004282	HEK293-F (30ml)	3:2	34.25	99.09
PR004995	293-6E(40ml)	3:2	42	95.69
PR005183	Expi-CHOs(1000ml)	3:2	89.6	99.916
PR005184	293-6E(40ml)	3:2	7.15	90.77
PR005185	293-6E(40ml)	3:2	7.425	89.1
PR005186	293-6E(40ml)	3:2	10.5	83.89
PR005187	293-6E(40ml)	3:2	8	97.86
PR005188	293-6E(40ml)	3:2	10.15	94.19
PR005827	HEK293-F (100ml)	3:2	35.2	99.526
PR005828	HEK293-F (100ml)	3:2	38.4	99.311
PR005829	HEK293-F (100ml)	3:2	31.8	99.457
PR005830	HEK293-F (100ml)	3:2	27.3	99.680
PR005838	Expi-CHOs(2000ml)	3:2	11.5	98.833
PR005839	Expi-CHOs(2000ml)	3:2	33.2	98.104
PR005866	Expi-CHOs(2000ml)	3:2	5.3	98.241
PR007379	HEK293-F (40ml)	3:2	33.5	98.625
PR007380	HEK293-F (40ml)	3:2	38.0	98.453

表12-(C):IgG-VH-VH六價對稱結構的雙抗分子蛋白的表現和物理化學性質

雙抗分子	表現系統和體積	質體轉染比例 (短鏈 ：長鏈)	第一步純化後產量 (mg/L)	HPLC-SEC 純度 (%)
PR003487	HEK293-F (30ml)	3:2	19	84
PR003488	HEK293-F (30ml)	3:2	17.39	85
PR003489	HEK293-F (30ml)	3:2	16.03	76
PR004158	HEK293-F (30ml)	3:2	31.92	63
PR004358	HEK293-F (30ml)	3:2	18.9	98.72

表12-(D):Fab-HCAb四價對稱結構的雙抗分子蛋白的表現和物理化學性質

雙抗分子	表現系統和體積	質體轉染比例 (短鏈 ：長鏈)	第一步純化後產量 (mg/L)	HPLC-SEC 純度 (%)
PR004279	HEK293-F (30ml)	3:2	11.375	79.18
PR005189	HEK293-F (100ml)	3:2	4	97.59
PR005649	HEK293-F (100ml)	3:2	30.4	91.928
PR007165	HEK293-F (100ml)	3:2	39	94.70

表12-(E):Fab-Fc-VH(n)非對稱結構的雙抗分子蛋白的表現和物理化學性質

雙抗分子	表現系統和體積	質體轉染比例 (短鏈 ：長鏈)	第一步純化後產量 (mg/L)	HPLC-SEC 純度 (%)	DSF Tm1 (°C)
PR004160	HEK293-F (30ml)	1:1:1	29.36	89.41	64.4
PR004161	HEK293-F (30ml)	1:1:1	31.62	85.47	63.0
PR004181	HEK293-F (30ml)	1:1:1	87.25	87.19	64.2
PR004182	HEK293-F (30ml)	1:1:1	24.75	79.14	51

表12-(F):具有Fab-VH-Fc-VH對稱結構的雙抗分子蛋白的表現和物理化學性質

雙抗分子	表現系統和體積	質體轉染比例 (短鏈：長	第一步純化後產量 (mg/L)	HPLC-SEC 純度 (%)

		鏈)		
PR005650	HEK293-F (100ml)	3:2	21.5	97.476
PR005651	HEK293-F (100ml)	3:2	18.2	98.129

實施例5. FACS檢測B7-H4×4-1BB雙特異性抗體在過度表現人和食蟹猴4-1BB的CHO-K1細胞株上的體外結合

【0098】 本實施例為了研究B7-H4×4-1BB雙特異性抗體4-1BB臂體外結合人和食蟹猴4-1BB的活性。採用過度表現人4-1BB的CHO-K1細胞株(CHO-K1/hu 4-1BB, Genscript，#M00538)和過度表現食蟹猴4-1BB的CHO-K1細胞株(CHO-K1/cyno 4-1BB, Genscript，#M00569)進行細胞位準上的抗體結合實驗。簡言之，消化酶處理細胞CHO-K1/hu 4-1BB和CHO-K1/cyno 4-1BB細胞，並用F12K完全培養基重新懸浮，用PBS洗滌一次。用PBS將細胞密度分別調整為1×10^6細胞/ml。以100 μL細胞/孔接種於96孔V底盤(Corning, #3894)，隨後加入100 μL/孔，2倍於終濃度的3倍濃度梯度稀釋的待測抗體。將細胞放置於4℃，避光培育1小時。之後，加入100 μL/孔預冷PBS漂洗細胞兩次，於500 g、4℃下離心5分鐘，棄上清。再加入100 μL/孔螢光二抗(Alexa Fluor 488-conjugated AffiniPure Goat Anti-Human IgG, Fcγ Fragment Specific, Jackson ImmunoResearch, #:109-545-06, 1:500稀釋)或者(Alexa Fluor® 647, Goat Anti-Human IgG, Fcγ fragment specific，Jackson

ImmunoResearch, #: 109-605-098, 1:1000稀釋)，4℃，避光培育30分鐘。用100 μL /孔預冷PBS洗滌細胞兩次，於500 g、4℃下離心5分鐘，棄上清。最後，200 μL/孔預冷PBS重新懸浮細胞，使用BD FACS CANTOII或艾森ACEA NovoCyte系列流式細胞儀讀取螢光發光訊號值。

【0099】 圖6-(A)-(L): B7-H4×4-1BB雙特異性抗體在過度表現人4-1BB的CHO-K1細胞株上的體外結合;

【0100】 圖7-(A)-(C): B7-H4×4-1BB雙特異性抗體在過度表現食蟹猴4-1BB的CHO-K1細胞株上的體外結合;

【0101】 如圖6-(A)-(L)所示，本實例中的B7-H4×4-1BB雙特異性抗體均與過度表現人4-1BB的CHO-K1細胞特異性結合。PR002789，PR002972，PR003334，PR003335, PR003336, PR003337，PR003338，PR004160，PR004161，PR004158，PR004162，PR004357，PR004359，PR004279, PR004280, PR004281, PR004282, PR005829等與人4-1BB的結合強於陽性對照Urelumab。具體表現為，抗體PR003335結合曲線的Span值約為Urelumab的1.5倍，MFI最大值高於Urelumab。

【0102】 如圖7-(A)-(C)所示，本實例中的B7-H4×4-1BB雙特異性抗體均與過度表現猴4-1BB的CHO-K1細胞特異性結合。而參照抗體Urelumab不具有與猴4-1BB交叉結合的活性。

實施例6. FACS檢測B7-H4×4-1BB雙特異性抗體在高度表現B7-H4的SK-BR-3細胞株上的體外結合

【0103】 本實施例為了研究B7-H4×4-1BB雙特異性抗體B7-H4臂的結合人B7-H4的活性。採用高度表現B7-H4的SK-BR-3細胞株進行與人B7-H4細胞位準結合實驗。簡言之，收集SK-BR-3細胞懸浮液，將細胞密度分別調整為2×10^6細胞/mL。以50 μL細胞/孔接種於96孔V底盤(Corning, #: 3894)，隨後加入50 μL/孔，2倍於終濃度的3倍濃度梯度稀釋的待測抗體。將細胞放置於4℃，避光培育2小時。之後，加入100 μL/孔預冷PBS漂洗細胞兩次，於500g、4℃下離心5分鐘，棄上清。再加入100 μL/孔螢光二抗(Alexa Fluor 647-conjugated AffiniPure Goat Anti-Human IgG, Fcγ Fragment Specific, Jackson ImmunoResearch, #:109-605-098, 1:1000稀釋)，4℃，避光培育1小時。用100 μL/孔預冷PBS洗滌細胞兩次，於500 g，4℃下離心5分鐘，棄上清。最後，200 μL/孔預冷FACS重新懸浮細胞，使用ACEA Novocyte3000讀取螢光發光訊號值。

【0104】 圖8-(A)-(K):B7-H4×4-1BB雙特異性抗體在高度表現B7-H4的SK-BR-3細胞株上的體外結合;

【0105】 如圖8-(A)-(K)中所示，本實例中B7-H4×4-1BB雙特異性抗體均與SK-BR-3細胞株上人B7-H4特異性結合，結合曲線EC50大多為0.1-10 nM。

實施例7. B7-H4×4-1BB雙特異性抗體在B7-H4高度表現細胞株SK-BR-3存在時的T細胞活化實驗以及細胞激素的釋放

【0106】 為了研究B7-H4 × 4-1BB雙特異性抗體體外媒介標靶T細胞的活化能力，採用人pan T細胞作為效應細胞，高度表現B7-H4的細胞株SK-BR-3作為媒介交聯的細胞進行體外活化實驗以及細胞激素釋放的檢測。具體的，將96孔平底盤(Corning, #3599)用OKT3塗覆培養盤，將pan T的密度調整為2×10^6細胞/mL，SK-BR-3的密度調整為2×10^5細胞/mL，以兩種細胞懸浮液各50 μL細胞/孔接種於96孔平底盤(Corning, #3599)，隨後加入50 μL/孔，3倍於終濃度的不同梯度稀釋的待測抗體，其中抗體最高終濃度為100 nM或30 nM或20 nM或6 nM，每個抗體共6或3個或2個濃度，最終效應細胞-標的細胞比為10:1，設置兩個重複。同時，在盤內設置同型IgG對照組。96孔盤置於37 ℃二氧化碳培養箱培育2天或3天。培育完成後，取上清液，加入96孔盤(Corning, #3599)，於500 g、4℃下離心5分鐘。培育2天的上清，用於檢測細胞激素IL-2的釋放或者培育3天的上清檢測IFN-gamma的釋放。ELISA檢測方法參照IL-2 (IL-2 Human Uncoated ELISA Kit,

Thermo, #88-7025-88)套組和 IFN gamma (IFN gamma Human Uncoated ELISA Kit, Thermo, #88-7316-88)操作說明。

【0107】 圖9-(A)-(E)：B7-H4×4-1BB雙特異性抗體在B7-H4高度表現細胞株SK-BR-3存在時活化4-1BB途徑，並誘導活化T細胞釋放IFN-γ。

【0108】 圖10-(A)-(N)：B7-H4×4-1BB雙特異性抗體在B7-H4高度表現細胞株SK-BR-3存在時活化4-1BB途徑，並誘導活化T細胞釋放IL-2。

【0109】 如圖9-(A)-(E)和圖10-(A)-(N)所示，在高度表現B7-H4的細胞株SK-BR-3存在時，B7-H4×4-1BB雙特異性抗體能夠媒介的T細胞活化。並且PR002790、PR002791、PR002802、PR002804、PR002806、PR003334、PR003335、PR003336、PR003337、PR003338、PR003487、PR003488、PR003489、PR004158、PR004160、PR004161、PR004162、PR004181、PR004182、PR004279、PR004280、PR004281、PR004282、PR004357、PR004358、PR004359對4-1BB途徑的活化優於或相當於Urelumab。具體表現為產生的細胞激素IFN-γ或IL-2高於Urelumab。

【0110】 不同的連接子長度也會影響雙抗對T細胞的活化，比如PR004281和PR004282表現優於PR003338和Urelumab（圖10-K)。

【0111】 帶有不同抗原表位的B7H4臂會影響雙抗對T細胞的活化，比如PR004281和PR004282表現優於PR004995和Urelumab(圖10-L)。

【0112】 帶有不同的Fc突變位址會影響雙抗對T細胞的活化，如PR005185、PR005186及PR004282優於Urelumab (圖10-M)。

實施例8. B7-H4×4-1BB雙特異性抗體對T細胞的活化不依賴於FcγR細胞

【0113】 為了研究B7-H4×4-1BB雙特異性抗體活性是否依賴於FcγR的表現。採用人pan T細胞作為效應細胞，高度表現FcγRIIb的細胞株CHO-K1/CD32b或高度表現FcγRI的細胞株CHO-K1/CD64作為媒介交聯的細胞進行體外活化實驗以及細胞激素釋放的檢測。具體的，將96孔平底盤(Corning, #3599)用OKT3塗覆培養盤，將pan T的密度調整為2×10^6細胞/mL，FcγR細胞的密度調整為2×10^5細胞/mL，以兩種細胞懸浮液各50 μL細胞/孔接種於96孔平底盤(Corning, #3599)，隨後加入100 μL/孔，2倍於終濃度的不同梯度稀釋的待測抗體，最終效應細胞-標的細胞比為10:1，設置兩個重複。同時，在盤內設置同型IgG對照組。96孔盤

置於37℃二氧化碳培養箱培育2天。培育完成後，取100 μl上清液，加入96孔盤(Corning, #3894)，於500 g、4℃下離心5分鐘，取上清，用於檢測細胞激素IL-2的釋放。ELISA檢測方法參照IL-2 (IL-2 Human Uncoated ELISA Kit, Thermo, #88-7025-88)套組操作說明。

【0114】 圖11-(A)-(B)：B7-H4×4-1BB雙抗對T細胞活化特異性不依賴FcγR的表現。(A)高度表現FcγRIIb的細胞株CHO-K1/CD32b細胞存在時，B7-H4×4-1BB雙特異性抗體PR004282媒介的T細胞活化和同型IgG對照相當。(B)高度表現FcγRI的細胞株CHO-K1/CD64細胞存在時，B7-H4×4-1BB雙特異性抗體PR004282媒介的T細胞活化和同型IgG對照相當。

實施例9. B7-H4×4-1BB雙特異性抗體對T細胞的活化依賴於B7-H4的表現

【0115】 為了研究B7-H4×4-1BB雙特異性抗體活性是否依賴於B7-H4表現。採用人pan T細胞作為效應細胞，高度表現B7-H4的細胞株SK-BR-3和MDA-MB-468細胞以及不表現B7-H4的COV644和JIMT-1及MDA-MB-231細胞作為媒介交聯的細胞進行體外活化實驗以及細胞激素釋放的檢測。具體的，將96孔平底盤(Corning, #3599)用OKT3塗覆培養盤，將pan T的密度調整為2×10^6細胞/mL，腫瘤細胞的密度調整為2×10^5細胞/mL，以兩種細胞

懸浮液各50 μL細胞/孔接種於96孔平底盤(Corning, #3599)，隨後加入50 μL /孔，3倍於終濃度的待測抗體，最終效應細胞-標的細胞比為10：1，設置兩個重複。同時，在盤內設置同型IgG對照組。96孔盤置於37 ℃二氧化碳培養箱培育2天。培育完成後，取100 μl上清液，加入96孔盤(Corning, #3894)，於500 g、4℃下離心5分鐘，取上清，用於檢測細胞激素IL-2的釋放ELISA檢測方法參照IL-2(IL-2 Human Uncoated ELISA Kit, Thermo, #88-7025-88)套組操作說明。

【0116】 圖12：FACS檢測腫瘤細胞表面的B7-H4表現量。圖12-(A)用B7-H4陽性對照抗體1檢測腫瘤細胞表面的B7-H4表現量。圖12-(B)用B7-H4×4-1BB雙特異性抗體檢測腫瘤細胞表面的B7-H4表現量。如圖所示，SK-BR-3和MDA-MB-468是高度表現B7-H4的腫瘤細胞，JIMT-1和COV644 及MDA-MB-231是不表現B7-H4的腫瘤細胞。

【0117】 圖13-(A)-(H)：B7-H4×4-1BB雙抗對T細胞活化特異性依賴B7-H4的表現。(A),(B)高度表現B7-H4的細胞株SK-BR-3或MDA-MB-468細胞存在時，B7-H4×4-1BB雙特異性抗體PR003334媒介的T細胞活化優於陽性對照。(C),(D)不表現B7-H4的細胞株COV644或JIMT-1細胞存在時, PR003334媒介的 T細胞活化程度與同型IgG對照相當。(E),(F)高度表現B7-H4的細胞株

MDA-MB-468或SK-BR-3細胞存在時，B7-H4 x 4-1BB雙特異性抗體PR004282媒介的T細胞活化優於陽性對照Urelumab。(G),(H)不表現B7-H4的細胞株JIMT-1或MDA-MB-231細胞存在時，PR004282媒介的T細胞活化程度與同型IgG對照相當。

實施例10. B7-H4 x 4-1BB雙特異性抗體的血清穩定性研究

【0118】 為了研究B7-H4x4-1BB雙特異性抗體在高濃度人血清中的穩定性，PR0003334和PR0003335用90%人血清進行梯度稀釋，初始濃度為100 nM，1:3梯度稀釋8個濃度點。分成6份樣本，分別在37度培育0天、1天、2天、4天、7天、14天後，液態氮速凍後放置於-70度保存。FACS檢測B7-H4x4-1BB雙特異性抗體在高濃度血清中37度放置不同時間後，與高度表現B7-H4的SK-BR-3細胞株和CHO-K1-hu4-1BB細胞的體外結合，參照實施例3.3和實施例6。

【0119】 PR0004282用95%人血清進行梯度稀釋，分成5管，分別在37度培育0天、1天、2天、4天、7天、14天後，液態氮速凍後放置於-80度保存。在高濃度人血清中37度放置不同時間後的PR004282用FACS方法檢測與B7H4+細胞和4-1BB+細胞的體外結合，過程如下：

消化酶處理CHO-K1/h4-1BB、CHO-K1/cyno4-1BB、CHO-K1/hB7H4及CHO-K1/cynoB7H4細胞，並用DMEM完全培

養基重新懸浮，用PBS洗滌後將細胞密度分別調整為1×10^6細胞/mL。以100 μL細胞/孔接種於96孔V底盤(Corning, #3894)，隨後加入100 μL/孔，2倍於終濃度的3倍濃度梯度稀釋的待測人血清處理後PR004282抗體(不同處理時間的抗體的每個劑量均含有4.5%人血清)。將細胞放置於4℃，避光培育2小時。再加入100 μL/孔預冷含2% FBS的PBS 漂洗細胞兩次，於500 g、4℃下離心5分鐘，棄上清。再加入100 μL/孔螢光二抗(Alexa Fluor 647-conjugated AffiniPure Goat Anti-Human IgG, Fcγ Fragment Specific, Jackson, #109-545-06, 1:1000稀釋)，4℃，避光培育1小時。用100 μL/孔預冷含2%FBS的PBS洗滌細胞兩次，於500 g、4℃下離心5分鐘，棄上清。最後，200 μL/孔預冷含2% FBS的PBS重新懸浮細胞，使用艾森ACEA NovoCyte系列流式細胞儀讀取螢光發光訊號值。

【0120】 圖14-(A-D)：B7-H4 x 4-1BB雙抗PR003334和PR003335的血清穩定性。在不同的人血清培育時間，PR003334和PR003335在90%血清中與高度表現B7-H4的SK-BR-3細胞和CHO-K1-人4-1BB細胞的結合沒有改變，說明PR003334和PR003335具有很好的血清穩定性。

【0121】 圖14-(E-H)：B7-H4x4-1BB雙抗PR004282的血清穩定性。在不同的血清培育時間，PR004282在95%血清中與高度表

現B7H4或4-1BB的CHO-K1細胞的結合沒有改變，說明PR004282具有很好的血清穩定性。

實施例11. FACS檢測B7-H4×4-1BB雙特異性抗體PR004282在4-1BB+細胞位準的結合能力

【0122】 本實施例是為了研究B7-H4×4-1BB雙特異性抗體PR004282體外結合人/食蟹猴/小鼠4-1BB的活性。採用過度表現人4-1BB的CHO-K1細胞株(CHO-K1/h4-1BB，Gensript, #M00538)、食蟹猴4-1BB的CHO-K1細胞株(CHO-K1/cyno4-1BB, Genscript, #M00569)、過度表現小鼠4-1BB的CHO-K1細胞株(CHO-K1/m4-1BB, Genscript,#M00568)進行細胞位準上的抗體結合實驗。簡言之，消化酶處理CHO-K1/h4-1BB細胞、CHO-K1/cyno 4-1BB細胞及CHO-K1/m 4-1BB細胞，並用含2% FBS的PBS重新懸浮。將細胞密度分別調整為1×10^6細胞/mL。以100 μL細胞/孔接種於96孔V底盤(Corning, #3894)，隨後加入100 μL/孔，2倍於終濃度的3倍濃度梯度稀釋的待測抗體。將細胞放置於4℃，避光培育2小時。之後，加入100 μL/孔預冷含2% FBS的PBS的FACS緩衝液漂洗細胞兩次，於500 g、4℃下離心5分鐘，棄上清。再加入100 μL/孔螢光二抗(Alexa Fluor® 647, Goat Anti-Human IgG, Fcγ fragment specific，Jackson ImmunoResearch, #109-605-098, 1:1000稀

釋)，4℃，避光培育1小時。用100 μL/孔預冷FACS緩衝液洗滌細胞兩次，於500 g、4℃下離心5分鐘，棄上清。最後，200 μL/孔預冷FACS緩衝液重新懸浮細胞，使用ACEA Novocyte3000 流式細胞儀讀取螢光發光訊號值。

【0123】 如圖15-(A)所示：B7-H4/4-1BB雙特異性抗體PR004282在高度表現人4-1BB的CHO-K1細胞株上的體外結合情況；PR004282與CHO-K1/h4-1BB細胞株結合活性優於對照抗體Urelumab。

【0124】 如圖15-(B)所示：PR004282在高度表現食蟹猴4-1BB的CHO-K1細胞株上的體外結合情況；PR004282可以結合猴4-1BB，而Urelumab不具有與猴的交叉反應。

【0125】 如圖15-(C)所示：PR004282在高度表現鼠4-1BB的CHO-K1細胞株上的體外結合情況；PR004282不具有小鼠4-1BB結合能力。

實施例12. FACS檢測B7-H4×4-1BB雙特異性抗體PR004282在B7H4+細胞位準的結合能力

【0126】 本實施例是為了研究B7-H4×4-1BB雙特異性抗體PR004282體外結合人/食蟹猴/小鼠B7-H4的活性。採用過度表現人B7H4的CHO-K1細胞株(CHO-K1/hB7-H4，和鉑自製)食蟹猴B7-H4的CHO-K1細胞株(CHO-K1/cynoB7-H4，和鉑自製)、過度

表現小鼠B7-H4的CHO-K1細胞株(CHO-K1/mB7-H4，和鉑自製)進行細胞位準上的抗體結合實驗。簡言之，消化酶處理CHO-K1/hB7H4細胞、CHO-K1/cyno B7-H4細胞及CHO-K1/mB7-H4細胞，並用含2% FBS的PBS重新懸浮。將細胞密度分別調整為1×10^6細胞/mL。以100 μL細胞/孔接種於96孔V底盤(Corning, #3894)，隨後加入100 μL/孔，2倍於終濃度的3倍濃度梯度稀釋的待測抗體。將細胞放置於4℃，避光培育2小時。之後，加入100 μL/孔預冷含2%FBS的PBS漂洗細胞兩次，於500 g、4℃下離心5分鐘，棄上清。再加入100 μL/孔螢光二抗(Alexa Fluor® 647, Goat Anti-Human IgG, Fcγ fragment specific，Jackson ImmunoResearch, #109-605-098, 1:1000稀釋)，4℃，避光培育1小時。用100 μL/孔預冷含2% FBS的PBS洗滌細胞兩次，於500 g、4℃下離心5分鐘，棄上清。最後，200 μL/孔預冷含2% BSA的PBS重新懸浮細胞，使用ACEA Novocyte3000 流式細胞儀讀取螢光發光訊號值。

【0127】 如圖16-(A)所示：B7-H4/4-1BB雙特異性抗體PR004282在高度表現人B7-H4的CHO-K1細胞株上的體外結合；PR004282與CHO-K1/hB7H4細胞株結合活性高於B7H4單抗抗體PR002408。

【0128】 如圖16-(B)所示：B7-H4抗體在高度表現食蟹猴B7-H4的CHO-K1細胞株上的體外結合；PR004282和PR002408與CHO-K1-食蟹猴B7-H4細胞株結合活性相當。

【0129】 如圖16-(C)所示：B7-H4抗體在高度表現鼠B7-H4的CHO-K1細胞株上的體外結合；PR004282有微弱的小鼠B7H4結合能力。

實施例13. FACS檢測B7-H4×4-1BB雙特異性抗體PR004282同時結合CHO-K1/h4-1BB和SK-BR-3的能力

【0130】 本實施例是為了研究B7-H4×4-1BB雙特異性抗體PR004282同時結合CHO-K1/h4-1BB和SK-BR-3的能力。簡言之，消化酶處理CHO-K1/h4-1BB 細胞和SK-BR-3細胞，並用PBS將細胞密度分別調整為1 x 10^6 細胞/mL，用0.5 μM Far-red(lifetechnologies, #C34572)對SK-BR-3，用0.5 μM CFSE(lifetechnologies, #C34544)對CHO-K1/h4-1BB細胞在室溫染色5分鐘。離心染色後的細胞，用>20 ml的含1%FBS培養基洗滌一次。重新懸浮洗滌後的細胞於FACS緩衝液中，並調整細胞密度均為2*10^6 /ml。在96孔V型盤內(Corning, #3894)每孔加入50 μl SK-BR-3細胞(每孔細胞數為1*10^5)和25 μl CHO-K1/h4-1BB(每孔細胞數為1*10^5)以及25ul 4倍梯度FACS緩衝液稀釋的待測抗體，混勻完全。4℃培育1小時。使用ACEA Novocyte3000流式細

胞儀，辨識FITC+ CHO-K1/h4-1BB細胞和Alexa647+SK-BR-3雙陽性百分比。數據用FlowJo軟體(Tree Star, Ashland, OR)分析，雙染細胞的百分比用於確定雙抗媒介的共結合率=(Q2/(Q1+Q2)。

【0131】 圖17顯示僅有PR004282具有同時結合CHO-K1/h4-1BB和SK-BR-3的能力。單抗均無該能力。

實施例14. FACS檢測B7-H4×4-1BB雙特異性抗體PR004282在原代細胞位準的結合能力

【0132】 本實施例是為了研究B7-H4×4-1BB雙特異性抗體PR004282體外結合活化後的人/食蟹猴原代T細胞的活性。用非人的靈長目CD3分離套組(Miltenyi，#130-092-012)從凍存的猴PBMC (PharmaLegacy，#SC1702051)分離出猴CD3+ T細胞，用培養基RPMI1640+10% FBS+1%丙酮酸鈉(Thermo, #11360-070)+1%非必需胺基酸溶液(Thermo, #11140-050)重新懸浮至2^10^6/ml,分別取1 ml至6孔盤內，加入1 ml含有20 ng/ml PMA (Sigma,#P1585-1MG)和5 nM Ionomycin (Sigma, #407952-5MG)的培養基，37℃ CO_2培養箱16h。用人CD3分離套組(Miltenyi，#130-096-535)從凍存的人PBMC (Saily，XFB-HP100B)分離出人CD3+ T細胞，其他操作同猴CD3+ T細胞的活化。

【0133】 活化後的猴T細胞密度用含2% FBS的PBS調整至1×10^6細胞/mL，以100 μL CD3+ T細胞/孔接種於96孔V底盤(Corning, #3894)，隨後加入100 μL/孔，2倍於終濃度的3倍濃度梯度稀釋的待測抗體PR004282/hIgG1/Urelumab/hIgG4，將細胞放置於4℃，避光培育2小時。之後，加入100 μL/孔預冷含2% FBS的PBS漂洗細胞兩次，於500 g、4℃下離心5分鐘，棄上清。再加入100 μL/孔螢光二抗(Alexa Fluor® 647, Goat Anti-Human IgG, Fcγ fragment specific，Jackson ImmunoResearch, #109-605-098, 1:1000稀釋)，4℃，避光培育1小時。用100 μL/孔預冷含2% FBS的PBS洗滌細胞兩次，於500 g、4℃下離心5分鐘，棄上清。最後，100 μL/孔預冷含2% FBS的PBS重新懸浮細胞，使用ACEA Novocyte3000流式細胞儀讀取螢光發光訊號值。

【0134】 Zombie NIR™染料(Biolegend，#77184)與活化後的人T細胞室溫暗處培育15-30分鐘，FACS緩衝液洗滌一次細胞，將細胞密度分別調整為1×10^6細胞/mL。以100 μL CD3+ T細胞/孔接種於96孔V底盤(Corning, #3894)，隨後加入100 μL/孔，2倍於終濃度的3倍濃度梯度稀釋的待測抗體PR004282/hIgG1, 將細胞放置於4℃，避光培育2小時。之後，加入100 μL/孔預冷含2% FBS的PBS漂洗細胞兩次，於500 g、4℃下離心5分鐘，棄上清。再加入100 μL/孔螢光二抗(Alexa Fluor® 488，Goat Anti-Human

IgG，Fcγ fragment specific，Jackson ImmunoResearch，#109-545-098，1:1000稀釋)，4℃，避光培育1小時。用100 μL/孔預冷含2% FBS的PBS洗滌細胞兩次，於500 g、4℃下離心5分鐘，棄上清。最後，100 μL/孔預冷含2% FBS的PBS重新懸浮細胞，使用ACEA Novocyte3000 流式細胞儀讀取螢光發光訊號值。

【0135】 如圖18-(A-B)所示：B7-H4/4-1BB雙特異性抗體PR004282可以與活化後的人或猴CD3+ T細胞結合。

實施例15. ELISA檢測B7-H4×4-1BB雙特異性抗體PR004282與B7家族或TNFR家族其他成員的交叉反應性

15.1 ELISA檢測B7-H4×4-1BB雙特異性抗體PR004282與B7家族其他成員的交叉反應性

【0136】 將B7家族的蛋白(表13)分別用PBS稀釋為1 μg/ml，加至96孔盤(Corning，#9018)中，每孔100μl，4℃下培育過夜。棄去液體後用PBST緩衝液(pH 7.4，含0.05% tween-20)洗盤3次，加入250 μl 2% BSA封阻液，37℃條件下培育1小時。棄去封阻液，並用PBST緩衝液洗盤3次，將待測抗原結合蛋白，稀釋成100 nM、10 nM和1 nM 3個濃度，每個孔加入100 μl，37℃培育1小時。PBST緩衝液清洗3次後，加入稀釋5000倍的羊抗人HRP二抗(Invitrogen，#A18805)，37℃條件下，避光培育1小時。PBST緩衝液清洗3次後，添加100 μl/孔TMB (Biopanda, #TMB-S-003)，

室溫避光放置約30分鐘；每孔加入50 μl/孔終止液(BBI life sciences，#E661006-0200)終止反應，置酵素標示讀取儀(PerkinElemer，#Enspire)中測定450 nm吸光度(OD450)值。

【0137】 圖19-(A)說明本發明的抗體PR004282不與B7家族其它成員蛋白發生交叉反應。

表13. B7家族其它成員供應商資訊

B7家族其它成員	供應商	目錄號	別稱
人B7-1/CD80蛋白, Fc Tag (HPLC-verified)	Acrobiosystem	B71-H5259	CD80
人B7-2 / CD86蛋白, Fc Tag	Acrobiosystem	CD6-H5257	CD86
人B7-DC/PD-L2/CD273重組蛋白(Fc Tag)	Sino Biological	H10292-H02H	PD-L2
人PD-L1/B7-H1 Protein, His Tag (HPLC verified)	Acrobiosystem	PD1-H5229	PD-L1
人CD275/ICOS配體重組蛋白 (Fc Tag)	Sino Biological	11559-H02H	ICOS-L
人B7-H3/CD276重組蛋白(ECD, Fc Tag)	Sino Biological	11188-H02H	
人B7H4 Fc嵌合重組蛋白	R&D	8870-B7-050	B7S1
人VISTA/B7H5/PD-1H Fc嵌合重組蛋白	R&D	7126-B7-050	VISTA
人B7-H6/NCR3LG1重組蛋白(Fc Tag)	Sino Biological	16140-H02H	
人B7H7/HHLA2嵌合重組蛋白(Fc Tag)	R&D	8084-B7-050	HHLA2

15.2 ELISA檢測B7-H4×4-1BB雙特異性抗體PR004282與TNFR家族其他成員的交叉反應性

【0138】 將TNFR家族的蛋白(表14)分別用PBS稀釋為1 μg/ml，加至96孔盤(Corning，#9018)中，每孔100 μl，4℃下培

育過夜。棄去液體後用PBST緩衝液(pH 7.4，含0.05% tween-20)洗盤3次，加入250 µl 2% BSA封阻液，37℃條件下培育1小時。棄去封阻液，並用PBST緩衝液洗盤3次，將待測抗原結合蛋白，稀釋成100 nM、10 nM和1 nM 3個濃度，每個孔加入100 µl，37℃培育1小時，同型抗體作為對照。PBST緩衝液清洗3次後，加入稀釋5000倍的羊抗人HRP二抗(Invitrogen，#A18805)，37℃條件下，避光培育1小時。PBST緩衝液清洗3次後，添加100 µl/孔TMB (Biopanda, #TMB-S-003)，室溫避光放置約30分鐘；每孔加入50 µl/孔終止液(BBI life sciences#E661006-0200)終止反應，置酵素標示讀取儀(PerkinElemer #Envision)中測定450 nm吸光度(OD450)值。

表14. TNFR家族其它成員供應商資訊

TNFR 家族其它成員	供應商	貨號
CD30	Acrobiosystems	CD0-H5229
CD27	Acrobiosystems	CD7-H522b
HVEM	Acrobiosystems	HVM-H52E9
GITR	Acrobiosystems	GIR-H5228
OX40	Acrobiosystems	OX0-H5224
4-1BB	Acrobiosystems	41B-H5227
CD40	Sino Biological	10774-H08H

【0139】 圖19-(B)說明本發明的抗體PR004282不與TNFR家族其它成員蛋白發生交叉反應。

實施例16. B7-H4×4-1BB雙特異性抗體PR004282的ADCC效果檢測

16.1 本實施例是透過ADCC報告基因細胞株來檢測PR004282的ADCC效果

【0140】 使用Jurkat FcγRIIIa-V158/NFAT-Luc細胞(和鉑自製)，檢測PR004282對CHO-K1/h4-1BB或SK-BR-3的ADCC效應的活性。CHO-K1/h4-1BB或SK-BR-3於300 g離心5分鐘，然後用RPMI1640 + 4% FBS血清培養基重新懸浮。將細胞的密度調整到6×10^5細胞/ml，在96孔盤的各孔內加入50 μl細胞懸浮液，於37℃培育過夜。Jurkat FcγRIIIa-V158/NFAT-Luc細胞於400 g離心4分鐘，然後用RPMI1640 + 4% FBS血清培養基重新懸浮。將細胞的密度調整到3×10^6細胞/ml，在96孔盤的各孔內加入50 μl細胞懸浮液。抗體用RPMI1640 + 4% FBS培養基稀釋，最高終濃度為100 nM，每個抗體共4個濃度，5倍稀釋，設置兩個重複，在96孔盤的各孔內加入50 μl抗體稀釋液。同時，在盤內設置同型IgG對照組和空白培養基對照組。細胞與抗體於37℃培育5小時。將96孔盤於常溫靜置30分鐘，加入60 μl/孔的室溫One-Glo顯色液(Promega,#E6110)。之後樣品避光常溫培育10分鐘。用PE Enspire進行Luminscence讀值。倍數=抗體孔的Luminscence讀值/空白培養基對照組的Luminscence讀值，用Prism 8軟體作圖。PR004469

及PR003369 (親和力成熟變體的B7H4單抗，具有ADCC增強效應，重鏈序列如SEQ ID NO: 290所示，輕鏈序列如SEQ ID NO: 291所示)作為陽性對照，human Iso IgG1 (CrownBio，#C0001-4)抗體作為陰性對照。

【0141】 圖20-(A)-(B)示出PR004282對CHO-K1/h4-1BB及SK-BR-3細胞無明顯的ADCC活性。而陽性對照PR004469及PR003369能以劑量依賴的方式分別對CHO-K1/4-1BB或SK-BR-3產生較強ADCC效應。

16.2 本實施例是為了研究B7H4/4-1BB雙抗PR004282透過ADCC效應媒介NK細胞毒殺標靶細胞的活性。

【0142】 本實驗採用人NK作為效應細胞，高度表現B7H4的細胞株SK-BR-3作為標靶細胞。使用ACEA公司的RTCA儀器檢測標靶細胞的電導率反應毒殺效率。96孔盤E-plate先用50 μl完全培養基平衡。消化酶處理SK-BR-3細胞，重新懸浮於含10%胎牛血清的RPM1640完全培養基中，稀釋至$4*10^5$/ml，平盤培養50μl/孔於E-plate 96盤中，即$2*10^4$/孔，37°C培養過夜。次日用EasySep™ Human CD56正向篩選套組(Stem cell，#17855)分選出NK，每孔加入新鮮50 μl含$1*10^5$ PBMC的培養液，隨後加入50 μl 4×的濃度梯度稀釋的抗體，抗體最高終濃度為100 nM，每個抗體共4個濃度，5倍稀釋，設置兩個重複。PR003369作為陽性對照，human Iso IgG1

(CrownBio，C0001-4)抗體作為陰性對照。即時檢測標靶細胞的電導率，取24小時時間點的數據計算標靶細胞毒殺效率 = (1-樣品/ iso對照) x 100%。

【0143】 圖20-(C)結果顯示PR004282與PR003369相比，PR004282沒有明顯的毒殺。 說明PR004282對SK-BR-3標靶細胞不具有ADCC活性。

實施例17. 利用BLI方法檢測抗體與人、小鼠、食蟹猴Fcγ受體蛋白的親和力

【0144】 測試使用Octet Red 96e分子相互作用分析儀，實驗緩衝液為稀釋至1x的動力學緩衝液(ForteBio，#18-1105)。

【0145】 設置儀器轉動速度為1000轉/分鐘，先將置於一列的FAB2G感測器(Fortebio，#18-5125)在測試緩衝液中平衡10分鐘，然後用FAB2G感測器捕捉抗體，捕捉高度1 nm；FAB2G感測器在緩衝液中平衡120s後與2倍梯度稀釋的Fcγ受體蛋白結合，設置結合時間60s、解離時間30s，蛋白濃度見表15。最後將FAB2G感測器浸入10 mM甘胺酸-鹽酸pH 1.5溶液進行再生，以洗提結合在感測器上的蛋白。對於抗體與FcRn的親和力測試，在緩衝液pH6.0和7.4兩個條件下分別進行。對於帶有avi標籤的食蟹猴CD32b和CD64，使用SA感測器(Fortebio,18-5019)捕捉受體蛋白，抗體為分析物。

表15.Fcγ受體蛋白資訊及分析物濃度

受體蛋白	供應商	貨號	濃度
人 CD64	Novo Protein	CM60	800-25
人 CD32a (H)		CS35	8000-500
人 CD32b		C444	8000-250
人 CD16a (V158)		C441	8000-250
人 CD16a (F158)		CS11	8000-250
人 CD16b		CB62	8000-250
人 FcRn		CI01	800-50
小鼠 CD32 (C-6his)		C767	8000-250
小鼠 CD16 (C-6his)		CS29	4000-250
小鼠 CD64 (his)	Acro Biosystems	CD4-M5227	1000-125
食蟹猴 FcRn		FCM-C52W9	800-25
食蟹猴 CD32a		CDA-C52H7	8000-250
食蟹猴 CD32b		CDB-C82E4	3000-187.5
食蟹猴 CD16		FC6-C52H9	2000-125
食蟹猴 CD64		FCA-C82E8	400-12.5

【0146】 使用Octet Data Analysis軟體(Fortebio，版本11.0)進行數據分析時，以0 nM為參照孔，扣除參照訊號(reference subtraction)，選擇“1:1 Global fitting”方法進行數據擬合，計算出蛋白與抗體結合的動力學參數，得到kon(1/Ms)值、kdis(1/s)值和KD(M)值；對於快結合快解離的相互作用，選用“steady state”方法擬合數據，得到KD(M)值。

【0147】 從表16-18可以看出，PR004282的KD值均高於對參照抗體Urelumab，表明其與人鼠猴Fcγ受體蛋白結合較弱。

表16. PR004282與人Fcγ受體的親和力

KD(M)	人 Fcγ 受體						
抗體名稱	CD64	CD16a(v)	CD16a(F)	CD16b	CD32a (H)	CD32b	FcRn (pH 6.0)
PR002408	2.68E-11	1.23E-07	1.62E-06	3.80E-06	4.40E-07	3.30E-06	2.64E-07
PR004282	1.20E-07	1.52E-06	不結合		>8E-06	不結合	2.35E-07
Urelumab	6.52E-10	2.39E-06			2.80E-06	3.20E-06	1.94E-07

表17. PR004282與猴Fcγ 受體的親和力

KD (M)	猴 Fcγ 受體					
抗體	CD64	CD32b	CD32a	CD16	FcRn(pH7.4)	FcRn(pH6.0)
PR002408	3.67E-10	1.51E-06	2.10E-06	1.29E-07	不結合	1.59E-07
PR004282	9.77E-08	5.10E-06	不結合	7.47E-07		1.43E-07
Urelumab	1.74E-10	5.97E-07	4.82E-06	8.92E-07		1.39E-07

表18. PR004282與小鼠Fcγ 受體的親和力

KD (M)	小鼠 Fcγ 受體		
抗體名稱	CD16	CD32	CD64
PR002408	1.28E-07	6.10E-07	3.60E-08
PR004282	1.41E-06	>8E-06	不結合
urelumab	7.81E-07	2.10E-06	1.63E-07

實施例18. B7-H4 x 4-1BB雙特異性抗體的非特異性細胞激素的釋放檢測

【0148】 為了評估B7-H4x4-1BB雙特異性抗體是否引起細胞激素的非特異性釋放。用人CD14分離套組(Meltenyi, #130-050-201)分離出單核細胞，將其或同一供體的PBMC重新懸浮於含10%胎牛血清的RPM1640完全培養基中，稀釋至2E6/ml，平盤培養100 µl/孔於平底96盤(Costar, #3599)中，即2E5/孔，隨後加入100ul 2x終濃度的梯度稀釋的抗體，抗體最高濃度為300

nM，10倍稀釋，共三個濃度，設置兩個重複，37°C培養過夜。Urelumab作為陽性對照，Utomilumab和human Iso IgG1 (CrownBio，C0001-4)抗體作為陰性對照。培育24h收取上清檢測TNF-a (Thermo, 88-7066-88)和IL-6 (Thermo，88-7346-77)的釋放，培育72h收上清檢測IFN-gamma (Thermo,88-7316-77)的釋放。

【0149】 圖21-(A)-(C)：B7-H4 × 4-1BB雙特異性抗體PR004282與PBMC或單核細胞共培育後細胞激素的釋放情況。不管是PBMC還是單核細胞，Urelumab均表現出較強的TNF-a和IL-6的釋放，IFN-gamma則僅表現在與PBMC共培育的情況下。而PR004282則與Utomilumab一樣顯示出較好的安全性，不管是與PBMC或單核細胞培育，均為顯示出明顯的細胞激素釋放。

實施例19. B7-H4×4-1BB雙特異性抗體在正常小鼠中的藥代動力學研究

【0150】 本實施例測試融合蛋白的藥代動力學性能。其方法如下，選取體重18~22克的雌性C57BL/6小鼠6隻，按5 mg/kg PR003334或5 mg/kg PR003335或5 mg/kg PR004282的劑量透過靜脈注射給與雙特異性抗體藥物；一組3隻於給藥前以及給藥後15分鐘、24小時(1天)、第4天、和第10天採集全血，另一組3隻於只於給藥前以及給藥後5小時、第2天、第7天、和第14天採集全血。

將全血靜置30分鐘使其凝固，隨後在4℃下以2,000 rpm離心5分鐘並將分離的血清樣品在-80℃下凍存直至分析。本實施例採用兩種ELISA方法來定量測定小鼠血清中的藥物濃度。ELISA方法一，即總體檢測方法，透過塗覆於96孔盤的山羊抗人Fc多株抗體來捕捉小鼠血清中的含有人Fc的融合蛋白，然後加入HRP標記的山羊抗人Fc第二抗體來檢測；ELISA方法二，即功能結構域檢測方法，透過塗覆於96孔盤的人4-1BB蛋白來捕捉小鼠血清中的含有人4-1BB HCAb的雙特異性抗體，然後加入HRP標記的山羊抗人Fc第二抗體來檢測。使用Phoenix WinNonlin軟體8.2版，選用非房室模型(NCA)對血藥濃度數據進行分析以評價其藥代動力學。

【0151】 圖22-(A)-(F)和表19顯示的是B7-H4×4-1BB雙特異性抗體PR003334和PR003335和PR004282的藥代動力學數據。圖22-(A)結果表明，總體檢測方法下，PR003334在小鼠體內的半衰期約為8天。圖22-(B)功能域檢測方法顯示，PR003334在小鼠體內的半衰期約為9天。圖22-(C)總體檢測方法下，PR003335在小鼠體內的半衰期約為14天。圖22-(D)功能域檢測方法顯示，PR003335在小鼠體內的半衰期約為12天。圖22-(E)總體檢測方法下，PR004282在小鼠體內的半衰期約為11天。圖22-(F)功能域檢測方法顯示，PR004282在小鼠體內的半衰期約為8天。

表19. PR003334和PR003335和PR004282的藥代動力學

	PR003334	PR003334	PR003335	PR003335	PR004282	PR004282
PK 參數	總體檢測	功能結構域檢測	總體檢測	功能結構域檢測	總體檢測	功能結構域檢測
$T_{1/2}$ (hr)	193	218	336	295	274	197
V_d (mL/kg)	76	89	81	81	133	119
AUC_{all} (μg/mL hr)	12,680±428	11,471±497	14,813±683	14,286±560	8,363±102	8,125±150
AUC (%)*	100	90	100	96	100	97
Cl (mL/hr/kg)	0.28	0.28	0.17	0.19	0.36	0.43
C_0 (μg/mL)	111	114	123	124	71	71

實施例20. B7H4/4-1BB雙抗PR004282在食蟹猴體內的藥代動力學研究

【0152】 本實施例測試B7-H4/4-1BB雙特異性抗體在食蟹猴體內的藥代動力學過程進行研究。具體的，將PR004282以0.9%生理鹽水稀釋，按照1 mg/kg的劑量靜脈注射入雄性食蟹猴體內，採集給藥前及給藥後0.5，1，2，4，8，12，24，48，72，168，336，504，672，840，1008小時的血樣。血樣在室溫靜置30分鐘後離心分離得到血清，利用建立的特異性ELISA方法(總體檢測法)檢測血清中B7-H4/4-1BB雙特異性抗體的含量。

【0153】 圖23和表20所示，B7-H4/4-1BB雙特異性抗體在靜脈注射給予食蟹猴後顯示出典型的IgG樣藥代動力學曲線。PR004282在雄性猴體內的半衰期約為3天。

表20. PR004282在正常猴體內的藥代動力學(單劑量)

PK參數		1號猴	2號猴	平均值
C_{max}	μg/mL	32.1	48	40
Terminal $t_{1/2}$	hr	45.3	82.3	63.8
$AUC_{0\text{-}last}$	hr*μg/mL	1472	2300	1886
$AUC_{0\text{-}INF}$	hr*μg/mL	1574	2932	2253
CL	mL/hr/kg	0.635	0.341	0.488
V_{ss}	mL/kg	35.1	35.5	35.3

實施例21. BALB/c-hCD137/CT26-B7-H4小鼠模型中B7-H4 × 4-1BB雙特異性抗體的抗腫瘤藥效評估

【0154】 為了評估B7-H4×4-1BB雙特異性抗體的體內抗腫瘤藥效，採用6-8周雌性BALB/c-hCD137小鼠，然後於腫瘤細胞接種當天每隻實驗小鼠皮下接種5×10^5 CT26/hB7-H4細胞。當平均腫瘤體積達到80 mm^3時對小鼠進行隨機分組，每組6隻小鼠。分組後將特定濃度經PBS稀釋的藥物以腹腔注射(i.p.)、每週給藥2次總共給藥6次(BIW*3)的方式進行給藥，以PBS為空白對照組。在初次給藥當天及之後第4、7、11、14和18天對腫瘤體積和小鼠體重進行測量。腫瘤大小計算公式：腫瘤體積(mm^3)=0.5×(腫瘤長徑×腫瘤短徑^2)。

【0155】 圖24所示B7-H4 × 4-1BB雙特異性抗體在BALB/c-hCD137/CT26-B7-H4小鼠模型中的抗腫瘤藥效。如圖24-(A)所示，B7-H4×4-1BB雙特異性抗體PR003334在18 mpk和6 mpk濃度下對小鼠均有抑制腫瘤生長的藥效。如圖24-(B)所示，受試各組小鼠體重變化均在正常範圍內。

實施例22. MDA-MB-468異種移植小鼠模型中B7-H4×4-1BB雙特異性抗體的抗腫瘤藥效評估

【0156】 為了評估B7-H4×4-1BB雙特異性抗體的體內抗腫瘤藥效。採用6-8周雌性NCG小鼠，然後於腫瘤細胞接種當天每隻實驗小鼠皮下接種5×10^6 MDA-MB-468細胞。當平均腫瘤體積達到120 mm^3時對小鼠進行隨機分組，每組6隻小鼠。分組後接種人5×10^6 PBMC細胞，第二天將特定濃度經PBS稀釋的藥物以腹腔注射(i.p.)、每週給藥2次總共給藥6次(BIW*3)的方式進行給藥，以同型對照IgG為對照組。在初次給藥當天及之後第7、12、15、19、22、26和29天對腫瘤體積和小鼠體重進行測量。腫瘤大小計算公式：腫瘤體積(mm^3)= 0.5×(腫瘤長徑×腫瘤短徑^2)。

【0157】 圖25所示B7-H4 × 4-1BB雙特異性抗體在MDA-MB-468異種移植小鼠模型中的抗腫瘤藥效。如圖25-(A)所示，B7-H4×4-1BB雙特異性抗體PR003338在18 mpk濃度下對小鼠有抑制腫瘤生長的藥效，且優於Urelumab在15 mpk濃度下的藥效。如圖25-(B)所示，受試各組小鼠體重變化均在正常範圍內。

實施例23. OVCAR3異種移植小鼠模型中B7-H4×4-1BB雙特異性抗體的抗腫瘤藥效評估

【0158】 為了評估B7-H4 × 4-1BB雙特異性抗體的體內抗腫瘤藥效。採用6-8周雌性NCG小鼠，然後於腫瘤細胞接種當天每隻實

驗小鼠皮下接種5 × 10^6 OVCAR3細胞。當平均腫瘤體積達到120 mm^3時對小鼠進行隨機分組，每組6隻小鼠。分組後接種人5 × 10^6 PBMC細胞，第二天將特定濃度經PBS稀釋的藥物以腹腔注射(i.p.)、每週給藥2次總共給藥6次(BIW*3)的方式進行給藥，以PBS為對照組。在初次給藥當天及之後第7、12、15、19、22、26和29天對腫瘤體積和小鼠體重進行測量。腫瘤大小計算公式：腫瘤體積(mm^3)=0.5×(腫瘤長徑×腫瘤短徑^2)。

【0159】 圖26所示B7-H4 × 4-1BB雙特異性抗體PR004282在OVCAR3異種移植小鼠模型中的抗腫瘤藥效。如圖26-(A)所示，B7-H4 × 4-1BB雙特異性抗體PR004282在18 mpk濃度下對小鼠有抑制腫瘤生長的藥效。如圖26-(B)所示，受試各組小鼠體重變化均在正常範圍內。

實施例24. BALB/c-hCD137/CT26-hB7-H4小鼠模型中B7-H4×4-1BB雙特異性抗體的抗腫瘤藥效和記憶性免疫效應評估

【0160】 為了評估B7-H4×4-1BB雙特異性抗體的體內抗腫瘤藥效。採用6-8周雌性BALB/c-hCD137小鼠，然後於腫瘤細胞接種當天每隻實驗小鼠皮下接種5 ×10^5 CT26-B7-H4細胞。當平均腫瘤體積達到80 mm^3時對小鼠進行隨機分組，每組6隻小鼠。分組後將特定濃度經PBS稀釋的藥物以腹腔注射(i.p.)、每週給藥2次總共給

藥6次(BIW*3)的方式進行給藥，以同型對照為對照組，Urelumab作為陽性對照組。在初次給藥當天及之後持續45天內一週三次對腫瘤體積和小鼠體重進行測量。腫瘤大小計算公式：腫瘤體積(mm^3)=0.5×(腫瘤長徑 × 腫瘤短徑^2)。給藥後45天對腫瘤消除的小鼠的另一側皮下接種5×10^5 CT26/hB7H4細胞，以同齡小鼠作為新接種對照組。一週三次對腫瘤體積和小鼠體重進行測量，第66天處死老鼠。

【0161】 圖27所示B7-H4 × 4-1BB雙特異性抗體PR004282在BALB/c-hCD137/CT26-B7-H4小鼠模型中的抗腫瘤藥效和記憶性免疫效果。如圖27-(A)-(D)所示，B7-H4 x 4-1BB雙特異性抗體PR004282在1 mpk濃度下對小鼠有抑制腫瘤生長的藥效，與Urelumab藥效相當。如圖27-(E)所示，受試各組小鼠體重變化均在正常範圍內。如圖27--(F)-(I)所示，腫瘤消除後的小鼠新接種同樣的腫瘤後與未接種未打藥的同齡的小鼠相比，腫瘤不再生長，說明PR004282能夠誘導記憶性免疫T細胞的產生從而可以持續長效的毒殺腫瘤。

實施例25. B7-H4 × 4-1BB雙特異性抗體的抗腫瘤藥效特異性評估

25.1 JIMT-1異種移植小鼠模型評估B7-H4x4-1BB雙特異性抗體的抗腫瘤藥效特異性

【0162】 採用6-8周雌性NCG小鼠，然後於腫瘤細胞接種當天每隻實驗小鼠皮下接種5 x 10^6 JIMT-1細胞。當平均腫瘤體積達到120 mm^3時對小鼠進行隨機分組，每組6隻小鼠。分組後接種人5 x 10^6 PBMC細胞，第二天將特定濃度經PBS稀釋的藥物以腹腔注射(i.p.)、每週給藥2次總共給藥6次(BIW*3)的方式進行給藥，以PBS為對照組。在初次給藥當天及之後第7、12、15、19、22、26和29天對腫瘤體積和小鼠體重進行測量。腫瘤大小計算公式：腫瘤體積(mm^3)=0.5×(腫瘤長徑×腫瘤短徑^2)。

【0163】 圖28－(A) PR004282在JIMT-1異種移植小鼠模型中的抗腫瘤藥效。如圖所示，PR004282在18 mpk濃度下對小鼠無抑制腫瘤生長的藥效，而Urelumab在15 mpk濃度下則顯示出一定的藥效，JIMT-1是不表現B7H4的細胞，說明PR004282不能毒殺不表現B7H4的腫瘤細胞。

25.2 BALB/c-hCD137/CT26小鼠模型評估B7-H4 x 4-1BB雙特異性抗體的抗腫瘤藥效特異性

【0164】 為了評估B7-H4×4-1BB雙特異性抗體的體內抗腫瘤藥效的特異性。採用6-8周雌性BALB/c-hCD137小鼠，然後於腫瘤細胞接種當天每隻實驗小鼠皮下接種5 x10^5 CT26野生型細胞。當平均腫瘤體積達到80 mm^3時對小鼠進行隨機分組，每組6隻小鼠。分組後將特定濃度經PBS稀釋的藥物以腹腔注射(i.p.)、每週給藥2

次總共給藥6次(BIW*3)的方式進行給藥，以同型對照為對照組。在初次給藥當天及之後第4、7、11、14和18天對腫瘤體積和小鼠體重進行測量。腫瘤大小計算公式：腫瘤體積(mm^3)=0.5×(腫瘤長徑 × 腫瘤短徑^2)。

【0165】 圖28-(B)：B7-H4 x 4-1BB 雙特異性抗體PR004282在BALB/c-hCD137 / CT26小鼠模型中沒有顯示出對小鼠較強的抑制腫瘤生長的藥效，而Urelumab顯示出很強的藥效。由於CT26是不表現B7H4的細胞，說明PR004282不能毒殺不表現B7H4的細胞。另一方面，根據實施例24中的結果，在CT26細胞上過度表現人B7H4以後，該CT26-hB7-H4腫瘤細胞的生長會受到PR004282的抑制。結合兩個實驗可以推論出，PR004282對腫瘤細胞的毒殺是B7H4表現依賴的。

【0166】 雖然以上描述了本發明的具體實施方式，但是本領域的技術人員應當理解，這些僅是舉例說明，在不背離本發明的原理和實質的前提下，可以對這些實施方式做出多種變更或修改。因此，本發明的保護範圍由所附申請專利範圍限定。

【序列表】

<110> 大陸商和鉑醫藥（上海）有限責任公司(HARBOUR BIOMED (SHANGHAI) CO.,LTD)

<120> 一種雙特異性抗體及其用途

<150> CN202010618149.1

<151> 2020-06-30

<160> 291

<170> PatentIn version 3.5

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20 25

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Ser Leu Arg Leu Ser Cys Ala Ala Ser

20 25

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20 25

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20 25

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Gly Phe Thr Phe Ser Arg Tyr

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<223> PR001760 HCDR1 Chothia, PR001763 HCDR1 Chothia, PR001768 HCDR1 Chothia

<400> 18

Gly Phe Thr Phe Ser Asn Tyr

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Gly Phe Thr Phe Ser Ser Tyr

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<400> 20

Gly Phe Thr Val Ser Ser Asn

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<400> 21

Gly Phe Thr Phe Ser Ser Phe

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<400> 22

Gly Phe Ile Phe Ser Asn Phe

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<400> 23

Glu Asp Thr Phe Ser Ser Tyr

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<223> PR000157 HFWR2 Chothia

<400> 24

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

1 5 10 15

Gly Asp Ile

<210> 25

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<213> 人工的序列

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<400> 25

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile

1 5 10 15

Gly Glu Ile

<210> 26

<211> 19

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<213> 人工的序列

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<223> PR000483 HFWR2 Chothia

<400> 26

Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

1 5 10 15

Gly Lys Ile

<210> 27

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<213> 人工的序列

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<223> PR000628 HFWR2 Chothia

<400> 27

Tyr Trp Ser Trp Ile Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Ile

1 5 10 15

Gly Glu Ile

<210> 28

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<213> 人工的序列

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<223> PR001476 HFWR2 Chothia, PR002408 HFWR2 Chothia

<400> 28

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

1 5 10 15

Ala Val Ile

<210> 29

<211> 19

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<220>

<223> PR001758 HFWR2 Chothia, PR001760 HFWR2 Chothia, PR001781 HFWR2 Chothia

<400> 29

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

1 5 10 15

Ser Ser Ile

<210> 30

<211> 19

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

1 5 10 15

Ser Ser Ile

<210> 31

<211> 19

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<400> 31

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

1 5 10 15

Ser Ala Ile

<210> 32

<211> 19

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<400> 32

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

1 5 10 15

Ser Val Ile

<210> 33

<211> 19

<212> PRT

<213> 人工的序列

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<400> 33

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

1 5 10 15

Ser Ser Ile

<210> 34

<211> 19

<212> PRT

<213> 人工的序列

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<223> PR001771 HFWR2 Chothia

<400> 34

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

1 5 10 15

Ser Ser Ile

<210> 35

<211> 19

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<213> 人工的序列

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<223> PR001774 HFWR2 Chothia

<400> 35

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

1 5 10 15

Ser Thr Ile

<210> 36

<211> 19

<212> PRT

<213> 人工的序列

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<223> PR001780 HFWR2 Chothia

<400> 36

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

1 5 10 15

Ser Thr Ile

<210> 37

<211> 19

<212> PRT

<213> 人工的序列

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<223> PR001836 HFWR2 Chothia

<400> 37

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

1 5 10 15

Ser Ser Ile

<210> 38

<211> 19

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<220>

<223> PR001838 HFWR2 Chothia, PR004469 HFWR2 Chothia

<400> 38

Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val

1 5 10 15

Ser Ser Ile

<210> 39

<211> 19

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<223> PR001840 HFWR2 Chothia

<400> 39

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

1 5 10 15

Ser Arg Ile

<210> 40

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<213> 人工的序列

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<223> PR001842 HFWR2 Chothia

<400> 40

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

1 5 10 15

Ser Ala Ile

<210> 41

<211> 19

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<213> 人工的序列

<220>

<223> PR002037 HFWR2 Chothia, PR002410 HFWR2 Chothia

<400> 41

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

1 5 10 15

Gly Gly Thr

<210> 42

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<212> PRT

<213> 人工的序列

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<223> PR000157 HCDR2 Chothia

<400> 42

Tyr Pro Gly Gly Gly Tyr

1 5

<210> 43

<211> 5

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<223> PR000448 HCDR2 Chothia

<400> 43

Gln His Ser Gly Ser

1 5

<210> 44

<211> 6

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<223> PR000483 HCDR2 Chothia

<400> 44

Tyr Pro Gly Asp Ser Tyr

1 5

<210> 45

<211> 5

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<213> 人工的序列

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<223> PR000628 HCDR2 Chothia

<400> 45

Asn His Gly Gly Tyr

1 5

<210> 46

<211> 6

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<213> 人工的序列

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<223> PR001476 HCDR2 Chothia

<400> 46

Ser Tyr Asp Gly Ser Asn

1 5

<210> 47

<211> 6

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<213> 人工的序列

<220>

<223> PR001758 HCDR2 Chothia

<400> 47

Ser Gly Ser Gly Asp Asp

1 5

<210> 48

<211> 6

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<213> 人工的序列

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<223> PR001760 HCDR2 Chothia

<400> 48

Ser Gly Ser Gly Val Ser

1 5

<210> 49

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<213> 人工的序列

<220>

<223> PR001763 HCDR2 Chothia, PR001771 HCDR2 Chothia, PR001830 HCDR2 Chothia

<400> 49

Ser Gly Ser Gly Gly Ser

1 5

<210> 50

<211> 6

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<223> PR001764 HCDR2 Chothia

<400> 50

Ser Gly Gly Gly Gly Ser

1 5

<210> 51

<211> 5

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<223> PR001767 HCDR2 Chothia

<400> 51

Tyr Ser Asp Gly Ser

1 5

<210> 52

<211> 6

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<213> 人工的序列

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<223> PR001768 HCDR2 Chothia

<400> 52

Ser Gly Ser Gly Asp Ser

1 5

<210> 53

<211> 6

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<223> PR001774 HCDR2 Chothia

<400> 53

Ser Gly Ser Gly Asp Thr

1 5

<210> 54

<211> 6

<212> PRT

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<223> PR001780 HCDR2 Chothia

<400> 54

Ser Gly Ser Gly Asp Asn

1 5

<210> 55

<211> 6

<212> PRT

<213> 人工的序列

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<223> PR001781 HCDR2 Chothia

<400> 55

Ser Gly Ser Gly Gly Asn

1 5

<210> 56

<211> 6

<212> PRT

<213> 人工的序列

<220>

<223> PR001836 HCDR2 Chothia

<400> 56

Asn Gly Ser Gly Phe Asn

1 5

<210> 57

<211> 6

<212> PRT

<213> 人工的序列

<220>

<223> PR001838 HCDR2 Chothia

<400> 57

Asp Gly Ser Gly Gly Asp

1 5

<210> 58

<211> 6

<212> PRT

<213> 人工的序列

<220>

<223> PR001840 HCDR2 Chothia

<400> 58

Asn Ser Asp Gly Ser Ser

1 5

<210> 59

<211> 6

<212> PRT

<213> 人工的序列

<220>

<223> PR002037 HCDR2 Chothia, PR002410 HCDR2 Chothia

<400> 59

Ala Pro Ile Phe Gly Thr

1 5

<210> 60

<211> 6

<212> PRT

<213> 人工的序列

<220>

<223> PR002408 HCDR2 Chothia

<400> 60

Ser Tyr Asp Ala Ser Asn

1 5

<210> 61

<211> 6

<212> PRT

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<223> PR004469 HCDR2 Chothia, PR007381 HCDR2 Chothia

<400> 61

Asp Ala Ser Gly Gly Asp

1 5

<210> 62

<211> 41

<212> PRT

<213> 人工的序列

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<223> PR000157 HFWR3 Chothia

<400> 62

Thr Asn Tyr Asn Glu Lys Phe Lys Gly Arg Val Thr Ile Thr Arg Asp

1 5 10 15

Thr Ser Thr Ser Thr Ala Tyr Leu Glu Leu Ser Ser Leu Arg Ser Glu

20 25 30

Asp Thr Ala Val Tyr Tyr Cys Ala Arg

35 40

<210> 63

<211> 41

<212> PRT

<213> 人工的序列

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<223> PR000448 HFWR3 Chothia

<400> 63

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

1 5 10 15

Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Asn Ser Val Thr Ala Ala

20 25 30

Asp Thr Ala Val Tyr Tyr Cys Ala Arg

35 40

<210> 64

<211> 41

<212> PRT

<213> 人工的序列

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<223> PR000483 HFWR3 Chothia

<400> 64

Thr Asn Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp

1 5 10 15

Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser

20 25 30

Asp Thr Ala Met Tyr Tyr Cys Ala Arg

35 40

<210> 65

<211> 41

<212> PRT

<213> 人工的序列

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<223> PR000628 HFWR3 Chothia

<400> 65

Val Thr Tyr Asn Pro Ser Leu Glu Ser Arg Val Thr Ile Ser Val Asp

1 5 10 15

Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala

20 25 30

Asp Thr Ala Val Tyr Tyr Cys Ala Arg

35 40

<210> 66

<211> 41

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<223> PR001476 HFWR3 Chothia, PR002408 HFWR3 Chothia

<400> 66

Glu Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp

1 5 10 15

Asn Ser Lys Asp Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Gly

20 25 30

Asp Thr Ala Val Tyr Tyr Cys Ala Lys

35 40

<210> 67

<211> 41

<212> PRT

<213> 人工的序列

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<223> PR001758 HFWR3 Chothia

<400> 67

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

1 5 10 15

Asn Ser Gln Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

20 25 30

Asp Thr Ala Val Tyr Phe Cys Ala Lys

35 40

<210> 68

<211> 41

<212> PRT

<213> 人工的序列

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<223> PR001760 HFWR3 Chothia

<400> 68

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

1 5 10 15

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Thr Arg Leu Thr Ala Glu

20 25 30

Asp Thr Ala Val Tyr Phe Cys Ala Lys

35 40

<210> 69

<211> 41

<212> PRT

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<223> PR001763 HFWR3 Chothia

<400> 69

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

1 5 10 15

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Arg Leu Thr Ala Glu

20 25 30

Asp Thr Ala Val Tyr Tyr Cys Ala Lys

35 40

<210> 70

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<223> PR001764 HFWR3 Chothia

<400> 70

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

1 5 10 15

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

20 25 30

Asp Thr Ala Val Tyr Tyr Cys Ala Lys

35 40

<210> 71

<211> 41

<212> PRT

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<223> PR001767 HFWR3 Chothia

<400> 71

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

1 5 10 15

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

20 25 30

Asp Thr Ala Val Tyr Tyr Cys Ala Arg

35 40

<210> 72

<211> 41

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<223> PR001768 HFWR3 Chothia, PR001771 HFWR3 Chothia, PR001781 HFWR3 Chothia

<400> 72

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

1 5 10 15

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

20 25 30

Asp Thr Ala Val Tyr Tyr Cys Ala Lys

35 40

<210> 73

<211> 41

<212> PRT

<213> 人工的序列

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<223> PR001774 HFWR3 Chothia

<400> 73

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

1 5 10 15

Ser Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

20 25 30

Asp Ser Ala Val Tyr Phe Cys Ala Lys

35 40

<210> 74

<211> 41

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<223> PR001780 HFWR3 Chothia

<400> 74

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

1 5 10 15

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

20 25 30

Asp Thr Ala Val Tyr Phe Cys Ala Lys

35 40

<210> 75

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<212> PRT

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<223> PR001830 HFWR3 Chothia, PR001833 HFWR3 Chothia

<400> 75

Thr Phe Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
1 5 10 15

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
20 25 30

Asp Thr Ala Val Tyr Phe Cys Ala Lys
35 40

<210> 76

<211> 41

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<213> 人工的序列

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<223> PR001836 HFWR3 Chothia

<400> 76

Thr Tyr Tyr Thr Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
1 5 10 15

Asn Ser Arg Asn Thr Leu Tyr Leu Gln Met Asn Arg Leu Thr Ala Glu
20 25 30

Asp Thr Ala Val Tyr Phe Cys Ala Lys
35 40

<210> 77

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001840 HFWR3 Chothia

<400> 77

Thr Ser Tyr Ala Asp Ser Val Gln Gly Arg Phe Thr Ile Ser Arg Asp

1 5 10 15

Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

20 25 30

Asp Thr Ala Val Tyr Tyr Cys Val Arg

35 40

<210> 78

<211> 41

<212> PRT

<213> 人工的序列

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<223> PR001842 HFWR3 Chothia

<400> 78

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

1 5 10 15

Asn Ser Lys Asn Thr Leu Tyr Leu His Met Asn Ser Leu Arg Ala Glu

20 25 30

Asp Thr Ala Val Tyr Tyr Cys Ala Lys

35 40

<210> 79

<211> 41

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<213> 人工的序列

<220>

<223> PR002037 HFWR3 Chothia, PR002410 HFWR3 Chothia

<400> 79

Thr Asn Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp

1 5 10 15

Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu

20 25 30

Asp Thr Ala Val Tyr Tyr Cys Ala Arg

35 40

<210> 80

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<223> PR000157 HCDR3 Chothia

<400> 80

Leu Ala Gly Ser Ser Tyr Arg Gly Ala Met Asp Ser

1 5 10

<210> 81

<211> 7

<212> PRT

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<223> PR000448 HCDR3 Chothia

<400> 81

Leu Thr Gly Pro Phe Asp Tyr

1 5

<210> 82

<211> 7

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<213> 人工的序列

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<223> PR000483 HCDR3 Chothia

<400> 82

Gly Tyr Gly Ile Phe Asp Tyr

1 5

<210> 83

<211> 13

<212> PRT

<213> 人工的序列

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<223> PR000628 HCDR3 Chothia

<400> 83

Asp Tyr Gly Pro Gly Asn Tyr Asp Trp Tyr Phe Asp Leu

1 5 10

<210> 84

<211> 10

<212> PRT

<213> 人工的序列

<220>

<223> PR001476 HCDR3 Chothia, PR002408 HCDR3 Chothia

<400> 84

Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr

1 5 10

<210> 85

<211> 15

<212> PRT

<213> 人工的序列

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<223> PR001758 HCDR3 Chothia

<400> 85

Glu Lys Ala Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val Asp Val

1 5 10 15

<210> 86

<211> 15

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<213> 人工的序列

<220>

<223> PR001760 HCDR3 Chothia, PR001830 HCDR3 Chothia, PR001836 HCDR3 Chothia

<400> 86

Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp Val

1 5 10 15

<210> 87

<211> 15

<212> PRT

<213> 人工的序列

<220>

<223> PR001763 HCDR3 Chothia

<400> 87

Glu Gly Ser Asn Gly Thr Asp Asp Tyr His Tyr Asp Ile Asp Val

1 5 10 15

<210> 88

<211> 15

<212> PRT

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<223> PR001764 HCDR3 Chothia

<400> 88

Glu Gly Thr Thr Glu Thr Asp Asp Tyr His Tyr Asn Met Asp Val

1 5 10 15

<210> 89

<211> 18

<212> PRT

<213> 人工的序列

<220>

<223> PR001767 HCDR3 Chothia

<400> 89

Asp Arg Tyr Tyr Gly Ser Gly Asn Tyr Pro Thr Ala Tyr Tyr Gly Met

1 5 10 15

Asp Val

<210> 90

<211> 15

<212> PRT

<213> 人工的序列

<220>

<223> PR001768 HCDR3 Chothia, PR001771 HCDR3 Chothia

<400> 90

Glu Gly Thr Gly Thr Thr Ser Asp Tyr Tyr Tyr Asn Val Asp Val

1 5 10 15

<210> 91

<211> 15

<212> PRT

<213> 人工的序列

<220>

<223> PR001774 HCDR3 Chothia

<400> 91

Glu Ala Thr Ala Met Ala Ser Asp Tyr Tyr Tyr Gly Val Asp Val

1 5 10 15

<210> 92

<211> 15

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<213> 人工的序列

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<223> PR001780 HCDR3 Chothia

<400> 92

Glu Asp Thr Ala Val Ala Ser Asp Tyr Tyr Tyr Asn Ile Asp Val

1 5 10 15

<210> 93

<211> 15

<212> PRT

<213> 人工的序列

<220>

<223> PR001781 HCDR3 Chothia

<400> 93

Glu Arg Thr Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val Asp Val

1 5 10 15

<210> 94

<211> 15

<212> PRT

<213> 人工的序列

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<223> PR001833 HCDR3 Chothia

<400> 94

Glu Gly Ala Thr Glu Thr Asp Asp Tyr His Phe Asn Thr Asp Val

1 5 10 15

<210> 95

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<220>

<223> PR001838 HCDR3 Chothia, PR004469 HCDR3 Chothia, PR007381 HCDR3 Chothia

<400> 95

Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp Val

1 5 10 15

<210> 96

<211> 14

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<213> 人工的序列

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<223> PR001840 HCDR3 Chothia

<400> 96

Lys Gly Ser Ser Ser Tyr Tyr His Tyr Ser Ile Glu Asp Asp

1 5 10

<210> 97

<211> 15

<212> PRT

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<223> PR001842 HCDR3 Chothia

<400> 97

Glu Lys Val Ala Thr Thr Gly Asp Tyr Tyr Tyr Asp Met Asp Val

1 5 10 15

<210> 98

<211> 7

<212> PRT

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<223> PR002037 HCDR3 Chothia, PR002410 HCDR3 Chothia

<400> 98

Gly Gly Pro Tyr Phe Asp Tyr

1 5

<210> 99

<211> 11

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<220>

<223> PR000157 HFWR4 Chothia, PR000448 HFWR4 Chothia, PR000483 HFWR4 Chothia

<400> 99

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

1 5 10

<210> 100

<211> 11

<212> PRT

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<223> PR000628 HFWR4 Chothia

<400> 100

Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser

1 5 10

<210> 101

<211> 11

<212> PRT

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<400> 101

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

1 5 10

<210> 102

<211> 11

<212> PRT

<213> 人工的序列

<220>

<223> PR001767 HFWR4 Chothia

<400> 102

Arg Gly Gln Gly Thr Thr Val Thr Val Ser Ser

1 5 10

<210> 103

<211> 23

<212> PRT

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<220>

<223> PR000157 LFWR1 Chothia

<400> 103

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

20

<210> 104

<211> 23

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<220>

<223> PR000448 LFWR1 Chothia, PR001476 LFWR1 Chothia, PR002408 LFWR1 Chothia

<400> 104

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

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys

20

<210> 105

<211> 22

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<223> PR000483 LFWR1 Chothia

<400> 105

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln

1 5 10 15

Thr Ala Ser Ile Thr Cys

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<210> 106

<211> 23

<212> PRT

<213> 人工的序列

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<223> PR000628 LFWR1 Chothia

<400> 106

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys

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<210> 107

<211> 23

<212> PRT

<213> 人工的序列

<220>

<223> PR002037 LFWR1 Chothia, PR002410 LFWR1 Chothia

<400> 107

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

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys

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<210> 108

<211> 11

<212> PRT

<213> 人工的序列

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<223> PR000157 LCDR1 Chothia

<400> 108

Lys Ala Ser Gln Gly Phe Asn Lys Tyr Val Ala

1 5 10

<210> 109

<211> 11

<212> PRT

<213> 人工的序列

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<223> PR000448 LCDR1 Chothia

<400> 109

Arg Ala Ser Gln Ser Ile Ser Ser Ile Leu Ala

1 5 10

<210> 110

<211> 11

<212> PRT

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<223> PR000483 LCDR1 Chothia

<400> 110

Ser Gly Asp Asn Ile Gly Asp Gln Tyr Ala His

1 5 10

<210> 111

<211> 11

<212> PRT

<213> 人工的序列

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<223> PR000628 LCDR1 Chothia

<400> 111

Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala

1 5 10

<210> 112

<211> 11

<212> PRT

<213> 人工的序列

<220>

<223> PR001476 LCDR1 Chothia, PR002408 LCDR1 Chothia

<400> 112

Arg Ala Ser Gln Ser Ile Ser Ser Asn Leu Gly

1 5 10

<210> 113

<211> 11

<212> PRT

<213> 人工的序列

<220>

<223> PR002037 LCDR1 Chothia, PR002410 LCDR1 Chothia

<400> 113

Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala

1 5 10

<210> 114

<211> 15

<212> PRT

<213> 人工的序列

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<223> PR000157 LFWR2 Chothia

<400> 114

Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr

1 5 10 15

<210> 115

<211> 15

<212> PRT

<213> 人工的序列

<220>

<223> PR000448 LFWR2 Chothia, PR000628 LFWR2 Chothia, PR001476 LFWR2 Chothia

<400> 115

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr

1 5 10 15

<210> 116

<211> 15

<212> PRT

<213> 人工的序列

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<223> PR000483 LFWR2 Chothia

<400> 116

Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr

1 5 10 15

<210> 117

<211> 7

<212> PRT

<213> 人工的序列

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<223> PR000157 LCDR2 Chothia

<400> 117

Tyr Thr Ser Thr Leu Gln Pro

1 5

<210> 118

<211> 7

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<223> PR000448 LCDR2 Chothia, PR001476 LCDR2 Chothia, PR002037 LCDR2 Chothia

<400> 118

Gly Ala Ser Thr Arg Ala Thr

1 5

<210> 119

<211> 7

<212> PRT

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<220>

<223> PR000483 LCDR2 Chothia

<400> 119

Gln Asp Lys Asn Arg Pro Ser

1 5

<210> 120

<211> 7

<212> PRT

<213> 人工的序列

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<223> PR000628 LCDR2 Chothia

<400> 120

Asp Ala Ser Asn Arg Ala Thr

1 5

<210> 121

<211> 32

<212> PRT

<213> 人工的序列

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<223> PR000157 LFWR3 Chothia

<400> 121

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

1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys

20 25 30

<210> 122

<211> 32

<212> PRT

<213> 人工的序列

<220>

<223> PR000448 LFWR3 Chothia, PR001476 LFWR3 Chothia, PR002408 LFWR3 Chothia

<400> 122

Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr

1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys

20 25 30

<210> 123

<211> 32

<212> PRT

<213> 人工的序列

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<223> PR000483 LFWR3 Chothia

<400> 123

Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr

1 5 10 15

Leu Thr Ile Ser Gly Thr Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys

20 25 30

<210> 124

<211> 32

<212> PRT

<213> 人工的序列

<220>

<223> PR000628 LFWR3 Chothia

<400> 124

Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr

1 5 10 15

Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys

20 25 30

<210> 125

<211> 32

<212> PRT

<213> 人工的序列

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<223> PR002037 LFWR3 Chothia

<400> 125

Gly Ile Pro Ala Arg Val Ser Gly Gly Gly Ser Gly Thr Glu Phe Thr

1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Cys Cys

20 25 30

<210> 126

<211> 32

<212> PRT

<213> 人工的序列

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<223> PR002410 LFWR3 Chothia

<400> 126

Gly Ile Pro Ala Arg Val Ser Gly Gly Gly Ser Gly Thr Glu Phe Thr

1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys

20 25 30

<210> 127

<211> 9

<212> PRT

<213> 人工的序列

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<223> PR000157 LCDR3 Chothia

<400> 127

Leu Gln Tyr Gly Asp Leu Leu Tyr Ala

1 5

<210> 128

<211> 9

<212> PRT

<213> 人工的序列

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<223> PR000448 LCDR3 Chothia

<400> 128

Gln Gln Tyr Tyr Asn Trp Pro Leu Thr

1 5

<210> 129

<211> 11

<212> PRT

<213> 人工的序列

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<223> PR000483 LCDR3 Chothia

<400> 129

Ala Thr Tyr Thr Gly Phe Gly Ser Leu Ala Val

1 5 10

<210> 130

<211> 11

<212> PRT

<213> 人工的序列

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<223> PR000628 LCDR3 Chothia

<400> 130

Gln Gln Arg Ser Asn Trp Pro Pro Ala Leu Thr

1 5 10

<210> 131

<211> 10

<212> PRT

<213> 人工的序列

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<223> PR001476 LCDR3 Chothia

<400> 131

Gln Gln Tyr Asn Ser Trp Pro Pro Leu Thr

1 5 10

<210> 132

<211> 9

<212> PRT

<213> 人工的序列

<220>

<223> PR002037 LCDR3 Chothia, PR002410 LCDR3 Chothia

<400> 132

Gln Gln Tyr Lys Asn Trp Pro Phe Thr

1 5

<210> 133

<211> 10

<212> PRT

<213> 人工的序列

<220>

<223> PR002408 LCDR3 Chothia

<400> 133

Gln Gln Tyr Gln Ser Trp Pro Pro Leu Thr

1 5 10

<210> 134

<211> 10

<212> PRT

<213> 人工的序列

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<223> PR000157 LFWR4 Chothia

<400> 134

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

1 5 10

<210> 135

<211> 10

<212> PRT

<213> 人工的序列

<220>

<223> PR000448 LFWR4 Chothia, PR000628 LFWR4 Chothia, PR001476 LFWR4 Chothia

<400> 135

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

1 5 10

<210> 136

<211> 10

<212> PRT

<213> 人工的序列

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<223> PR000483 LFWR4 Chothia

<400> 136

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu

1 5 10

<210> 137

<211> 10

<212> PRT

<213> 人工的序列

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<223> PR002037 LFWR4 Chothia, PR002410 LFWR4 Chothia

<400> 137

Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys

1 5 10

<210> 138

<211> 121

<212> PRT

<213> 人工的序列

<220>

<223> PR000157 VH

<400> 138

Glu 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 Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Asp Ile Tyr Pro Gly Gly Gly Tyr Thr Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Leu Ala Gly Ser Ser Tyr Arg Gly Ala Met Asp Ser Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 139

<211> 115

<212> PRT

<213> 人工的序列

<220>

<223> PR000448 VH

<400> 139

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Gln His Ser Gly Ser Thr Asp Ser Asn Pro Ser Leu Lys
50 55 60

Gly Arg Val Thr Phe Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Leu Thr Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 140

<211> 116

<212> PRT

<213> 人工的序列

<220>

<223> PR000483 VH

<400> 140

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Thr Tyr
20 25 30

Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Lys Ile Tyr Pro Gly Asp Ser Tyr Thr Asn Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Tyr Gly Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 141

<211> 121

<212> PRT

<213> 人工的序列

<220>

<223> PR000628 VH

<400> 141

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn His Gly Gly Tyr Val Thr Tyr Asn Pro Ser Leu Glu
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Asp Tyr Gly Pro Gly Asn Tyr Asp Trp Tyr Phe Asp Leu Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 142

<211> 119

<212> PRT

<213> 人工的序列

<220>

<223> PR001476 VH

<400> 142

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 143

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001758 VH

<400> 143

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Leu Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Asp Asp Thr Tyr Tyr Gly Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Gln Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Lys Glu Lys Ala Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 144

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001760 VH

<400> 144

Glu 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 Tyr
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 145

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001763 VH

<400> 145

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

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

Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Glu Gly Ser Asn Gly Thr Asp Asp Tyr His Tyr Asp Ile Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 146

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001764 VH

<400> 146

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ser Ala Ile Ser Gly Gly Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asp Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Glu Gly Thr Thr Glu Thr Asp Asp Tyr His Tyr Asn Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 147

<211> 126

<212> PRT

<213> 人工的序列

<220>

<223> PR001767 VH

<400> 147

Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Tyr Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

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

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

Met Asp Val Arg Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 148

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001768 VH

<400> 148

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Asp Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Glu Gly Thr Gly Thr Thr Ser Asp Tyr Tyr Tyr Asn Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 149

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001771 VH

<400> 149

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Thr Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Glu Gly Thr Gly Thr Thr Ser Asp Tyr Tyr Tyr Asn Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 150

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001774 VH

<400> 150

Glu 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 Ser Phe
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Gly Ser Gly Asp Thr Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Lys Glu Ala Thr Ala Met Ala Ser Asp Tyr Tyr Tyr Gly Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 151

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001780 VH

<400> 151

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Gly Ser Gly Asp Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Lys Glu Asp Thr Ala Val Ala Ser Asp Tyr Tyr Tyr Asn Ile Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 152

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001781 VH

<400> 152

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Leu Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Glu Arg Thr Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 153

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001830 VH

<400> 153

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

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

Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 154

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001833 VH

<400> 154

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Lys Glu Gly Ala Thr Glu Thr Asp Asp Tyr His Phe Asn Thr Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 155

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001836 VH

<400> 155

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn Phe
20 25 30

Ala Met Thr Trp Val Arg Gln Pro Pro Glu Lys Gly Leu Lys Trp Val
35 40 45

Ser Ser Ile Asn Gly Ser Gly Phe Asn Thr Tyr Tyr Thr Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 156

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001838 VH

<400> 156

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val
35 40 45

Ser Ser Ile Asp Gly Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 157

<211> 123

<212> PRT

<213> 人工的序列

<220>

<223> PR001840 VH

<400> 157

Glu 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 Ser Tyr
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val
35 40 45

Ser Arg Ile Asn Ser Asp Gly Ser Ser Thr Ser Tyr Ala Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

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

Val Arg Lys Gly Ser Ser Ser Tyr Tyr His Tyr Ser Ile Glu Asp Asp
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 158

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR001842 VH

<400> 158

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu His Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Glu Lys Val Ala Thr Thr Gly Asp Tyr Tyr Tyr Asp Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 159

<211> 116

<212> PRT

<213> 人工的序列

<220>

<223> PR002037 VH, PR002410 VH

<400> 159

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Met Arg Val Ser Cys Lys Ala Ser Glu Asp Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Thr Ala Pro Ile Phe Gly Thr Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 160

<211> 119

<212> PRT

<213> 人工的序列

<220>

<223> PR002408 VH

<400> 160

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 161

<211> 124

<212> PRT

<213> 人工的序列

<220>

<223> PR004469 VH

<400> 161

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val
35 40 45

Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 162

<211> 107

<212> PRT

<213> 人工的序列

<220>

<223> PR000157 VL

<400> 162

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 Lys Ala Ser Gln Gly Phe Asn Lys Tyr
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

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

Ser Gly Ser Gly Arg Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Gly Asp Leu Leu Tyr
85 90 95

Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 163

<211> 107

<212> PRT

<213> 人工的序列

<220>

<223> PR000448 VL

<400> 163

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ile
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 164

<211> 108

<212> PRT

<213> 人工的序列

<220>

<223> PR000483 VL

<400> 164

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln

1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Asn Ile Gly Asp Gln Tyr Ala

20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr

35 40 45

Gln Asp Lys Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser

50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met

65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Tyr Thr Gly Phe Gly Ser Leu

85 90 95

Ala Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu

100 105

<210> 165

<211> 109

<212> PRT

<213> 人工的序列

<220>

<223> PR000628 VL

<400> 165

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

1 5 10 15

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

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro

85 90 95

Ala Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

100 105

<210> 166

<211> 108

<212> PRT

<213> 人工的序列

<220>

<223> PR001476 VL

<400> 166

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

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn

20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Ser Trp Pro Pro

85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

100 105

<210> 167

<211> 107

<212> PRT

<213> 人工的序列

<220>

<223> PR002037 VL

<400> 167

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

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Val Ser Gly

50 55 60

Gly Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser

65 70 75 80

Glu Asp Phe Ala Val Tyr Cys Cys Gln Gln Tyr Lys Asn Trp Pro Phe

85 90 95

Thr Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys

100 105

<210> 168

<211> 108

<212> PRT

<213> 人工的序列

<220>

<223> PR002408 VL

<400> 168

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

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn

20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro Pro

85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

100 105

<210> 169

<211> 107

<212> PRT

<213> 人工的序列

<220>

<223> PR002410 VL

<400> 169

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

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Val Ser Gly

50 55 60

Gly Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Lys Asn Trp Pro Phe

85 90 95

Thr Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys

100 105

<210> 170

<211> 451

<212> PRT

<213> 人工的序列

<220>

<223> PR000157 HC

<400> 170

Glu 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 Ser Tyr

20 25 30

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

35 40 45

Gly Asp Ile Tyr Pro Gly Gly Gly Tyr Thr Asn Tyr Asn Glu Lys Phe

50 55 60

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

65 70 75 80

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

85 90 95

Ala Arg Leu Ala Gly Ser Ser Tyr Arg Gly Ala Met Asp Ser Trp Gly

100 105 110

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

115 120 125

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

130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val

145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala

165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val

180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His

195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys

210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly

225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met

245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His

260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val

275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr

290 295 300

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

305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile

325 330 335

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

340 345 350

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

355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu

370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro

385 390 395 400

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

405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met

420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser

435 440 445

Pro Gly Lys

450

<210> 171

<211> 442

<212> PRT

<213> 人工的序列

<220>

<223> PR000448 HC

<400> 171

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Gln His Ser Gly Ser Thr Asp Ser Asn Pro Ser Leu Lys
50 55 60

Gly Arg Val Thr Phe Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Leu Thr Gly Pro Phe Asp 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 Leu Gly Gly Pro Ser 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 Asn 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 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 His Tyr Thr

420 425 430

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys

435 440

<210> 172

<211> 442

<212> PRT

<213> 人工的序列

<220>

<223> PR000483 HC

<400> 172

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

1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Thr Tyr

20 25 30

Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Lys Ile Tyr Pro Gly Asp Ser Tyr Thr Asn Tyr Ser Pro Ser Phe

50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Gly Tyr Gly Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val

100 105 110

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

115 120 125

Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu

130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly

145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser

165 170 175

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

180 185 190

Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr

195 200 205

Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro

210 215 220

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser 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 His 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 Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val

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 Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly

325 330 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg 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 Met 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 Gln 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 Lys Ser Leu Ser Leu Ser Pro Gly Lys

435 440

<210> 173

<211> 448

<212> PRT

<213> 人工的序列

<220>

<223> PR000628 HC

<400> 173

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

1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr

20 25 30

Tyr Trp Ser Trp Ile Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Ile

35 40 45

Gly Glu Ile Asn His Gly Gly Tyr Val Thr Tyr Asn Pro Ser Leu Glu

50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu

65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala

85 90 95

Arg Asp Tyr Gly Pro Gly Asn Tyr Asp Trp Tyr Phe Asp Leu Trp Gly

100 105 110

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

115 120 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala

130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val

145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala

165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val

180 185 190

Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His

195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly

210 215 220

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser

225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg

245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro

260 265 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala

275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val

290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr

305 310 315 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr

325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu

340 345 350

Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys

355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser

370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp

385 390 395 400

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

405 410 415

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala

420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys

435 440 445

<210> 174

<211> 449

<212> PRT

<213> 人工的序列

<220>

<223> PR001476 HC

<400> 174

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Lys

<210> 175

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR001758 HC

<400> 175

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Leu Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Asp Asp Thr Tyr Tyr Gly Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Gln Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Lys Glu Lys Ala Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
130 135 140

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 176

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR001760 HC

<400> 176

Glu 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 Tyr
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

130 135 140

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

145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 177

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR001763 HC

<400> 177

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

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

20 25 30

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

35 40 45

Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Glu Gly Ser Asn Gly Thr Asp Asp Tyr His Tyr Asp Ile Asp

100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser

115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

130 135 140

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

145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 178

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR001764 HC

<400> 178

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

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

20 25 30

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

35 40 45

Ser Ala Ile Ser Gly Gly Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

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

85 90 95

Ala Lys Glu Gly Thr Thr Glu Thr Asp Asp Tyr His Tyr Asn Met Asp

100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser

115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

130 135 140

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

145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 179

<211> 358

<212> PRT

<213> 人工的序列

<220>

<223> PR001767 HC

<400> 179

Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Tyr Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

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

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

Met Asp Val Arg Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro
115 120 125

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
130 135 140

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
145 150 155 160

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
165 170 175

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly

180 185 190

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

195 200 205

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp

210 215 220

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

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

290 295 300

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

305 310 315 320

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

325 330 335

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

340 345 350

Ser Leu Ser Pro Gly Lys

355

<210> 180

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR001768 HC

<400> 180

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Asp Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Glu Gly Thr Gly Thr Thr Ser Asp Tyr Tyr Tyr Asn Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

130 135 140

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

145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 181

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR001771 HC

<400> 181

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

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

20 25 30

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

35 40 45

Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Glu Gly Thr Gly Thr Thr Ser Asp Tyr Tyr Tyr Asn Val Asp

100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser

115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

130 135 140

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

145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 182

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR001774 HC

<400> 182

Glu 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 Ser Phe

20 25 30

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

35 40 45

Ser Thr Ile Ser Gly Ser Gly Asp Thr Thr Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr Phe Cys

85 90 95

Ala Lys Glu Ala Thr Ala Met Ala Ser Asp Tyr Tyr Tyr Gly Val Asp

100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser

115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

130 135 140

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

145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 183

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR001780 HC

<400> 183

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Gly Ser Gly Asp Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Lys Glu Asp Thr Ala Val Ala Ser Asp Tyr Tyr Tyr Asn Ile Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
130 135 140

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 184

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR001781 HC

<400> 184

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Leu Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Glu Arg Thr Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

130 135 140

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

145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 185

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR001830 HC

<400> 185

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

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

20 25 30

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

35 40 45

Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys

85 90 95

Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp

100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser

115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

130 135 140

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

145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 186

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR001833 HC

<400> 186

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

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

20 25 30

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

35 40 45

Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys

85 90 95

Ala Lys Glu Gly Ala Thr Glu Thr Asp Asp Tyr His Phe Asn Thr Asp

100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser

115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

130 135 140

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

145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 187

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR001836 HC

<400> 187

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn Phe
20 25 30

Ala Met Thr Trp Val Arg Gln Pro Pro Glu Lys Gly Leu Lys Trp Val
35 40 45

Ser Ser Ile Asn Gly Ser Gly Phe Asn Thr Tyr Tyr Thr Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
130 135 140

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 188

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR001838 HC

<400> 188

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val
35 40 45

Ser Ser Ile Asp Gly Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

130 135 140

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

145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 189

<211> 355

<212> PRT

<213> 人工的序列

<220>

<223> PR001840 HC

<400> 189

Glu 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 Ser Tyr

20 25 30

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

35 40 45

Ser Arg Ile Asn Ser Asp Gly Ser Ser Thr Ser Tyr Ala Asp Ser Val

50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Val Arg Lys Gly Ser Ser Ser Tyr Tyr His Tyr Ser Ile Glu Asp Asp

100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Glu Pro Lys Ser Cys

115 120 125

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly

130 135 140

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met

145 150 155 160

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His

165 170 175

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val

180 185 190

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr

195 200 205

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

210 215 220

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile

225 230 235 240

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

245 250 255

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

260 265 270

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu

275 280 285

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro

290 295 300

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

305 310 315 320

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met

325 330 335

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser

340 345 350

Pro Gly Lys

355

<210> 190

<211> 356

<212> PRT

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

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

20 25 30

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

35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu His Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Glu Lys Val Ala Thr Thr Gly Asp Tyr Tyr Tyr Asp Met Asp

100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser

115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

130 135 140

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

145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 191

<211> 446

<212> PRT

<213> 人工的序列

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<223> PR002037 HC, PR002410 HC

<400> 191

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Met Arg Val Ser Cys Lys Ala Ser Glu Asp Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Thr Ala Pro Ile Phe Gly Thr Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

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

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr

195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr

210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe

225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

305 310 315 320

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

325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

355 360 365

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

370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

405 410 415

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

420 425 430

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

435 440 445

<210> 192

<211> 449

<212> PRT

<213> 人工的序列

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<223> PR002408 HC

<400> 192

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Lys

<210> 193

<211> 356

<212> PRT

<213> 人工的序列

<220>

<223> PR004469 HC

<400> 193

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

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

20 25 30

Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val

35 40 45

Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp

100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser

115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

130 135 140

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

145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 194

<211> 214

<212> PRT

<213> 人工的序列

<220>

<223> PR000157 LC

<400> 194

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 Lys Ala Ser Gln Gly Phe Asn Lys Tyr

20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

35 40 45

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

50 55 60

Ser Gly Ser Gly Arg Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro

65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Gly Asp Leu Leu Tyr

85 90 95

Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala

100 105 110

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

115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala

130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln

145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser

165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr

180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser

195 200 205

Phe Asn Arg Gly Glu Cys

210

<210> 195

<211> 214

<212> PRT

<213> 人工的序列

<220>

<223> PR000448 LC

<400> 195

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ile
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln

145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser

165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr

180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser

195 200 205

Phe Asn Arg Gly Glu Cys

210

<210> 196

<211> 214

<212> PRT

<213> 人工的序列

<220>

<223> PR000483 LC

<400> 196

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln

1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Asn Ile Gly Asp Gln Tyr Ala

20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr

35 40 45

Gln Asp Lys Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser

50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met

65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Tyr Thr Gly Phe Gly Ser Leu

85 90 95

Ala Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys

100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln

115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly

130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly

145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala

165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser

180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val

195 200 205

Ala Pro Thr Glu Cys Ser

210

<210> 197

<211> 216

<212> PRT

<213> 人工的序列

<220>

<223> PR000628 LC

<400> 197

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Ala Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val
100 105 110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
115 120 125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
130 135 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn

145 150 155 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser

165 170 175

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

180 185 190

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr

195 200 205

Lys Ser Phe Asn Arg Gly Glu Cys

210 215

<210> 198

<211> 215

<212> PRT

<213> 人工的序列

<220>

<223> PR001476 LC, PR002789鏈, PR002790鏈, PR002791鏈, PR002792

<400> 198

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

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn

20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Ser Trp Pro Pro

85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala

100 105 110

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

115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu

130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser

145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val

180 185 190

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

195 200 205

Ser Phe Asn Arg Gly Glu Cys

210 215

<210> 199

<211> 214

<212> PRT

<213> 人工的序列

<220>

<223> PR002037 LC

<400> 199

Glu Ile Val Met Thr Gln Ser Pro Ala Ser Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Val Ser Gly
50 55 60

Gly Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Cys Cys Gln Gln Tyr Lys Asn Trp Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln

145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser

165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr

180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser

195 200 205

Phe Asn Arg Gly Glu Cys

210

<210> 200

<211> 215

<212> PRT

<213> 人工的序列

<220>

<223> PR002408 LC, PR003334鏈, PR003335鏈, PR003336鏈, PR003337

<400> 200

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

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn

20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro Pro

85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala

100 105 110

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

115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu

130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser

145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val

180 185 190

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

195 200 205

Ser Phe Asn Arg Gly Glu Cys

210 215

<210> 201

<211> 214

<212> PRT

<213> 人工的序列

<220>

<223> PR002410 LC, PR002972鏈, PR004158鏈, PR004160鏈, PR004161

<400> 201

Glu Ile Val Met Thr Gln Ser Pro Ala Ser Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Val Ser Gly
50 55 60

Gly Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Lys Asn Trp Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln

145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser

165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr

180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser

195 200 205

Phe Asn Arg Gly Glu Cys

210

<210> 202

<211> 702

<212> PRT

<213> 人工的序列

<220>

<223> PR002789鏈

<400> 202

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser

465 470 475 480

Glu Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly

485 490 495

Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp

500 505 510

Ile Gly Glu Ile Gln His Ser Gly Ser Thr Asp Ser Asn Pro Ser Leu

515 520 525

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

530 535 540

Leu Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys

545 550 555 560

Ala Arg Leu Thr Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val

565 570 575

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly

580 585 590

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

595 600 605

Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile

610 615 620

Ser Ser Ile Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg

625 630 635 640

Leu Leu Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg

645 650 655

Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser

660 665 670

Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn

675 680 685

Trp Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

690 695 700

<210> 203

<211> 589

<212> PRT

<213> 人工的序列

<220>

<223> PR002790鏈

<400> 203

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Leu Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Asp Asp Thr Tyr Tyr Gly Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe

545 550 555 560

Cys Ala Lys Glu Lys Ala Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

<210> 204

<211> 589

<212> PRT

<213> 人工的序列

<220>

<223> PR002791鏈

<400> 204

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe

545 550 555 560

Cys Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

<210> 205

<211> 589

<212> PRT

<213> 人工的序列

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<223> PR002792鏈

<400> 205

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Asn Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Tyr

545 550 555 560

Cys Ala Lys Glu Gly Ser Asn Gly Thr Asp Asp Tyr His Tyr Asp Ile

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

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<212> PRT

<213> 人工的序列

<220>

<223> PR002793鏈

<400> 206

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ala Ile Ser Gly Gly Gly Gly Ser Thr Tyr Tyr Ala Asp Ser

515 520 525

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

530 535 540

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

545 550 555 560

Cys Ala Lys Glu Gly Thr Thr Glu Thr Asp Asp Tyr His Tyr Asn Met

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

<210> 207

<211> 591

<212> PRT

<213> 人工的序列

<220>

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<400> 207

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Ile Gln Pro Gly

465 470 475 480

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

485 490 495

Asn Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp

500 505 510

Val Ser Val Ile Tyr Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val

515 520 525

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

530 535 540

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

545 550 555 560

Ala Arg Asp Arg Tyr Tyr Gly Ser Gly Asn Tyr Pro Thr Ala Tyr Tyr

565 570 575

Gly Met Asp Val Arg Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585 590

<210> 208

<211> 589

<212> PRT

<213> 人工的序列

<220>

<223> PR002795鏈

<400> 208

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Asp Ser Thr Tyr Tyr Ala Asp Ser

515 520 525

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

530 535 540

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

545 550 555 560

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

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

<210> 209

<211> 589

<212> PRT

<213> 人工的序列

<220>

<223> PR002798鏈

<400> 209

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

465 470 475 480

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

485 490 495

Phe Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Thr Ile Ser Gly Ser Gly Asp Thr Thr Tyr Tyr Ala Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr Phe

545 550 555 560

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

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

<210> 210

<211> 589

<212> PRT

<213> 人工的序列

<220>

<223> PR002800鏈

<400> 210

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly

465 470 475 480

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

485 490 495

Phe Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp

500 505 510

Val Ser Thr Ile Ser Gly Ser Gly Asp Asn Thr Tyr Tyr Ala Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe

545 550 555 560

Cys Ala Lys Glu Asp Thr Ala Val Ala Ser Asp Tyr Tyr Tyr Asn Ile

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

<210> 211

<211> 589

<212> PRT

<213> 人工的序列

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Leu Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser

515 520 525

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

530 535 540

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

545 550 555 560

Cys Ala Lys Glu Arg Thr Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

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<213> 人工的序列

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

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

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe

545 550 555 560

Cys Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

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<213> 人工的序列

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<400> 213

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe

545 550 555 560

Cys Ala Lys Glu Gly Ala Thr Glu Thr Asp Asp Tyr His Phe Asn Thr

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

<210> 214

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<212> PRT

<213> 人工的序列

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<400> 214

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

465 470 475 480

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

485 490 495

Phe Ala Met Thr Trp Val Arg Gln Pro Pro Glu Lys Gly Leu Lys Trp

500 505 510

Val Ser Ser Ile Asn Gly Ser Gly Phe Asn Thr Tyr Tyr Thr Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Asn Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe

545 550 555 560

Cys Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

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<213> 人工的序列

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

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

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp

500 505 510

Val Ser Ser Ile Asp Gly Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser

515 520 525

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

530 535 540

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

545 550 555 560

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

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

<210> 216

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<212> PRT

<213> 人工的序列

<220>

<223> PR002808鏈

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Ser Trp Gly Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp

500 505 510

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser

515 520 525

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

530 535 540

Tyr Leu His Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr

545 550 555 560

Cys Ala Lys Glu Lys Val Ala Thr Thr Gly Asp Tyr Tyr Tyr Asp Met

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

<210> 217

<211> 699

<212> PRT

<213> 人工的序列

<220>

<223> PR002972鏈

<400> 217

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

1 5 10 15

Ser Met Arg Val Ser Cys Lys Ala Ser Glu Asp Thr Phe Ser Ser Tyr

20 25 30

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

35 40 45

Gly Gly Thr Ala Pro Ile Phe Gly Thr Thr Asn Tyr Ala Gln Lys Phe

50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

65 70 75 80

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

85 90 95

Ala Arg Gly Gly Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val

100 105 110

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

115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu

130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly

145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser

165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr

195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr

210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe

225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

305 310 315 320

Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser

325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

355 360 365

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

370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

405 410 415

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

420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Glu Pro Lys

435 440 445

Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg Thr Gln Val

450 455 460

Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu Thr Leu

465 470 475 480

Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr Tyr Trp

485 490 495

Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Glu

500 505 510

Ile Gln His Ser Gly Ser Thr Asp Ser Asn Pro Ser Leu Lys Gly Arg

515 520 525

Val Thr Phe Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu

530 535 540

Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg Leu

545 550 555 560

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

565 570 575

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser

580 585 590

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

595 600 605

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ile

610 615 620

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

625 630 635 640

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

645 650 655

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser

660 665 670

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn Trp Pro Leu

675 680 685

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

690 695

<210> 218

<211> 589

<212> PRT

<213> 人工的序列

<220>

<223> PR003334鏈

<400> 218

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Leu Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Asp Asp Thr Tyr Tyr Gly Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe

545 550 555 560

Cys Ala Lys Glu Lys Ala Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

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

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe

545 550 555 560

Cys Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

<210> 220

<211> 589

<212> PRT

<213> 人工的序列

<220>

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<400> 220

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe

545 550 555 560

Cys Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

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

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe

545 550 555 560

Cys Ala Lys Glu Gly Ala Thr Glu Thr Asp Asp Tyr His Phe Asn Thr

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

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<213> 人工的序列

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<400> 222

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp

500 505 510

Val Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser

515 520 525

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

530 535 540

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

545 550 555 560

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

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

<210> 223

<211> 713

<212> PRT

<213> 人工的序列

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<223> PR003487鏈

<400> 223

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

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

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe

545 550 555 560

Cys Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Val Gln

580 585 590

Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly Ser Leu Arg

595 600 605

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Thr

610 615 620

Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val Ser Ser Ile

625 630 635 640

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

645 650 655

Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met

660 665 670

Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Lys Glu

675 680 685

Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp Val Trp Gly

690 695 700

Gln Gly Thr Thr Val Thr Val Ser Ser

705 710

<210> 224

<211> 718

<212> PRT

<213> 人工的序列

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

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

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe

545 550 555 560

Cys Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly

580 585 590

Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro

595 600 605

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

610 615 620

Asn Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu

625 630 635 640

Trp Val Ser Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp

645 650 655

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

660 665 670

Leu Tyr Leu Gln Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr

675 680 685

Phe Cys Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn

690 695 700

Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

705 710 715

<210> 225

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<220>

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<400> 225

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

450 455 460

Thr Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly

465 470 475 480

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

485 490 495

Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp

500 505 510

Val Ser Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser

515 520 525

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

530 535 540

Tyr Leu Gln Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe

545 550 555 560

Cys Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val

565 570 575

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly

580 585 590

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu

595 600 605

Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly Ser Leu Arg Leu

610 615 620

Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Thr Trp

625 630 635 640

Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val Ser Ser Ile Ser

645 650 655

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

660 665 670

Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Thr

675 680 685

Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Lys Glu Gly

690 695 700

Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp Val Trp Gly Gln

705 710 715 720

Gly Thr Thr Val Thr Val Ser Ser

725

<210> 226

<211> 715

<212> PRT

<213> 人工的序列

<220>

<223> PR004158鏈

<400> 226

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

1 5 10 15

Ser Met Arg Val Ser Cys Lys Ala Ser Glu Asp Thr Phe Ser Ser Tyr

20 25 30

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

35 40 45

Gly Gly Thr Ala Pro Ile Phe Gly Thr Thr Asn Tyr Ala Gln Lys Phe

50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

65 70 75 80

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

85 90 95

Ala Arg Gly Gly Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val

100 105 110

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

115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu

130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly

145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser

165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr

195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr

210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe

225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

305 310 315 320

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

325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

355 360 365

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

370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

405 410 415

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

420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Glu Pro Lys

435 440 445

Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg Thr Glu Val

450 455 460

Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly Ser Leu

465 470 475 480

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

485 490 495

Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val Ser Ser

500 505 510

Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly

515 520 525

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln

530 535 540

Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Lys

545 550 555 560

Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp Val Trp

565 570 575

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu

580 585 590

Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly Ser

595 600 605

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

610 615 620

Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val Ser

625 630 635 640

Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser Val Lys

645 650 655

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu

660 665 670

Gln Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala

675 680 685

Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp Val

690 695 700

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

705 710 715

<210> 227

<211> 446

<212> PRT

<213> 人工的序列

<220>

<223> PR004160鏈，PR004161鏈，PR004181鏈，PR004182鏈

<400> 227

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Met Arg Val Ser Cys Lys Ala Ser Glu Asp Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Thr Ala Pro Ile Phe Gly Thr Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

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

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr

195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr

210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe

225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

305 310 315 320

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

325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

340 345 350

Cys Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val

355 360 365

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

370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

405 410 415

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

420 425 430

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

435 440 445

<210> 228

<211> 497

<212> PRT

<213> 人工的序列

<220>

<223> PR004160鏈

<400> 228

Glu 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 Tyr

20 25 30

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

35 40 45

Ser Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys

85 90 95

Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp

100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly

115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val

130 135 140

Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly Ser Leu Arg Leu Ser

145 150 155 160

Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Thr Trp Val

165 170 175

Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Gly

180 185 190

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

195 200 205

Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Thr Arg

210 215 220

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

225 230 235 240

Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp Val Trp Gly Gln Gly

245 250 255

Thr Thr Val Thr Val Ser Ser Ala Ser Glu Pro Lys Ser Ser Asp Lys

260 265 270

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

275 280 285

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser

290 295 300

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp

305 310 315 320

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

325 330 335

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val

340 345 350

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu

355 360 365

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys

370 375 380

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr

385 390 395 400

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

405 410 415

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu

420 425 430

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu

435 440 445

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys

450 455 460

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu

465 470 475 480

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly

485 490 495

Lys

<210> 229

<211> 638

<212> PRT

<213> 人工的序列

<220>

<223> PR004161鏈

<400> 229

Glu 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 Tyr

20 25 30

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

35 40 45

Ser Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys

85 90 95

Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp

100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly

115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val

130 135 140

Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly Ser Leu Arg Leu Ser

145 150 155 160

Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Thr Trp Val

165 170 175

Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Gly

180 185 190

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

195 200 205

Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Thr Arg

210 215 220

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

225 230 235 240

Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp Val Trp Gly Gln Gly

245 250 255

Thr Thr Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly

260 265 270

Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly

275 280 285

Gly Gly Val Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala

290 295 300

Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Thr Trp Val Arg Gln Ala

305 310 315 320

Pro Glu Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Gly Ser Gly Val

325 330 335

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

340 345 350

Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Thr Arg Leu Thr Ala

355 360 365

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

370 375 380

Asp Asp His Tyr Tyr Asn Val Asp Val Trp Gly Gln Gly Thr Thr Val

385 390 395 400

Thr Val Ser Ser Ala Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr

405 410 415

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe

420 425 430

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

435 440 445

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

450 455 460

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

465 470 475 480

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

485 490 495

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

500 505 510

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

515 520 525

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro

530 535 540

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val

545 550 555 560

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

565 570 575

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

580 585 590

Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

595 600 605

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

610 615 620

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

625 630 635

<210> 230

<211> 586

<212> PRT

<213> 人工的序列

<220>

<223> PR004162鏈

<400> 230

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

1 5 10 15

Ser Met Arg Val Ser Cys Lys Ala Ser Glu Asp Thr Phe Ser Ser Tyr

20 25 30

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

35 40 45

Gly Gly Thr Ala Pro Ile Phe Gly Thr Thr Asn Tyr Ala Gln Lys Phe

50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

65 70 75 80

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

85 90 95

Ala Arg Gly Gly Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val

100 105 110

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

115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu

130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly

145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser

165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr

195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr

210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe

225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

305 310 315 320

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

325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

355 360 365

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

370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

405 410 415

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

420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Glu Pro Lys

435 440 445

Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg Thr Glu Val

450 455 460

Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly Ser Leu

465 470 475 480

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

485 490 495

Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val Ser Ser

500 505 510

Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly

515 520 525

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln

530 535 540

Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Lys

545 550 555 560

Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp Val Trp

565 570 575

Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

<210> 231

<211> 636

<212> PRT

<213> 人工的序列

<220>

<223> PR004181鏈

<400> 231

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

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

20 25 30

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

35 40 45

Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Glu Gly Thr Gly Thr Thr Ser Asp Tyr Tyr Tyr Asn Val Asp

100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly

115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu

130 135 140

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser

145 150 155 160

Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Thr Trp Val

165 170 175

Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Gly

180 185 190

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

195 200 205

Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser

210 215 220

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

225 230 235 240

Gly Thr Thr Ser Asp Tyr Tyr Tyr Asn Val Asp Val Trp Gly Gln Gly

245 250 255

Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly

260 265 270

Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly

275 280 285

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly

290 295 300

Phe Thr Phe Ser Asn Tyr Ala Met Thr Trp Val Arg Gln Pro Pro Gly

305 310 315 320

Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr

325 330 335

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

340 345 350

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

355 360 365

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

370 375 380

Tyr Tyr Tyr Asn Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val

385 390 395 400

Ser Ser Ala Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro

405 410 415

Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe

420 425 430

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val

435 440 445

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe

450 455 460

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro

465 470 475 480

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

485 490 495

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val

500 505 510

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

515 520 525

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

530 535 540

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly

545 550 555 560

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

565 570 575

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

580 585 590

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

595 600 605

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

610 615 620

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

625 630 635

<210> 232

<211> 633

<212> PRT

<213> 人工的序列

<220>

<223> PR004182鏈

<400> 232

Glu 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 Ser Tyr

20 25 30

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

35 40 45

Ser Arg Ile Asn Ser Asp Gly Ser Ser Thr Ser Tyr Ala Asp Ser Val

50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Val Arg Lys Gly Ser Ser Ser Tyr Tyr His Tyr Ser Ile Glu Asp Asp

100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser

115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu

130 135 140

Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys

145 150 155 160

Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Trp Met His Trp Val Arg

165 170 175

Gln Ala Pro Gly Lys Gly Leu Val Trp Val Ser Arg Ile Asn Ser Asp

180 185 190

Gly Ser Ser Thr Ser Tyr Ala Asp Ser Val Gln Gly Arg Phe Thr Ile

195 200 205

Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu

210 215 220

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

225 230 235 240

Ser Tyr Tyr His Tyr Ser Ile Glu Asp Asp Trp Gly Gln Gly Thr Leu

245 250 255

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

260 265 270

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val

275 280 285

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr

290 295 300

Phe Ser Ser Tyr Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly

305 310 315 320

Leu Val Trp Val Ser Arg Ile Asn Ser Asp Gly Ser Ser Thr Ser Tyr

325 330 335

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

340 345 350

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala

355 360 365

Val Tyr Tyr Cys Val Arg Lys Gly Ser Ser Ser Tyr Tyr His Tyr Ser

370 375 380

Ile Glu Asp Asp Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala

385 390 395 400

Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro

405 410 415

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

420 425 430

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

435 440 445

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr

450 455 460

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu

465 470 475 480

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His

485 490 495

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys

500 505 510

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln

515 520 525

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

530 535 540

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

545 550 555 560

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

565 570 575

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

580 585 590

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

595 600 605

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

610 615 620

Lys Ser Leu Ser Leu Ser Pro Gly Lys

625 630

<210> 233

<211> 222

<212> PRT

<213> 人工的序列

<220>

<223> PR004279鏈, PR005189鏈, PR005190鏈, PR005649鏈, PR0056

<400> 233

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys

210 215 220

<210> 234

<211> 586

<212> PRT

<213> 人工的序列

<220>

<223> PR004279鏈

<400> 234

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

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn

20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro Pro

85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala

100 105 110

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

115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu

130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser

145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val

180 185 190

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

195 200 205

Ser Phe Asn Arg Gly Glu Cys Glu Pro Lys Ser Ser Asp Lys Thr His

210 215 220

Thr Pro Pro Pro Pro Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly

225 230 235 240

Val Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly

245 250 255

Phe Thr Phe Ser Asn Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Glu

260 265 270

Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Gly Ser Gly Val Ser Thr

275 280 285

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

290 295 300

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

305 310 315 320

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

325 330 335

His Tyr Tyr Asn Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val

340 345 350

Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys

355 360 365

Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro

370 375 380

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

385 390 395 400

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp

405 410 415

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

420 425 430

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu

435 440 445

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

450 455 460

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly

465 470 475 480

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

485 490 495

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

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

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

565 570 575

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

580 585

<210> 235

<211> 578

<212> PRT

<213> 人工的序列

<220>

<223> PR004280鏈

<400> 235

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

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

450 455 460

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly

465 470 475 480

Phe Thr Phe Ser Asn Tyr Ala Met Ser Trp Phe Arg Gln Pro Pro Glu

485 490 495

Thr Gly Leu Lys Trp Val Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

Ser His Tyr Asp Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val

565 570 575

Ser Ser

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<211> 572

<212> PRT

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<223> PR004281鏈

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

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

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

450 455 460

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

465 470 475 480

Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val

485 490 495

Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val

500 505 510

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

515 520 525

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

530 535 540

Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp

545 550 555 560

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

565 570

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<223> PR004282鏈

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

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

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Gly Gly Ser Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly

450 455 460

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly

465 470 475 480

Phe Thr Phe Ser Asn Tyr Ala Met Ser Trp Phe Arg Gln Pro Pro Glu

485 490 495

Thr Gly Leu Lys Trp Val Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

Ser His Tyr Asp Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val

565 570 575

Ser Ser

<210> 238

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<212> PRT

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Met Arg Val Ser Cys Lys Ala Ser Glu Asp Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Thr Ala Pro Ile Phe Gly Thr Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

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

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly

145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser

165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr

195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr

210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe

225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

305 310 315 320

Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser

325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

355 360 365

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

370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

405 410 415

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

420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Glu Pro Lys

435 440 445

Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg Thr Glu Val

450 455 460

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu

465 470 475 480

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Trp Met

485 490 495

His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val Ser Arg

500 505 510

Ile Asn Ser Asp Gly Ser Ser Thr Ser Tyr Ala Asp Ser Val Gln Gly

515 520 525

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln

530 535 540

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

545 550 555 560

Lys Gly Ser Ser Ser Tyr Tyr His Tyr Ser Ile Glu Asp Asp Trp Gly

565 570 575

Gln Gly Thr Leu Val Thr Val Ser Ser

580 585

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<212> PRT

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

1 5 10 15

Ser Met Arg Val Ser Cys Lys Ala Ser Glu Asp Thr Phe Ser Ser Tyr

20 25 30

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

35 40 45

Gly Gly Thr Ala Pro Ile Phe Gly Thr Thr Asn Tyr Ala Gln Lys Phe

50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

65 70 75 80

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

85 90 95

Ala Arg Gly Gly Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val

100 105 110

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

115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu

130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly

145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser

165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr

195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr

210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe

225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

305 310 315 320

Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser

325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

355 360 365

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

370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

405 410 415

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

420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Glu Pro Lys

435 440 445

Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg Thr Glu Val

450 455 460

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu

465 470 475 480

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Trp Met

485 490 495

His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val Ser Arg

500 505 510

Ile Asn Ser Asp Gly Ser Ser Thr Ser Tyr Ala Asp Ser Val Gln Gly

515 520 525

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln

530 535 540

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

545 550 555 560

Lys Gly Ser Ser Ser Tyr Tyr His Tyr Ser Ile Glu Asp Asp Trp Gly

565 570 575

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu Val

580 585 590

Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu

595 600 605

Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Trp Met

610 615 620

His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val Ser Arg

625 630 635 640

Ile Asn Ser Asp Gly Ser Ser Thr Ser Tyr Ala Asp Ser Val Gln Gly

645 650 655

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln

660 665 670

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

675 680 685

Lys Gly Ser Ser Ser Tyr Tyr His Tyr Ser Ile Glu Asp Asp Trp Gly

690 695 700

Gln Gly Thr Leu Val Thr Val Ser Ser

705 710

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<211> 586

<212> PRT

<213> 人工的序列

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<223> PR004359鏈

<400> 240

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

1 5 10 15

Ser Met Arg Val Ser Cys Lys Ala Ser Glu Asp Thr Phe Ser Ser Tyr

20 25 30

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

35 40 45

Gly Gly Thr Ala Pro Ile Phe Gly Thr Thr Asn Tyr Ala Gln Lys Phe

50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

65 70 75 80

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

85 90 95

Ala Arg Gly Gly Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val

100 105 110

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

115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu

130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly

145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser

165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr

195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr

210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe

225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

305 310 315 320

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

325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

355 360 365

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

370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

405 410 415

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

420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Glu Pro Lys

435 440 445

Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg Thr Glu Val

450 455 460

Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu

465 470 475 480

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

485 490 495

Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val Ser Ser

500 505 510

Ile Asp Gly Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val Lys Gly

515 520 525

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln

530 535 540

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys

545 550 555 560

Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp Val Trp

565 570 575

Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

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<400> 241

Gly Ser Gly Ser

1

<210> 242

<211> 5

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<400> 242

Gly Gly Gly Gly Ser

1 5

<210> 243

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Gly Gly Ser Gly Gly Ser

1 5

<210> 244

<211> 7

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<400> 244

Gly Gly Gly Gly Ser Gly Ser

1 5

<210> 245

<211> 15

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<223> GS_15

<400> 245

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser

1 5 10 15

<210> 246

<211> 20

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<213> 人工的序列

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<223> GS_20

<400> 246

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

1 5 10 15

Gly Gly Gly Ser

20

<210> 247

<211> 25

<212> PRT

<213> 人工的序列

<220>

<223> GS_25

<400> 247

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser

20 25

<210> 248

<211> 15

<212> PRT

<213> 人工的序列

<220>

<223> 人類IgG1樞紐

<400> 248

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro

1 5 10 15

<210> 249

<211> 15

<212> PRT

<213> 人工的序列

<220>

<223> 人類IgG1樞紐(C220S)

<400> 249

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro

1 5 10 15

<210> 250

<211> 15

<212> PRT

<213> 人工的序列

<220>

<223> H1_15

<400> 250

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro

1 5 10 15

<210> 251

<211> 15

<212> PRT

<213> 人工的序列

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<223> G5-LH

<400> 251

Gly Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro

1 5 10 15

<210> 252

<211> 17

<212> PRT

<213> 人工的序列

<220>

<223> H1_15-RT

<400> 252

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg

1 5 10 15

Thr

<210> 253

<211> 18

<212> PRT

<213> 人工的序列

<220>

<223> L-GS_15-RT

<400> 253

Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser

1 5 10 15

Arg Thr

<210> 254

<211> 18

<212> PRT

<213> 人工的序列

<220>

<223> L-H1_15-RT

<400> 254

Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro

1 5 10 15

Arg Thr

<210> 255

<211> 19

<212> PRT

<213> 人工的序列

<220>

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<400> 255

Lys Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro

1 5 10 15

Pro Arg Thr

<210> 256

<211> 19

<212> PRT

<213> 人工的序列

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<223> KL-H1_15-AS

<400> 256

Lys Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro

1 5 10 15

Pro Ala Ser

<210> 257

<211> 9

<212> PRT

<213> 人工的序列

<220>

<223> RT-GS_5-KL

<400> 257

Arg Thr Gly Gly Gly Gly Ser Lys Leu

1 5

<210> 258

<211> 19

<212> PRT

<213> 人工的序列

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<223> RT-GS_15-KL

<400> 258

Arg Thr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly

1 5 10 15

Ser Lys Leu

<210> 259

<211> 29

<212> PRT

<213> 人工的序列

<220>

<223> RT-GS_25-KL

<400> 259

Arg Thr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly

1 5 10 15

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Lys Leu

20 25

<210> 260

<211> 6

<212> PRT

<213> 人工的序列

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<223> EPKSSD

<400> 260

Glu Pro Lys Ser Ser Asp

1 5

<210> 261

<211> 17

<212> PRT

<213> 人工的序列

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<223> AS-GS_15

<400> 261

Ala Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly

1 5 10 15

Ser

<210> 262

<211> 569

<212> PRT

<213> 人工的序列

<220>

<223> PR004995鏈

<400> 262

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

1 5 10 15

Ser Met Arg Val Ser Cys Lys Ala Ser Glu Asp Thr Phe Ser Ser Tyr

20 25 30

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

35 40 45

Gly Gly Thr Ala Pro Ile Phe Gly Thr Thr Asn Tyr Ala Gln Lys Phe

50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

65 70 75 80

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

85 90 95

Ala Arg Gly Gly Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val

100 105 110

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

115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu

130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly

145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser

165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr

195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr

210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe

225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

305 310 315 320

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

325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

355 360 365

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

370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

405 410 415

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

420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Glu Val Gln

435 440 445

Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg

450 455 460

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Ser

465 470 475 480

Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val Ser Ser Ile

485 490 495

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

500 505 510

Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met

515 520 525

Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Glu

530 535 540

Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp Val Trp Gly

545 550 555 560

Gln Gly Thr Thr Val Thr Val Ser Ser

565

<210> 263

<211> 572

<212> PRT

<213> 人工的序列

<220>

<223> PR005183鏈

<400> 263

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Gly Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

450 455 460

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

465 470 475 480

Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val

485 490 495

Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val

500 505 510

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

515 520 525

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

530 535 540

Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp

545 550 555 560

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

565 570

<210> 264

<211> 569

<212> PRT

<213> 人工的序列

<220>

<223> PR005184鏈

<400> 264

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Gly Gly Pro Ser Val Phe

225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

305 310 315 320

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

325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

355 360 365

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

370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

405 410 415

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

420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Glu Val Gln

435 440 445

Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg

450 455 460

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Ser

465 470 475 480

Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val Ser Ser Ile

485 490 495

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

500 505 510

Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met

515 520 525

Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Glu

530 535 540

Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp Val Trp Gly

545 550 555 560

Gln Gly Thr Thr Val Thr Val Ser Ser

565

<210> 265

<211> 569

<212> PRT

<213> 人工的序列

<220>

<223> PR005185鏈

<400> 265

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro

210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe

225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val

260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser

325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

340 345 350

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

355 360 365

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

370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp

405 410 415

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

420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Glu Val Gln

435 440 445

Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg

450 455 460

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Ser

465 470 475 480

Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val Ser Ser Ile

485 490 495

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

500 505 510

Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met

515 520 525

Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Glu

530 535 540

Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp Val Trp Gly

545 550 555 560

Gln Gly Thr Thr Val Thr Val Ser Ser

565

<210> 266

<211> 572

<212> PRT

<213> 人工的序列

<220>

<223> PR005186鏈

<400> 266

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Ala Gly Ala Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

450 455 460

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

465 470 475 480

Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val

485 490 495

Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val

500 505 510

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

515 520 525

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

530 535 540

Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp

545 550 555 560

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

565 570

<210> 267

<211> 572

<212> PRT

<213> 人工的序列

<220>

<223> PR005187鏈

<400> 267

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr

245 250 255

Arg Glu Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

450 455 460

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

465 470 475 480

Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val

485 490 495

Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val

500 505 510

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

515 520 525

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

530 535 540

Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp

545 550 555 560

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

565 570

<210> 268

<211> 572

<212> PRT

<213> 人工的序列

<220>

<223> PR005188鏈

<400> 268

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val

290 295 300

Val Ser Val Leu Thr Val Asp His His Asp Trp Leu Asn Gly Lys Glu

305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu

420 425 430

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

435 440 445

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

450 455 460

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

465 470 475 480

Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val

485 490 495

Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val

500 505 510

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

515 520 525

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

530 535 540

Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp

545 550 555 560

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

565 570

<210> 269

<211> 571

<212> PRT

<213> 人工的序列

<220>

<223> PR005189鏈

<400> 269

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro Pro
85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val

180 185 190

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

195 200 205

Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu Val Glu Ser Gly Gly

210 215 220

Gly Val Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser

225 230 235 240

Gly Phe Thr Phe Ser Asn Tyr Ala Met Thr Trp Val Arg Gln Ala Pro

245 250 255

Glu Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Gly Ser Gly Val Ser

260 265 270

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

275 280 285

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Thr Arg Leu Thr Ala Glu

290 295 300

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

305 310 315 320

Asp His Tyr Tyr Asn Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr

325 330 335

Val Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro

340 345 350

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro

355 360 365

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr

370 375 380

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn

385 390 395 400

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg

405 410 415

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val

420 425 430

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

435 440 445

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

450 455 460

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

465 470 475 480

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe

485 490 495

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

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

565 570

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<223> PR005190鏈

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Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
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Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro Pro
85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

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

115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu

130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser

145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val

180 185 190

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

195 200 205

Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu Leu Glu Ser Gly Gly

210 215 220

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser

225 230 235 240

Gly Phe Thr Phe Ser Asn Tyr Ala Met Ser Trp Phe Arg Gln Pro Pro

245 250 255

Glu Thr Gly Leu Lys Trp Val Ser Ser Ile Asp Ala Ser Gly Gly Asp

260 265 270

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

275 280 285

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

290 295 300

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

305 310 315 320

Asp Ser His Tyr Asp Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr

325 330 335

Val Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro

340 345 350

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro

355 360 365

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr

370 375 380

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn

385 390 395 400

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg

405 410 415

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val

420 425 430

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

435 440 445

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

450 455 460

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

465 470 475 480

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe

485 490 495

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

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

565 570

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

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn

20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro Pro

85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala

100 105 110

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

115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu

130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser

145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val

180 185 190

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

195 200 205

Ser Phe Asn Arg Gly Glu Cys Glu Pro Lys Ser Ser Asp Lys Thr His

210 215 220

Thr Pro Pro Pro Pro Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly

225 230 235 240

Val Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly

245 250 255

Phe Thr Phe Ser Asn Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Glu

260 265 270

Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Gly Ser Gly Val Ser Thr

275 280 285

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

290 295 300

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

305 310 315 320

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

325 330 335

His Tyr Tyr Asn Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val

340 345 350

Ser Ser Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro

355 360 365

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

370 375 380

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val

385 390 395 400

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp

405 410 415

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr

420 425 430

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp

435 440 445

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu

450 455 460

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

465 470 475 480

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

485 490 495

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

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

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

565 570 575

Leu Ser Leu Ser Pro Gly Lys

580

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Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro Pro
85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val

180 185 190

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

195 200 205

Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu Val Glu Ser Gly Gly

210 215 220

Gly Val Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser

225 230 235 240

Gly Phe Thr Phe Ser Asn Tyr Ala Met Thr Trp Val Arg Gln Ala Pro

245 250 255

Glu Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Gly Ser Gly Val Ser

260 265 270

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

275 280 285

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Thr Arg Leu Thr Ala Glu

290 295 300

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

305 310 315 320

Asp His Tyr Tyr Asn Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr

325 330 335

Val Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro

340 345 350

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro

355 360 365

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr

370 375 380

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn

385 390 395 400

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg

405 410 415

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val

420 425 430

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

435 440 445

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

450 455 460

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

465 470 475 480

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe

485 490 495

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

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

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

565 570 575

Ser Gly Gly Gly Val Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys

580 585 590

Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Thr Trp Val Arg

595 600 605

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

610 615 620

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

625 630 635 640

Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Thr Arg Leu

645 650 655

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

660 665 670

Glu Thr Asp Asp His Tyr Tyr Asn Val Asp Val Trp Gly Gln Gly Thr

675 680 685

Thr Val Thr Val Ser Ser

690

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<211> 694

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Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro Pro
85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val

180 185 190

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

195 200 205

Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu Leu Glu Ser Gly Gly

210 215 220

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser

225 230 235 240

Gly Phe Thr Phe Ser Asn Tyr Ala Met Ser Trp Phe Arg Gln Pro Pro

245 250 255

Glu Thr Gly Leu Lys Trp Val Ser Ser Ile Asp Ala Ser Gly Gly Asp

260 265 270

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

275 280 285

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

290 295 300

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

305 310 315 320

Asp Ser His Tyr Asp Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr

325 330 335

Val Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro

340 345 350

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro

355 360 365

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr

370 375 380

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn

385 390 395 400

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg

405 410 415

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val

420 425 430

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

435 440 445

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

450 455 460

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

465 470 475 480

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe

485 490 495

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

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

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

565 570 575

Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys

580 585 590

Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Ser Trp Phe Arg

595 600 605

Gln Pro Pro Glu Thr Gly Leu Lys Trp Val Ser Ser Ile Asp Ala Ser

610 615 620

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

625 630 635 640

Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu

645 650 655

Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Glu Gly Ser His

660 665 670

Gly Thr Asp Asp Ser His Tyr Asp Val Asp Val Trp Gly Gln Gly Thr

675 680 685

Thr Val Thr Val Ser Ser

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<400> 274

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu

450 455 460

Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys

465 470 475 480

Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Ser Trp Phe Arg

485 490 495

Gln Pro Pro Glu Thr Gly Leu Lys Trp Val Ser Ser Ile Asp Ala Ser

500 505 510

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

515 520 525

Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu

530 535 540

Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Glu Gly Ser His

545 550 555 560

Gly Thr Asp Asp Ser His Tyr Asp Val Asp Val Trp Gly Gln Gly Thr

565 570 575

Thr Val Thr Val Ser Ser

580

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

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

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu

450 455 460

Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser

465 470 475 480

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

485 490 495

Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val Ser

500 505 510

Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val Lys

515 520 525

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu

530 535 540

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala

545 550 555 560

Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp Val

565 570 575

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

580 585

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

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

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

450 455 460

Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val

465 470 475 480

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr

485 490 495

Phe Ser Asn Tyr Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly

500 505 510

Leu Lys Trp Val Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr

515 520 525

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

530 535 540

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala

545 550 555 560

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

565 570 575

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

580 585 590

<210> 277

<211> 597

<212> PRT

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<220>

<223> PR005830鏈

<400> 277

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

450 455 460

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser

465 470 475 480

Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala

485 490 495

Ala Ser Gly Phe Thr Phe Ser Asn Tyr Ala Met Ser Trp Phe Arg Gln

500 505 510

Pro Pro Glu Thr Gly Leu Lys Trp Val Ser Ser Ile Asp Ala Ser Gly

515 520 525

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

530 535 540

Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg

545 550 555 560

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

565 570 575

Thr Asp Asp Ser His Tyr Asp Val Asp Val Trp Gly Gln Gly Thr Thr

580 585 590

Val Thr Val Ser Ser

595

<210> 278

<211> 578

<212> PRT

<213> 人工的序列

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<223> PR005838鏈

<400> 278

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Gly Gly Ser Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly

450 455 460

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly

465 470 475 480

Phe Thr Phe Ser Asn Tyr Ala Met Ser Trp Phe Arg Gln Pro Pro Glu

485 490 495

Thr Gly Leu Lys Trp Val Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

Ser His Tyr Asp Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val

565 570 575

Ser Ser

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<211> 578

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<400> 279

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Ala Gly Ala Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Gly Gly Ser Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly

450 455 460

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly

465 470 475 480

Phe Thr Phe Ser Asn Tyr Ala Met Ser Trp Phe Arg Gln Pro Pro Glu

485 490 495

Thr Gly Leu Lys Trp Val Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

Ser His Tyr Asp Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val

565 570 575

Ser Ser

<210> 280

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<212> PRT

<213> 人工的序列

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<223> PR005866鏈

<400> 280

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Gly Gly Ser Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly

450 455 460

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly

465 470 475 480

Phe Thr Phe Ser Asn Tyr Ala Met Ser Trp Phe Arg Gln Pro Pro Glu

485 490 495

Thr Gly Leu Lys Trp Val Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

Ser His Tyr Asp Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val

565 570 575

Ser Ser

<210> 281

<211> 578

<212> PRT

<213> 人工的序列

<220>

<223> PR007165鏈

<400> 281

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Glu Val

210 215 220

Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly Ser Leu

225 230 235 240

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

245 250 255

Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val Ser Ser

260 265 270

Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly

275 280 285

Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln

290 295 300

Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys Ala Lys

305 310 315 320

Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp Val Trp

325 330 335

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser Ser Asp

340 345 350

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly

355 360 365

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile

370 375 380

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu

385 390 395 400

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His

405 410 415

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg

420 425 430

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

435 440 445

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu

450 455 460

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr

465 470 475 480

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

485 490 495

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp

500 505 510

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val

515 520 525

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

530 535 540

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His

545 550 555 560

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro

565 570 575

Gly Lys

<210> 282

<211> 12

<212> PRT

<213> 人工的序列

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<223> 人類IgG2樞紐

<400> 282

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro

1 5 10

<210> 283

<211> 19

<212> PRT

<213> 人工的序列

<220>

<223> PR007381 HFWR2 Chothia

<400> 283

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

1 5 10 15

Ser Ser Ile

<210> 284

<211> 124

<212> PRT

<213> 人工的序列

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<223> PR007381 VH

<400> 284

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

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

20 25 30

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

35 40 45

Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp

100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

115 120

<210> 285

<211> 356

<212> PRT

<213> 人工的序列

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<223> PR007381 HC

<400> 285

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

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

20 25 30

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

35 40 45

Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp

100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser

115 120 125

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

130 135 140

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

145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

210 215 220

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

290 295 300

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

305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

325 330 335

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

340 345 350

Ser Pro Gly Lys

355

<210> 286

<211> 578

<212> PRT

<213> 人工的序列

<220>

<223> PR007379鏈

<400> 286

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 Arg Ser Phe

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Gly Gly Ser Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly

450 455 460

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly

465 470 475 480

Phe Thr Phe Ser Asn Tyr Ala Met Ser Trp Phe Arg Gln Pro Pro Glu

485 490 495

Thr Gly Leu Lys Trp Val Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

Ser His Tyr Asp Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val

565 570 575

Ser Ser

<210> 287

<211> 578

<212> PRT

<213> 人工的序列

<220>

<223> PR007380鏈

<400> 287

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 Arg Ser Phe
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Gly Gly Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro

225 230 235 240

Ser 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Gly Gly Ser Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly

450 455 460

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly

465 470 475 480

Phe Thr Phe Ser Asn Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly

485 490 495

Lys Gly Leu Glu Trp Val Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

Ser His Tyr Asp Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val

565 570 575

Ser Ser

<210> 288

<211> 6

<212> PRT

<213> 人工的序列

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<400> 288

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1 5

<210> 289

<211> 10

<212> PRT

<213> 人工的序列

<220>

<223> (G4S)2

<400> 289

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1 5 10

<210> 290

<211> 449

<212> PRT

<213> 人工的序列

<220>

<223> 重鏈序列

<400> 290

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

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

20 25 30

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

35 40 45

Ala Val Ile Ser Tyr Asp Ala Ser Asn Glu Tyr Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asp Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Lys Gly Gly Ala Leu Arg Trp Tyr Phe Ala Tyr Trp Gly Gln Gly

100 105 110

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

115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro

225 230 235 240

Asp 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 His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn 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 Ala Leu Pro Ala Pro Glu 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 Arg 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 Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln 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 Gly

435 440 445

Lys

<210> 291

<211> 215

<212> PRT

<213> 人工的序列

<220>

<223> 輕鏈序列

<400> 291

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1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Asn
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Arg Ser Trp Pro Pro
85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val

180 185 190

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

195 200 205

Ser Phe Asn Arg Gly Glu Cys

210 215

【發明申請專利範圍】

【請求項1】 一種雙特異性抗體，其包含標靶B7-H4的抗原結合結構域和標靶4-1BB的抗原結合結構域；所述的標靶B7-H4的抗原結合結構域含有序列如SEQ ID NO: 16所示的HCDR1、序列如SEQ ID NO: 46所示的HCDR2以及序列如SEQ ID NO: 84所示的HCDR3，序列如SEQ ID NO: 112所示的LCDR1、序列如SEQ ID NO: 118所示的LCDR2以及序列如SEQ ID NO: 131所示的LCDR3；或者，序列如SEQ ID NO: 16所示的HCDR1、序列如SEQ ID NO: 60所示的HCDR2以及序列如SEQ ID NO: 84所示的HCDR3，序列如SEQ ID NO: 112所示的LCDR1、序列如SEQ ID NO: 118所示的LCDR2以及序列如SEQ ID NO: 133所示的LCDR3。

【請求項2】 如請求項1所述的雙特異性抗體，其特徵在於，所述的標靶B7-H4的抗原結合結構域含有序列如SEQ ID NO: 142所示的VH和序列如SEQ ID NO: 166所示的VL；或者序列如SEQ ID NO: 160所示的VH和序列如SEQ ID NO: 168所示的VL。

【請求項3】 如請求項2所述的雙特異性抗體，其特徵在於，所述標靶B7-H4的抗原結合結構域含有序列如SEQ ID NO: 174所示的重鏈和序列如SEQ ID NO: 198所示的輕鏈；或者，序列如SEQ ID NO: 192所示的重鏈和序列如SEQ ID NO: 200所示的輕鏈。

【請求項4】 如請求項1所述的雙特異性抗體，其特徵在於，所述的標靶4-1BB的抗原結合結構域含有：序列分別如SEQ ID NO: 17、47和85所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、48和86所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、49和87所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 19、50和88所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 20、51和89所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、52和90所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、49和90所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 21、53和91所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 21、54和92所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 19、55和93所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、49和86所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 19、49和94所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 22、56和86所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、57和95所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如 SEQ ID NO: 19、58和96所示的HCDR1、HCDR2和HCDR3；

或者，序列分別如SEQ ID NO: 18、61和95所示的HCDR1、HCDR2和HCDR3。

【請求項5】 如請求項4所述的雙特異性抗體，其特徵在於，所述的標靶4-1BB的抗原結合結構域含有一個或者多個序列如SEQ ID NO: 143~157、284或者161所示的重鏈可變區。

【請求項6】 如請求項5所述的雙特異性抗體，其特徵在於，所述的標靶4-1BB的抗原結合結構域包含序列如SEQ ID NO: 175~189、193、285或者171所示的重鏈。

【請求項7】 如請求項1所述的雙特異性抗體，其特徵在於，所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 14、43和81所示的HCDR1、HCDR2和HCDR3；和序列分別如SEQ ID NO: 109、118和128所示的LCDR1、LCDR2和LCDR3。

【請求項8】 如請求項7所述的雙特異性抗體，其特徵在於，所述的標靶4-1BB的抗原結合結構域包含序列如SEQ ID

NO: 139所示的重鏈可變區和序列如SEQ ID NO: 163所示的輕鏈可變區。

【請求項9】 如請求項8所述的雙特異性抗體，其特徵在於，所述的標靶4-1BB的抗原結合結構域包含序列如SEQ ID NO: 171所示的重鏈和序列如SEQ ID NO: 195所示的輕鏈。

【請求項10】 如請求項1所述的雙特異性抗體，其特徵在於，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 109、118和128所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 14、43和81所示的HCDR1、HCDR2和HCDR3；

所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 17、47和85所示的HCDR1、HCDR2和HCDR3；

所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46

和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、48和86所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、49和87所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 19、50和88所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 20、51和89所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46

和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、52和90所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 21、53和91所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 21、54和92所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 19、55和93所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46

和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、49和86所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 19、49和94所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 22、56和86所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、57和95所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和133所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、60

和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 17、47和85所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和133所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、60和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、48和86所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和133所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、60和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、49和86所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和133所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、60和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 19、49和94所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和133所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、60

和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 18、61和95所示的HCDR1、HCDR2和HCDR3；

或者，所述的標靶B7-H4的抗原結合結構域包含序列分別如SEQ ID NO: 112、118和131所示的LCDR1、LCDR2和LCDR3和序列分別如SEQ ID NO: 16、46和84所示的HCDR1、HCDR2和HCDR3；且所述的標靶4-1BB的抗原結合結構域包含序列分別如SEQ ID NO: 19、49和97所示的HCDR1、HCDR2和HCDR3。

【請求項11】 如請求項1所述的雙特異性抗體，其特徵在於，所述標靶B7-H4的抗原結構域為IgG的形式，所述標靶4-1BB的抗原結合結構域為單個VH的形式；

或者，所述標靶B7-H4的抗原結構域為IgG的形式，所述標靶4-1BB的抗原結合結構域為ScFv的形式；

或者，所述標靶B7-H4的抗原結構域為IgG的形式，所述標靶4-1BB的抗原結合結構域為2個或者3個VH串聯的形式；

或者，所述標靶B7-H4的抗原結構域為Fab的形式，所述標靶4-1BB的抗原結合結構域為HCAb的形式或者為HCAb的形式和VH的形式(HCAb-VH形式)；

或者，所述標靶B7-H4的抗原結構域為Fab的形式，所述標靶4-1BB的抗原結合結構域為單個VH、2個或者3個VH串聯的形式。

【請求項12】 如請求項11所述的雙特異性抗體，其特徵在於，所述的雙特異性抗體為如下形式：

(1) IgG的C端連接有ScFv，所述ScFv的VH連接於所述C端；

(2) IgG的C端連接有VH或者串聯VH；

(3) HCAb的N端連接有Fab；

(4) HCAb的N端連接有Fab，所述Fab的C端連接有VH；

或者(5) Fc的2個CH2的N端分別連接有Fab，以及VH或者串聯VH。

【請求項13】 如請求項12所述的雙特異性抗體，其特徵在於，(1)中雙特異性抗體的多肽鏈1如式：VLB7-H4-CL所示，多肽鏈2如式：VHB7-H4-CH1-樞紐-CH2-CH3-連接子-VH4-1BB-連接子-VL4-1BB所示；(2)中雙特異性抗體的多肽鏈1如式：VLB7-H4-CL所示，多肽鏈2如式：VHB7-H4-CH1-樞紐-CH2-CH3-連接子-(VH4-1BB)n所示；(3)中雙特異性抗體的多肽鏈1如式：VHB7-H4-CH1所示，多肽鏈2如式：VLB7-H4-CL-連接子-VH4-1BB-連接子-CH2-CH3所示；(4)中雙特異性抗體的多肽鏈1如式：VHB7-H4-CH1所示，多肽鏈2如式：VLB7-H4-CL-連接子-VH4-1BB-連接子-CH2-CH3- VH4-1BB所示；或者(5)中雙特異性抗體含三條多肽鏈：多肽鏈1如式：VLB7-H4-CL所示，多肽鏈2如式：VHB7-H4-CH1-樞紐-CH2-CH3所示，多

肽鏈3如式：VH4-1BB-連接子-CH2-CH3或者(VH4-1BB)n-連接子-CH2-CH3所示。

【請求項14】 如請求項13所述的雙特異性抗體，其特徵在於，所述的連接子選自由SEQ ID NO: 241~261、282以及288~289構成的群組。

【請求項15】 如請求項14所述的雙特異性抗體，其特徵在於：

(1)中所述的連接子含有如SEQ ID NO: 245所示的序列；

(2)中所述的連接子含有如SEQ ID NO: 243、245~247以及SEQ ID NO: 288~289任一所示的序列；

(3)中所述的連接子含有如SEQ ID NO: 250所示的序列；

(4)中所述的連接子含有如SEQ ID NO: 282所示的序列；

(5)中所述的連接子含有如SEQ ID NO: 245所示的序列。

【請求項16】 如請求項15所述的雙特異性抗體，其特徵在於，所述多肽鏈1的胺基酸序列如SEQ ID NO: 198所示，且所述多肽鏈2的胺基酸序列如SEQ ID NO: 202~216中任一個所示；

或者，所述多肽鏈1的胺基酸序列如SEQ ID NO: 200所示，且所述多肽鏈2的胺基酸序列如SEQ ID NO: 218~225、235~237中任一個所示；

或者，所述多肽鏈1的胺基酸序列如SEQ ID NO: 233所示，且所述多肽鏈2的胺基酸序列如SEQ ID NO: 234所示。

【請求項17】 一種分離的核酸，其編碼如請求項1~16任一項所述的雙特異性抗體。

【請求項18】 一種包含如請求項17所述的分離的核酸的表現載體。

【請求項19】 一種宿主細胞，其包含根據請求項18所述的表現載體。

【請求項20】 如請求項19所述的宿主細胞，其特徵在於，所述宿主細胞為原核細胞或真核細胞。

【請求項21】 一種雙特異性抗體的製備方法，其包含培養如請求項19或20所述的宿主細胞，從培養物中獲得所述雙特異性抗體。

【請求項22】 一種藥物組成物，其包含如請求項1~16任一項所述的雙特異性抗體。

【請求項23】 一種嵌合抗原受體，其包含如請求項1~16任一項所述的雙特異性抗體。

【請求項24】 一種抗體藥物偶聯物，其包含細胞毒性劑，以及如請求項1~16任一項所述的雙特異性抗體。

【請求項25】 如請求項24所述的抗體藥物偶聯物，其特徵在於，所述細胞毒性劑為MMAF或MMAE。

【請求項26】 一種套組，其包括如請求項1~16任一項所述的雙特異性抗體、如請求項23所述的嵌合抗原受體、如請求項24或25中所述的抗體藥物偶聯物和/或如請求項22所述的藥物組成物。

【請求項27】 如請求項26所述的套組，其特徵在於所述套組還包括(i)施用抗體或其抗原結合片段或抗體藥物偶聯物或藥物組成物的裝置；和/或(ii)使用說明。

【請求項28】 一種套裝藥盒，其包含藥盒A和藥盒B，其中：

所述藥盒A含有如請求項1~16任一項所述的雙特異性抗體、如請求項23所述的嵌合抗原受體、如請求項24或25所述的抗體藥物偶聯物和/或如請求項22所述的藥物組成物；

所述藥盒B含有其他抗腫瘤抗體或者包含所述其他抗腫瘤抗體的藥物組成物，和/或由激素製劑、標靶小分子製劑、蛋白酶體抑制劑、成像劑、診斷劑、化療劑、溶瘤藥物、細胞毒性劑、細胞激素、共刺激分子的活化劑、抑制性分子的抑制劑以及疫苗組成的群組中的一種或多種。

【請求項29】 一種如請求項1~16任一項所述的雙特異性抗體、如請求項23所述的嵌合抗原受體、如請求項24或25所述的抗體藥物偶聯物或如請求項22所述的藥物組成物，或者使用如請求項28所述的套裝藥盒在製備診斷、治療和/或預防4-1BB和/或B7-H4媒介的疾病或病症的藥物中的應用。

【請求項30】 如請求項29所述的應用，其特徵在於，所述的疾病或病症為乳腺癌、卵巢癌、子宮內膜癌、腎癌、黑色素瘤、肺癌、胃癌、肝癌、食道癌、子宮頸癌、頭頸部腫瘤、膽管癌、膽囊癌、膀胱癌、肉瘤或者結直腸癌。

【請求項31】 如請求項30所述的應用，其特徵在於，所述的疾病或病症為乳腺癌、卵巢癌、子宮內膜癌、腎癌或膽管癌。

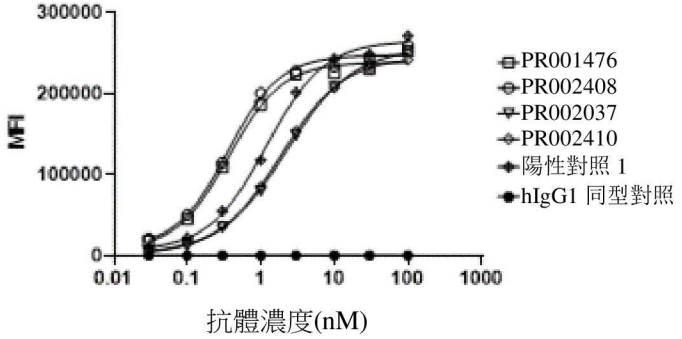
【請求項32】 如請求項31所述的應用，其特徵在於，所述的疾病或病症為乳腺癌。

【請求項33】 一種免疫檢測或者測定4-1BB或B7H4的方法，其包括使用如請求項1~16任一項所述的雙特異性抗體、如請求項23所述的嵌合抗原受體、如請求項24或25所述的抗體藥物偶聯物或如請求項22所述的藥物組成物，所述檢測為非診斷和/或治療目的的。

【發明圖式】

1-(A)

結合 SK-BR-3

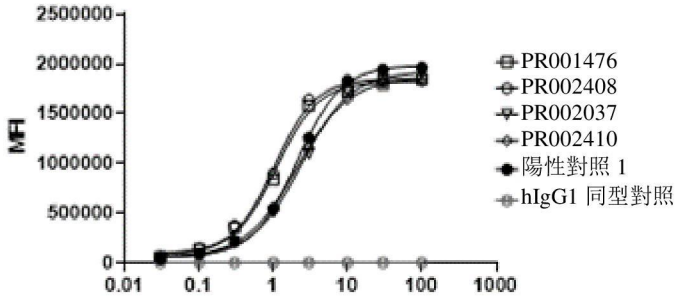


抗體濃度(nM)

抗體	EC50 (nM)	MFI 最大值
RP001476	0.367	238962
PR002408	0.3531	248060
PR002037	2.22	256727
PR002410	1.872	245482
陽性對照 1	1.199	265713

1-(B)

結合 CHO-K1/cyno B7H4

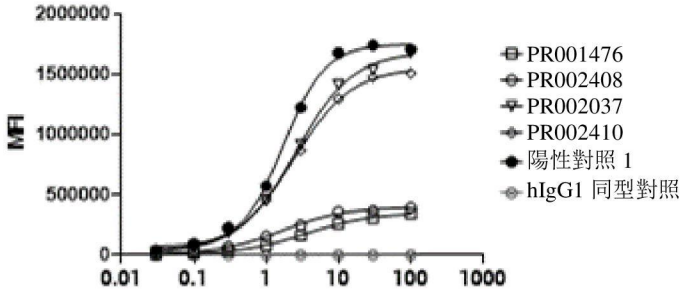


抗體濃度(nM)

抗體	EC50 (nM)	MFI 最大值
RP001476	1.097	1822000
PR002408	1.029	1852000
PR002037	2.382	1922000
PR002410	2.077	1862000
陽性對照 1	2.095	1986000

1-(C)

結合 CHO-K1/m B7H4



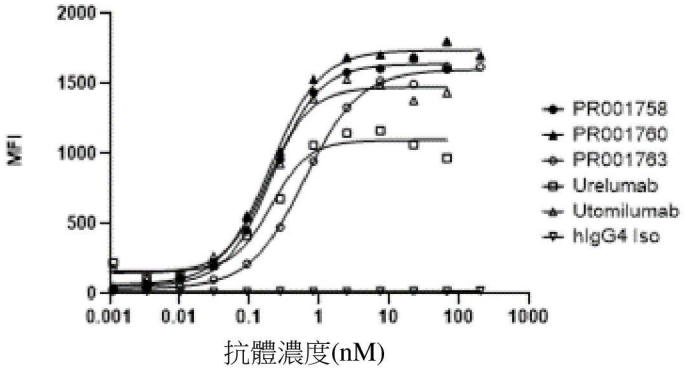
抗體濃度(nM)

抗體	EC50 (nM)	MFI 最大值
RP001476	3.614	353378
PR002408	1.678	398460
PR002037	2.57	1686000
PR002410	2.385	1554000
陽性對照 1	1.728	1749000

圖 1

2-(A)

結合 CHO-K1/hu 4-1BB

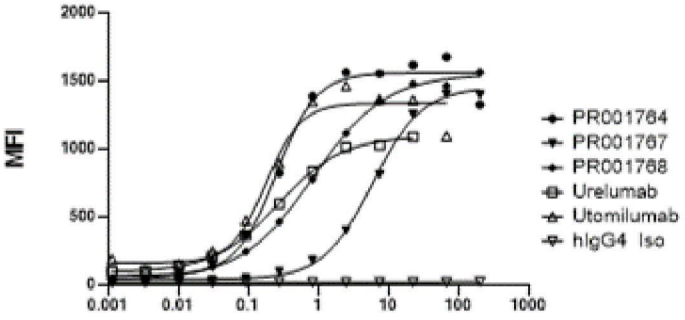


抗體濃度(nM)

抗體	EC50 (nM)	MFI 最大值
PR001758	0.2122	1644
PR001760	0.1981	1742
PR001763	0.616	1602
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

2-(B)

結合 CHO-K1/hu 4-1BB

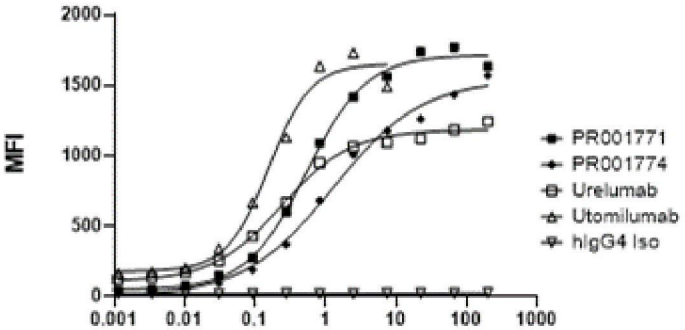


抗體濃度(nM)

抗體	EC50 (nM)	MFI 最大值
PR001764	0.2488	1562
PR001767	5.874	1453
PR001768	0.846	1552
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

2-(C)

結合 CHO-K1/hu 4-1BB

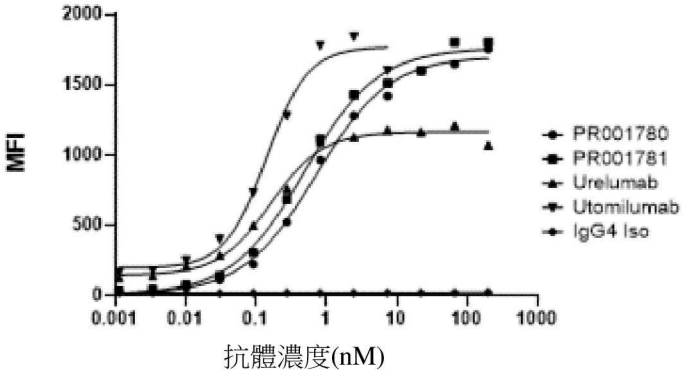


抗體濃度(nM)

抗體	EC50 (nM)	MFI 最大值
PR001771	0.5323	1716
PR001774	1.27	1544
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

2-(D)

結合 CHO-K1/hu 4-1BB

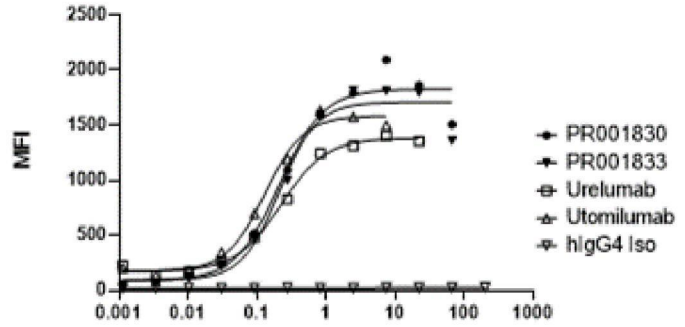


抗體濃度(nM)

抗體	EC50 (nM)	MFI 最大值
PR001780	0.7075	1703
PR001781	0.4917	1761
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

2-(E)

結合 CHO-K1/hu 4-1BB

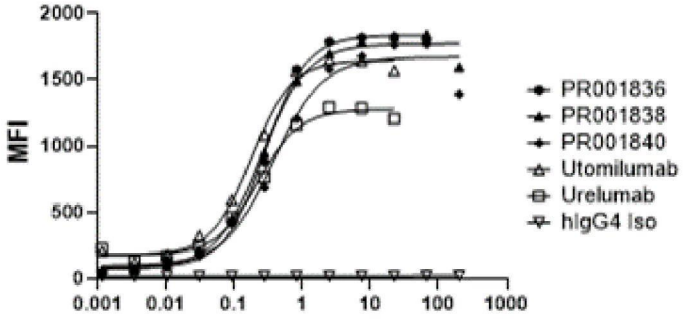


抗體濃度(nM)

抗體	EC50 (nM)	MFI 最大值
PR001830	0.2088	1826
PR001833	0.2099	1708
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

2-(F)

結合 CHO-K1/hu 4-1BB

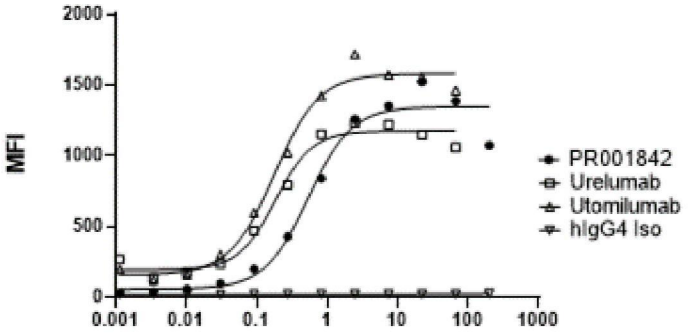


抗體濃度(nM)

抗體	EC50 (nM)	MFI 最大值
PR001836	0.2798	1833
PR001838	0.2482	1770
PR001840	0.3696	1669
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

2-(G)

結合 CHO-K1/hu 4-1BB

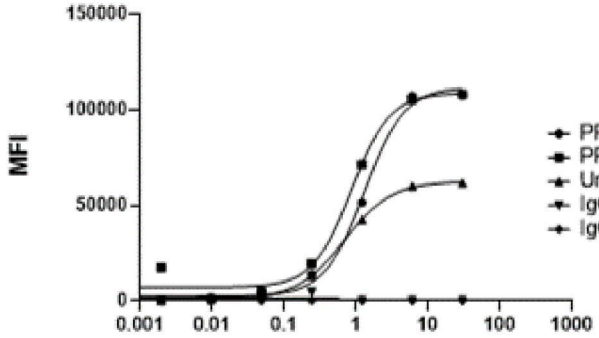


抗體濃度(nM)

抗體	EC50 (nM)	MFI 最大值
PR001842	0.5372	1346
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

2-(H)

結合 CHO-K1/hu 4-1BB

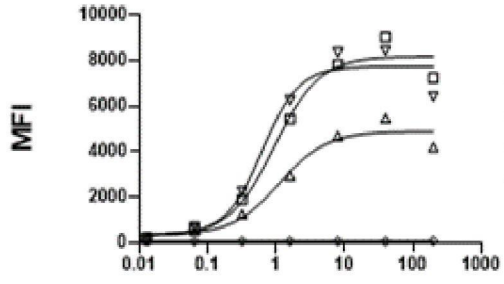


抗體濃度(nM)

抗體	EC50 (nM)	MFI 最大值
PR001838	0.8512	101674
PR004469	1.295	109216
Urelumab	0.6834	61805

2-(I)

結合 CHO-K1/hu 4-1BB



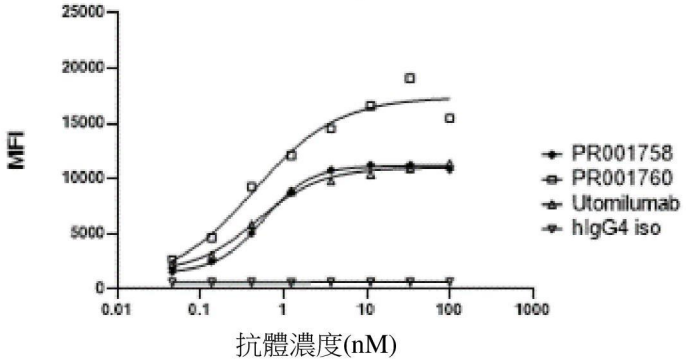
抗體濃度(nM)

抗體	EC50(nM)	最大結合值
PR000448	0.9473	8182
Urelumab	1.114	4898
Utomilumab	0.6271	7747

圖 2

3-(A)

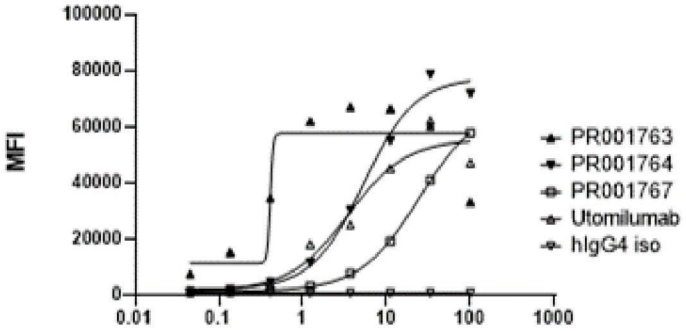
結合 CHO-K1/cyno 4-1BB



抗體	EC50 (nM)	MFI 最大值
PR001758	0.5747	11167
PR001760	0.4428	17361
Utomilumab	0.4848	10978

3-(B)

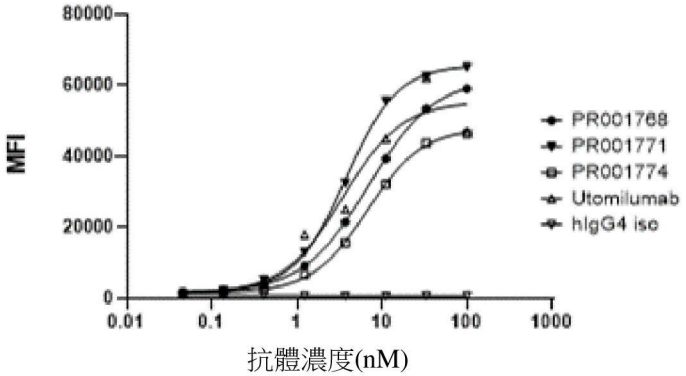
結合 CHO-K1/cyno 4-1BB



抗體	EC50 (nM)	MFI 最大值
PR001763	n.d.	57664
PR001764	5.325	77340
PR001767	25	68419
Utomilumab	3.459	55506

3-(C)

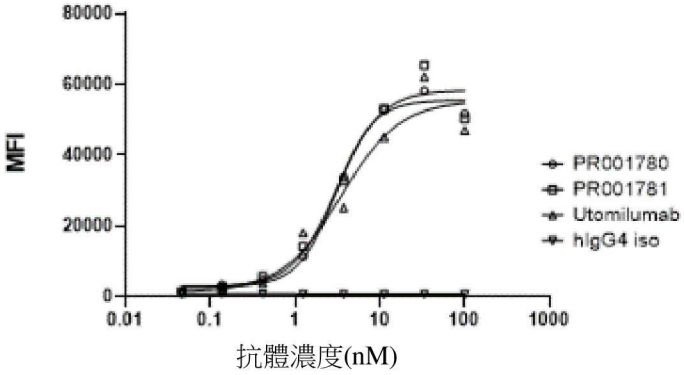
結合 CHO-K1/cyno 4-1BB



抗體	EC50 (nM)	MFI 最大值
PR001768	6.969	62154
PR001771	3.77	65713
PR001774	6.728	48008
Utomilumab	3.459	55506

3-(D)

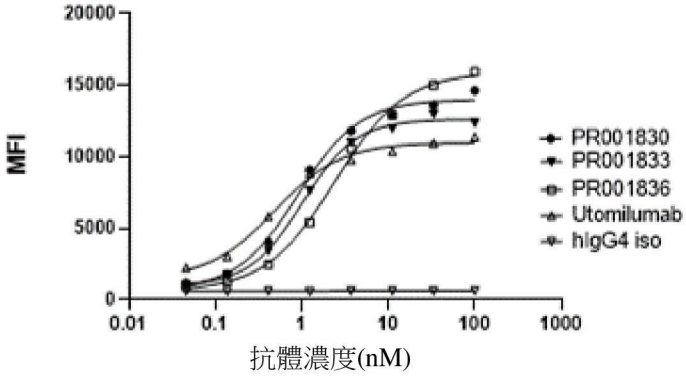
結合 CHO-K1/cyno 4-1BB



抗體	EC50 (nM)	MFI 最大值
PR001780	2.99	55516
PR001781	3.099	58329
Utomilumab	3.459	55506

3-(E)

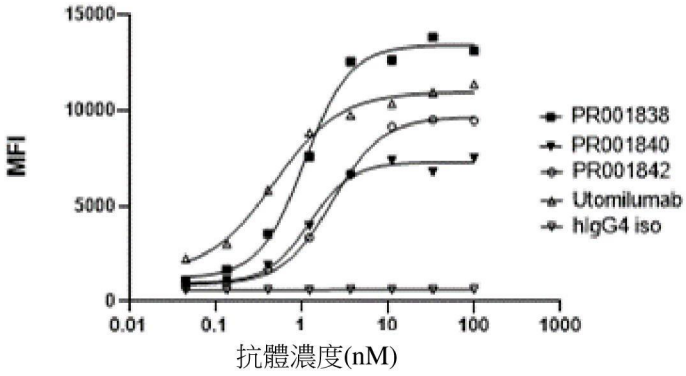
結合 CHO-K1/cyno 4-1BB



抗體	EC50 (nM)	MFI 最大值
PR001830	0.8991	13968
PR001833	1.018	12610
PR001836	2.410	15913
Utomilumab	0.4848	10978

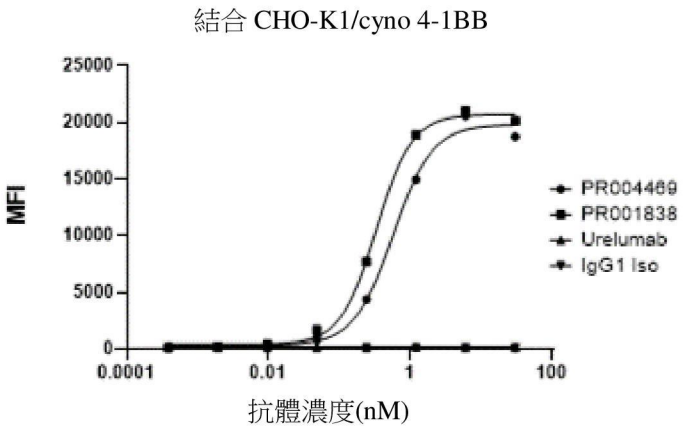
3-(F)

結合 CHO-K1/cyno 4-1BB



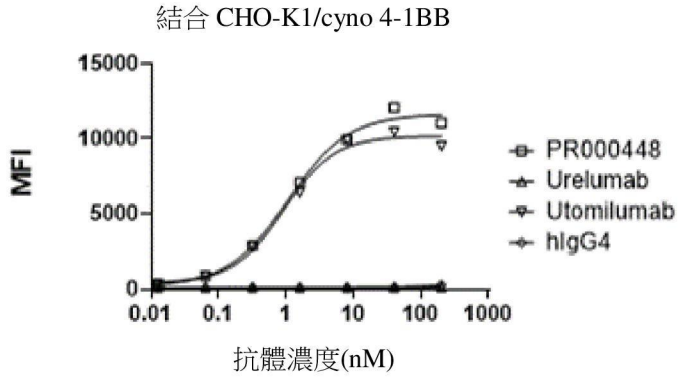
抗體	EC50 (nM)	MFI 最大值
PR001838	1.089	13431
PR001840	1.246	7303
PR001842	2.285	9660
Utomilumab	0.4848	10978

3-(G)



抗體	EC50 (nM)	MFI 最大值
PR001838	0.3287	20294
PR004469	0.5678	19472
Urelumab	不結合	

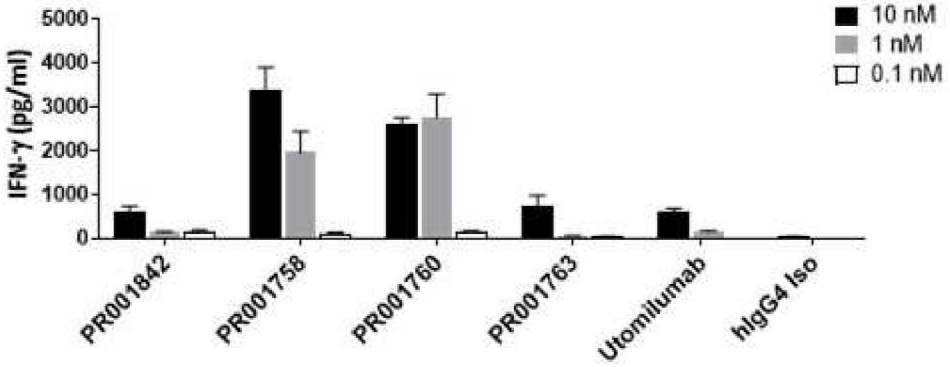
3-(H)



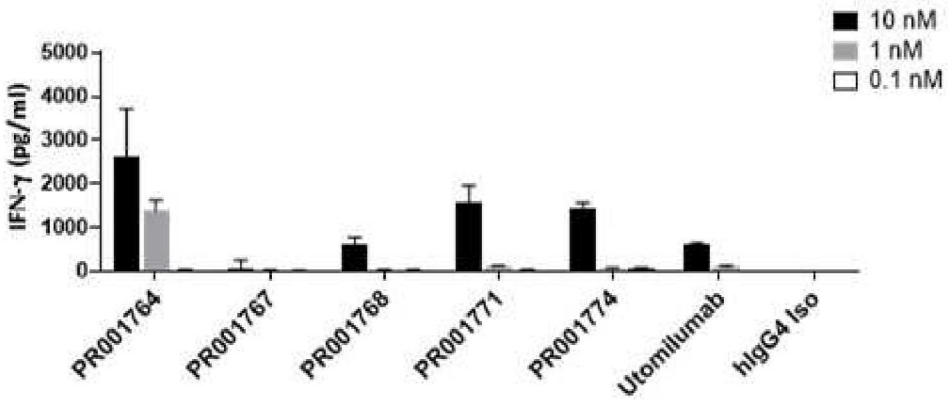
抗體	EC50 (nM)	最大結合值
PR000448	1.064	11657
Urelumab	不結合	
Utomilumab	0.9293	10188

圖 3

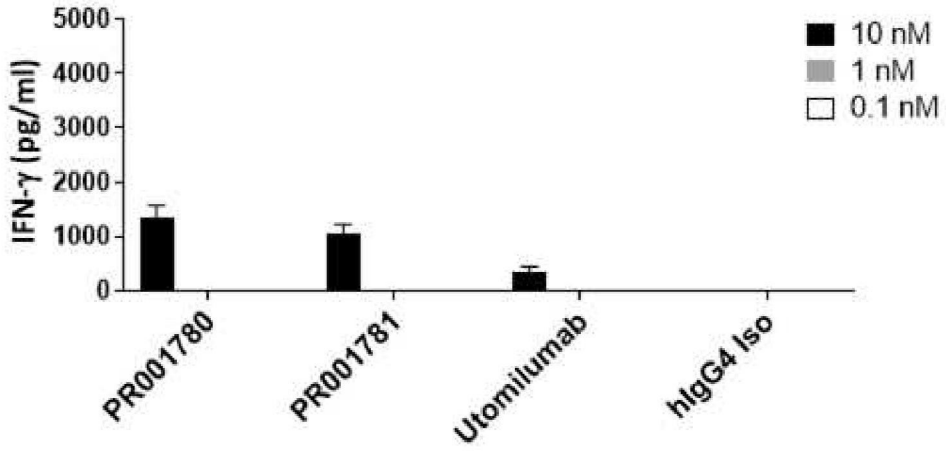
4-(A)


10 nM
1 nM
0.1 nM
IFN-γ (pg/ml)
5000
4000
3000
2000
1000
0
PR001842
PR001758
PR001760
PR001763
Utomilumab
hIgG4 Iso

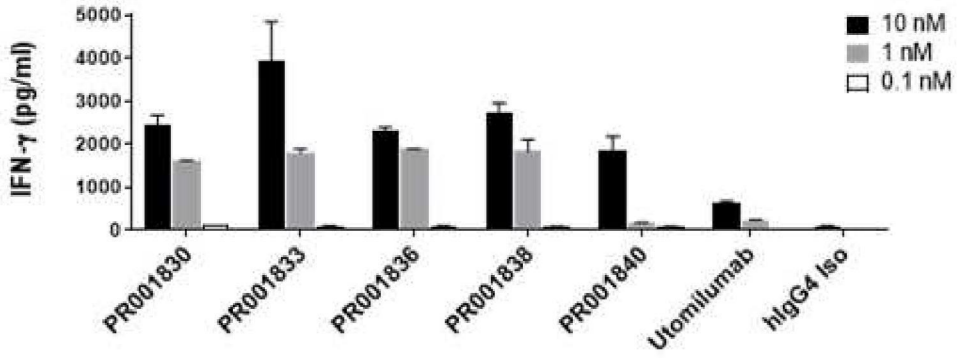
4-(B)


10 nM
1 nM
0.1 nM
IFN-γ (pg/ml)
5000
4000
3000
2000
1000
0
PR001764
PR001767
PR001768
PR001771
PR001774
Utomilumab
hIgG4 Iso

4-(C)


IFN-γ (pg/ml)
5000
4000
3000
2000
1000
0
10 nM
1 nM
0.1 nM
PR001780
PR001781
Utomilumab
hIgG4 Iso

4-(D)


IFN-γ (pg/ml)
5000
4000
3000
2000
1000
0
10 nM
1 nM
0.1 nM
PR001830
PR001833
PR001836
PR001838
PR001840
Utomilumab
hIgG4 Iso

4-(E)

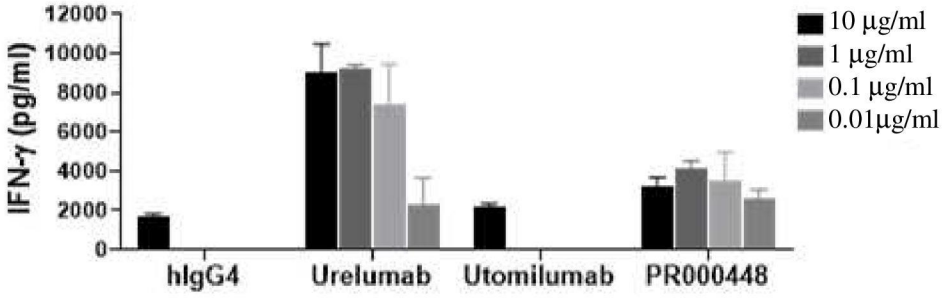
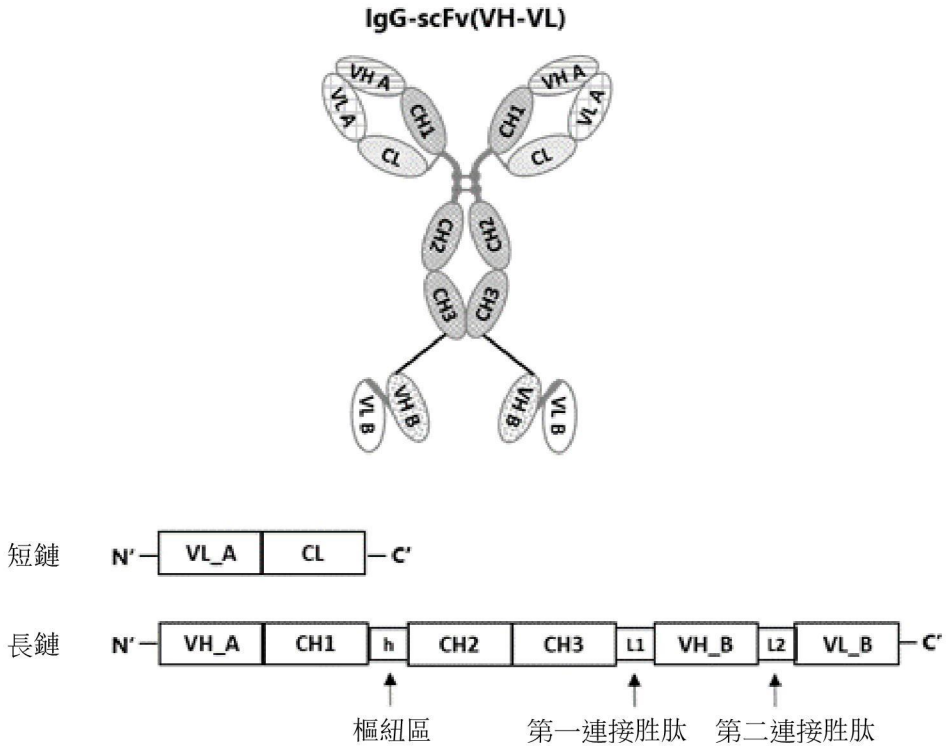
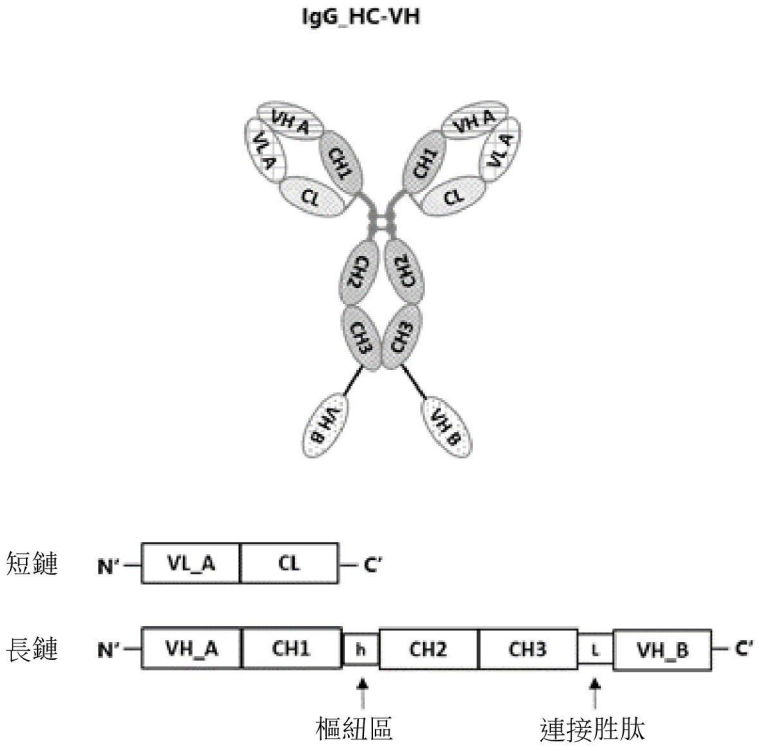

IFN-γ (pg/ml)
12000
10000
8000
6000
4000
2000
0
10 µg/ml
1 µg/ml
0.1 µg/ml
0.01µg/ml
hIgG4
Urelumab
Utomilumab
PR000448

圖 4

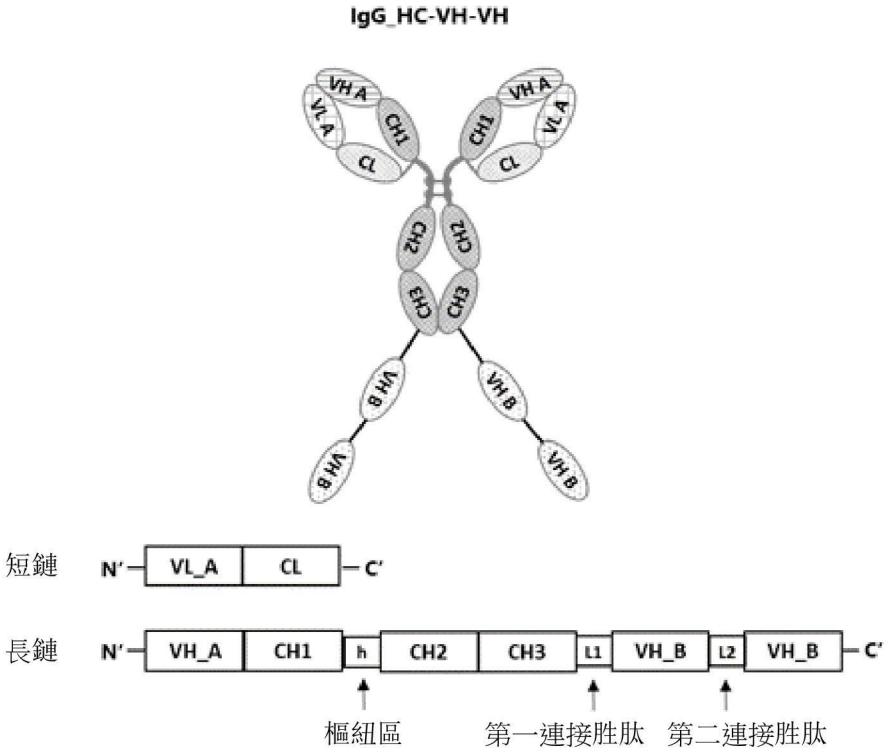
5-(A)


IgG-scFv(VH-VL)
VH A
VL A
CH1
CL
CH2
CH3
VL B
VH B
短鏈
N'
VL_A
CL
C'
長鏈
VH_A
h
L1
VH_B
L2
VL_B
樞紐區
第一連接胜肽
第二連接胜肽

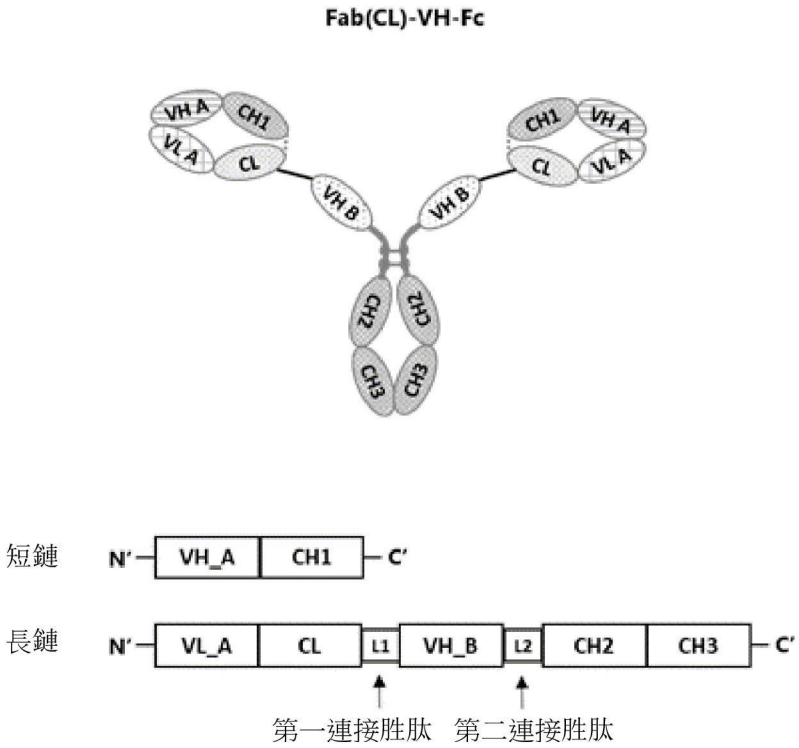
5-(B)


IgG_HC-VH
VH A
VL A
CH1
CL
CH2
CH3
VH B
短鏈
N'
VL_A
CL
C'
長鏈
VH_A
h
L
VH_B
樞紐區
連接胜肽

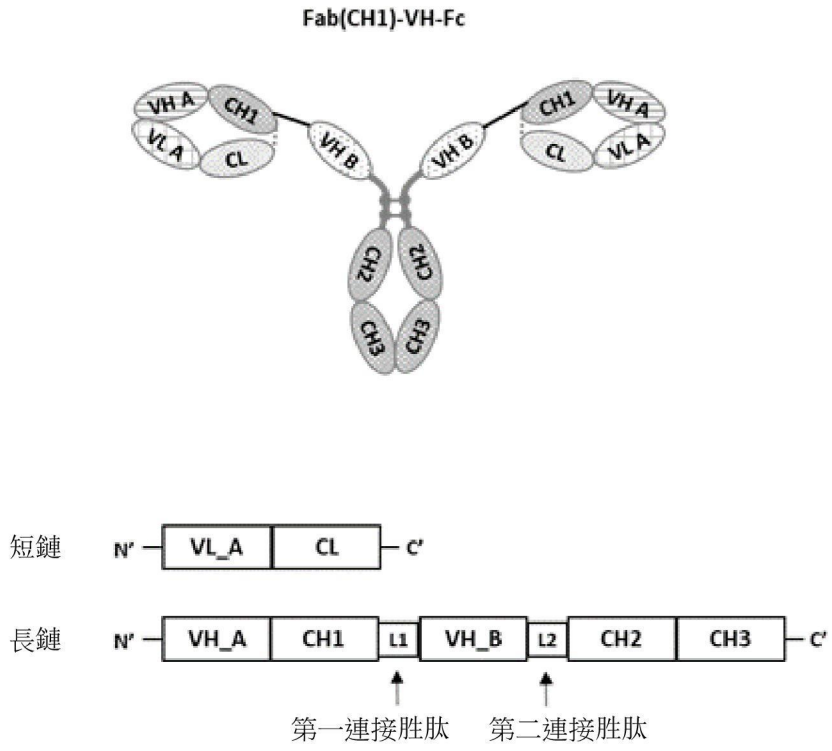
5-(C)


IgG_HC-VH-VH
VH A
VL A
CH1
CL
CH2
CH3
VH B
短鏈
N'
VL_A
CL
C'
長鏈
VH_A
CH1
h
CH2
CH3
L1
VH_B
L2
樞紐區
第一連接胜肽
第二連接胜肽

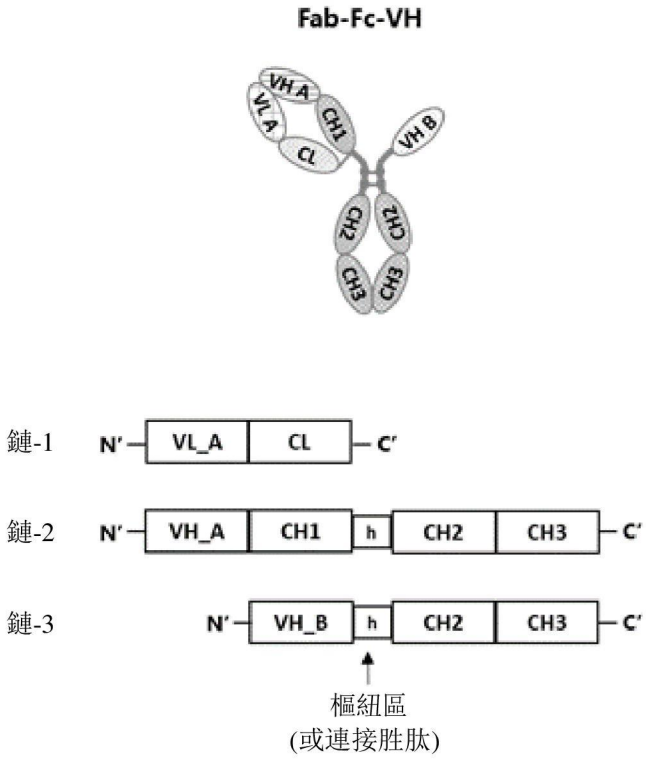
5-(D)


Fab(CL)-VH-Fc
VH A
CH1
VL A
CL
VH B
CH2
CH3
短鏈
N'
VH_A
CH1
C'
長鏈
VL_A
CL
L1
VH_B
L2
CH2
CH3
第一連接胜肽
第二連接胜肽

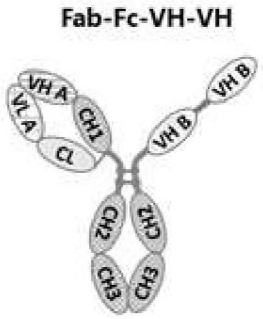
5-(E)

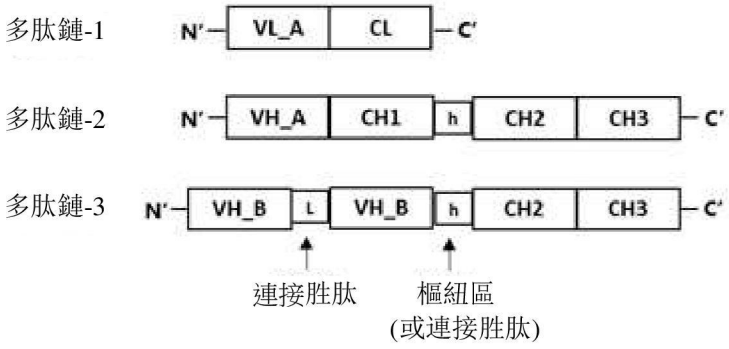

Fab(CH1)-VH-Fc
VH A
CH1
VL A
CL
VH B
VH B
CH1
VH A
CL
VL A
CH2
CH2
CH3
CH3
短鏈
N'
VL_A
CL
C'
長鏈
N'
VH_A
CH1
L1
VH_B
L2
CH2
CH3
C'
第一連接胜肽
第二連接胜肽

5-(F)

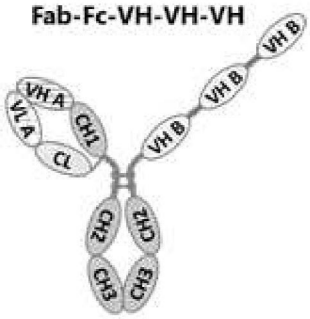

Fab-Fc-VH
VH A
VL A
CH1
CL
VH B
CH2
CH2
CH3
CH3
鏈-1
N'
VL_A
CL
C'
鏈-2
N'
VH_A
CH1
h
CH2
CH3
C'
鏈-3
N'
VH_B
h
CH2
CH3
C'
樞紐區
(或連接胜肽)

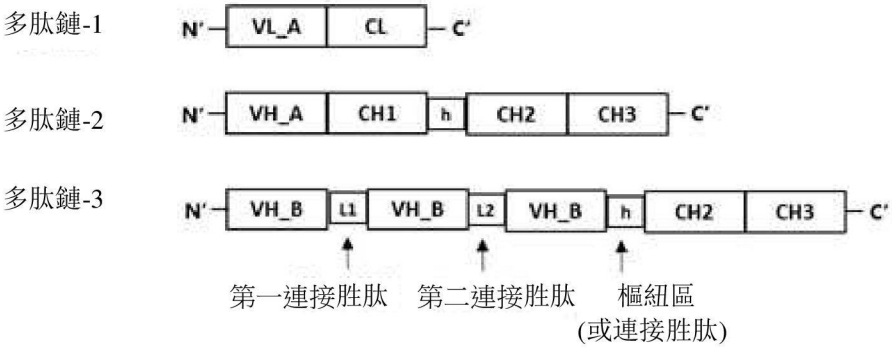
5-(G)


Fab-Fc-VH-VH
VH A
VL A
CH1
CL
VH B
VH B
CH2
CH2
CH3
CH3


多肽鏈-1
N'
VL_A
CL
C'
多肽鏈-2
N'
VH_A
CH1
h
CH2
CH3
C'
多肽鏈-3
N'
VH_B
L
VH_B
h
CH2
CH3
C'
連接胜肽
樞紐區
(或連接胜肽)

5-(H)


Fab-Fc-VH-VH-VH
VH A
VL A
CH1
CL
VH B
VH B
VH B
CH2
CH2
CH3
CH3


多肽鏈-1
N'
VL_A
CL
C'
多肽鏈-2
N'
VH_A
CH1
h
CH2
CH3
C'
多肽鏈-3
N'
VH_B
L1
VH_B
L2
VH_B
h
CH2
CH3
C'
第一連接胜肽
第二連接胜肽
樞紐區
(或連接胜肽)

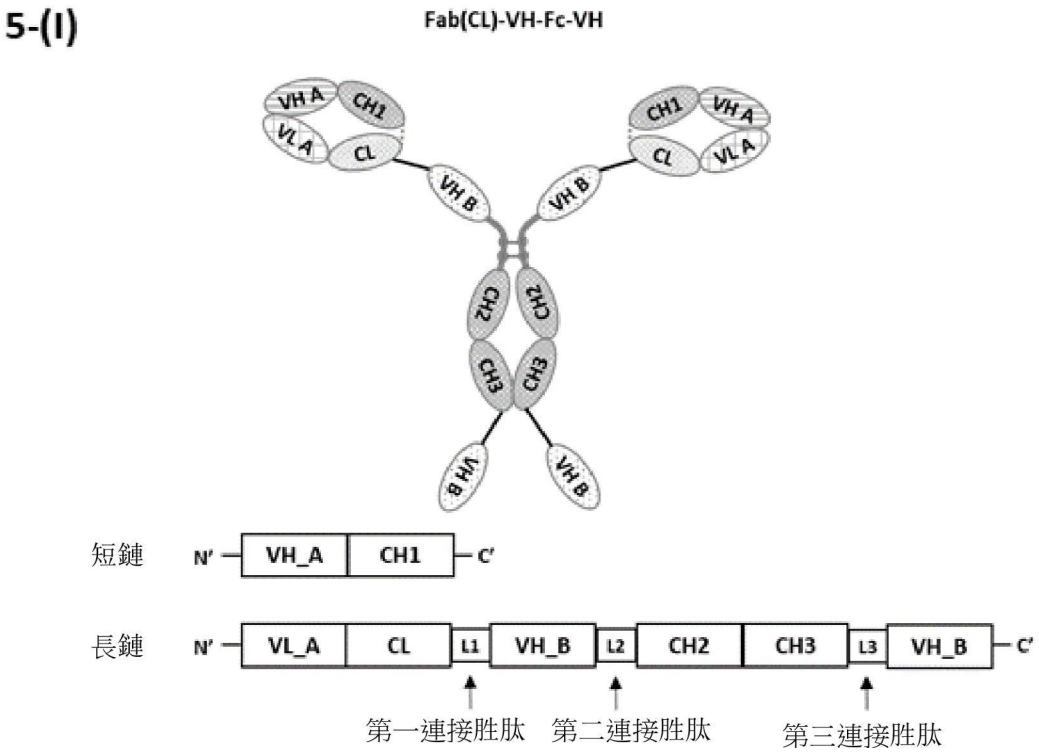
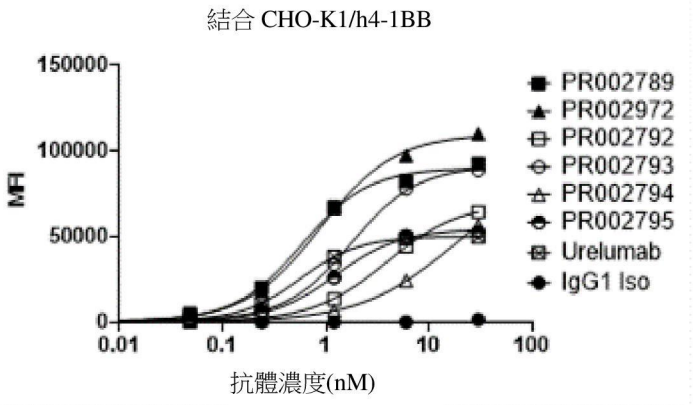

5-(I)
Fab(CL)-VH-Fc-VH
VH A
CH1
VL A
CL
VH B
CH2
CH3
短鏈
N'
VH_A
CH1
C'
長鏈
VL_A
CL
L1
VH_B
L2
CH2
CH3
L3
第一連接胜肽
第二連接胜肽
第三連接胜肽

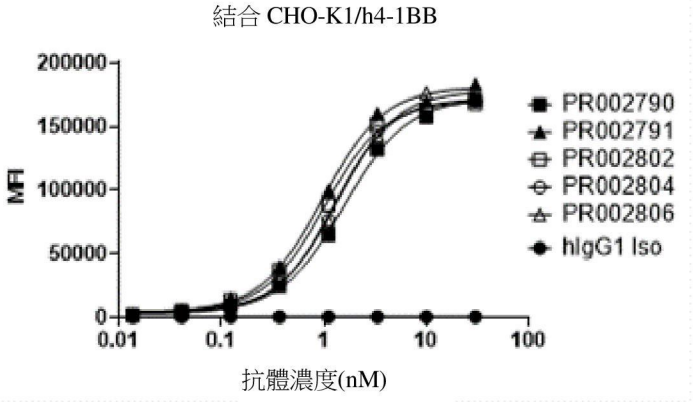
圖 5

6-(A)



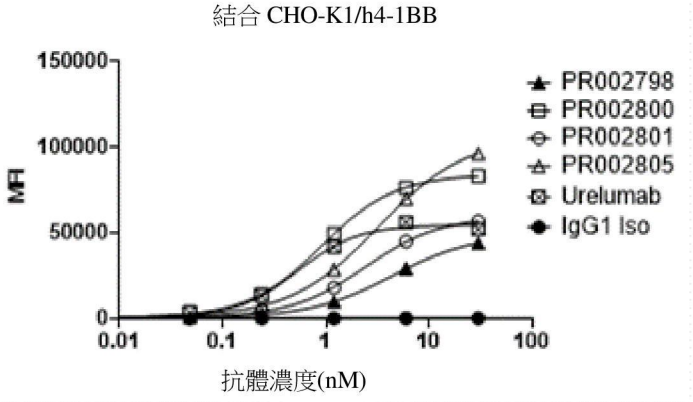
抗體	EC50 (nM)	MFI 最大值
PR002789	0.5832	89905
PR002972	0.8787	109696
PR002792	3.867	69629
PR002793	1.757	91136
PR002794	17.26	89715
PR002795	1.242	54263
Urelumab	0.5638	50027

6-(B)



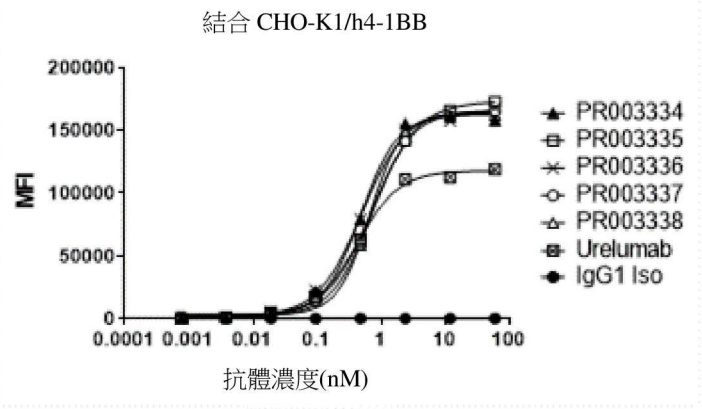
抗體	EC50 (nM)	MFI 最大值
PR002790	1.569	172452
PR002791	0.964	181267
PR002802	1.011	169767
PR002804	1.248	171989
PR002806	1.346	178189

6-(C)



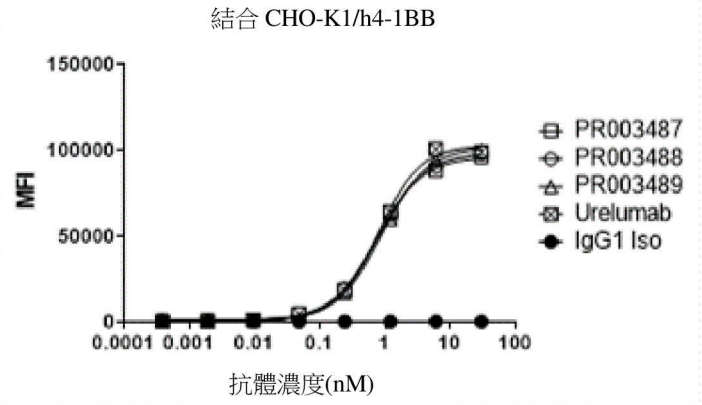
抗體	EC50 (nM)	MFI 最大值
PR002798	4.383	49377
PR002800	0.909	84135
PR002801	2.412	59629
PR002805	3.204	106201
Urelumab	0.5328	54570

6-(D)



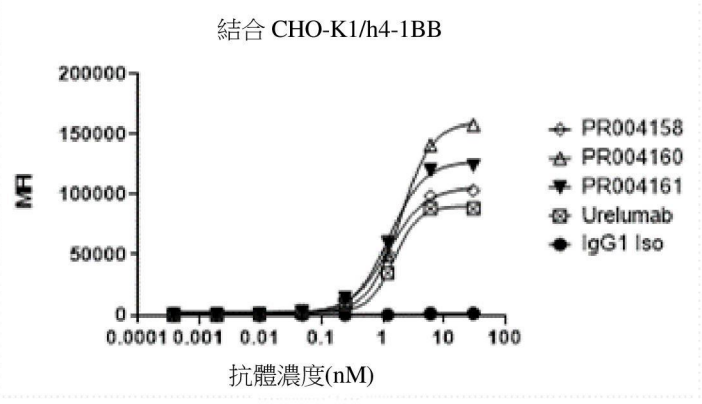
抗體	EC50 (nM)	MFI 最大值
PR003334	0.4831	162519
PR003335	0.7395	173076
PR003336	0.5000	165948
PR003337	0.7215	165538
PR003338	0.6708	163354
Urelumab	0.4241	118060

6-(E)



抗體	EC50 (nM)	MFI 最大值
PR003487	0.755	95740
PR003488	0.7735	98153
PR003489	0.8951	100804
urelumab	0.7945	101473

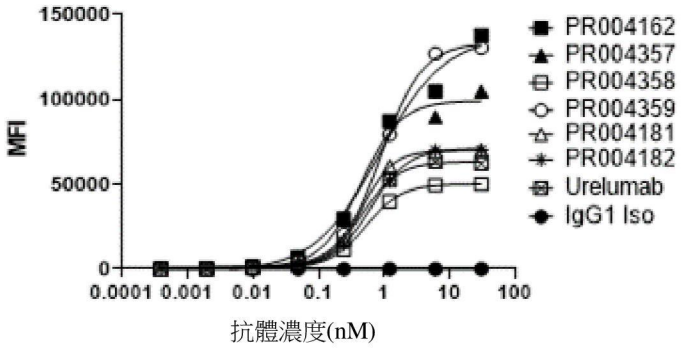
6-(F)



抗體	EC50 (nM)	MFI 最大值
PR004158	1.23	104982
PR004160	1.943	158311
PR004161	1.266	126124
Urelumab	1.506	88235

6-(G)

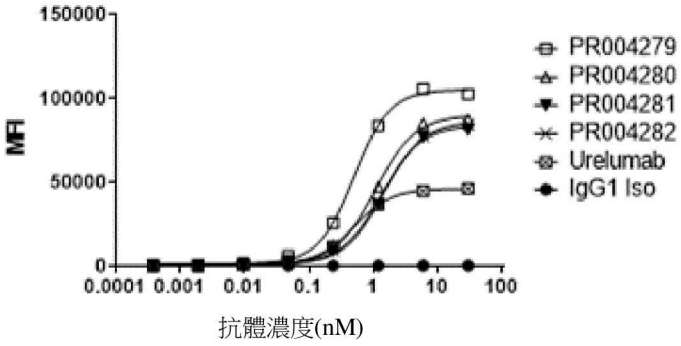
結合 CHO-K1/h4-1BB



抗體	EC50 (nM)	MFI 最大值
PR004162	0.8384	137301
PR004357	0.4317	99202
PR004358	0.5194	50246
PR004359	0.89	133337
PR004181	0.4487	69865
PR004182	0.6107	71139
Urelumab	0.4488	63326

6-(H)

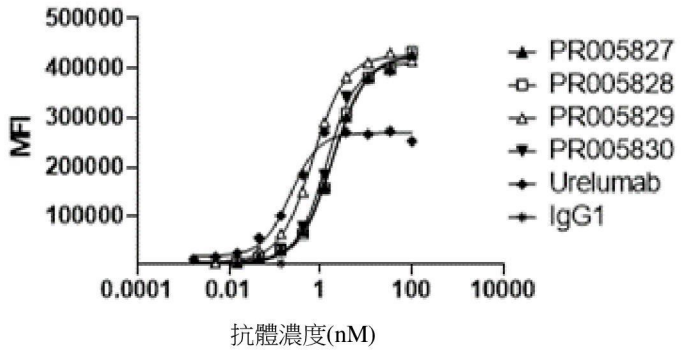
結合 CHO-K1/h4-1BB



抗體	EC50 (nM)	MFI 最大值
PR004279	0.5035	104957
PR004280	1.086	89959
PR004281	1.394	83574
PR004282	1.408	86442
Urelumab	0.4989	45925

6-(I)

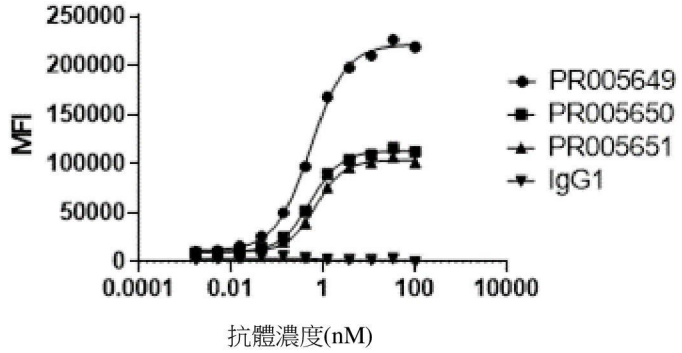
結合 CHO-K1/h4-1BB 細胞



抗體	EC50 (nM)	MFI最大值
PR005827	1.853	424725
PR005828	1.844	423994
PR005829	0.6776	425447
PR005830	1.373	410829
Urelumab	0.2218	269486

6-(J)

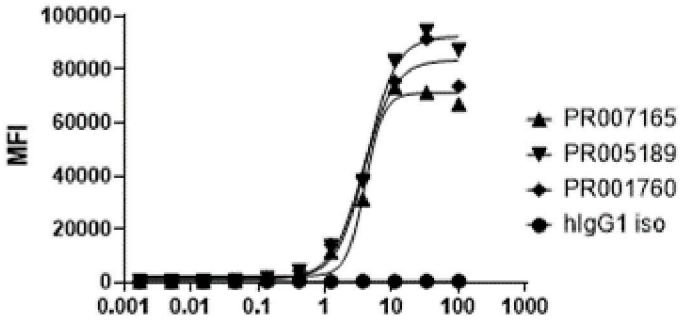
結合 CHO-K1/h4-1BB 細胞



抗體	EC50 (nM)	MFI最大值
PR005649	0.5333	221290
PR005650	0.5313	112860
PR005651	0.6893	103596

6-(K)

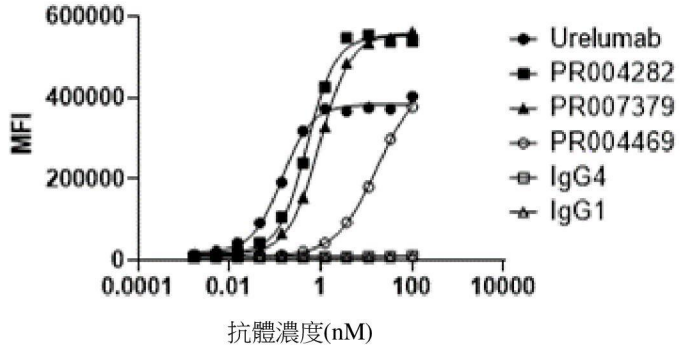
結合 CHO-K1/hu 4-1BB



抗體	EC50 (nM)	MFI 最大值
PR007165	3.996	71246
PR005189	4.255	92381
PR001760	3.761	83588

6-(L)

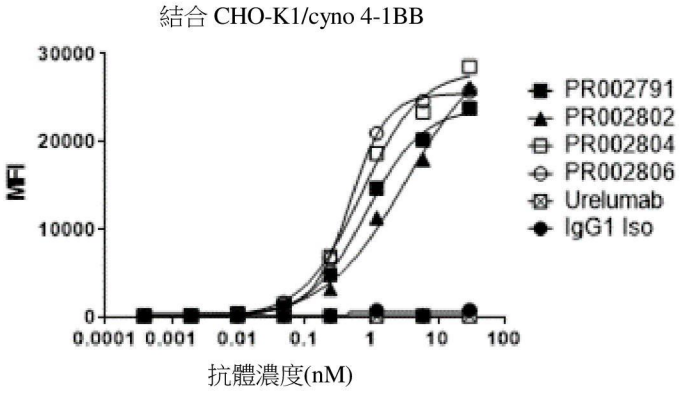
結合 CHO-K1/h4-1BB 細胞



抗體	EC50(nM)	MFI最大值
Urelumab	0.1404	383660
PR004282	0.5024	552940
PR007379	0.9384	560073
PR004469	17.04	447078

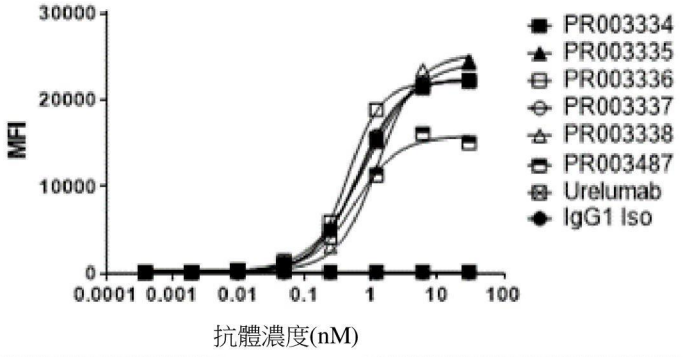
圖 6

7-(A)



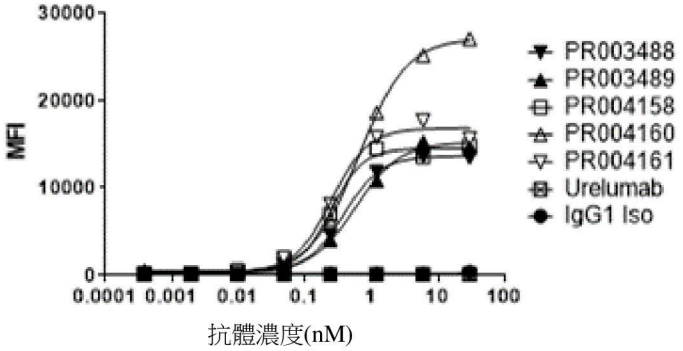
抗體	EC50 (nM)	MFI 最大值
PR002791	0.844	23881
PR002802	3.341	31349
PR002804	0.7054	28189
PR002806	0.4697	25505
urelumab	N.D	N.D

7-(B)



抗體	EC50 (nM)	MFI 最大值
PR003334	0.6581	22567
PR003335	0.7969	24442
PR003336	0.443	22090
PR003337	0.6307	22514
PR003338	1.289	25239
PR003487	0.5637	15834
urelumab	N.D	N.D

7-(C)

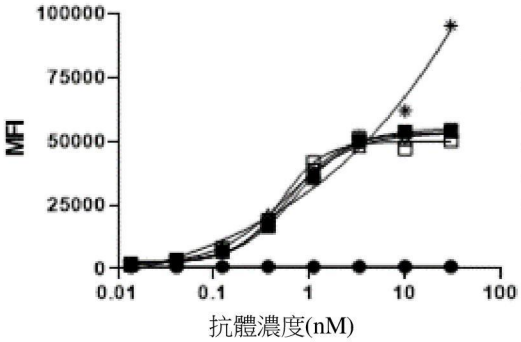


抗體	EC50 (nM)	MFI 最大值
PR003488	0.3824	13645
PR003489	0.576	15209
PR004158	0.2482	14511
PR004160	0.6447	27154
PR004161	0.2501	16822
urelumab	N.D	N.D

圖 7

8-(A)

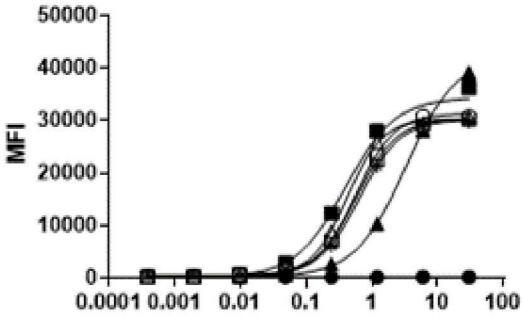
結合 SK-BR-3 細胞



抗體	EC50 (nM)	MFI 最大值
PR002790	0.7169	54647
PR002791	0.5540	53403
PR002802	0.4993	49937
PR002804	0.6150	53272
PR002806	n.d.	n.d.

8-(B)

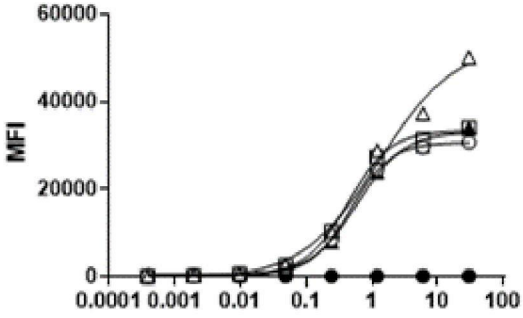
結合 SK-BR-3 細胞



抗體	EC50 (nM)	MFI 最大值
PR002789	0.3921	34336
PR002972	3.309	42339
PR002792	0.5752	30413
PR002793	0.5649	31288
PR002794	0.4177	30245
PR002795	0.6435	30137

8-(C)

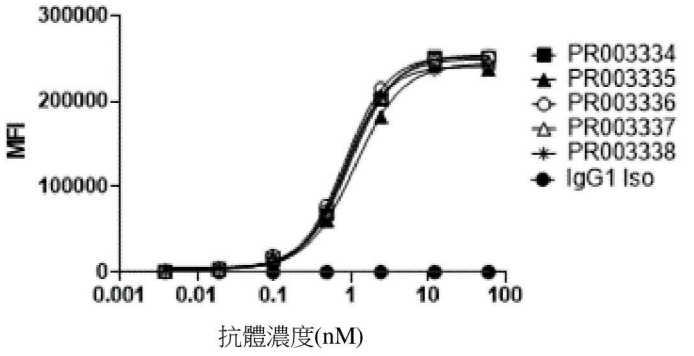
結合 SK-BR-3 細胞



抗體	EC50 (nM)	MFI 最大值
PR002798	0.5961	33151
PR002800	0.4285	33422
PR002801	0.4759	30648
PR002805	1.268	53448

8-(D)

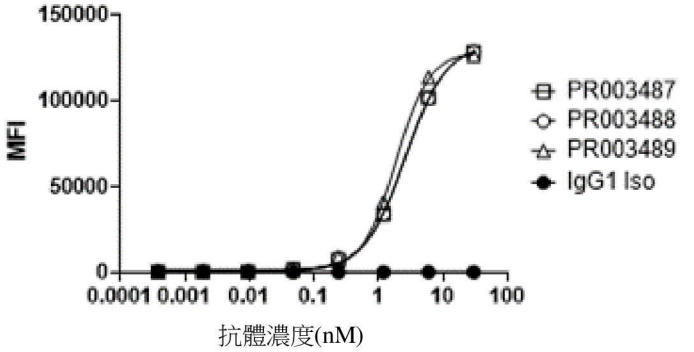
結合 SK-BR-3 細胞



抗體	EC50 (nM)	MFI 最大值
PR003334	0.9685	254417
PR003335	1.102	244159
PR003336	0.8208	252359
PR003337	0.9001	249524
PR003338	0.8207	241092

8-(E)

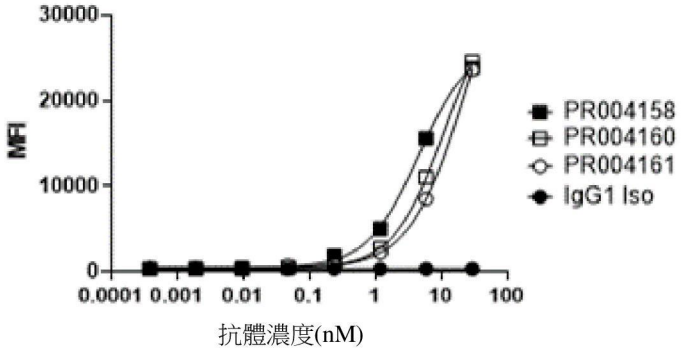
結合 SK-BR-3 細胞



抗體	EC50 (nM)	MFI 最大值
PR003487	2.593	131617
PR003488	2.626	132285
PR003489	1.877	126775

8-(F)

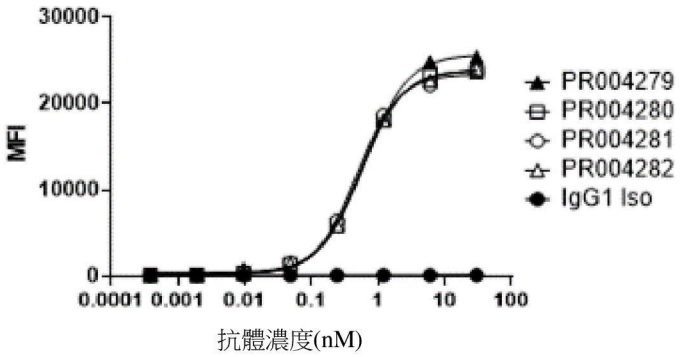
結合 SK-BR-3 細胞



抗體	EC50 (nM)	MFI 最大值
PR004158	4.614	26398
PR004160	11.33	32312
PR004161	23.44	41230

8-(G)

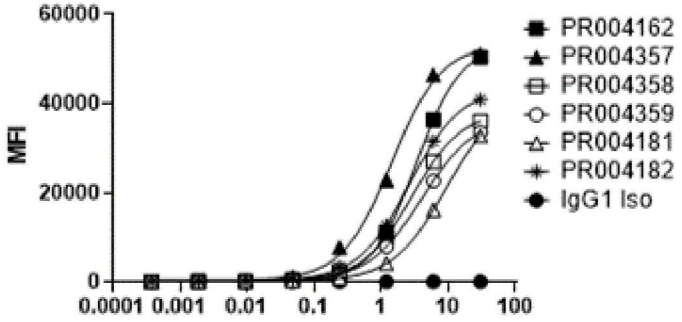
結合 SK-BR-3 細胞



抗體	EC50 (nM)	MFI 最大值
PR004279	0.6201	25718
PR004280	0.5358	23858
PR004281	0.4801	23400
PR004282	0.5444	23879

8-(H)

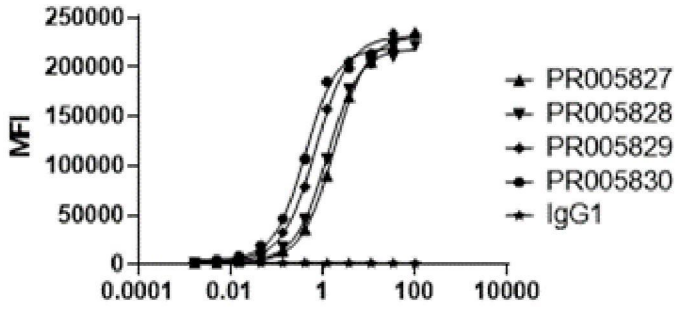
結合 SK-BR-3 細胞



抗體	EC50 (nM)	MFI 最大值
PR004162	3.342	53207
PR004357	1.433	53334
PR004358	2.909	38512
PR004359	4.051	37469
PR004181	9.254	41920
PR004182	2.616	43637

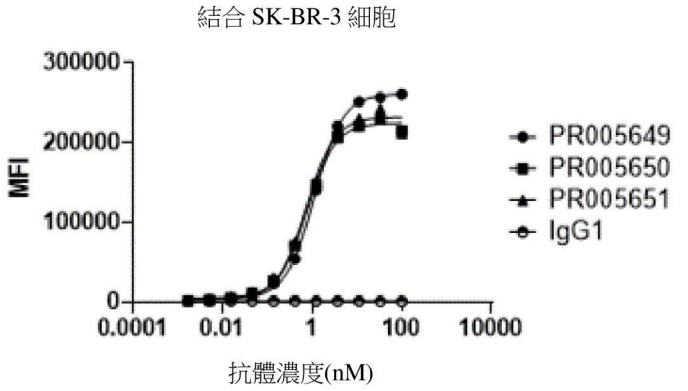
8-(I)

結合 SK-BR-3 細胞



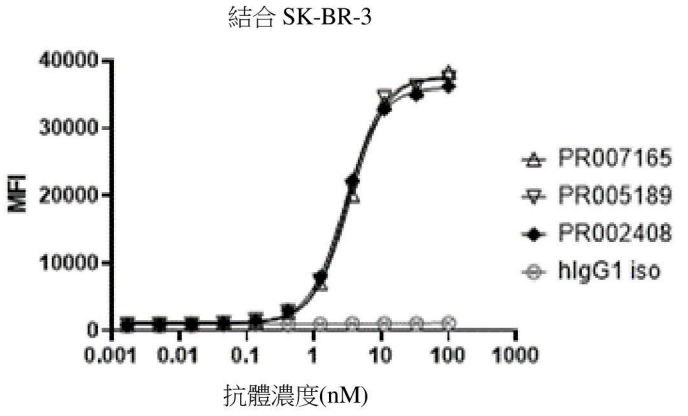
抗體	EC50 (nM)	MFI最大值
PR005827	1.767	231310
PR005828	1.259	218403
PR005829	0.7033	231300
PR005830	0.4168	219262

8-(J)



抗體	EC50 (nM)	MFI最大值
PR005649	1.126	261119
PR005650	0.7538	224628
PR005651	0.7379	231769

8-(K)

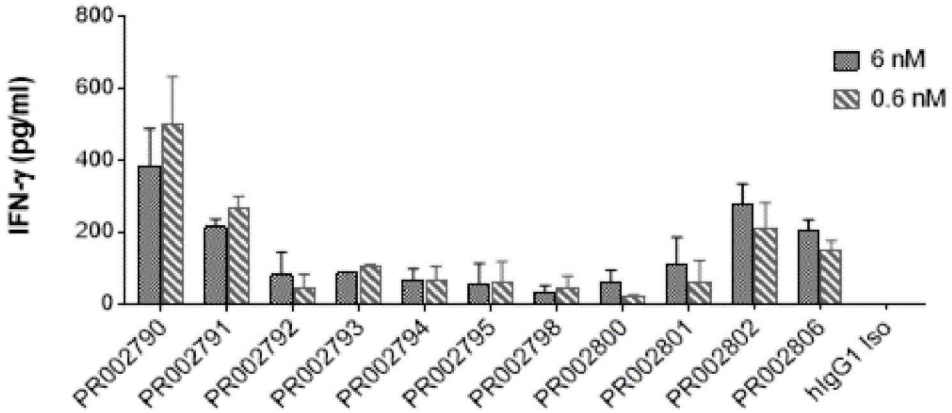


抗體	EC50 (nM)	MFI 最大值
PR007165	3.462	37793
PR005189	3.173	37457
PR002408	2.853	36029

圖 8

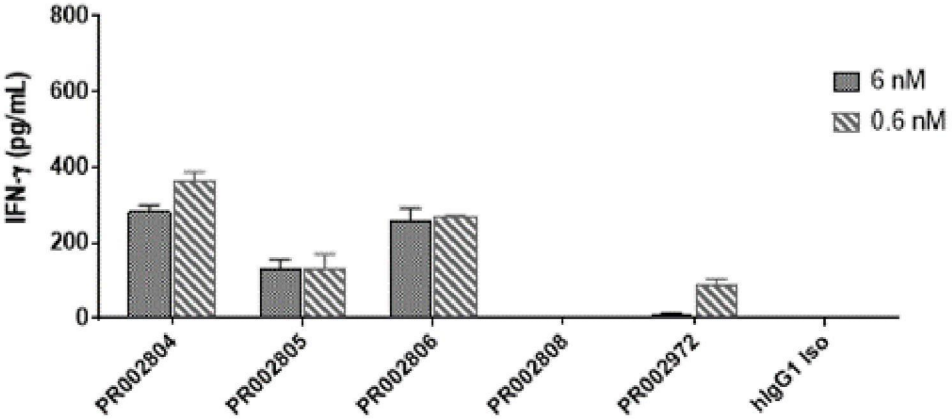
9-(A)

SK-BR-3 細胞媒介的 T 細胞活化



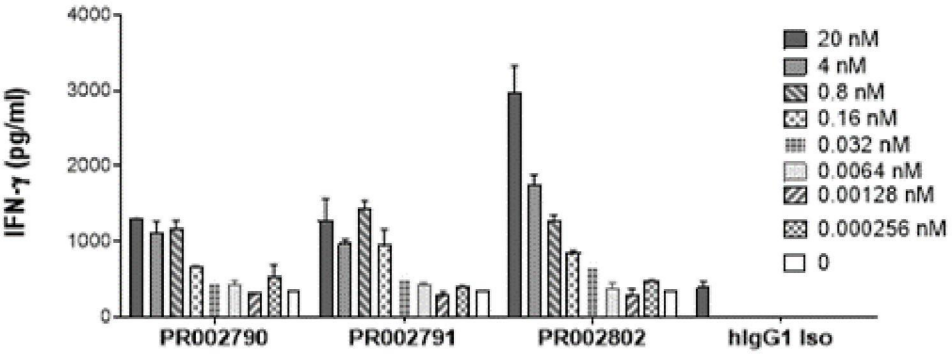
9-(B)

SK-BR-3 細胞媒介的 T 細胞活化

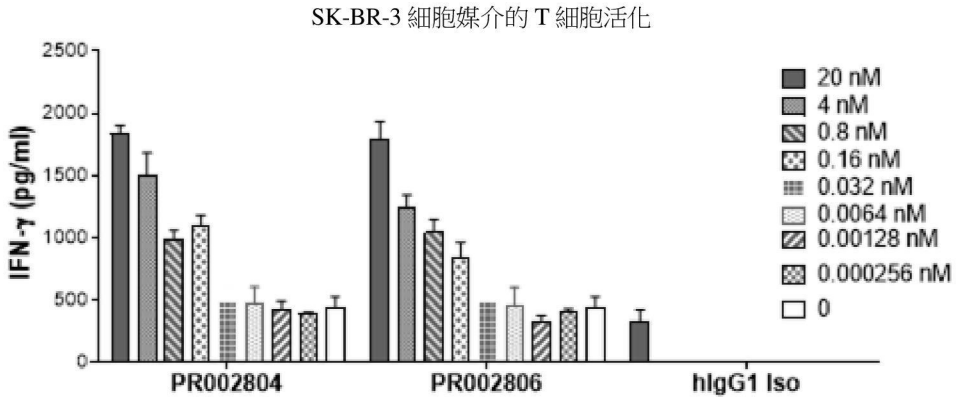


9-(C)

SK-BR-3 細胞媒介的 T 細胞活化



9-(D)


SK-BR-3 細胞媒介的 T 細胞活化
IFN-γ (pg/ml)
2500
2000
1500
1000
500
0
20 nM
4 nM
0.8 nM
0.16 nM
0.032 nM
0.0064 nM
0.00128 nM
0.000256 nM
0
PR002804
PR002806
hIgG1 Iso

9-(E)

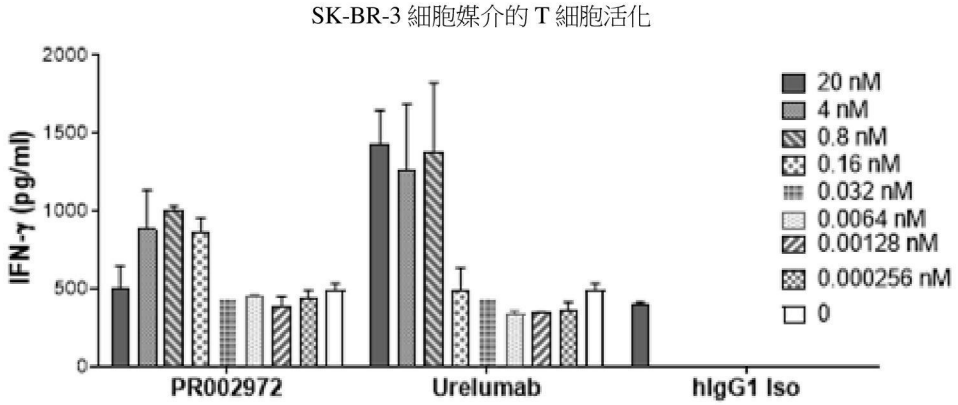
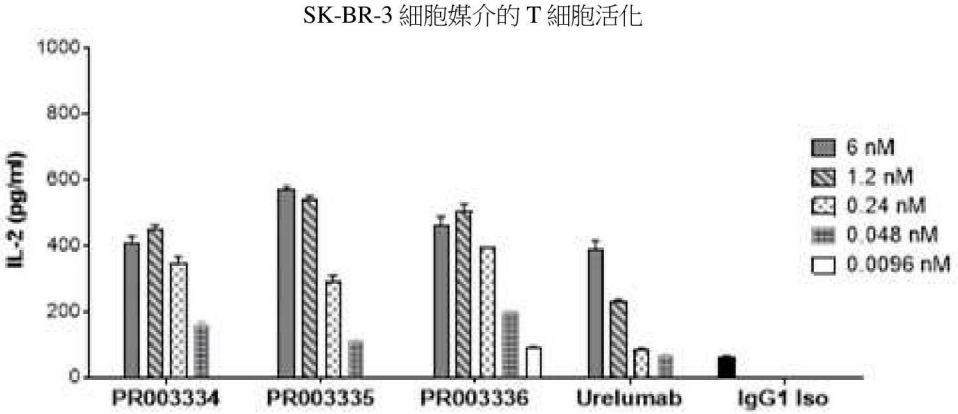

SK-BR-3 細胞媒介的 T 細胞活化
IFN-γ (pg/ml)
2000
1500
1000
500
0
20 nM
4 nM
0.8 nM
0.16 nM
0.032 nM
0.0064 nM
0.00128 nM
0.000256 nM
0
PR002972
Urelumab
hIgG1 Iso

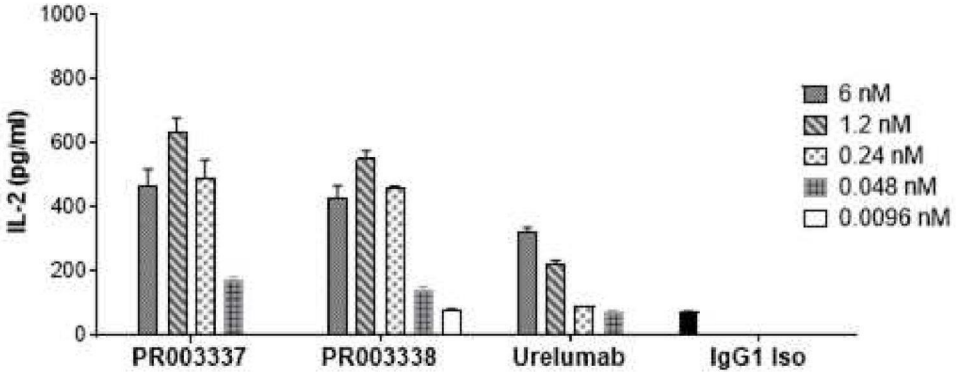
圖 9

10-(A)


SK-BR-3 細胞媒介的 T 細胞活化
IL-2 (pg/ml)
1000
800
600
400
200
0
6 nM
1.2 nM
0.24 nM
0.048 nM
0.0096 nM
PR003334
PR003335
PR003336
Urelumab
IgG1 Iso

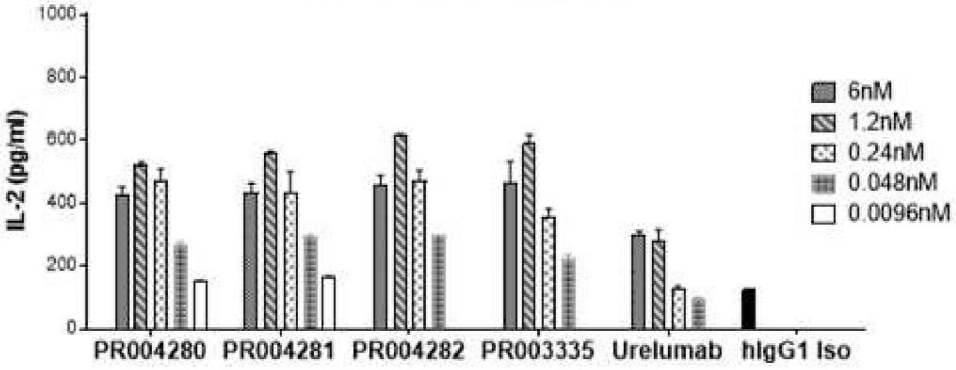
10-(B)

SK-BR-3 細胞媒介的 T 細胞活化



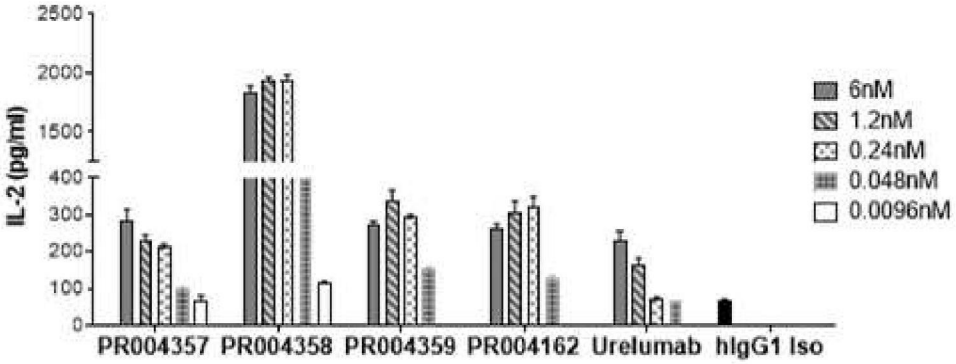
10-(C)

SK-BR-3 細胞媒介的 T 細胞活化



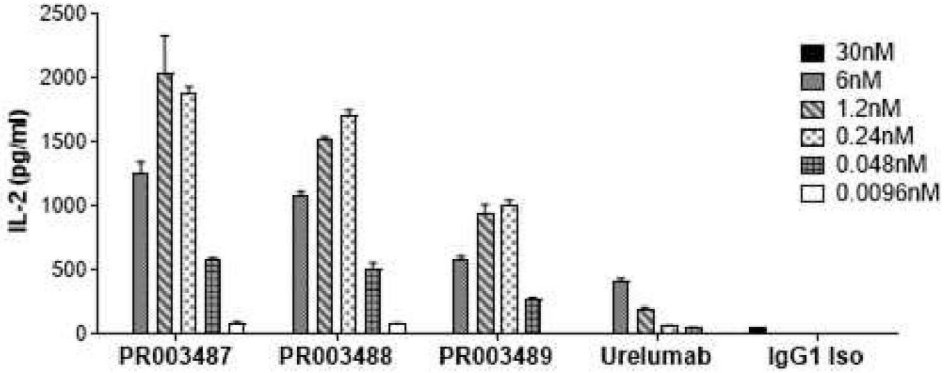
10-(D)

SK-BR-3 細胞媒介的 T 細胞活化



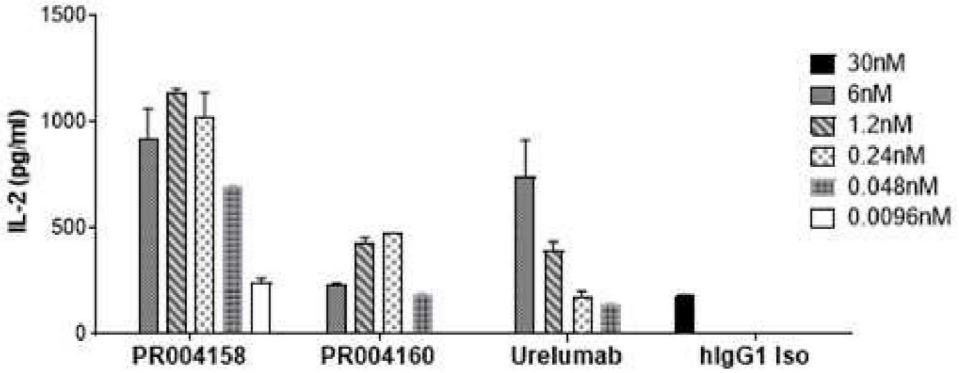
10-(E)

SK-BR-3 細胞媒介的 T 細胞活化



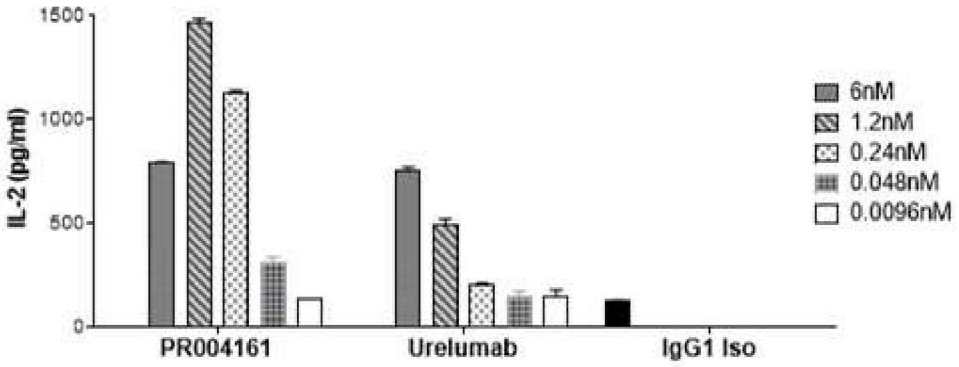
10-(F)

SK-BR-3 細胞媒介的 T 細胞活化



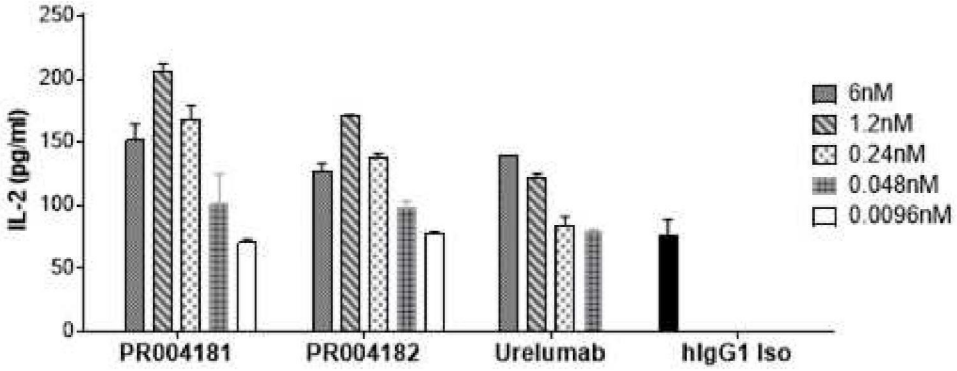
10-(G)

SK-BR-3 細胞媒介的 T 細胞活化



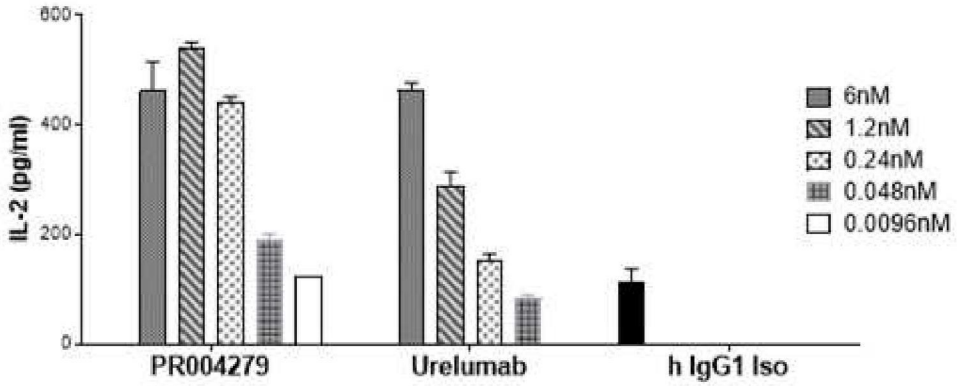
10-(H)

SK-BR-3 細胞媒介的 T 細胞活化



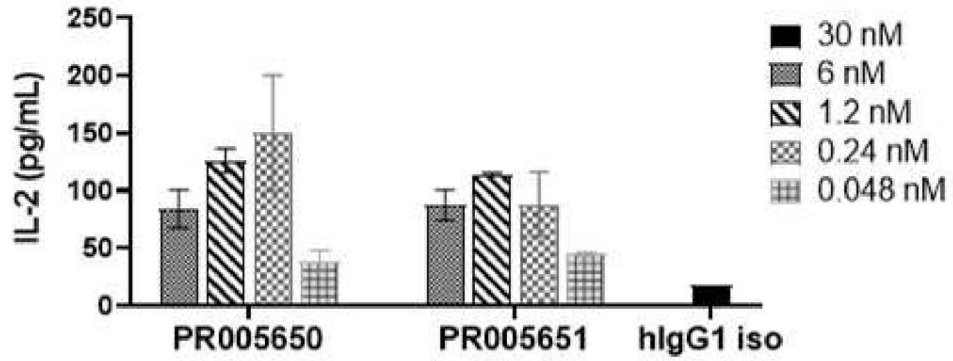
10-(I)

SK-BR-3 細胞媒介的 T 細胞活化



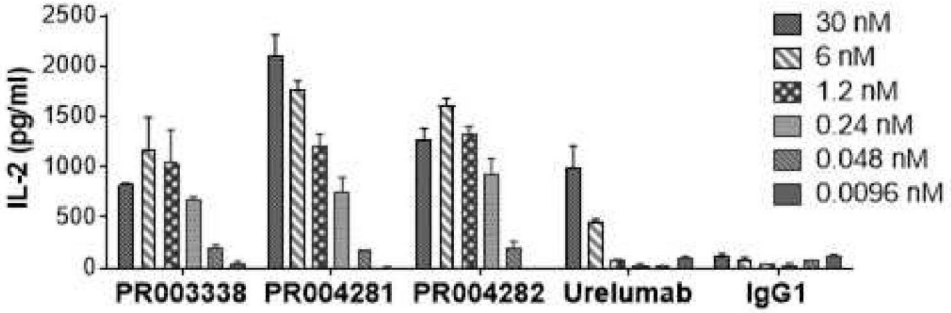
10-(J)

SK-BR-3 細胞媒介的 T 細胞活化



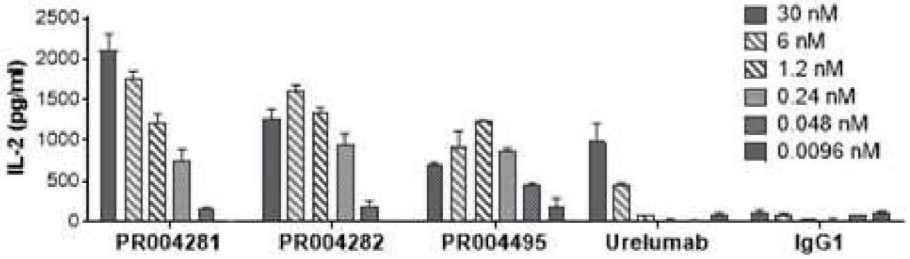
10-(K)

SK-BR-3 細胞媒介的 T 細胞活化



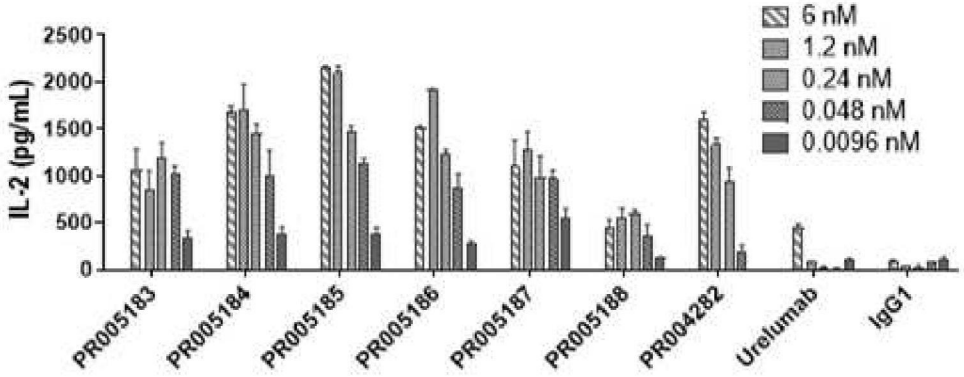
10-(L)

SK-BR-3 細胞媒介的 T 細胞活化



10-(M)

SK-BR-3 細胞媒介的 T 細胞活化



10-(N)

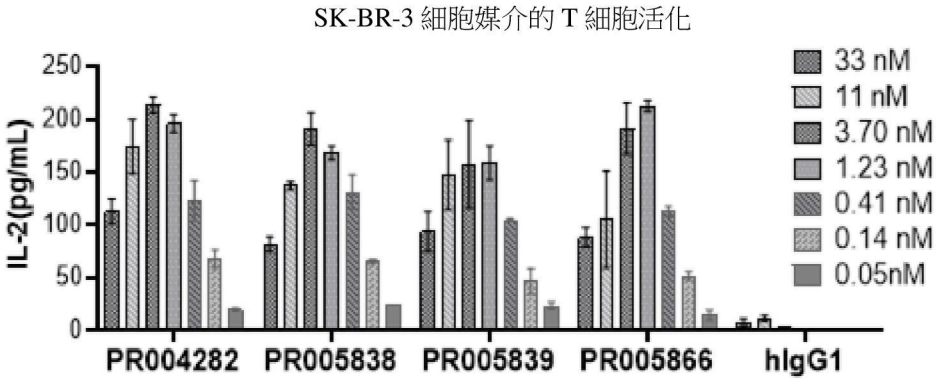
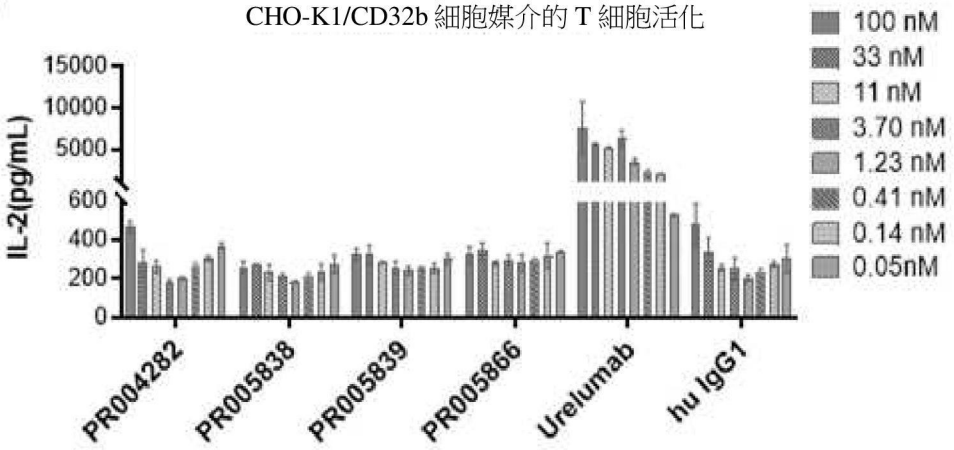


圖 10

11-(A)



11-(B)

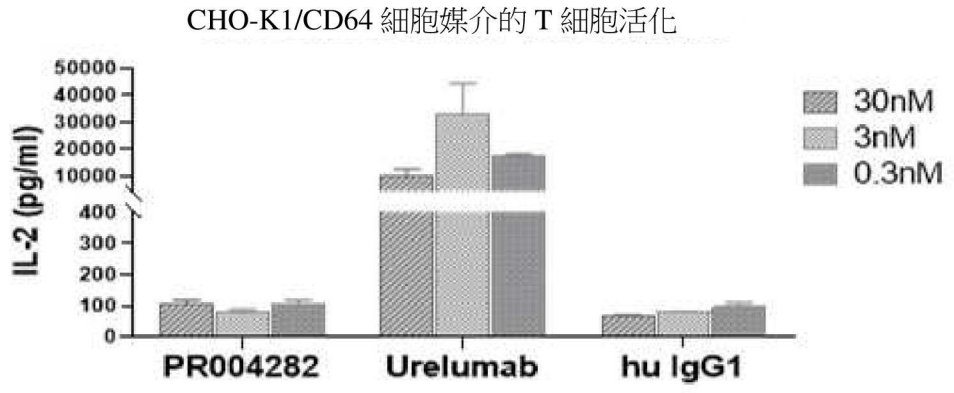
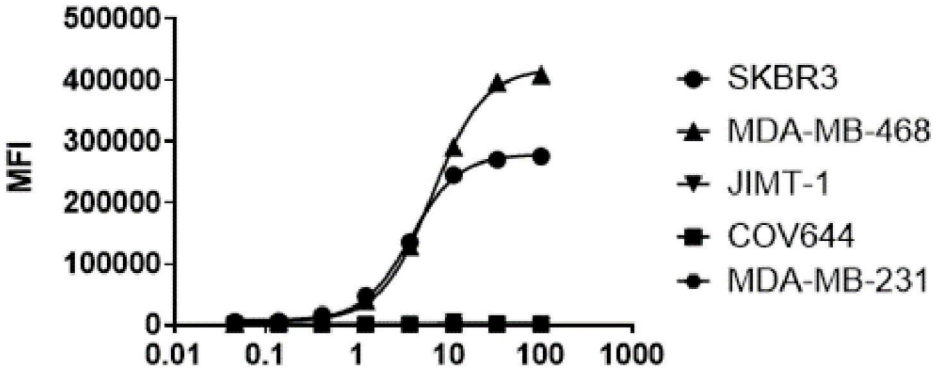


圖 11

12-(A)

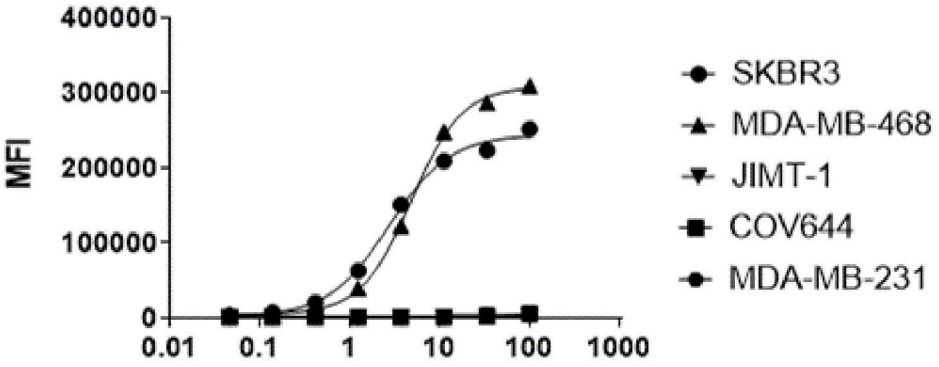
陽性對照抗體 1 檢測腫瘤細胞表現 B7H4 的表現量



抗體濃度(nM)

12-(B)

PR003334 檢測腫瘤細胞表面的 B7H4 的表現量

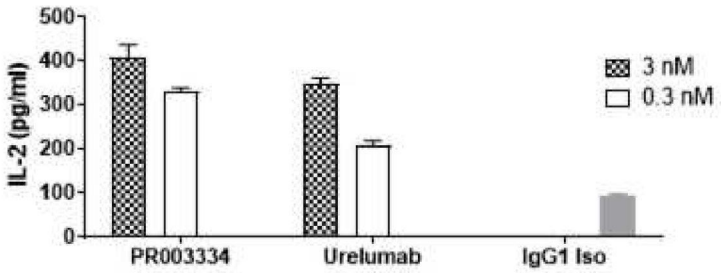


抗體濃度(nM)

圖 12

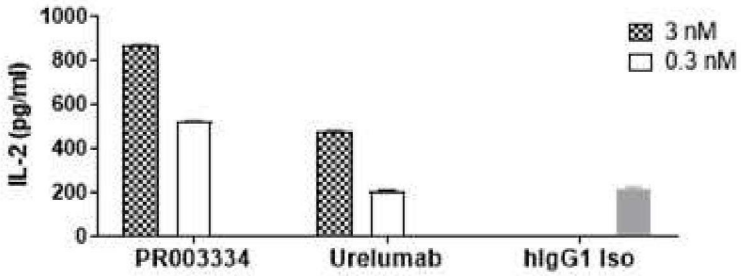
13-(A)

在高度表現 B7H4 的細胞 SK-BR-3 存在時，雙抗可以特異性地活化 T 細胞



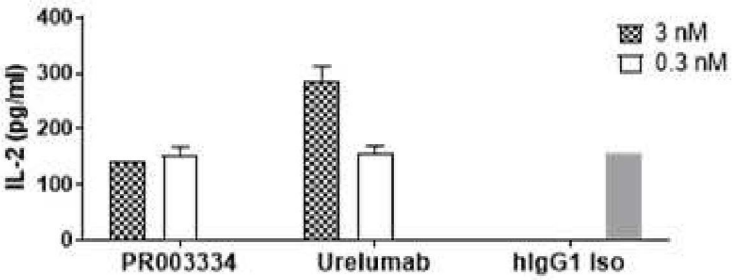
13-(B)

在高度表現 B7H4 的細胞 MDA-MB-468 存在時，雙抗可以特異性地活化 T 細胞



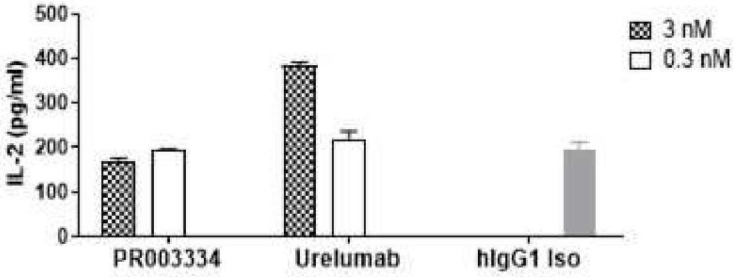
13-(C)

在不表現 B7H4 的細胞 COV644 存在時，雙抗不活化 T 細胞



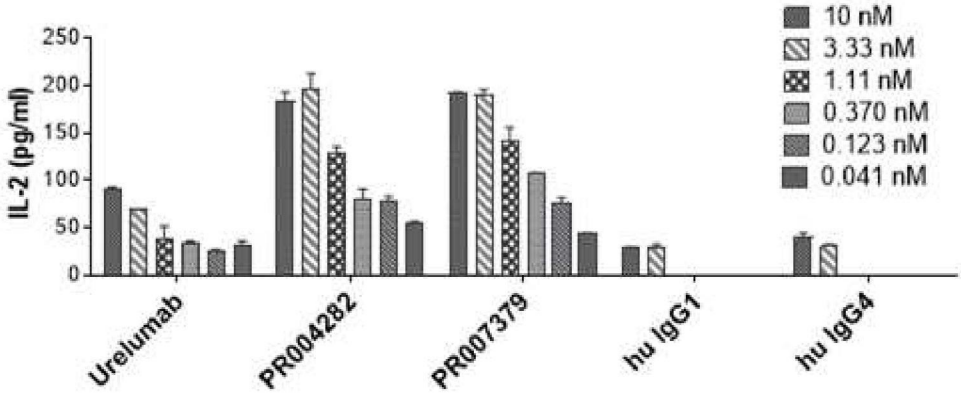
13-(D)

在不表現 B7H4 的細胞 Jimt-1 存在時，雙抗不活化 T 細胞



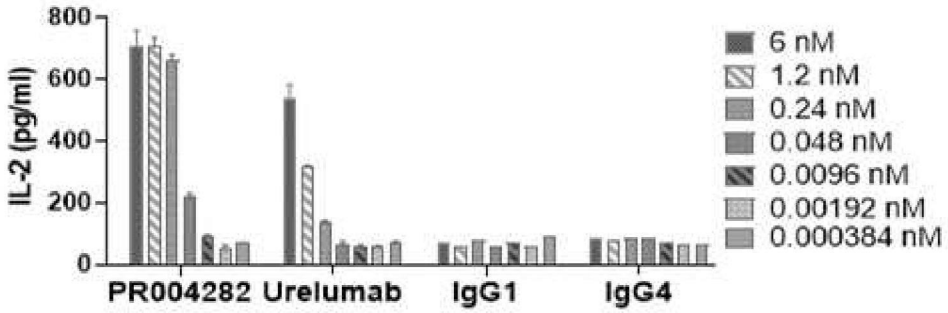
13-(E)

MDA-MB-468 細胞媒介的 T 細胞活化



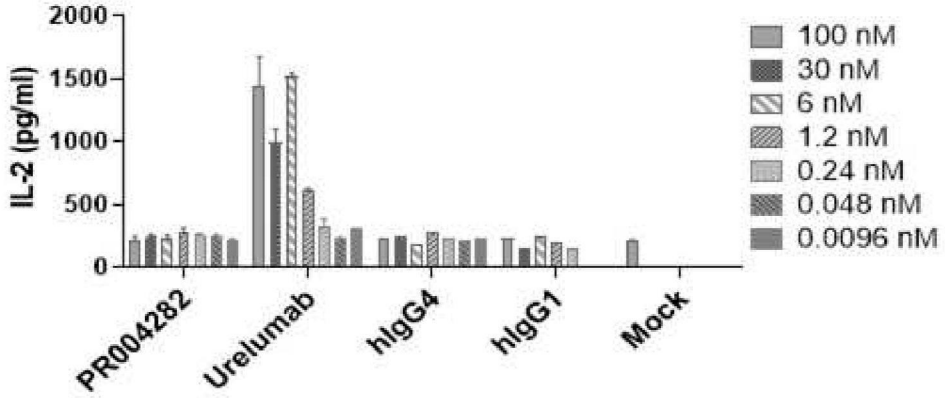
13-(F)

SK-BR-3 細胞媒介的 T 細胞活化



13-(G)

JIMT-1 細胞媒介的 T 細胞活化



13-(H)

MDA-MB-231 細胞媒介的 T 細胞活化

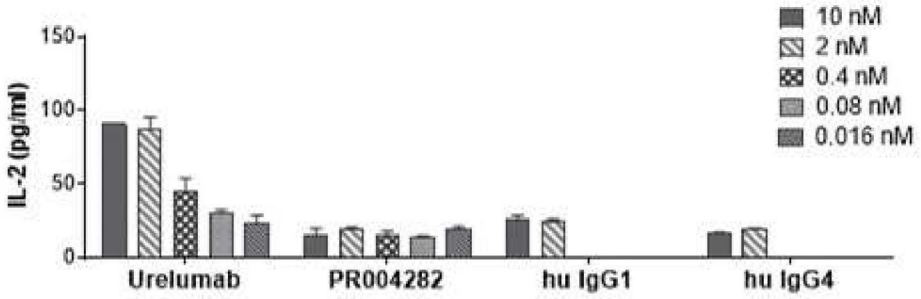
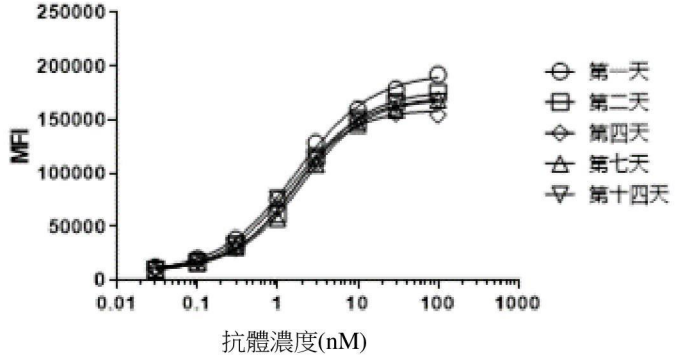


圖 13

14-(A)

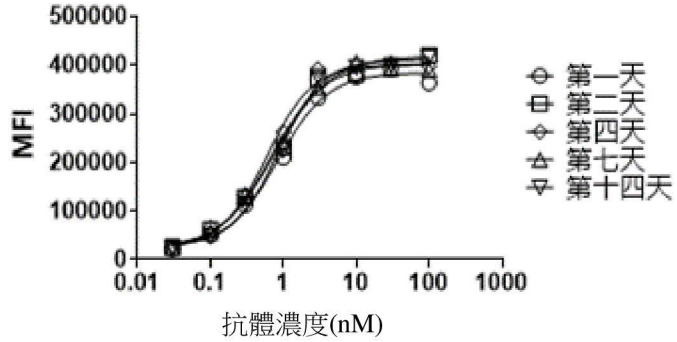
PR003334 結合 SK-BR-3 細胞



時間點	EC50(nM)	最大訊號值
第一天	1.707	186430
第二天	1.912	168183
第四天	1.562	147497
第七天	2.004	160471
第十四天	1.489	164959

14-(B)

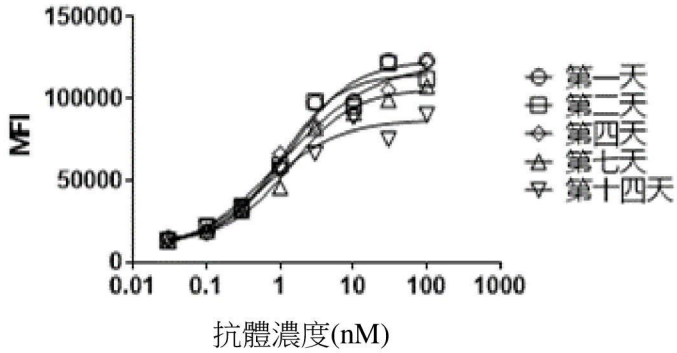
PR003334 結合 CHO-K1/hu 4-1BB 細胞



時間點	EC50(nM)	最大訊號值
第一天	0.841	360239
第二天	0.769	397943
第四天	0.607	374153
第七天	0.680	381546
第十四天	0.851	383431

14-(C)

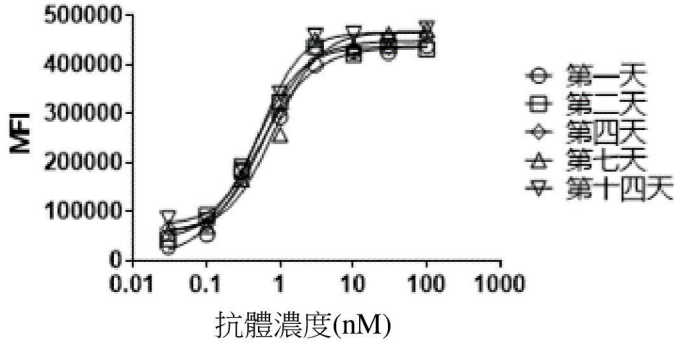
PR003335 結合 SK-BR-3 細胞



時間點	EC50(nM)	最大訊號值
第一天	1.285	112575
第二天	1.039	102557
第四天	1.072	120474
第七天	1.41	93520
第十四天	0.6645	78631

14-(D)

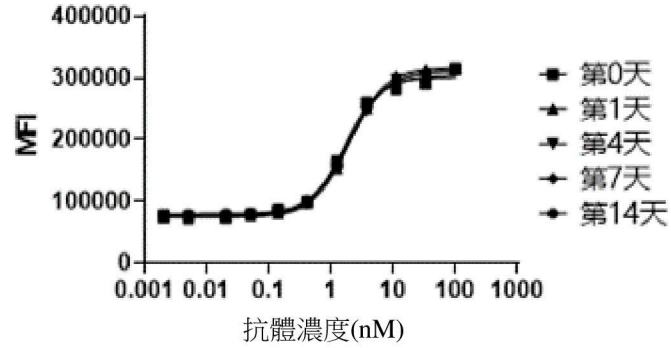
PR003335 結合 CHO-K1/h4-1BB 細胞



時間點	EC50(nM)	最大訊號值
第一天	0.4700	432153
第二天	0.4572	396669
第四天	0.6241	389379
第七天	0.8201	410577
第十四天	0.5605	391641

14-(E)

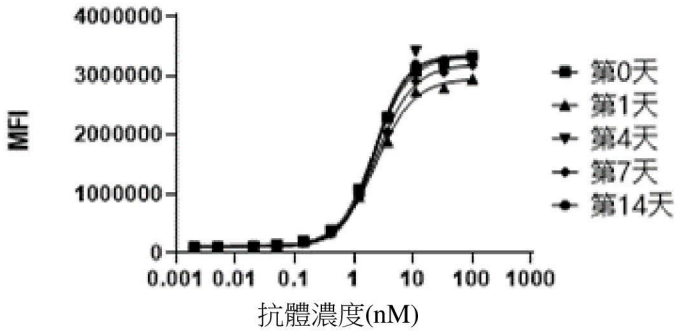
PR004282 結合 CHO-K1/人 4-1BB 細胞



時間點	EC50(nM)	最大訊號值
第0天	1.613	300719
第一天	1.954	316913
第四天	1.813	312597
第七天	1.766	304656
第十四天	1.953	311639

14-(F)

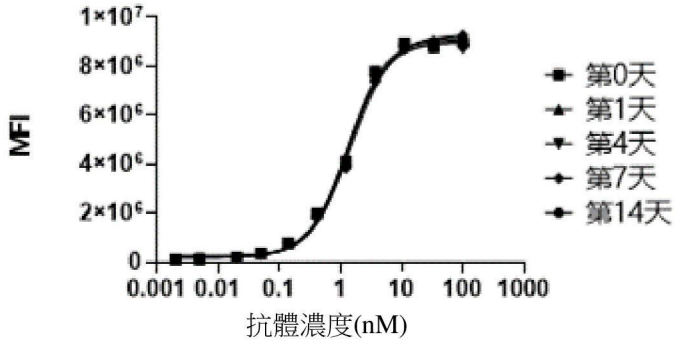
PR004282 結合 CHO-K1/猴 4-1BB 細胞



時間點	EC50(nM)	最大訊號值
第0天	2.18	3314024
第一天	2.386	2942971
第四天	2.185	3320789
第七天	2.416	3184374
第十四天	2.329	3344662

14-(G)

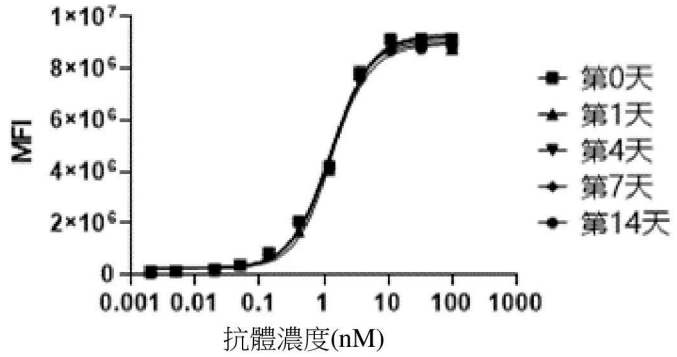
PR004282 結合 CHO-K1/人 B7H4 細胞



時間點	EC50(nM)	最大訊號值
第0天	1.297	9300606
第一天	1.344	9028383
第四天	1.331	9334816
第七天	1.294	9206150
第十四天	1.276	8974801

14-(H)

PR004282 結合 CHO-K1/猴 B7H4 細胞

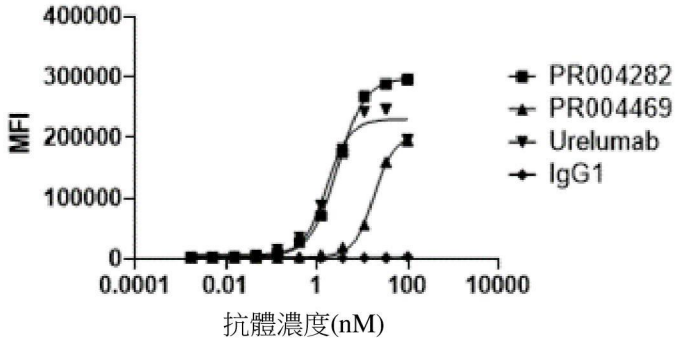


時間點	EC50(nM)	最大訊號值
第0天	1.305	9090977
第一天	1.356	9217138
第四天	1.292	9000287
第七天	1.496	9295882
第十四天	1.346	8990780

圖 14

15-(A)

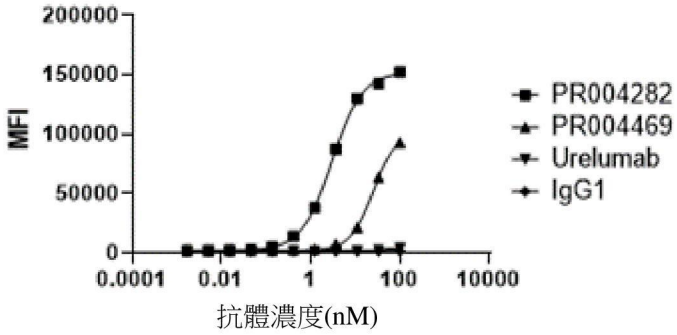
PR004282 結合 CHO-K1/h4-1BB 細胞



抗體	EC50 (nM)	MFI最大值
PR004282	2.851	299284
PR004469	18.01	203998
Urelumab	1.63	230882

15-(B)

PR004282 結合 CHO-K1/cyno-4-1BB 細胞



抗體	EC50 (nM)	MFI最大值
PR004282	2.99	151967
PR004469	25.38	102035
Urelumab	~ 39.92	3842

15-(C)

PR004282 結合 CHO-K1/m4-1BB 細胞

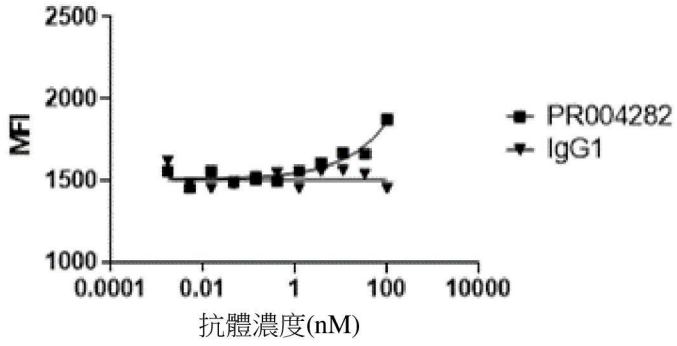
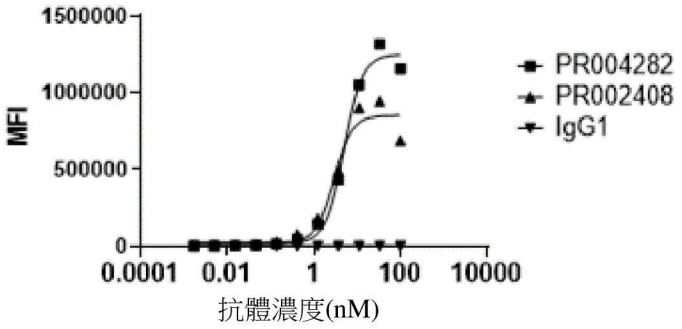


圖 15

16-(A)

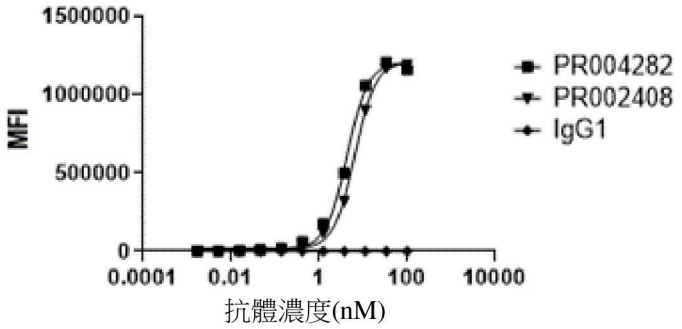
結合 CHO-K1/人 B7H4 細胞



抗體	EC50 (nM)	MFI最大值
PR004282	4.961	1249032
PR002408	2.925	853508

16-(B)

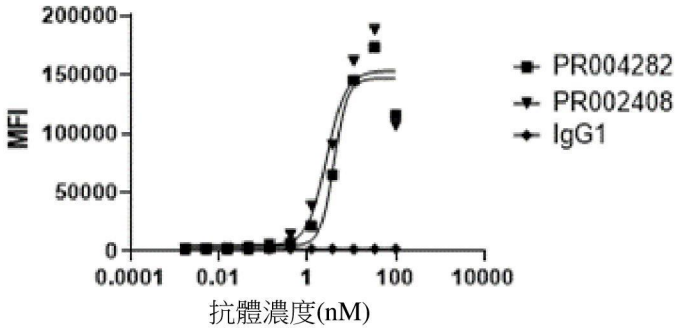
結合 CHO-K1/猴 B7H4 細胞



抗體	EC50 (nM)	MFI最大值
PR004282	4.272	1202740
PR002408	6.395	1208645

16-(C)

結合 CHO-K1/小鼠 B7H4 細胞



抗體	EC50 (nM)	MFI最大值
PR004282	3.997	146939
PR002408	2.714	153281

圖 16

PR004282 同時結合
CHO-K1/h4-1BB 和 SK-BR-3 細胞

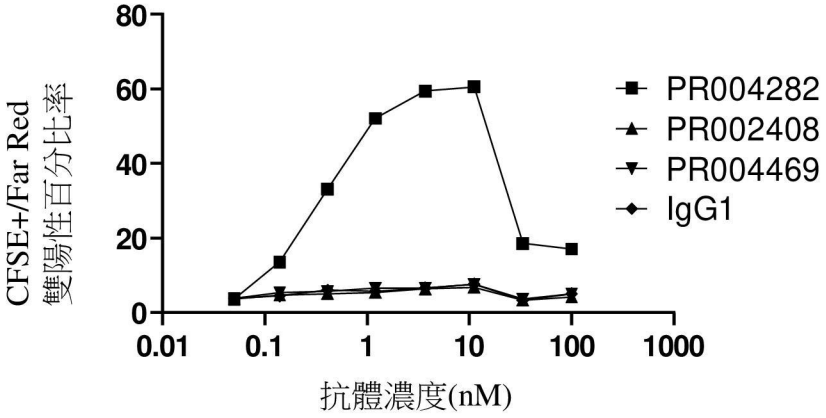
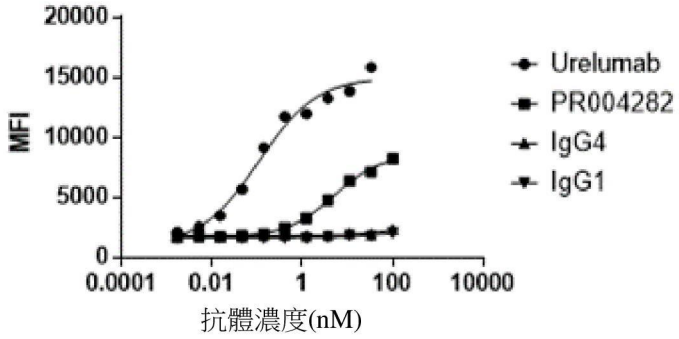


圖 17

18-(A)

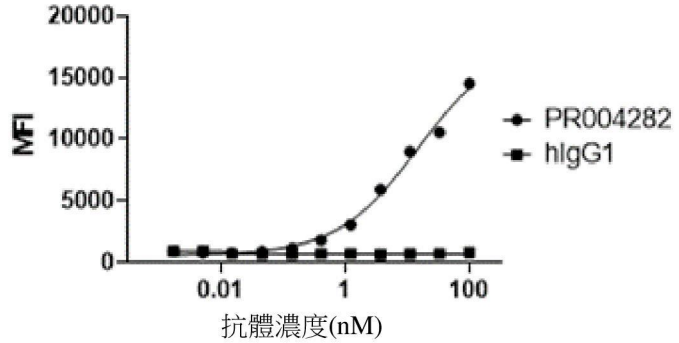
PR004282 結合活化後的人 Pan T 細胞



抗體	EC50(nM)	最大訊號值
Urelumab	0.1076	14978
PR004282	5.048	8585

18-(B)

PR004282 結合活化後的猴 Pan T 細胞

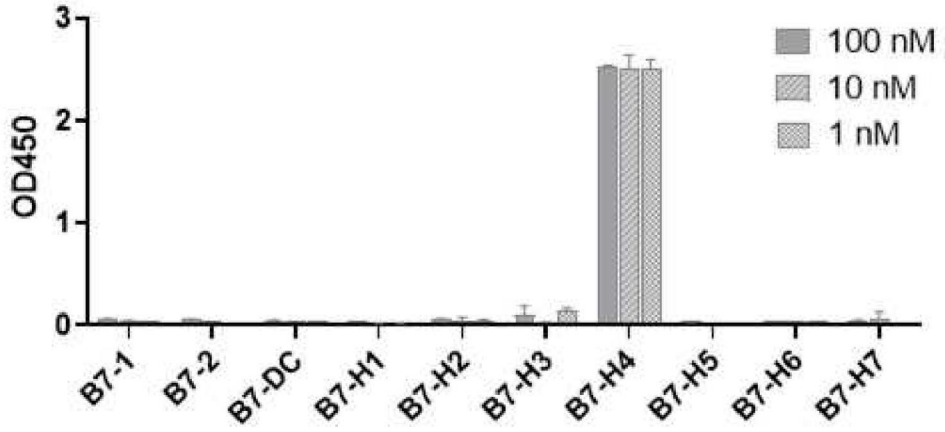


抗體	EC50(nM)	最大訊號值
PR004282	14.95	17991

圖 18

19-(A)

PR004282 與 B7 家族其他成員的交叉反應



19-(B)

PR004282 與 TNFR 家族其他成員的交叉反應

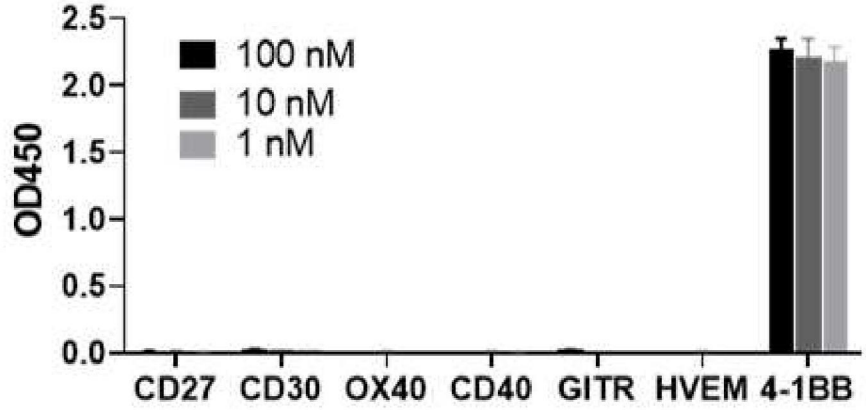
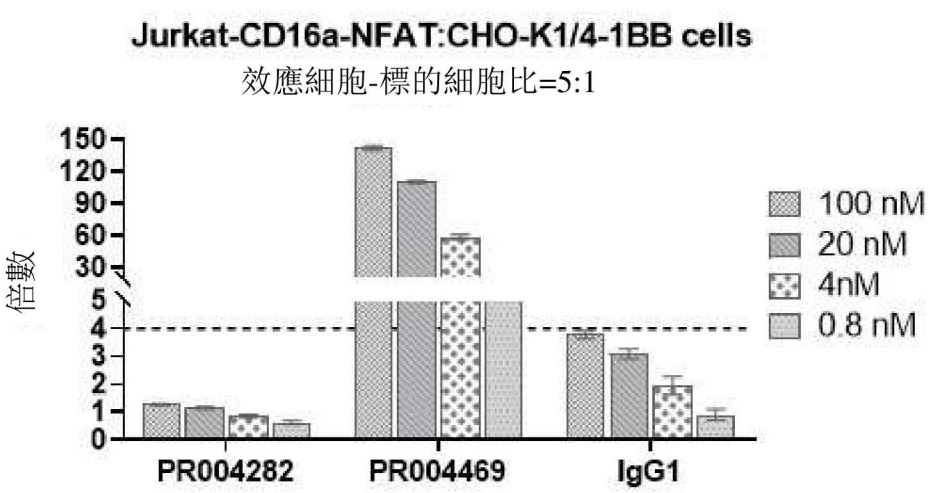
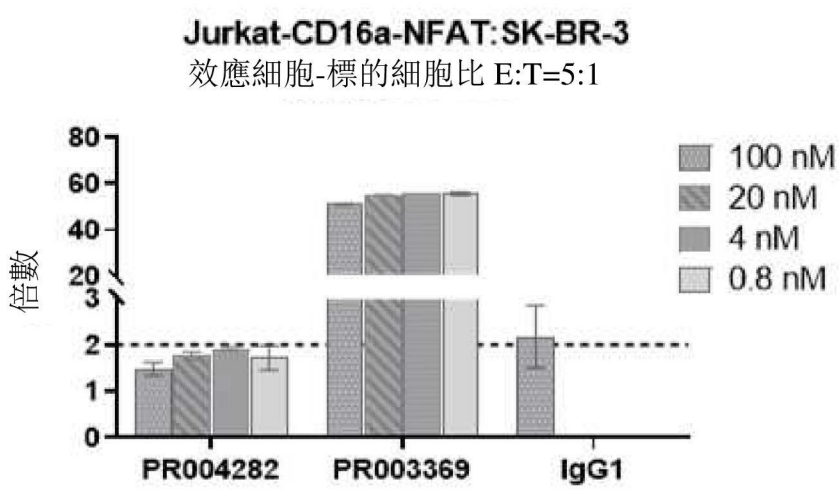


圖 19

20-(A)



20-(B)



20-(C)

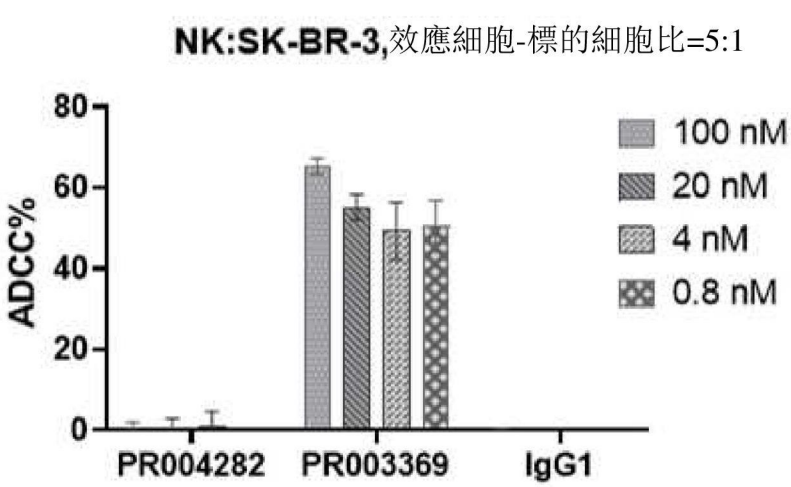
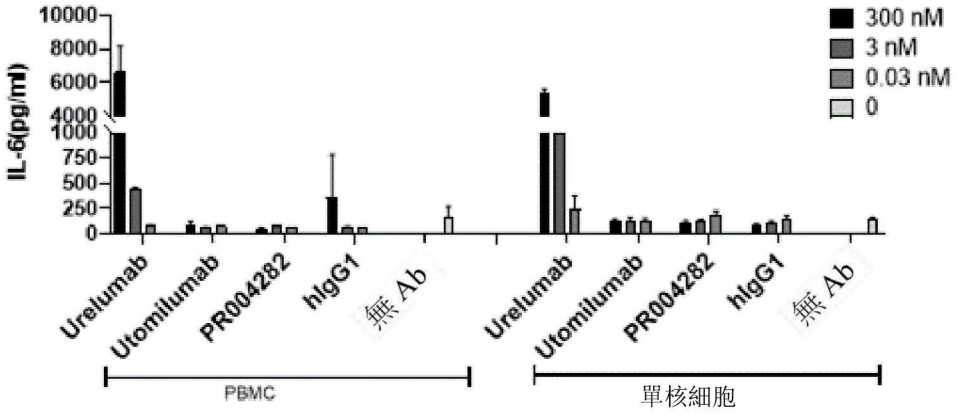


圖 20

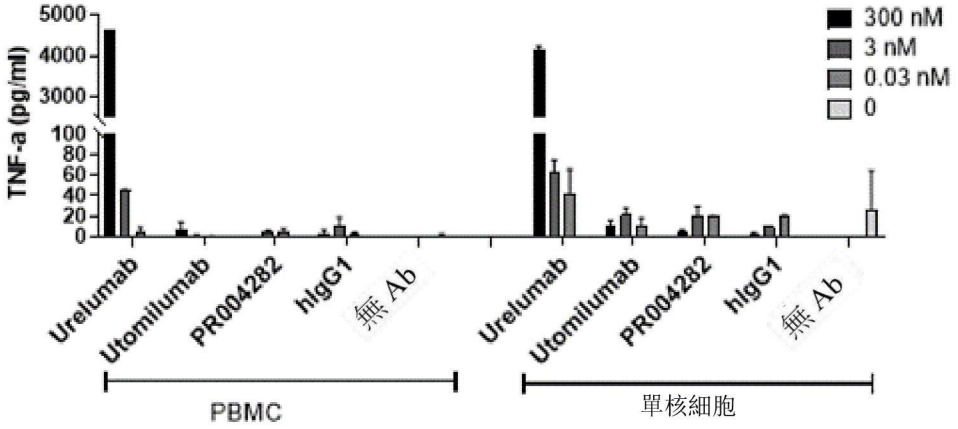
21-(A)

PBMC 或單核細胞與 PR004282 培育 24h 後上清中 IL-6 的釋放



21-(B)

PBMC 或單核細胞與 PR004282 培育 24h 後上清中 TNF-a 的釋放



21-(C)

PBMC 或單核細胞與 PR004282 培育 24h 後上清中 IFN-γ的釋放

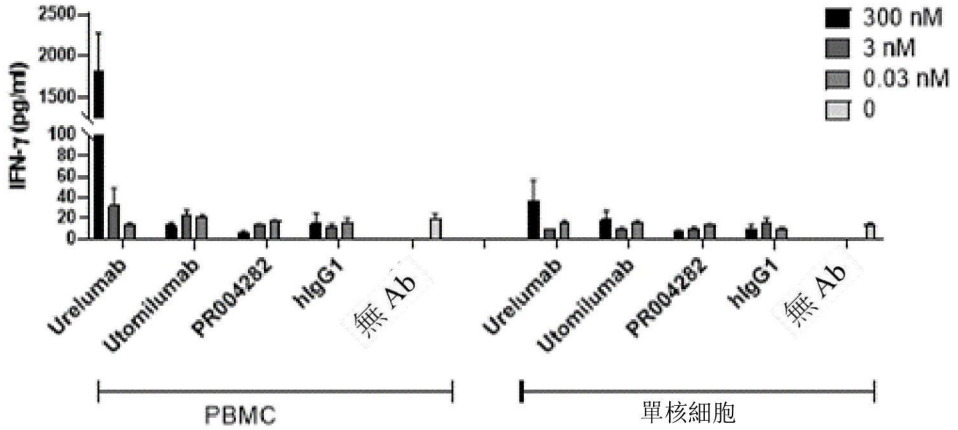
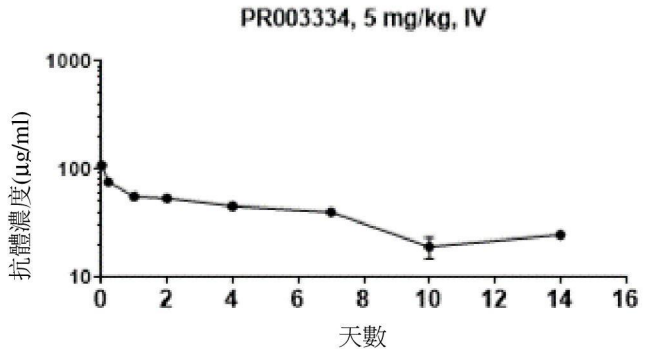


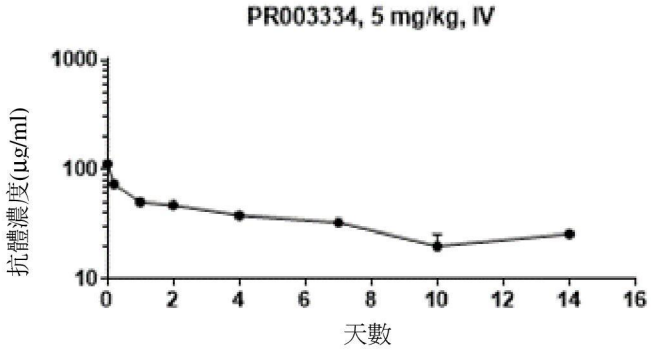
圖 21

22-(A)



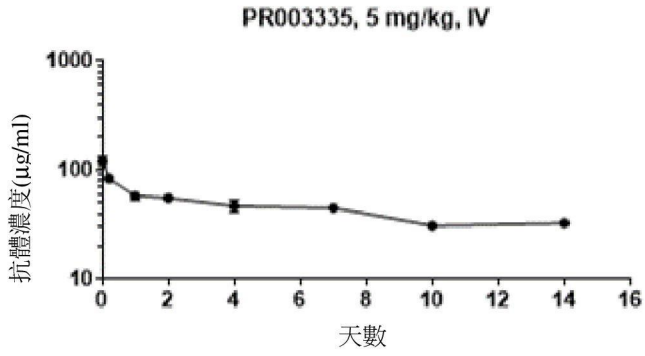
PK 參數	單位	平均值
$T_{1/2}$	小時	193
V_d	mL/kg	76
AUC_{all}	µg*小時/mL	12,680
AUC *	%	100
CL	mL/小時/kg	0.28
C_0	µg/mL	111

22-(B)



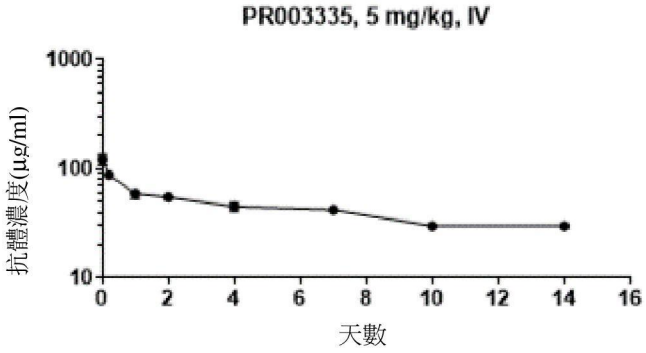
PK 參數	單位	平均值
$T_{1/2}$	小時	218
V_d	mL/kg	89
AUC_{all}	µg*小時/mL	11,471
AUC *	%	90
CL	mL/小時/kg	0.28
C_0	µg/mL	114

22-(C)



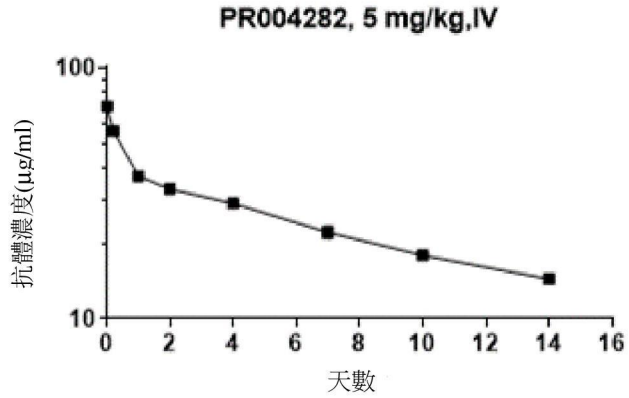
PK 參數	單位	平均值
$T_{1/2}$	小時	336
V_d	mL/kg	81
AUC_{all}	µg*小時/mL	14,813
AUC *	%	100
CL	mL/小時/kg	0.17
C_0	µg/mL	123

22-(D)



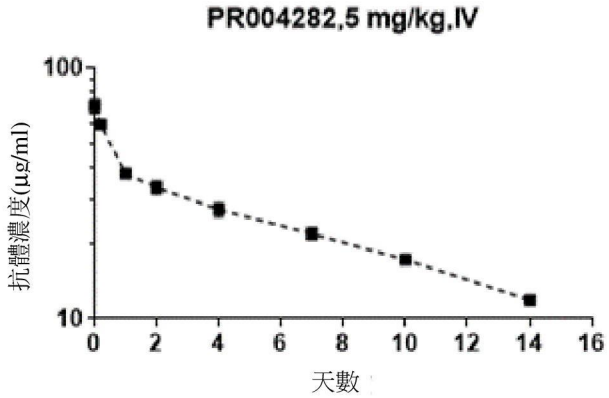
PK 參數	單位	平均值
$T_{1/2}$	小時	295
V_d	mL/kg	81
AUC_{all}	µg*小時/mL	14,286
AUC *	%	96
CL	mL/小時/kg	0.19
C_0	µg/mL	124

22-(E)



PK 參數	單位	平均值
$T_{1/2}$	小時	274
V_d	mL/kg	133
AUC_{all}	µg*小時/mL	8,363±102
AUC *	%	100
CL	mL/小時/kg	0.36
C_0	µg/mL	71

22-(F)



PK 參數	單位	平均值
$T_{1/2}$	小時	197
V_d	mL/kg	119
AUC_{all}	µg*小時/mL	8,125±150
AUC *	%	97
CL	mL/小時/kg	0.43
C_0	µg/mL	71

圖 22

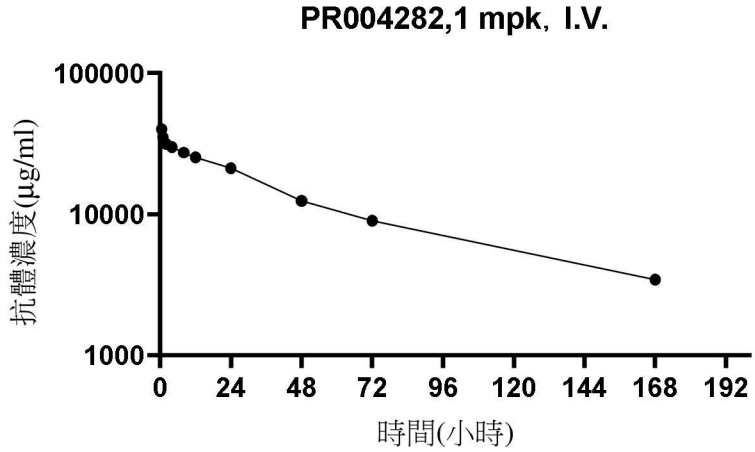
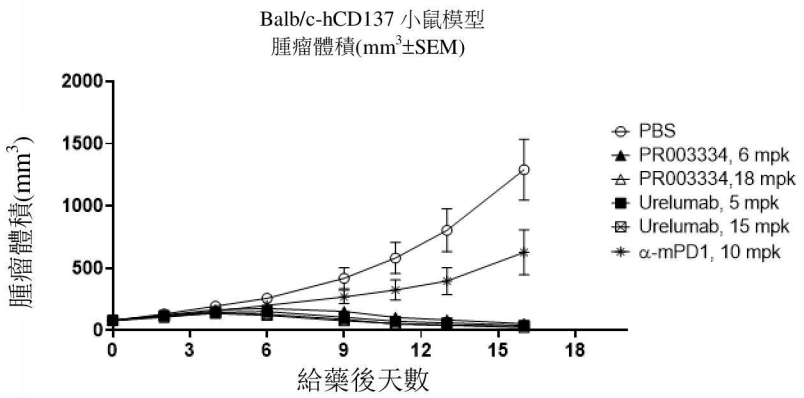


圖 23

24-(A)



24-(B)

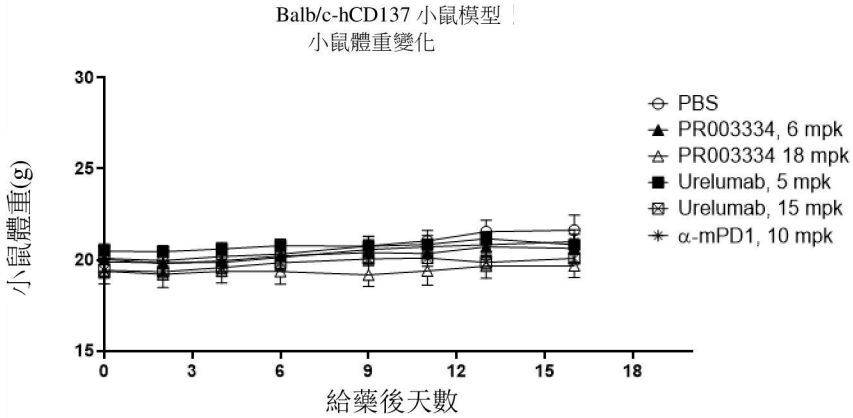
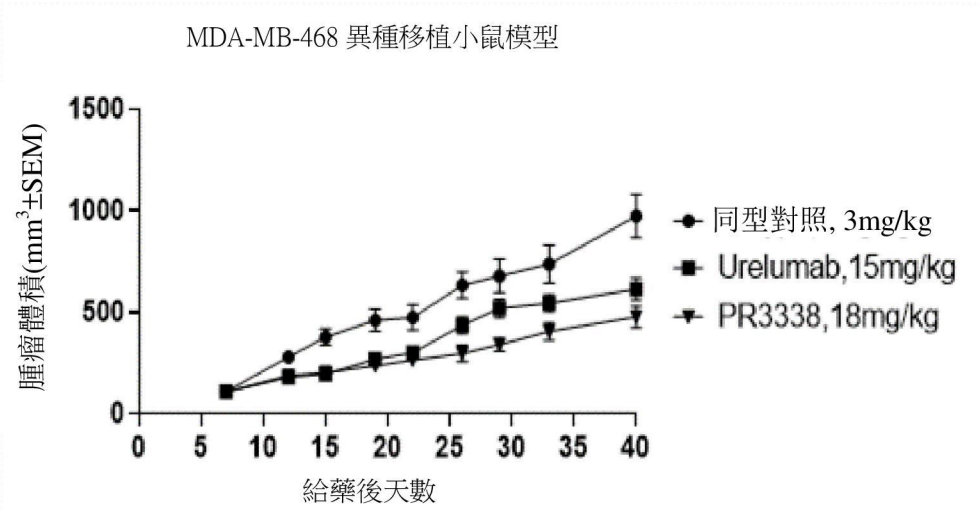


圖 24

25-(A)


MDA-MB-468 異種移植小鼠模型
腫瘤體積(mm3±SEM)
1500
1000
500
0
0 5 10 15 20 25 30 35 40
給藥後天數
同型對照, 3mg/kg
Urelumab,15mg/kg
PR3338,18mg/kg

25-(B)

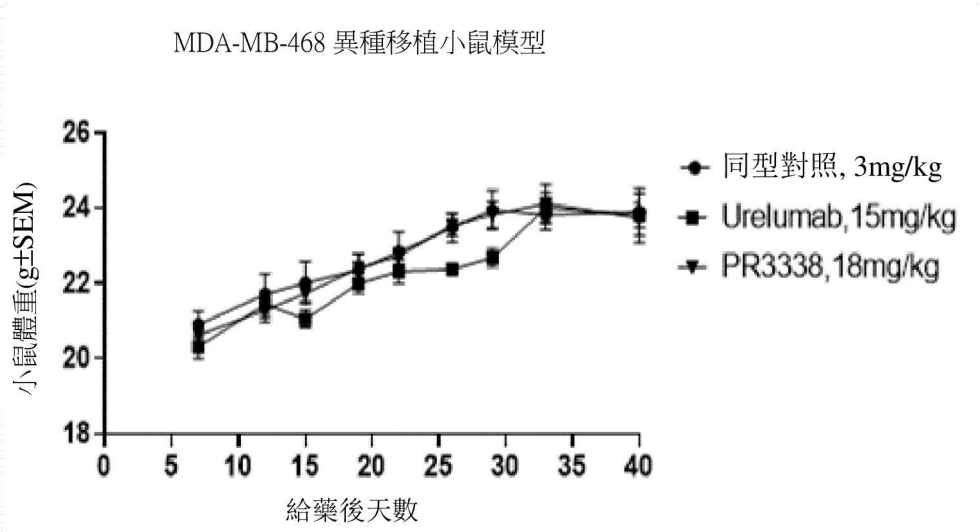
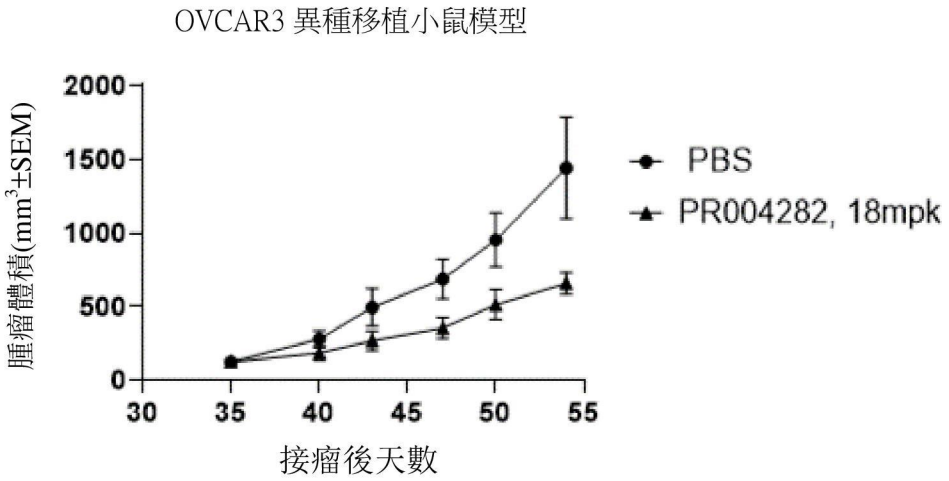

MDA-MB-468 異種移植小鼠模型
小鼠體重(g±SEM)
26
24
22
20
18
0 5 10 15 20 25 30 35 40
給藥後天數
同型對照, 3mg/kg
Urelumab,15mg/kg
PR3338,18mg/kg

圖 25

26-(A)


OVCAR3 異種移植小鼠模型
腫瘤體積(mm3±SEM)
2000
1500
1000
500
0
30
35
40
45
50
55
接瘤後天數
PBS
PR004282, 18mpk

26-(B)

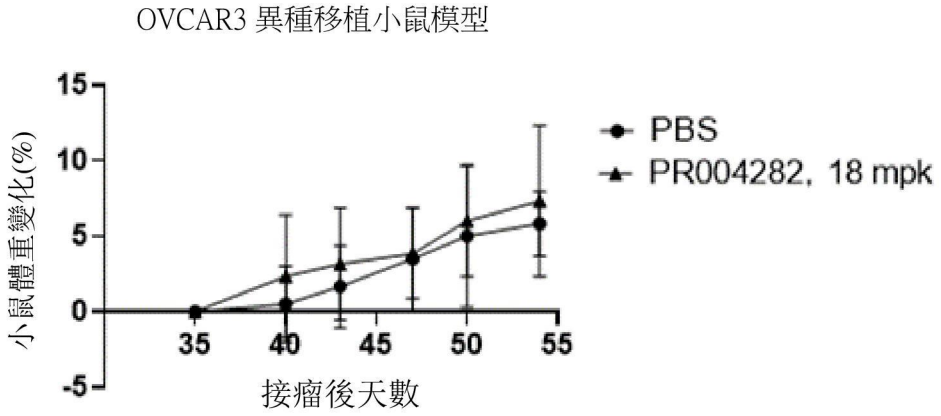
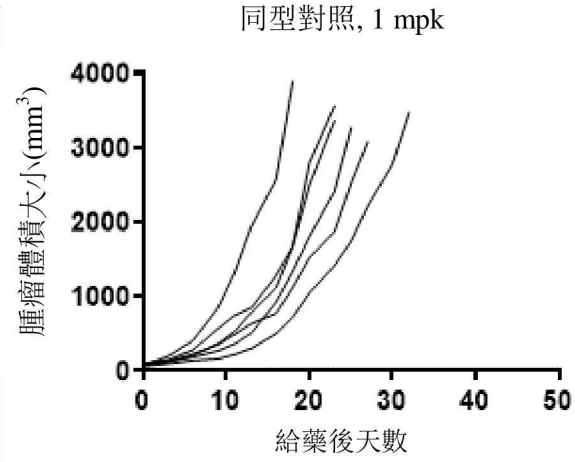
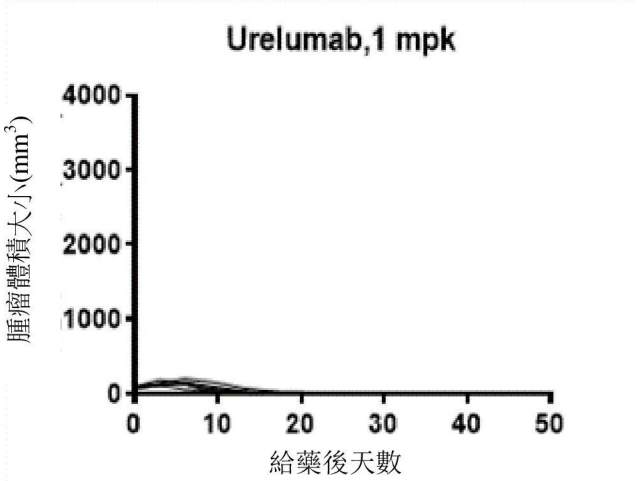

OVCAR3 異種移植小鼠模型
小鼠體重變化(%)
15
10
5
0
-5
35
40
45
50
55
接瘤後天數
PBS
PR004282, 18 mpk

圖 26

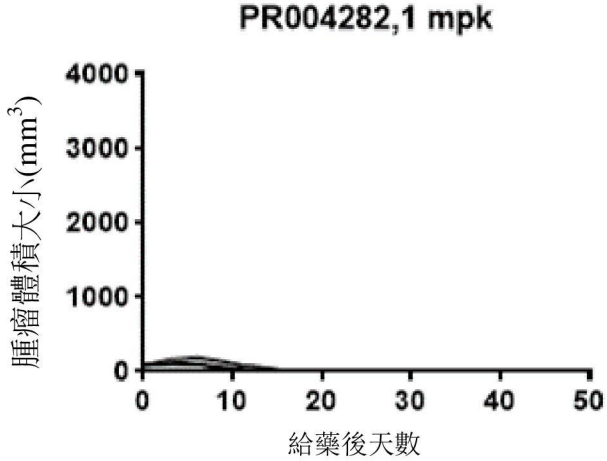
27-(A)


同型對照, 1 mpk
腫瘤體積大小(mm3)
4000
3000
2000
1000
0
0
10
20
30
40
50
給藥後天數

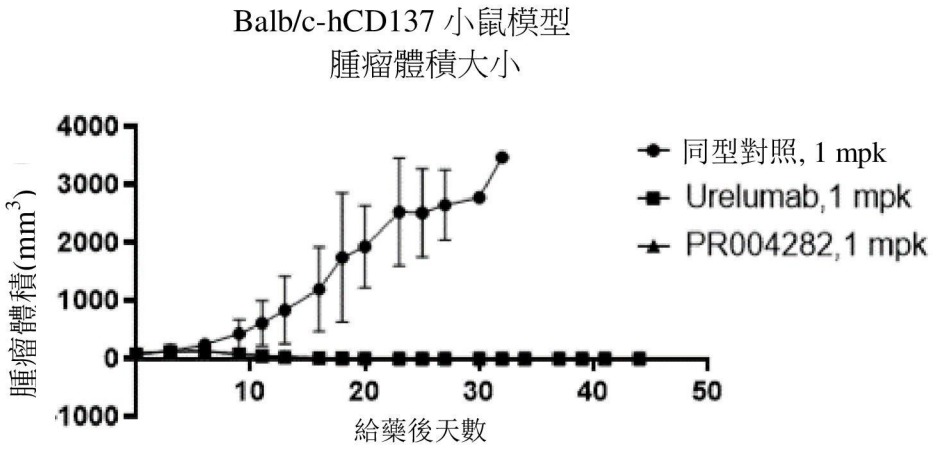
27-(B)


Urelumab,1 mpk
腫瘤體積大小(mm3)
4000
3000
2000
1000
0
0
10
20
30
40
50
給藥後天數

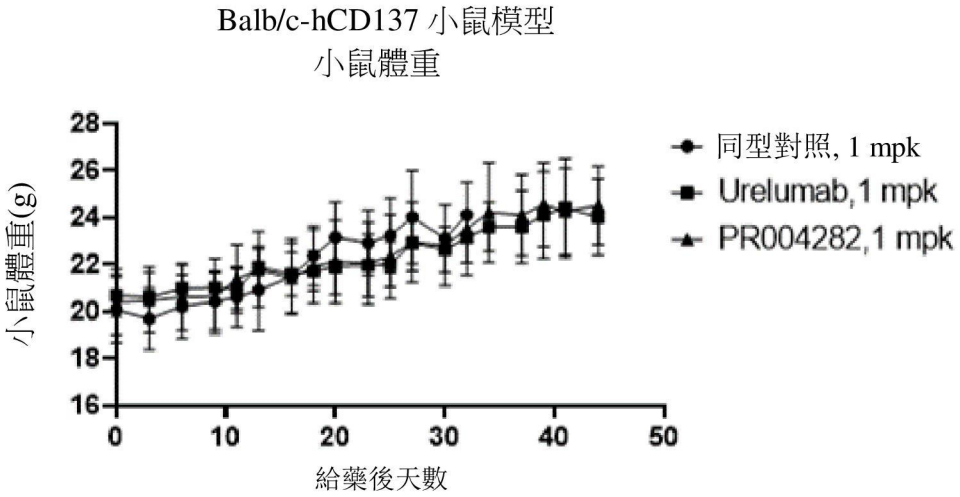
27-(C)


PR004282,1 mpk
腫瘤體積大小(mm3)
4000
3000
2000
1000
0
0
10
20
30
40
50
給藥後天數

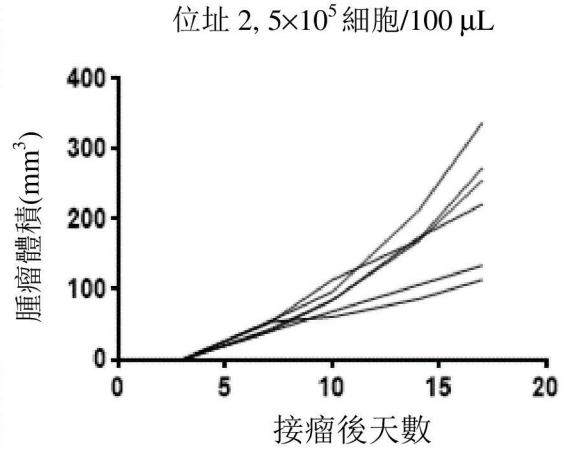
27-(D)


Balb/c-hCD137 小鼠模型
腫瘤體積大小
腫瘤體積(mm3)
4000
3000
2000
1000
0
-1000
10
20
30
40
50
給藥後天數
同型對照, 1 mpk
Urelumab,1 mpk
PR004282,1 mpk

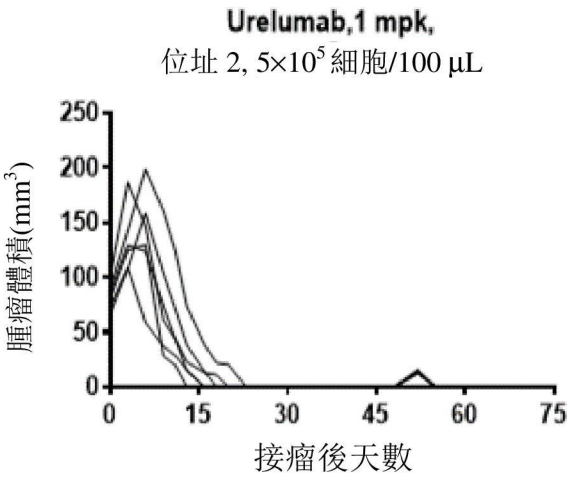
27-(E)


Balb/c-hCD137 小鼠模型
小鼠體重
小鼠體重(g)
28
26
24
22
20
18
16
0
10
20
30
40
50
給藥後天數
同型對照, 1 mpk
Urelumab,1 mpk
PR004282,1 mpk

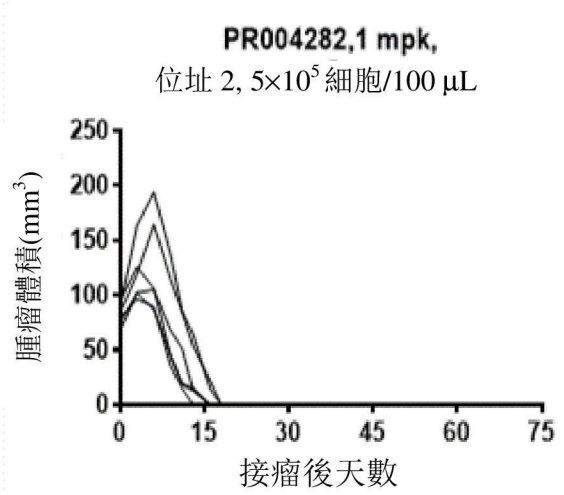
27-(F)


位址 2, 5×10^5 細胞/100 μL
腫瘤體積(mm^3)
400
300
200
100
0
0
5
10
15
20
接瘤後天數

27-(G)


Urelumab,1 mpk,
位址 2, 5×10^5 細胞/100 μL
腫瘤體積(mm^3)
250
200
150
100
50
0
0
15
30
45
60
75
接瘤後天數

27-(H)


PR004282,1 mpk,
位址 2, 5×10^5 細胞/100 μL
腫瘤體積(mm^3)
250
200
150
100
50
0
0
15
30
45
60
75
接瘤後天數

27-(I)

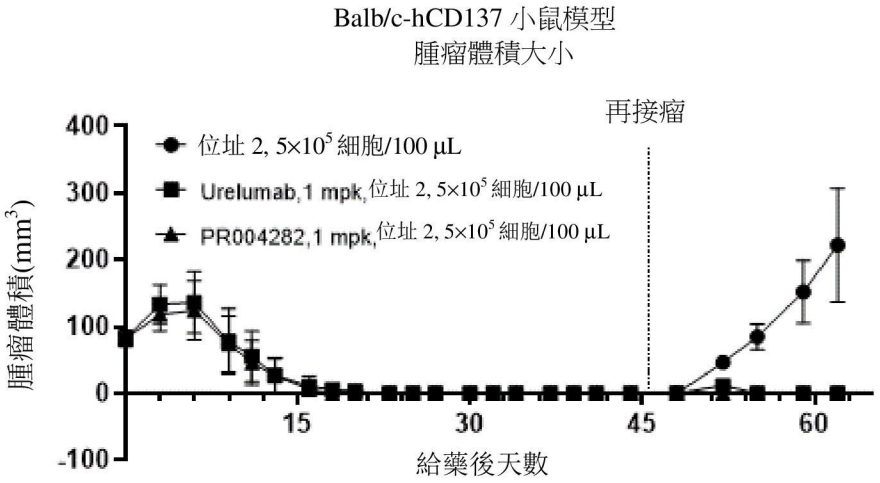
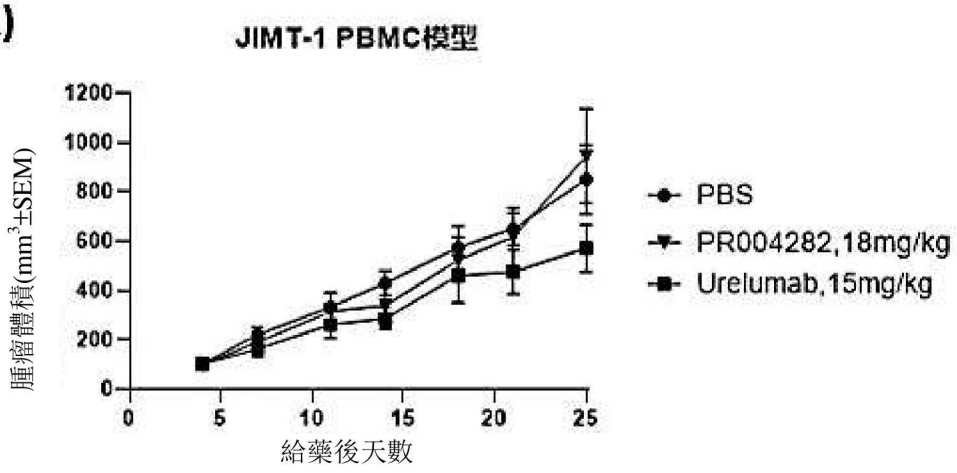


圖 27

28-(A)



28-(B)

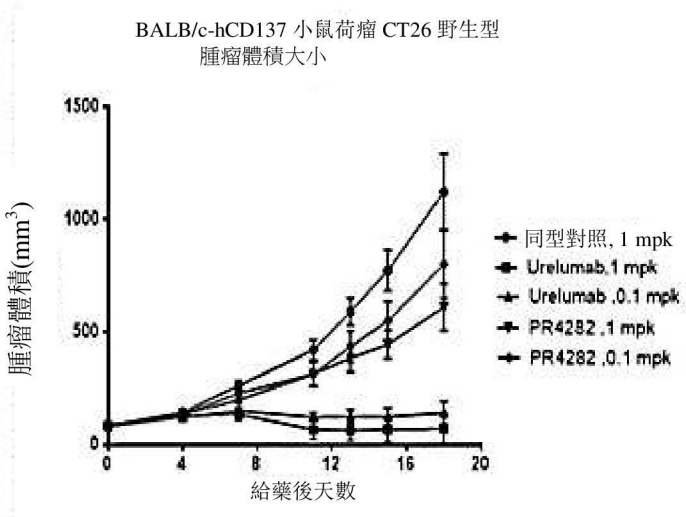


圖 28