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(56)參考文獻：

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(54)名稱

標靶 R O R 1 的抗體或其抗原結合片段及製備方法和應用

(57)摘要

本發明公開了標靶 ROR1 的抗體或其抗原結合片段及製備方法和應用，其中所述標靶 ROR1 的抗體或其抗原結合片段包含 VL 和 VH；所述 VL 包含以下的 CDR 或其突變：分別如 SEQ ID NO: 69、78、84 所示的 VL CDR1、VL CDR2、VL CDR3；所述 VH 包含以下的 CDR 或其突變：分別如 SEQ ID NO: 12、33、53 所示的 VH CDR1、VH CDR2、VH CDR3。上述抗體或其抗原結合片段對 ROR1 具有良好結合親和力；與 ROR2 幾乎沒有交叉反應性，其 KD 值均與參考的現有技術抗體相當；且具有顯著的內吞作用，在腫瘤細胞中具有 ADCC 效應。

指定代表圖：

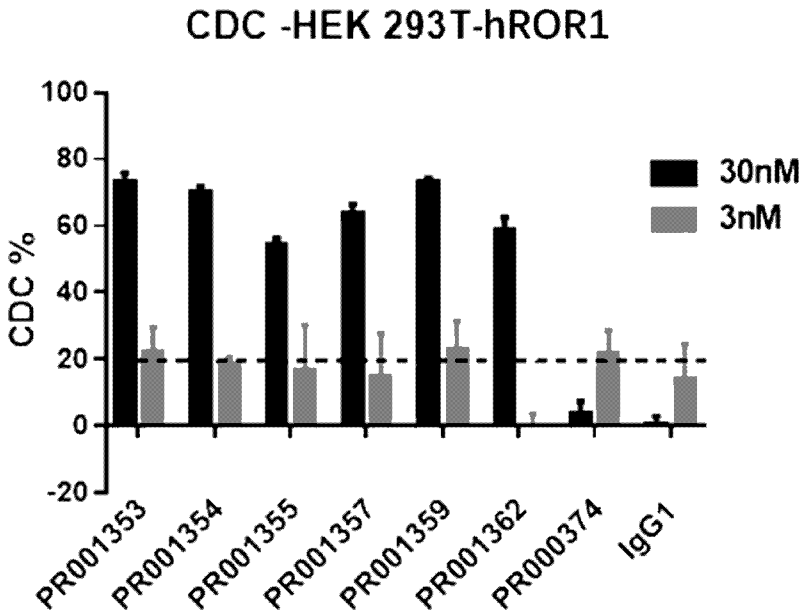


圖 10



I818308

【發明摘要】

【中文發明名稱】 標靶ROR1的抗體或其抗原結合片段及製備方法和應用

【中文】

本發明公開了標靶ROR1的抗體或其抗原結合片段及製備方法和應用，其中所述標靶ROR1的抗體或其抗原結合片段包含VL和VH；所述VL包含以下的CDR或其突變：分別如SEQ ID NO: 69、78、84所示的VL CDR1、VL CDR2、VL CDR3；所述VH包含以下的CDR或其突變：分別如SEQ ID NO: 12、33、53所示的VH CDR1、VH CDR2、VH CDR3。上述抗體或其抗原結合片段對ROR1具有良好結合親和力；與ROR2幾乎沒有交叉反應性，其KD值均與參考的現有技術抗體相當；且具有顯著的內吞作用，在腫瘤細胞中具有ADCC效應。

【指定代表圖】 圖10

【發明說明書】

【中文發明名稱】 標靶ROR1的抗體或其抗原結合片段及製備方法和應用

【技術領域】

【0001】 本申請主張申請日為2020/9/3的中國專利申請2020109183287的優先權。本申請引用上述中國專利申請的全文。

【0002】 本申請涉及生物醫藥領域，尤其涉及一種標靶ROR1的抗體或其抗原結合片段及製備方法和應用。

【先前技術】

【0003】 受體酪胺酸激酶樣孤兒受體1(ROR1，Recombinant Receptor Tyrosine Kinase Like Orphan Receptor 1)，又稱NTRKR1，是一種無活性的酪胺酸蛋白激酶跨膜蛋白，其在許多腫瘤中過度表現，但在正常組織中幾乎不表現。ROR1總共含有937個胺基酸，整個蛋白質的分子量約為105KDa(信號胜肽(第1-29位胺基酸)被切除)，但其存在一個短的同種型，只含有393個胺基酸組成的細胞外結構域，由於缺乏跨膜域與信號胜肽，此同種型定位於細胞質或細胞核。此外，還有文獻報導了一種“截短的ROR1”，其膜上只有跨膜結構域和胞內結構域。

【0004】 目前眾所周知，全長ROR1作為受體與Wnt5a相互作用後，傳遞Wnt信號途徑，從而有助於慢性淋巴細胞白血病(CLL)中的細胞增殖和遷移，並且有助於固態腫瘤中的上皮-間質-轉變(EMT)。

【0005】 現有的抗體(例如emergent公司的專利申請WO_2016_094873_A2中的序列R11H18L9)與ROR1的結合能力均較弱，考慮到ROR1抗原本身表現量的局限，其作為單抗和雙抗的開發空間有限。因此本領域缺乏與ROR1抗原具有高親和力的同時不與ROR2交叉反應，且ADCC活性、內吞活性等更好的抗體(特別是全人源抗體)。

【發明內容】

【0006】 本發明所要解決的技術問題是克服本領域標靶ROR1的抗體與ROR1的結合能力較弱、與ROR2有交叉反應性、ADCC活性和內吞活性不足等缺陷，提供了一種標靶ROR1的抗體或其抗原結合片段、及其製備方法和應用。

【0007】 為了解決上述技術問題，本發明第一方面提供了一種標靶ROR1的抗體或其抗原結合片段，其包含輕鏈可變區(VL)和/或重鏈可變區(VH)；其中，

所述VL包含以下的CDR或其突變：如SEQ ID NO: 69的胺基酸序列所示的VL CDR1，如SEQ ID NO: 78的胺基酸序列所示的VL CDR2，如SEQ ID NO: 84的胺基酸序列所示的VL CDR3；

所述VH包含以下的CDR或其突變：如SEQ ID NO: 12的胺基酸序列所示的VH CDR1，如SEQ ID NO: 33的胺基酸序列所示的VH CDR2，如SEQ ID NO: 53的胺基酸序列所示的VH CDR3；

其中所述突變為在所述CDR的胺基酸序列上具有3、2或1個胺基酸插入、缺失或替換。

【0008】 本申請中，在類似“具有3、2或1個胺基酸的插入、缺失或替換”中“胺基酸突變”是指相較於原胺基酸序列而言，變異體的序列存在胺基酸的突變，包括在原胺基酸序列的基礎上發生胺基酸的插入、缺失或替換。示例性的解釋是對CDR的突變可以包含3個、2個或1個胺基酸的突變，這些CDR之間可以任選地選擇相同或不同數目的胺基酸殘基進行突變，例如可以是對CDR1進行1個胺基酸的突變，對CDR2和CDR3不進行胺基酸突變。

【0009】 本申請中，所述突變可以包括目前如本領域技術人員公知的突變，例如在抗體的生產或者應用過程中，可能會對抗體進行的一些突變，例如對可能存在的，特別是CDR區的轉錄後修飾(Potential post-translational modifications, PTMs)的位址進行突變，包括抗體的聚集、脫醯胺基(asparagine deamidation)

敏感位址(NG, NS, NH等)、天門冬胺酸異構(DG, DP)敏感位址、N糖基化(N-{P}S/T)敏感位址及氧化敏感位址等相關突變。

【0010】 優選地，所述的VL CDR1的突變為在如SEQ ID NO: 69所示的胺基酸序列上具有T5S、I6M/V、N7S和N8S中的4、3、2或1個胺基酸替換；其胺基酸序列優選如SEQ ID NO: 70-74任一所示。

【0011】 優選地，所述的VL CDR2的突變為在如SEQ ID NO: 78所示的胺基酸序列上具有S4N的胺基酸替換，所述胺基酸序列如SEQ ID NO: 79所示。

【0012】 優選地，所述的VL CDR3的突變為在如SEQ ID NO: 84所示的胺基酸序列上具有N4K/Q和S5L/I/A中的2或1個胺基酸替換；其胺基酸序列優選如SEQ ID NO: 85-87、SEQ ID NO: 184和SEQ ID NO: 185任一所示。

【0013】 優選地，所述的VH CDR1的突變為在如SEQ ID NO: 12所示的胺基酸序列上具有T3S、S6T/R/N和Y7F/S中的3、2或1個胺基酸替換；其胺基酸序列優選如SEQ ID NO: 13-18任一所示。

【0014】 優選地，所述的VH CDR2的突變為在如SEQ ID NO: 33所示的胺基酸序列上具有D3E、G4A、S5I/V/G和D6S/N中的4、3、2或1個胺基酸替換；其胺基酸序列優選如SEQ ID NO: 32、SEQ ID NO: 34-36和SEQ ID NO: 178-183任一所示。

【0015】 優選地，所述的VH CDR3的突變為在如SEQ ID NO: 53所示的胺基酸序列上具有E1D、Q2L和L8I中的3、2或1個胺基替換；其胺基酸序列優選如SEQ ID NO: 52、54或55所示。

【0016】 以上所述的VL CDR1的突變T5S一般是指如SEQ ID NO: 69所示的胺基酸序列的第5位胺基酸T突變為S，其他的胺基酸替換例如I6M/V、N7S和N8S，以及VL CDR2、VL CDR3、VH CDR1~3的突變等等均以此類推，本領域人員都應當理解其含義。例如，VL CDR3的突變N4K/Q和S5L/I/A亦可分別表述為下文表10中在整個VL序列上計算突變位址的N92K/Q和S93L/I/A；VH CDR2的突變D3E和G4A亦可分別表述為在整個VH序列上計算突變位址的D54E和G55A。

【0017】 優選地，所述VL CDR1的胺基酸序列如SEQ ID NO: 69所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 84所示；或者所述VL CDR1的胺基酸序列如SEQ ID NO: 70所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 85所示；或者所述VL CDR1的胺基酸序列如SEQ ID NO: 71所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 84所示；所述VL CDR1的胺基酸序列如SEQ ID NO: 72所示，所述VL CDR2

的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 85所示；或者所述VL CDR1的胺基酸序列如SEQ ID NO: 69所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 86所示；或者所述VL CDR1的胺基酸序列如SEQ ID NO: 73所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 79所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 85所示；或者所述VL CDR1的胺基酸序列如SEQ ID NO: 74所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 85所示；或者所述VL CDR1的胺基酸序列如SEQ ID NO: 69所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 87所示；或者所述VL CDR1的胺基酸序列如SEQ ID NO: 73所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 85所示；或者所述VL CDR1的胺基酸序列如SEQ ID NO: 72所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 84所示；或者所述VL CDR1的胺基酸序列如SEQ ID NO: 73所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 84所示；或者所述VL CDR1的胺基酸序列如SEQ

ID NO: 70所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 84所示；或，所述VL CDR1的胺基酸序列如SEQ ID NO: 69所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 184所示；或，所述VL CDR1的胺基酸序列如SEQ ID NO: 69所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 185所示；或，所述VL CDR1的胺基酸序列如SEQ ID NO: 72所示，所述VL CDR2的胺基酸序列如SEQ ID NO: 78所示，且所述VL CDR3的胺基酸序列如SEQ ID NO: 85所示。

【0018】 優選地，所述VH CDR1的胺基酸序列如SEQ ID NO: 12所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 32所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 52所示；或者所述VH CDR1的胺基酸序列如SEQ ID NO: 12所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 32所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或者所述VH CDR1的胺基酸序列如SEQ ID NO: 12所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 33所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或者所述VH CDR1的胺基酸序列如SEQ ID NO: 12所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 34所示，且所述VH CDR3的

胺基酸序列如SEQ ID NO: 53所示；或者所述VH CDR1的胺基酸序列如SEQ ID NO: 12所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 35所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或者所述VH CDR1的胺基酸序列如SEQ ID NO: 13所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 33所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或者所述VH CDR1的胺基酸序列如SEQ ID NO: 14所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 35所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或者所述VH CDR1的胺基酸序列如SEQ ID NO: 13所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 33所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 54所示；或者所述VH CDR1的胺基酸序列如SEQ ID NO: 15所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 36所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或者所述VH CDR1的胺基酸序列如SEQ ID NO: 16所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 33所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或者所述VH CDR1的胺基酸序列如SEQ ID NO: 12所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 32所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 55所示；或者所述VH CDR1的胺基酸序列如SEQ ID NO: 17所示，所述VH CDR2的胺基酸序列如SEQ

ID NO: 34所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或者所述VH CDR1的胺基酸序列如SEQ ID NO: 18所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 34所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或，所述VH CDR1的胺基酸序列如SEQ ID NO: 12所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 178所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或，所述VH CDR1的胺基酸序列如SEQ ID NO: 12所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 179所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或，所述VH CDR1的胺基酸序列如SEQ ID NO: 12所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 180所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或，所述VH CDR1的胺基酸序列如SEQ ID NO: 12所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 181所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或，所述VH CDR1的胺基酸序列如SEQ ID NO: 16所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 178所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或，所述VH CDR1的胺基酸序列如SEQ ID NO: 16所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 179所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或，所述VH CDR1的胺基酸序列如SEQ ID NO: 17所示，

所述VH CDR2的胺基酸序列如SEQ ID NO: 182所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示；或，所述VH CDR1的胺基酸序列如SEQ ID NO: 17所示，所述VH CDR2的胺基酸序列如SEQ ID NO: 183所示，且所述VH CDR3的胺基酸序列如SEQ ID NO: 53所示。

【0019】 在某一較佳實施例中，所述抗體或其抗原結合片段中，所述VL包含的VL CDR1、VL CDR2和VL CDR3的胺基酸序列分別如下表所示；所述VH包含的VH CDR1、VH CDR2和VH CDR3的胺基酸序列分別如下表所示。

LCDR1 (SEQ ID NO:)	LCDR2 (SEQ ID NO:)	LCDR3 (SEQ ID NO:)	HCDR1 (SEQ ID NO:)	HCDR2 (SEQ ID NO:)	HCDR3 (SEQ ID NO:)
69	78	84	12	32	52
70	78	85	12	32	53
71	78	84	12	34	53
72	78	85	12	35	53
69	78	86	12	34	53
73	79	85	12	34	53
74	78	85	13	33	53
69	78	87	12	33	53
73	78	85	14	35	53
73	78	85	13	33	54
69	78	84	15	36	53
69	78	84	16	33	53
69	78	86	12	33	53
73	78	85	12	32	55
73	78	85	13	33	53
69	78	84	17	34	53

72	78	84	12	32	52
69	78	84	12	35	53
69	78	84	18	34	53
69	78	84	13	33	53
73	78	84	15	36	53
70	78	84	12	32	53
69	78	184	12	33	53
69	78	185	12	33	53
69	78	84	12	178	53
69	78	184	12	178	53
69	78	185	12	178	53
69	78	84	12	179	53
69	78	184	12	179	53
69	78	185	12	179	53
72	78	85	12	180	53
72	78	85	12	181	53
69	78	184	16	33	53
69	78	185	16	33	53
69	78	84	16	178	53
69	78	184	16	178	53
69	78	185	16	178	53
69	78	84	16	179	53
69	78	184	16	179	53
69	78	185	16	179	53
69	78	184	17	34	53
69	78	185	17	34	53
69	78	84	17	182	53
69	78	184	17	182	53
69	78	185	17	182	53
69	78	84	17	183	53
69	78	184	17	183	53
69	78	185	17	183	53

【0020】 優選地，所述輕鏈可變區(VL)還包括輕鏈可變區框架區(VL FWR)，所述VL FWR優選為人抗體的輕鏈可變區框架區。

更優選地，所述VL FWR包括胺基酸序列如SEQ ID NO: 59-67或其突變所示的VL FWR1、胺基酸序列如SEQ ID NO: 76或其突變所示的VL FWR2、胺基酸序列如SEQ ID NO: 81或82或其突變所示的VL FWR3和胺基酸序列如SEQ ID NO: 89-91或其突變所示的VL FWR4。

【0021】 優選地，所述重鏈可變區(VH)還包括重鏈可變區框架區(VH FWR)，所述VH FWR優選為人抗體的重鏈可變區框架區，更優選地，所述VH FWR包括胺基酸序列如SEQ ID NO: 2-10或其突變所示的VHFWR1、胺基酸序列如SEQ ID NO: 20-30或其突變所示的VHFWR2、胺基酸序列如SEQ ID NO: 38-50或其突變所示的VHFWR3和胺基酸序列如SEQ ID NO: 57或其突變所示的VHFWR4。其中所述的突變為在所述VH FWR的胺基酸序列上具有3、2或1個胺基酸插入、缺失、替換和重複。

【0022】 在某一較佳實施例中，所述VL包括如下表或其突變所示的胺基酸序列；所述VH包括如下表或其突變所示的胺基酸序列。

VL(SEQ ID NO:)	VH(SEQ ID NO:)
117	93
118	94
119	95
120	96
121	97
122	98
123	99

124	100
125	101
126	102
127	103
128	104
129	105
130	106
126	107
128	108
127	109
129	110
131	93
117	111
129	112
129	113
132	108
133	114
134	115
194	95
195	95
119	186
194	186
195	186
119	187
194	187
195	187
121	188
121	189
196	105
197	105
129	190
196	190
197	190
129	191
196	191

197	191
196	110
197	110
129	192
196	192
197	192
129	193
196	193
197	193

【0023】 上述突變為所述VH和/或VL的胺基酸序列上發生了一個或多個胺基酸殘基的缺失、取代或添加，且所述突變的胺基酸序列與所述VH和/或VL的胺基酸序列具有至少85%序列相同性，並保持或改善了所述抗體與ROR1的結合；所述至少85%序列相同性優選為至少90%序列相同性，更優選為至少95%、96%、97%、98%序列相同性，最優選為至少99%序列相同性。

【0024】 在本申請中，上述所列CDR的胺基酸序列均是按照Chothia定義規則所示出的(本申請的請求項中也是按照Chothia定義規則所示出的序列)。但是，本領域人員公知，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，馬裏蘭州(1991))和基於結構環區域位置的Chothia定義規則(參見JMol Biol 273:927-48,1997)。在本申請中，還可以使用包含了Kabat定義和Chothia定義的Combined定義規則確定可變結構域序列中的胺基酸殘基。其中Combined定義規

則即是將Kabat定義和Chothia定義的範圍相結合，基於此取了一個更大的範圍，詳見表3。本領域技術人員應當理解的是，除非另有規定，否則術語給定抗體或其區(例如可變區)的“CDR”及“互補決定區”應瞭解為涵蓋如透過本發明描述的上述已知方案中的任何一種界定的互補決定區。雖然本發明中請求保護的範圍是基於Chothia定義規則所示出的序列，但是根據其他CDR的定義規則所對應的胺基酸序列也應當落在本發明的保護範圍中。

【0025】 優選地，所述的標靶ROR1的抗體或其抗原結合片段還包括重鏈恆定區和/或輕鏈恆定區。

【0026】 更優選地，所述重鏈恆定區選自hIgG1、hIgG2、hIgG3或hIgG4或其突變，所述輕鏈恆定區選自κ鏈或者λ鏈或其突變。更優選地，所述重鏈恆定區為hIgG1，且所述輕鏈恆定區為人源抗體的κ鏈。

【0027】 進一步更優選地，所述的標靶ROR1的抗體或其抗原結合片段為全長抗體、Fab、Fab'、F(ab')₂、Fv優選scFv、雙特异性抗體(例如可以與OX40、4-1BB、CD3等標的一起做雙抗)、多特异性抗體、重鏈抗體或單域抗體，或由上述抗體製得的單株抗體或多株抗體。

【0028】 本申請中，所述的“Fab片段”由一條輕鏈和一條重鏈的CH1及可變區組成。Fab分子的重鏈不能與另一個重鏈分子形成二

硫鍵。“Fc”區含有抗體的CH1和CH2結構域的兩個重鏈片段。兩個重鏈片段由兩個或多個二硫鍵並透過CH3結構域的疏水作用保持在一起。所述的“Fab片段”含有一條輕鏈和包含VH結構域和CH1結構域以及CH1和CH2結構域之間區域的一條重鏈的部分，由此可在兩個Fab'片段的兩條重鏈之間形成鏈間二硫鍵以形成F(ab')₂分子。所述的“F(ab')₂片段”含有兩條輕鏈和兩條包含CH1和CH2結構域之間的恆定區的部分的重鏈，由此在兩條重鏈間形成鏈間二硫鍵。因此F(ab')₂片段由透過兩條重鏈間的二硫鍵保持在一起的兩個Fab'片段組成。所述的術語“Fv”意指向抗體的單臂的VL和VH結構域組成的抗體片段，但缺少恆定區。

【0029】 本申請中，所述的scFv(single chain antibody fragment，單鏈抗體)可為本領域常規的單鏈抗體，其包括重鏈可變區、輕鏈可變區和15~20個胺基酸的短鏈胜肽。其中VL和VH結構域透過使其能够產生為單個多胜肽鏈的连接體配對形成單價分子[參見，例如，Bird等人，Science 242:423-426 (1988) 和Huston等人，Proc. Natl. Acad. Sci. USA 85:5879-5883(1988)]。此類scFv分子可具有一般結構：NH₂-VL-連接子-VH-COOH或NH₂-VH-連接子-VL-COOH。合適的現有技術連接子由重複的G4S胺基酸序列或其變異體組成。例如，可使用具有胺基酸序列(G₄S)₄或(G₄S)₃連接子，但也可使用其變異體。

【0030】 本申請中，術語“多特異性抗體”按其最廣義使用，涵蓋具有多表位特異性的抗體。這些多特異性抗體包括但不限於：包含重鏈可變區(VH)和輕鏈可變區(VL)的抗體，其中該VH-VL單元具有多表位特異性；具有兩個或多個VL和VH區的抗體，每個VH-VL單元與不同的標的或同一個標的的不同表位結合；具有兩個或更多個單可變區的抗體，每個單可變區與不同的標的或同一個標的的不同的表位結合；全長抗體、抗體片段、雙特異性抗體(diabodies)、和三抗體(triabodies)、共價或非共價連接在一起的抗體片段等。

【0031】 本申請中，所述的單株抗體或mAb或Ab，指由單一的選殖細胞株得到的抗體，所述的細胞株不限於真核的，原核的或噬菌體的選殖細胞株。

【0032】 本申請中，所述的“重鏈抗體”指的是只包含一個重鏈可變區(VHH)和兩個常規的CH2與CH3區的抗體，又稱為HCAbs。

【0033】 “單域抗體”，又稱為“奈米抗體”，指的是從重鏈抗體中選殖出來的VHH結構，是已知的可結合目標抗原的最小單位。

【0034】 優選地，所述的標靶ROR1的抗體或其抗原結合片段為全長抗體。

【0035】 在某一較佳實施例中，所述全長抗體包括重鏈和輕鏈；其中，所述重鏈包括如下表或其突變所示的胺基酸序列；所述輕鏈包括如下表或其突變所示的胺基酸序列。

輕鏈(SEQ ID NO:)	重鏈(SEQ ID NO:)
160	136
161	137
162	138
163	139
164	140
165	141
166	142
167	143
168	144
169	145
170	146
171	147
172	148
173	149
169	150
171	151
170	152
172	153
174	136
160	154
172	155
172	156
175	151
176	157
177	158
206	138
207	138
162	198

206	198
207	198
162	199
206	199
207	199
164	200
164	201
208	148
209	148
172	202
208	202
209	202
172	203
208	203
209	203
208	153
209	153
172	204
208	204
209	204
172	205
208	205
209	205

【0036】 上述的突變為所述重鏈和/或輕鏈的胺基酸序列上發生了一個或多個胺基酸殘基的缺失、取代或添加，且所述突變的胺基酸序列與所述重鏈和/或輕鏈的胺基酸序列具有至少85%序列相同性，並保持或改善了所述抗體與ROR1的結合；所述至少85%序列相同性優選為至少90%序列相同性；更優選為至少95%序列相同性；最優選為至少99%序列相同性。

【0037】 爲了解決上述技術問題，本發明第二方面提供了一種分離的核酸，其編碼如本發明第一方面所述的標靶ROR1的抗體或其抗原結合片段。

【0038】 所述核酸的製備方法爲本領域常規的製備方法，較佳地，包括以下的步驟：透過基因選殖技術獲得編碼上述抗體的核酸分子，或者透過人工全序列合成的方法得到編碼上述抗體的核酸分子。

【0039】 本領域技術人員知曉，編碼上述抗體的胺基酸序列的鹼基序列可以適當引入替換、缺失、改變、插入或增加來提供一個多聚核苷酸的同系物。本發明中多聚核苷酸的同系物可以透過對編碼該抗體序列基因的一個或多個鹼基在保持抗體活性範圍內進行替換、缺失或增加來製得。

【0040】 爲了解決上述技術問題，本發明第三方面提供了一種重組表現載體，其包含如本發明第二方面所述的分離的核酸。

【0041】 所述重組表現載體可透過本領域常規方法獲得，即：將本申請所述的核酸分子連接於各種表現載體上建構而成。所述的表現載體爲本領域常規的各種載體，只要其能够容載前述核酸分子即可。

【0042】 優選地，所述表現載體包含真核細胞表現載體和/或原核細胞表現載體。

【0043】 爲了解決上述技術問題，本發明第四方面提供了一種轉形體，其包含如本發明第三方面所述的重組表現載體。

【0044】 所述轉形體的製備方法可爲本領域常規的製備方法，例如爲：將上述重組表現載體轉形至宿主細胞中製得。所述轉形體的宿主細胞爲本領域常規的各種宿主細胞，只要能滿足使上述重組表現載體穩定地自行複製，且所攜帶所述的核酸可被有效表現即可。優選地，所述宿主細胞爲原核細胞和/或真核細胞，所述原核細胞優選E. coli 細胞如TG1、BL21(表現單鏈抗體或Fab抗體)，所述真核細胞優選HEK293細胞或CHO細胞(表現全長IgG抗體)。將前述重組表現質體轉形至宿主細胞中，即可得本發明優選的重組表現轉形體。其中所述轉形方法爲本領域常規轉形方法，較佳地爲化學轉形法，熱休克法或電穿孔法。

【0045】 爲了解決上述技術問題，本發明第五方面提供了一種嵌合抗原受體，其包含如本發明第一方面所述的標靶ROR1的抗體或其抗原結合片段。

【0046】 爲了解決上述技術問題，本發明第六方面提供了一種基因修飾的細胞，其包含如本發明第五方面所述的嵌合抗原受體。

【0047】 優選地，所述基因修飾的細胞爲真核細胞，優選分離的人細胞；更優選免疫細胞如T細胞，或NK細胞。

【0048】 爲了解決上述技術問題，本發明第七方面提供了一種標靶ROR1的抗體或其抗原結合片段的製備方法，所述製備方法包括以下步驟：培養如本發明第四方面所述的轉形體，從培養物中獲得標靶ROR1的抗體或其抗原結合片段。

【0049】 爲了解決上述技術問題，本發明第八方面提供了一種抗體藥物偶聯物，其包含細胞毒性劑，以及如本發明第一方面所述的標靶ROR1的抗體或其抗原結合片段。

【0050】 爲了解決上述技術問題，本發明第九方面提供了一種藥物組成物，其包含如本發明第一方面所述的標靶ROR1的抗體或其抗原結合片段、和/或如本發明第八方面所述的抗體藥物偶聯物。

【0051】 優選地，所述藥物組成物還包括其他抗腫瘤抗體作爲活性成分。

【0052】 優選地，所述藥物組成物還包括藥學上可接受的載體。

【0053】 所述的藥學上可接受的載體可爲本領域常規的載體，所述的載體可以爲任意合適的生理學或藥學上可接受的藥物賦形劑。所述的藥物賦形劑爲本領域常規的藥物賦形劑，優選地包括藥學上可接受的賦形劑、填充劑或稀釋劑等。更優選地，所述的藥物組成物包括0.01~99.99%的上述蛋白質和/或上述的抗體藥物偶聯物，和0.01~99.99%的藥用載體，所述百分比爲占所述藥物組成物的質量百分比。

【0054】 本發明所述的藥物組成物的給藥途徑優選地為非經腸道施用、注射給藥或口服給藥。所述注射給藥優選地包括靜脈注射、肌肉注射、腹腔注射、皮內注射或皮下注射等途徑。所述的藥物組成物為本領域常規的各種劑型，較佳地為固體、半固體或液體的形式，即可以為水溶液、非水溶液或混合懸浮液，更佳的為片劑、膠囊、顆粒劑、注射劑或輸注劑等。更優選地為經由血管內、皮下、腹膜內或肌內施用。較佳地，所述藥物組成物還可以作為氣霧劑或粗噴霧劑施用，即經鼻施用；或者，鞘內、髓內或心室內施用。更優選地，所述的藥物組成物還可以透皮、經皮、局部、腸內、陰道內、舌下或經直腸施用。本發明的藥物組成物可根據需要製成各種劑型，並可由醫師根據患者種類、年齡、體重和大致疾病狀況、給藥方式等因素確定對病人有益的劑量進行施用。給藥方式例如可以採用注射或其它治療方式。

【0055】 本發明所述的藥物組成物的給藥劑量位準可以根據達到所需診斷或治療結果的組成物量而調整。施用方案也可以為單次注射或多次注射，或進行調整。所選擇的劑量位準和方案依賴於包括所述藥物組成物的活性和穩定性(即，半衰期)、製劑、施用途徑、與其他藥物或治療的組合、待檢測和/或治療的疾病或病症、以及待治療的受試者的健康狀況和先前醫療史等各種因素而進行合理地調整。

【0056】 對於本發明的所述藥物組成物的治療有效劑量可以最初在細胞培養實驗或動物模型例如啮齒類動物、兔、犬、豬和/或靈長類動物中進行估計。動物模型也可以用於測定合適的施用濃度範圍和途徑。隨後可以用於確定在人中施用的有用劑量和途徑。一般地，施用有效量或劑量的確定和調整以及何時和如何進行此類調整的評估為本領域技術人員已知。

【0057】 對於組合療法，上述標靶ROR1的抗體或其抗原結合片段、上述抗體藥物偶聯物和/或另外的治療或診斷劑可以各自作為單一藥劑，在適合於執行預期治療或診斷的任何時間範圍內進行使用。因此，這些單一藥劑可以基本上同時(即作為單一制劑或在數分鐘或數小時內)或以按順序連續施用。

【0058】 關於製劑、劑量、施用方案和可測量的治療結果的另外指導，參見Berkow等人(2000)The Merck Manual of Medical Information(Merck 醫學資訊手冊)和 Merck&Co.Inc., Whitehouse Station, New Jersey; Ebadi (1998) CRC Desk Reference of Clinical Pharmacology(臨床藥理學手冊)等著作。

【0059】 為了解決上述技術問題，本發明第十方面提供了如本發明第一方面所述的標靶ROR1的抗體或其抗原結合片段、如本發明第五方面所述的嵌合抗原受體、如本發明第六方面所述的基因修飾的細胞、如本發明第八方面所述的抗體藥物偶聯物和/或如本發明

第九方面所述的藥物組成物在製備治療和/或預防癌症的藥物中的應用。

【0060】 優選地，所述癌症為結腸癌、肺癌、前列腺癌、肝癌、腎癌、胰腺癌、乳腺癌、子宮頸癌、卵巢癌、甲狀腺腫瘤、慢性淋巴細胞白血病、急性淋巴細胞白血病、急性骨髓白血病、非何杰金氏淋巴瘤、慢性骨髓性淋巴細胞白血病、多發性骨髓瘤、黑色素瘤、結腸直腸癌、成膠質細胞瘤和/或子宮內膜癌。

【0061】 為了解決上述技術問題，本發明第十一方面提供了一種套組，其包括如本發明第一方面所述的標靶ROR1的抗體或其抗原結合片段、如本發明第五方面所述的嵌合抗原受體、如本發明第六方面所述的基因修飾的細胞、本發明第八方面所述的抗體藥物偶聯物和/或如本發明第九方面所述的藥物組成物。

【0062】 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。

【0063】 為了解決上述技術問題，本發明還提供了一種檢測樣品中ROR1的方法，其包括使用如本發明第一方面所述的標靶ROR1的抗體或其抗原結合片段進行檢測。

【0064】 優選地，所述檢測為診斷。

【0065】 為了解決上述技術問題，本發明還提供了如本發明第一方面所述的標靶ROR1的抗體或其抗原結合片段、如本發明第五

方面所述的嵌合抗原受體、如本發明第六方面所述的基因修飾的細胞、本發明第八方面所述的抗體藥物偶聯物和/或如本發明第九方面所述的藥物組成物在診斷、預防和/或治療癌症中的應用。優選地，所述癌症如本發明第十方面所述。

【0066】 爲了解決上述技術問題，本發明還提供一種套裝藥盒，其包含藥盒A和藥盒B，所述的藥盒A包含如本發明第一方面所述的標靶ROR1的抗體或其抗原結合片段、如本發明第五方面所述的嵌合抗原受體、如本發明第六方面所述的基因修飾的細胞、本發明第八方面所述的抗體藥物偶聯物和/或如本發明第九方面所述的藥物組成物，所述的藥盒B爲其他藥物優選大分子藥物例如抗癌症(腫瘤)抗體或者包含所述其他抗癌症(腫瘤)抗體的藥物組成物，或小分子藥物。

【0067】 所述的藥盒A和藥盒B可以同時使用，也可以先使用藥盒A再使用藥盒B，還可以先使用藥盒B再使用藥盒A，可以根據具體應用時的實際需求而定。

【0068】 爲了解決上述技術問題，本發明還提供一種在有需要的受試者中治療癌症的方法，其包括向有需要的受試者施用如本發明第一方面所述的標靶ROR1的抗體或其抗原結合片段、如本發明第五方面所述的嵌合抗原受體、如本發明第六方面所述的基因修飾

的細胞、本發明第八方面所述的抗體藥物偶聯物和/或如本發明第九方面所述的藥物組成物。優選地，所述癌症如本發明第十方面所述。

【0069】 較佳地，還包括施用其他藥物優選大分子藥物例如其他抗癌症(腫瘤)抗體或者包含所述其他抗癌症(腫瘤)抗體的藥物組成物，或小分子藥物，例如與其他藥物進行聯合用藥，例如可以與化學治療劑等進行聯合用藥。

【0070】 在本申請中，除非另有說明，否則本申請中使用的科學和技術名詞具有本領域技術人員所通常理解的含義。並且，本申請中所用的細胞培養、分子遺傳學、核酸化學、免疫學實驗室操作步驟均為對應領域內廣泛使用的常規步驟。同時，為了更好地理解本發明，下面提供相關術語的定義和解釋。

【0071】 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布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，被稱為互補決定區(CDR)或高度變異區(HVR)。可變域中更高度守恆的部分被稱為框架(FWR)。天然重鏈和輕鏈的可變結構域各自包含四個FWR區，大部分採用 β -折疊構型，透過三個CDRs連接，形成環連接，並且在一些情況下形成 β -折疊結構的一部分。每條鏈中的CDRs透過FWR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。

【0072】 本申請所用胺基酸三字母代碼和單字母代碼如本領域技術人員知曉，或J. Biol. Chem, 243, p3558(1968)中所述。

【0073】 如本申請使用的，術語“包括”或“包含”旨在表示組成物和方法包括所述的元素但不排除其他元素，但根據上下文的理解，也包括“由... ..組成”的情況。

【0074】 本申請所述的術語“抗體”可以是包括免疫球蛋白，其是由兩條相同的重鏈和兩條相同的輕鏈透過鏈間二硫鍵連接而成的四胜肽鏈結構。免疫球蛋白重鏈恆定區的胺基酸組成和排列順序不同，故其抗原性也不同。據此，可將免疫球蛋白分為五類，或稱為免疫球蛋白的同種型，即IgM、IgD、IgG、IgA和IgE，其對應的重鏈分別為 μ 鏈、 δ 鏈、 γ 鏈、 α 鏈和 ϵ 鏈。同一類Ig根據其樞紐區胺基酸組成和重鏈二硫鍵的數目和位置的差別，又可分為不同的亞型，如IgG可分為IgG1、IgG2、IgG3和IgG4。輕鏈透過恆定區的不同分為 κ 鏈或 λ 鏈。五類Ig中第每類Ig都可以有 κ 鏈或 λ 鏈。

【0075】 在本申請中，本申請所述的抗體輕鏈可變區可進一步包含輕鏈恆定區，所述的輕鏈恆定區包含人源的 κ 、 λ 鏈或其變異體。

在本申請中，本申請所述的抗體重鏈可變區可進一步包含重鏈恆定區，所述的重鏈恆定區包含人源的IgG1、2、3、4或其變異體。

【0076】 在輕鏈和重鏈內，可變區和恆定區透過大約12或更多個胺基酸的“J”區連接，重鏈還包含大約3個或更多個胺基酸的“D”區。各重鏈由重鏈可變區(VH)和重鏈恆定區(CH)組成。重鏈恆定區由3個結構域(CH1、CH2和CH3)組成。各輕鏈由輕鏈可變區(VL)和輕鏈恆定區(CL)組成。輕鏈恆定區由一個結構域CL組成。抗體的恆定區可媒介免疫球蛋白與宿主組織或因子，包括免疫系統的各种細胞(例如，效應細胞)和經典補體系統的第一組分(C1q)的結合。抗體重鏈和輕鏈靠近N端的約110個胺基酸的序列變化很大，為可變區(V區)；靠近C端的其餘胺基酸序列相對穩定，為恆定區(C區)。可變區包括3個高度變異區(HVR)和4個序列相對守恆的框架區(FWR)。3個高度變異區決定抗體的特異性，又稱為互補性決定區(CDR)。每條輕鏈可變區(VL)和重鏈可變區(VH)由3個CDR區4個FWR區組成，從胺基端到羧基端依次排列的順序為：FWR1、CDR1、FWR2、CDR2、FWR3、CDR3、FWR4。輕鏈的3個CDR區指VL CDR1、VL CDR2和VL CDR3；重鏈的3個CDR區指VH CDR1、VH CDR2和VH CDR3。

【0077】 術語“人源抗體”包括具有人種系免疫球蛋白序列的可變和恆定區的抗體。本申請的人抗體可包括不由人種系免疫球蛋白

序列編碼的胺基酸殘基(如透過體外隨機或位址特異性誘變或透過體內體細胞突變所引入的突變)。然而，術語“人抗體”不包括這樣的抗體，即其中已將衍生自另一種哺乳動物物種(諸如小鼠)種系的CDR序列移植到人框架序列上(即“人源化抗體”)。

【0078】 如本申請所用，關於抗體的術語“特異性”意指辨識特異性抗原但基本上不辨識或結合樣品中的其他分子的抗體。例如，特異性結合來自一個物種的抗原的抗體也可以結合來自一個或更多個物種的該抗原。但是，這種種間交叉反應性本身不改變抗體根據特異性的分類。在另一個實例中，特異性結合抗原的抗體也可以結合該抗原的不同等位基因形式。然而，這種交叉反應性本身不改變抗體根據特異性的分類。在一些情況下，術語“特異性”或“特異性結合”可用於指抗體、蛋白質或胜肽與第二化學物質的相互作用，意味著該相互作用取決於化學物質上特定結構(例如，抗原決定位或表位)的存在；例如，抗體一般辨識並結合特定的蛋白質結構，而不是蛋白質。如果抗體對表位“A”具有特異性，則在含有經標記的“A”和抗體的反應中，含有表位A的分子(或游離的，未標記的A)的存在將減少結合於抗體的標記的A的量。

【0079】 本申請中，術語“抗原結合片段”是指抗體的抗原結合片段及抗體類似物，其通常包括至少部分母體抗體(parental antibody)的抗原結合區或可變區(例如一個或多個CDR)。抗體片段

保留母體抗體的至少某些結合特異性。通常，當基於莫耳來表示活性時，抗體片段保留至少10%的母體結合活性。優選地，抗體片段保留至少50%、60%、70%、80%、90%、95%、99%或100%或更多的母體抗體對標的的結合親和力。抗原結合片段實例包括但不限於：Fab、Fab'、F(ab')₂、Fv片段、線性抗體(linear antibody)、單(重)鏈抗體、奈米抗體、結構域抗體和多特異性抗體等。工程改造的抗體變異體綜述於 Holliger 和 Hudson(2005)Nat. Biotechnol. 23: 1126-1136中。

【0080】 本文中使用的術語“嵌合抗原受體”或“CAR”指：包含能够結合抗原的胞外域(胞外結合結構域)、樞紐結構域、跨膜結構域(跨膜區)和使胞質信號傳到結構域的多肽(即胞內信號域)。樞紐結構域可以被認為是用於向細胞外抗原結合區提供柔性的一部分。胞內信號域指經由確定的信號傳導途徑透過產生第二信使而將資訊傳遞到細胞內以調節細胞活性的蛋白質、或透過對應於此類信使而作為效應子發揮作用的蛋白質，產生可以促進CAR的細胞(例如CAR-T細胞)的免疫效應子功能的信號。胞內信號域包含信號傳導結構域，還可以包括源自共刺激分子的共刺激胞內結構域。

【0081】 “相同性”、“突變”是指兩個多核苷酸序列之間或兩個多肽之間的序列相似性。當兩個比較序列中的位置均被相同鹼基或胺基酸單體殘基占據時，例如如果兩個DNA分子的每一個位置都被

腺嘌呤占據時，那麼所述分子在該位置是同源的。兩個序列之間的相同性百分率是兩個序列共有的匹配或同源位置數除以比較的位置數 $\times 100$ 的函數。例如，在序列最佳比對時，如果兩個序列中的10個位置有6個匹配或同源，那麼兩個序列為60%同源。一般而言，當比對兩個序列而得到最大的相同性百分率時進行比較。

【0082】 術語“多肽”、“胜肽”和“蛋白質”(如果為單鏈)在本申請中互換地使用。術語“核酸”、“核酸序列”，“核苷酸序列”或“多核苷酸序列”和“多核苷酸”互換使用。

【0083】 本文使用的術語“載體”是包含分離的核酸並可用於將分離的核酸遞送至細胞內部的組成物。在本領域中已知許多載體，包括但不限於線性多核苷酸、與離子或兩親化合物相關的多核苷酸、質體和病毒。因此，術語“載體”包括自主複製的質體或病毒。該術語還應被解釋為包括促進核酸轉移到細胞中的非質體和非病毒化合物，例如聚離胺酸化合物、脂質體等。病毒載體的實例包括但不限於腺病毒載體、腺相關病毒載體、反轉錄病毒載體等。

【0084】 本申請使用的表述“細胞”、“細胞株”可互換使用，並且所有這類名稱都包括後代。術語“宿主細胞”是指，可用於導入載體的細胞，其包括但不限於，如大腸桿菌等原核細胞，如酵母細胞等的真菌細胞，或者如纖維原細胞、CHO細胞、COS細胞、NSO細胞、HeLa細胞、BHK細胞、HEK 293細胞或人細胞等的動物細胞。

【0085】 術語“轉染”是指將外源核酸引入真核細胞。轉染可以透過本領域已知的各種手段來實現，包括磷酸鈣-DNA共沉澱、DEAE-葡聚糖媒介的轉染、聚凝胺媒介的轉染、電穿孔、顯微注射、脂質體融合、脂質轉染、原生質體融合、反轉錄病毒感染和生物彈道技術(biolistics)。

【0086】 術語“免疫細胞”指可以引發免疫反應的細胞，“免疫細胞”及其語法上的其他形式可以指任何來源的免疫細胞。“免疫細胞”包括例如衍生自在骨髓中產生的造血幹細胞(HSC)的白血細胞(白血球)、淋巴細胞(T細胞、B細胞、自然殺手(NK)細胞和骨髓來源的細胞(嗜中性顆粒細胞、嗜酸性顆粒細胞、嗜鹼性顆粒細胞、單核細胞、巨噬細胞、樹突狀細胞)。術語“免疫細胞”也可以是人或非人的。例如，免疫細胞可以是來自血液的，如自體的T細胞、異體T細胞、自體NK細胞、異體NK細胞，也可以來源自細胞株，如利用EBV病毒感染來製備NK細胞株，從胚胎幹細胞和iPSC誘導分化來的NK細胞以及NK92細胞株等。

【0087】 如本申請使用的，術語“T細胞”是指在胸腺中成熟的一類淋巴細胞。T細胞在細胞媒介的免疫中起重要作用，並且與其他淋巴細胞(例如B細胞)的不同點在於細胞表面上存在T細胞受體。“T細胞”包括表現CD3的所有類型的免疫細胞，包括T輔助細胞(CD4+細胞)、細胞毒性T細胞(CD8+細胞)、自然殺手T細胞、T調節細胞

(Treg)和 γ - δ T細胞。“細胞毒性細胞”包括CD8+T細胞、自然殺手(NK)細胞和嗜中性顆粒細胞，這些細胞能够媒介細胞毒性反應。如本文使用的，術語“NK細胞”是指起源於骨髓並且在先天免疫系統中起重要作用的一類淋巴細胞。NK細胞提供針對病毒感染的細胞、腫瘤細胞或其他遭受壓力的細胞的快速免疫反應，即使是細胞表面上不存在抗體和主要組織相容性複合體。

【0088】 “任選”、“任一”、“任意”或“任一項”意味著隨後所描述地事件或環境可以但不必發生，該說明包括該事件或環境發生或不發生地場合。例如，“任選包含1個抗體重鏈可變區”意味著特定序列的抗體重鏈可變區可以但不必須存在。本發明所用，“一個”和“一種”在本發明中用來指的一個或多於一個的語法對象。除非內容明確提示，否則術語“或”在本發明中用來意指術語“和/或”並且與之互換使用。“約”和“大約”應當通常意指鑒於測量的性質或精度，所測量的量的可接受誤差程度。示例性誤差程度一般在其10%範圍內和更一般在其5%範圍內。本發明揭示的方法和組成物涵蓋這樣的多肽和核酸，它們具有指定的序列，變異序列或與其基本上相同或相似的序列，例如，與序列指定至少85%、90%、95%、99%或更多相同的序列。在胺基酸序列的情況下，術語“基本上相同”在本發明中用來指第一胺基酸序列。

【0089】 如本文中所使用的，術語EC50是指半最大效應濃度 (concentration for 50% of maximal effect)，即能引起50%最大效應的濃度。

【0090】 如本發明所用，術語“癌”、“癌症”、“癌症病人”意在包括全部類型的癌性生長物或致瘤過程、轉移性組織或惡性轉化的細胞、組織或器官，無論組織病理學類型或侵襲力階段是什麼。例子包括但不限於固態腫瘤、血液學癌、軟組織腫瘤和轉移性病灶。

【0091】 本領域人員應當理解的是，包含本發明所述的標靶ROR1的抗體或其抗原結合片段的產品，例如CAR-T、TCR-T、雙抗、多抗、ADC等等都應當落在本發明保護的範圍內。

【0092】 在符合本領域常識的基礎上，上述各優選條件，可任意組合，即得本發明各較佳實例。

【0093】 本發明所用試劑和原料均市售可得。

【0094】 本發明的積極進步效果在於：本發明所述的標靶ROR1的抗體或其抗原結合片段對hROR1和cynoROR1具有良好的結合親和力；與ROR2幾乎沒有任何的交叉反應性。本發明所述的標靶ROR1的抗體或其抗原結合片段的KD值均顯示出與參考的現有技術抗體相當；且均顯示出具有顯著的內吞作用。本發明標靶ROR1的抗體或其抗原結合片段在腫瘤細胞中具有ADCC效應，沒有顯著的CDC/ADCP效應，後續可以基於ADCC方向上的應用開發單抗。

此外，本發明標靶ROR1的抗體或其抗原結合片段中絕大多數PTM位址的去除突變，並不會影響抗體的結合能力，更有利於下游生產成藥。在某一較佳實施例中，本發明所述的標靶ROR1的抗體或其抗原結合片段與腫瘤細胞株結合時，EC50值幾乎均顯示出比現有的現有技術抗體幾乎高出1個log。

【圖式簡單說明】

【0095】 圖1：噬菌體序列庫建立的工作流程。

【0096】 圖2：實施例3中的ELISA篩選結果。

【0097】 圖3：實施例3中的FACS篩選結果。

【0098】 圖4：重組抗體與293T-hROR1細胞株結合的ELISA試驗；其中，A顯示了PR001352-PR001371的結果圖；B顯示了PR001415-1419的結果圖。

【0099】 圖5：重組抗體與CHO-K1-cynoROR1細胞株結合的ELISA試驗；其中，A顯示了PR001352-PR001371的結合數據，B顯示了PR001415-PR001419的結合數據。

【0100】 圖6：重組抗體與A549細胞株結合的ELISA試驗；其中，A顯示了PR001352-PR001371的結合數據，B顯示了PR001415-PR001419的結合數據。

【0101】 圖7：PR001352-PR001371、PR001415-PR001419在HEK293T-hROR1細胞上內吞的數據。

【0102】 圖 8：PR001353、PR001354、PR001357 在更低濃度時在 HEK293T-hROR1 細胞上內吞的數據。

【0103】 圖 9：重組抗體對 A549 細胞株的 ADCC 效應；其中，A 和 B 分別為供體 1 和 2 的 PR001353、PR001354、PR001355、PR001357、PR001359 和 PR001362 的結果。

【0104】 圖 10：重組抗體對 HEK293T-hROR1 的 CDC 作用。

【0105】 圖 11：ADCP 對重組抗體對 A549 細胞的影響。

【實施方式】

具體實施方式

【0106】 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。

實施例 1 抗原和穩定表現細胞株的製備

a. 抗原和其他蛋白的製備

【0107】 Human ROR1-ECD-Fc(縮寫 hROR1-ECD-Fc) 蛋白，購自 Acrobiosystems，Cat#：RO1-H5250；

Human ROR1-ECD-his 蛋白(縮寫 hROR1-ECD-his)，購自 Acrobiosystems，Cat#：RO1-H522y；

生物素化的 ROR1(Biotin-ROR1)，購自 Acrobiosystems，Cat#：RO1-H821y；

hROR2ECD-his，購自Acrobiosystems，Cat#：RO2-H52E5；

mROR1ECD-his，購自Acrobiosystems，Cat#：
RO1-M5221。

b. 穩定表現細胞株的製備

【0108】 HEK293T-hROR1(人ROR1，human ROR1)購自康源博創，Cat#：KC-1018；

CHO-K1-cynoROR1(獼猴ROR1，cynomolgus ROR1)穩定表現株由實驗室製備，穩定表現株製備方法如下：

按密度為50000/ml接種2ml/孔的CHO-K1細胞懸浮液到6孔盤，培育過夜後加入polybrene(上海吉凱基因，貨號REVG0001，10mg/ml)，使終濃度為4μg/ml，混勻後加10μl病毒(LV-cynoROR1，購於上海吉凱基因，貨號：42582-1，效價1e9/ml，50μl/vial)，混勻後在37℃培育8小時，之後棄去上清液，更換為新鮮培養基，於37℃培養。24小時後消化酶處理來重新懸浮細胞，以含8μg/ml puromycin的完全培養基將細胞稀釋到5/ml，以100μl/孔接種10塊96孔盤，37℃培養10天，挑取單選殖株進行FACS驗證，驗證後將驗證的選殖株繼續擴大培養，凍存。

种

實施例2 噬菌體展示(Phage display)

a. ROR1免疫H2L2小鼠的噬菌體序列庫建構

【0109】 免疫小鼠：用hROR1-ECD-Fc融合蛋白免疫H2L2小鼠(購於和鉑醫藥，授權專利號為EP2379727B1)，具體為：第一次注射時，每隻小鼠注射50μg聯用的上述融合蛋白與CFA，然後分別在第15、29、43、57、71、86和100天時用Ribi佐劑加強免疫7次。在第50、78和107天時採血測試。在融合前3天，即第137天時，進行最後一次加強免疫。

【0110】 從上述免疫後的小鼠中收集脾細胞，並從中分離出脾臟B細胞，然後萃取RNA後參照產品說明書(Thermofisher, Cat.No.15596018)TRIZOL即可，進行RT-PCR參照產品說明書(Thermofisher, Cat.No.11756500)。以cDNA為模板，透過第一次PCR擴增出VH(重鏈可變區)和VL(輕鏈可變區)，然後進行重疊PCR並製備得到scFv片段。

【0111】 其中，上述第一次PCR(First PCR)的反應系統和反應程序如下表1-1和表1-2所示：

表1-1 反應系統

總 RNA-cDNA	1 μl/1 μl 水作為陰性對照
5×Q5 反應緩衝液	10 μl
2.5mM dNTPs	4μl
正向引子(10μM)	2μl
反向引子(10μM)	2μl
Q5 DNA 聚合酶	0.5μl
ddH ₂ O	30.5μl
總系統	50 μl

表1-2 PCR反應程序

98℃	30s	} 30 個循環
98℃	10s	
64℃	30s	
72℃	30s	
72℃	10mins	

【0112】 所述重疊PCR(Overlap PCR)的反應系統和反應程序

如下表2-1和表2-2所示：

表2-1 反應系統

VH 混合物(50ng)	X μl
Vκ 混合物(50ng)	Y μl
5×Q5 反應緩衝液	5μl
5×Q5 GC 增強	5μl
2.5mM dNTPs	2μl
Q5 DNA 聚合酶	0.25μl
ddH ₂ O Up to	25μl

【0113】 上表中，由於每個樣品的濃度不同，因此按質量來換算體積，所以每個反應的VH和VL體積都是不同的，在此用X和Y來代表，保證反應系統中每個基因的質量為50ng，且最終由水將總系統補充為25μl。

表2-2 PCR反應程序

98℃	30s	} 7 個循環
98℃	10s	
68℃	30s	
72℃	30s	
72℃	5mins	

【0114】 7次循環反應後，加入引子SfiF(1μl)/SfiR(1μl)進行重疊PCR(Overlap PCR)，反應程序如下表2-3所示。

表2-3 PCR反應程序

98℃	30s	
98℃	10s	} 25 個循環
66℃	30s	
72℃	40s	
72℃	5mins	

【0115】 將上述所得的連接產物轉形至MC1061F'(Lucigen，Cat#：60512-1)；然後製備噬菌體序列庫(噬菌體序列庫建立的工作流程和結果如圖1所示)。進行三輪生物淘選(步驟如下述b所示)，並用生物素化的ROR1透過ELISA(步驟如下述c所示)進行篩選，將所有篩選出的候選物(hit)送去定序(步驟如下所述)並生產出特定的選殖株。

b. 生物淘選(Bio-Panning)

【0116】 將上述所得噬菌體序列庫(1E13噬菌體顆粒)用鏈黴親和素(SA)塗佈的珠子(SA beads，Thermofisher，Cat#：11206)消除(deplete)，然後在室溫下與SA-Bio-ROR1珠培育(參照產品說明書Thermofisher，Cat#：11206)；然後用1×PBST洗滌14次。洗滌後，用pH3.0檸檬酸緩衝液加入磁珠噬菌體混合物室溫培育10分鐘，再加入pH9.0 Tris-HCl中和緩衝液，然後取上清液在37℃感染10ml的MC1061F'細胞，感染時間為15分鐘，感染的細胞極限稀

釋後塗布培養盤2×YT(含有100μg/ml Amp)，37度培養過夜生成菌落。然後在上述感染的細胞中加入50μl 2E12/ml的M13K07輔助噬菌體(NEB，Cat#：N0315S)，在37℃繼續培養15min。最後加入100ml的2×YT(含有100μg/ml Amp，50μg/ml Kan，1mM IPTG)，在30℃培育過夜。將100ml的過夜培養物離心，透過0.22μm過濾器進行過濾，加入7ml的20%PEG6000和2.5M的NaCl到35ml上清液(1：5，體積比)中，然後在4℃，8000rpm離心30min。將離心後所得的噬菌體沉澱重新懸浮於1ml 1×PBST中，以10000rpm離心5分鐘以丟棄碎片。將所得上清液(噬菌體顆粒)轉移到新管中，並準備進行第2輪淘選第3輪淘選。第2輪淘選和第3輪淘選的過程與前述步驟相同。

c. 初步篩選

【0117】 將上述的菌落挑選到含有YT/Amp培養基(Sangon Biotech，Cat#：A507016-0250)的96孔盤中，並在37℃下生長3小時。加入IPTG至終濃度為1mM，並在30℃下誘導過夜。然後將上清液離心沉澱後取上清液進行ELISA試驗。

【0118】 ELISA試驗篩選：將1μg/ml上述實施例1a中製備得到的用PBS配製的hROR1 ECD-his/hROR2 ECD-his/mROR1 ECD-his蛋白加入到96孔盤(Corning 9018)中，在4℃下塗佈過夜，然後棄除液體並用PBST洗滌3次。在室溫下用5%牛奶封阻2小

時，並用PBST洗滌3次。加入100 μ l/孔的上述所取上清液並在室溫下培育1小時，然後用PBST洗滌3次。加入100 μ l/孔的第二抗體(Sigma，Cat#：A8592)，在室溫下培育1小時，然後進行洗滌。接著將100 μ l/孔的TMB加入孔盤中並在室溫下培育15分鐘，然後終止反應並讀數。

【0119】 結果如圖2所示，圖中顯示了164個候選物(hit)的ELISA結果，其中71個候選物從第2輪淘選的結果挑出(如圖2中的A所示)，93個候選物從第3輪淘選的結果挑出(如圖2中的B所示)。

實施例3 抗體定序及FACS篩選驗證

a. 定序：

【0120】 噬菌體來源的候選物：直接將上述164個候選物進行定序(北京擎科生物科技有限公司上海分公司)，然後進行特定的序列分析。結果顯示其完全產生了89個獨特的候選物。

b. FACS篩選驗證：

【0121】 將上述89個獨特的候選物進行HEK293T-hROR1和CHO-K1-CynoROR1的FACS篩選實驗，所得結果分別顯示在圖3的A和B中。關於FACS(流式細胞術)篩選，包括：使用TrypLE消化酶處理貼壁上述細胞後，用FACS緩衝液洗滌細胞並計數，然後用封阻試劑稀釋至 $3-5 \times 10^6$ /ml密度。將100 μ l/孔的細胞加入96孔盤(Corning 3894)。封阻3-4分鐘後，加入100 μ l/孔上述實施例2c中

所述上清液，在4℃培育1小時。洗滌後加入第二抗體，於4℃培育。然後洗滌細胞並進行流式細胞術以進行FACS分析。按照圖3顯示的結果進行排名，將效果排名前25的選植株配對並進行後續的轉染和純化。

c. 排名前25的抗體序列資訊

【0122】 本領域人員公知，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，馬裏蘭州(1991))和基於結構環區域位置的Chothia定義規則(參見J Mol Biol 273:927-48,1997)。在本申請中，還可以使用包含了Kabat定義和Chothia定義的Combined定義規則確定可變結構域序列中的胺基酸殘基。其中Combined定義規則即是將Kabat定義和Chothia定義的範圍相結合，基於此取了一個更大的範圍，詳見表3。

表3 不同編號系統下本發明CDR在抗體輕鏈或重鏈中的位置

CDR\編號系統	Kabat	Chothia	Combined
VL CDR1	L24 - L34	L24 - L34	L24 - L34
VL CDR2	L50 - L56	L50 - L56	L50 - L56
VL CDR3	L89 - L97	L89 - L97	L89 - L97
VH CDR1	H31 - H35	H26 - H32	H26 - H35
VH CDR2	H50 - H65	H52 - H56	H50 - H65
VH CDR3	H95 - H102	H95 - H102	H95 - H102

表4 本發明抗體重鏈CDR的胺基酸序列(基於Chothia定義規則)

抗體編號	VH CDR1	SEQ ID NO.	VH CDR2	SEQ ID NO.	VH CDR3	SEQ ID NO.
陽性對照 (PR000374)	GSDINDY	11	NSGGS	31	GYSTYYRDFNI	51
PR001352	GFTFSSY	12	WYDGIS	32	DLARSFDL	52
PR001353	GFTFSSY	12	WYDGIS	32	EQARSFDL	53
PR001354	GFTFSSY	12	WYDGSD	33	EQARSFDL	53
PR001355	GFTFSSY	12	WYDGSN	34	EQARSFDL	53
PR001356	GFTFSSY	12	WYDGVS	35	EQARSFDL	53
PR001357	GFTFSSY	12	WYDGSN	34	EQARSFDL	53
PR001358	GFTFSSY	12	WYDGSN	34	EQARSFDL	53
PR001359	GFTFSTY	13	WYDGSD	33	EQARSFDL	53
PR001360	GFTFSSY	12	WYDGSD	33	EQARSFDL	53
PR001361	GFTFSRY	14	WYDGVS	35	EQARSFDL	53
PR001362	GFTFSTY	13	WYDGSD	33	DQARSFDL	54
PR001363	GFSFSSY	15	WYDGGD	36	EQARSFDL	53
PR001364	GFTFSSF	16	WYDGSD	33	EQARSFDL	53
PR001365	GFTFSSY	12	WYDGSD	33	EQARSFDL	53
PR001366	GFTFSSY	12	WYDGIS	32	DLARSFDI	55
PR001367	GFSFSSY	15	WYDGGD	36	EQARSFDL	53
PR001368	GFTFSTY	13	WYDGSD	33	EQARSFDL	53
PR001369	GFTFSNY	17	WYDGSN	34	EQARSFDL	53
PR001370	GFTFSSY	12	WYDGIS	32	DLARSFDL	52
PR001371	GFTFSSY	12	WYDGVS	35	EQARSFDL	53
PR001415	GFTFSNS	18	WYDGSN	34	EQARSFDL	53
PR001416	GFTFSTY	13	WYDGSD	33	EQARSFDL	53
PR001417	GFSFSSY	15	WYDGGD	36	EQARSFDL	53
PR001418	GFTFSSY	12	WYDGSD	33	EQARSFDL	53
PR001419	GFTFSSY	12	WYDGIS	32	EQARSFDL	53

表5 本發明抗體輕鏈CDR的胺基酸序列(基於Chothia定義規則)

抗體編號	VL CDR1	SEQ ID NO.	VL CDR2	SEQ ID NO.	VL CDR3	SEQ ID NO.
陽性對照抗體 (PR000374)	QASQSIDSNLA	68	RASNLAS	77	LGGVGAVSYRTS	83
PR001352	RASQTINNWLA	69	KASSLES	78	QQYNSYSPTYT	84
PR001353	RASQSISSWLA	70	KASSLES	78	QQYKSYSPMYT	85
PR001354	RASQTINNWLA	69	KASSLES	78	QQYNSYSPTYT	84
PR001355	RASQTMNNWLA	71	KASSLES	78	QQYNSYSPTYT	84
PR001356	RASQSINNWLA	72	KASSLES	78	QQYKSYSPMYT	85

PR001357	RASQTINNWLA	69	KASSLES	78	QQYKLYSPMYT	86
PR001358	RASQSINSWLA	73	KASNLES	79	QQYKSYSPMYT	85
PR001359	RASQSVNNWLA	74	KASSLES	78	QQYKSYSPMYT	85
PR001360	RASQTINNWLA	69	KASSLES	78	QQYNIYSPMYT	87
PR001361	RASQSINSWLA	73	KASSLES	78	QQYKSYSPMYT	85
PR001362	RASQSINSWLA	73	KASSLES	78	QQYKSYSPMYT	85
PR001363	RASQTINNWLA	69	KASSLES	78	QQYNSYSPMYT	84
PR001364	RASQTINNWLA	69	KASSLES	78	QQYNSYSPMYT	84
PR001365	RASQTINNWLA	69	KASSLES	78	QQYKLYSPMYT	86
PR001366	RASQSINSWLA	73	KASSLES	78	QQYKSYSPMYT	85
PR001367	RASQTINNWLA	69	KASSLES	78	QQYNSYSPMYT	84
PR001368	RASQSINSWLA	73	KASSLES	78	QQYKSYSPMYT	85
PR001369	RASQTINNWLA	69	KASSLES	78	QQYNSYSPMYT	84
PR001370	RASQSINNWLA	72	KASSLES	78	QQYNSYSPMYT	84
PR001371	RASQTINNWLA	69	KASSLES	78	QQYNSYSPMYT	84
PR001415	RASQTINNWLA	69	KASSLES	78	QQYNSYSPMYT	84
PR001416	RASQTINNWLA	69	KASSLES	78	QQYNSYSPMYT	84
PR001417	RASQSINSWLA	73	KASSLES	78	QQYNSYSPMYT	84
PR001418	RASQTINNWLA	69	KASSLES	78	QQYNSYSPMYT	84
PR001419	RASQSISSWLA	70	KASSLES	78	QQYNSYSPMYT	84

其中陽性對照抗體 (PR000374) 的具體資訊參見 WO2016094873(R11H18L9)。

d. 抗體可變區的框架區序列

【0123】 下表5-1為對照抗體及本發明優選的框架區序列組合。本發明獲得的抗體及對照抗體的輕鏈可變區和重鏈可變區如下表5-1所示。

e. 抗體輕鏈、重鏈的序列

【0124】 在得到編碼抗體分子的輕、重鏈可變結構域序列以後，可以採用常規的重組DNA技術，將輕、重鏈可變結構域序列和對應的人的抗體輕、重鏈恆定結構域序列進行融合表現，得到重組

抗體分子。本發明抗體的重鏈恆定區可選自hIgG1、hIgG2、hIgG3或hIgG4中的一種。在本實施例中，抗體重鏈可變結構域序列(VH)透過基因合成並選殖到編碼人IgG1抗體重鏈恆定結構域序列的哺乳動物細胞表現質體載體中，以編碼產生IgG1抗體的全長重鏈。抗體輕鏈可變結構域序列(VL)透過基因合成並選殖到編碼人抗體Igκ輕鏈恆定結構域序列的哺乳動物細胞表現質體載體中，以編碼產生抗體的全長輕鏈。在本實施例中，由於從免疫的和鉑醫藥H2L2小鼠得到的單株抗體分子可變結構域的序列是人源抗體序列，因而本實施例也得到全人源的抗ROR1重組IgG1抗體。

【0125】 例如，本發明獲得的抗體及對照抗體的重鏈序列和輕鏈序列可以如下表5-1所示。

表5-1 輕重鏈、可變區、框架區序列組合(SEQ ID NO，本發明後續以Chothia定義規則為例)

Accession	ChainType	可變區	輕重鏈	FWR1	FWR2	FWR3	FWR4
PR001352	HC(重鏈)	93	136	2	20	38	57
PR001352	LC(輕鏈)	117	160	59	76	81	89
PR001353	HC	94	137	3	21	39	57
PR001353	LC	118	161	60	76	81	89
PR001354	HC	95	138	4	22	40	57
PR001354	LC	119	162	61	76	81	89
PR001355	HC	96	139	5	23	41	57
PR001355	LC	120	163	62	76	82	90
PR001356	HC	97	140	6	24	42	57
PR001356	LC	121	164	60	76	81	89
PR001357	HC	98	141	4	23	40	57

PR001357	LC	122	165	63	76	81	89
PR001358	HC	99	142	4	25	43	57
PR001358	LC	123	166	60	76	81	91
PR001359	HC	100	143	6	26	40	57
PR001359	LC	124	167	60	76	81	89
PR001360	HC	101	144	6	23	44	57
PR001360	LC	125	168	64	76	81	89
PR001361	HC	102	145	7	27	45	57
PR001361	LC	126	169	65	76	81	91
PR001362	HC	103	146	8	23	46	57
PR001362	LC	127	170	60	76	81	89
PR001363	HC	104	147	6	28	47	57
PR001363	LC	128	171	66	76	81	89
PR001364	HC	105	148	2	23	40	57
PR001364	LC	129	172	60	76	81	89
PR001365	HC	106	149	4	23	40	57
PR001365	LC	130	173	67	76	81	89
PR001366	HC	107	150	9	20	38	57
PR001366	LC	126	169	65	76	81	91
PR001367	HC	108	151	6	28	48	57
PR001367	LC	128	171	66	76	81	89
PR001368	HC	109	152	6	23	49	57
PR001368	LC	127	170	60	76	81	89
PR001369	HC	110	153	6	29	43	57
PR001369	LC	129	172	60	76	81	89
PR001370	HC	93	136	2	20	38	57
PR001370	LC	131	174	60	76	81	91
PR001371	HC	111	154	6	27	45	57
PR001371	LC	117	160	59	76	81	89
PR001415	HC	112	155	10	22	40	57
PR001415	LC	129	172	60	76	81	89
PR001416	HC	113	156	6	23	40	57
PR001416	LC	129	172	60	76	81	89
PR001417	HC	108	151	6	28	48	57
PR001417	LC	132	175	66	76	81	89

PR001418	HC	114	157	6	23	40	57
PR001418	LC	133	176	60	76	81	90
PR001419	HC	115	158	6	30	50	57
PR001419	LC	134	177	65	76	81	89
陽性對照 (PR000374)		92	135				
陽性對照 (PR000374)		116	159				

實施例4 抗體生產、純化和驗證

a. 重組抗體生產和純化

【0126】 經上述定序分析後，得到編碼抗體分子的輕、重鏈可變結構域序列以後，可以採用常規的重組DNA技術，將重鏈和輕鏈配對並選殖到表現載體中。將上述效果排名前25的選植株配對並進行轉染和純化。然後透過轉染至293或CHO細胞以產生蛋白質。透過本領域常規步驟使用蛋白A純化抗體然後進行特徵鑑定。具體結果顯示在表6中。

表 6

AccessionID	AB_MW (Kda)	Ext. Coeff	AB_pI	產量 (mg/L)	SEC 純化	VH 生 殖系	VL 生 殖系	VH PTMs	VL PTMs
PR001352	145.3	1.45	9.28	26.86	100	IGHV 3-33	IGKV 1-5	DG (HCDR2)	NS (LCDR3)
PR001353	145.174	1.45	9.28	38.06	99.49			DG (HCDR2)	
PR001354	145.316	1.46	9.27	35.64	100			DG (HCDR2)	NS (LCDR3)
PR001355	145.138	1.47	9.27	39	100			DG (HCDR2)	NS (LCDR3)
PR001356	145.162	1.47	9.17	42.84	99			DG	

PR001357	145.504	1.48	9.42	33.66	100
PR001358	145.256	1.45	9.37	34.46	100
PR001359	145.258	1.46	9.27	40.99	99.56
PR001360	145.324	1.45	9.05	30.92	100
PR001361	145.136	1.45	9.29	36.69	98.91
PR001362	145.086	1.47	8.87	33.8	99.29
PR001363	145.212	1.45	8.64	44.43	99.38
PR001364	145.314	1.45	9.05	40.06	99.35
PR001365	145.542	1.48	9.34	21.82	100
PR001366	145.242	1.45	9.44	47.01	100
PR001367	145.364	1.46	8.63	38.08	99.06
PR001368	145.202	1.46	9.17	44.64	98.47
PR001369	145.276	1.45	9.18	38.9	99.44
PR001370	145.25	1.45	9.28	28.5	99.7
PR001371	144.993	1.45	8.88	41.52	99.11
PR001415	145.282	1.45	9.18	89.5	96.78
PR001416	145.31	1.46	9.17	94.25	97.35

(HCDR2)	
DG (HCDR2)	
DG (HCDR2)	NS (LCDR1)
DG (HCDR2)	
DG (HCDR2)	
DG (HCDR2)	NS (LCDR1)
DG (HCDR2)	NS (LCDR1)
DG (HCDR2)	NS (LCDR3)
DG (HCDR2)	NS (LCDR3)
DG (HCDR2)	
DG (HCDR2)	NS (LCDR1)
DG (HCDR2)	NS (LCDR3)
DG (HCDR2)	NS (LCDR1)
DG (HCDR2)	NS (LCDR3)
DG (HCDR2)	NS (LCDR3)
NS (HCDR1),D G (HCDR2)	NS (LCDR3)
DG	NS (LCDR3)

								(HCDR2)	
PR001417	145.282	1.46	8.63	94.5	96.45			DG (HCDR2)	NS (LCDR1),NS (LCDR3)
PR001418	145.31	1.46	9.17	74.5	97.17			DG (HCDR2)	NS (LCDR3)
PR001419	145.138	1.47	9.27	86	98.12			DG (HCDR2),N xS/T (HFR3)	NS (LCDR3)

b. 重組抗體的驗證

(1) 抗體結合特性的驗證

【0127】 使用FACS進行特徵鑑定，將上述所得重組抗體連續稀釋至9種不同濃度，並在培育1小時後分別在HEK293T-hROR1、CHO-K1-cynoROR1和A549細胞株(內源表現ROR1)上進行測試，然後培育第二抗體1小時。結果如圖4-6和下表7-2所示。

表 7-1

	HEK293T-hROR1		CHO-K1-cynoROR1		A549	
Ab No.	EC50	MAX(MFI)	EC50	MAX(MFI)	EC50	MAX(MFI)
PR000374	8.776	261573	3.449	31869	3.581	3846
PR001352	1.127	261573	0.4629	30743	0.1542	4520
PR001353	1.031	261573	0.3096	29027	0.1019	4331
PR001354	1.135	261573	0.4362	26956	0.1852	4305
PR001355	1.137	261573	0.4629	30016	0.1767	4240
PR001356	1.016	261573	0.4831	29730	0.1658	4631
PR001357	0.9739	261573	0.3244	24566	0.09886	4548
PR001358	1.031	261573	0.3388	27345	0.08687	4968
PR001359	1.134	261573	0.5516	27150	0.184	3929
PR001360	1.443	261573	0.6241	24978	0.2394	4051

PR001361	1.187	261573	0.4089	27215	0.1287	4520
PR001362	1.685	261573	1.947	17654	18.61	3754
PR001363	1.567	261573	0.5852	17205	0.2057	3697
PR001364	1.523	261573	0.4849	18158	0.1955	3965
PR001365	1.149	261573	0.4081	22079	0.1323	4398
PR001366	1.06	261573	0.2652	23316	0.1126	4746
PR001367	1.239	261573	0.4939	21210	0.2049	3447
PR001368	1.076	261573	0.4835	27806	0.1938	4214
PR001369	1.469	261573	0.4474	22184	0.1344	3893
PR001370	1.276	261573	0.4838	26010	0.1298	3917
PR001371	1.318	261573	0.7295	28410	0.2551	4113
hIgG1		226		140		119

表 7-2

	HEK293T-hROR1	CHO-K1-cyROR1	A549
Ab No.	EC50	EC50	EC50
PR000374	17.21	5.044	6.337
PR001415	2.522	0.8506	0.3761
PR001416	2.395	0.9467	0.3978
PR001417	2.831	1.491	0.9127
PR001418	3.005	1.105	0.5006
PR001419	2.679	0.7063	0.2472

【0128】 圖 4：重組抗體與 HEK293T-hROR1 細胞株結合的 ELISA 試驗；其中，A 顯示了 PR001352-PR001371 的結合，所有 20 個重組抗體的 EC50 的數據 (EC50 的數據參見表 7-1，其中由於陽性細胞表現太高，流式細胞儀完全飽和，故第 3 列 (MAX(MFI)) 的數據完全相同) 比參考的現有技術抗體 (PR000374，R11H18L9 from patent WO2016094873) 低 10 倍；B 顯示了 PR001415-1419 的 EC50 的數據 (EC50 的數據參見表 7-2) 也比參考的現有技術抗體

低10倍；其中iso1和iso2均為hIgG1，購自Crownbio，Cat#：C0001-4。

【0129】 圖5：重組抗體與CHO-K1-cynoROR1細胞株結合的ELISA試驗；其中，A顯示了PR001352-PR001371的結合數據(EC50的數據見表7-1)，說明了這些重組抗體都具有與cynoROR1的交叉反應性，除PR001362外均結合效果優於參考的現有技術抗體(PR000374)；B顯示了PR001415-PR001419的結合數據(EC50的數據見表7-2)，說明了這些重組抗體都具有與cynoROR1的交叉反應性，且效果均優於參考的現有技術抗體。

【0130】 圖6：重組抗體與A549細胞株結合的ELISA試驗；其中，A顯示了PR001352-PR001371的結合數據，結果顯示(EC50的數據見表7-1)除PR001362外，PR001352-PR001371均優於參考的現有技術抗體(PR000374)；B顯示了PR001415-PR001419的結合數據(EC50的數據見表7-2)，結果顯示所有5個重組抗體均具有比參考的現有技術抗體更好的親和力。

(2)內吞驗證

【0131】 關於內吞實驗，將HEK293T-hROR1細胞計數並以5000/孔接種到96孔黑壁透明底孔盤(PE 6005225)。將上述所得重組抗體連續稀釋至9種不同濃度，並使重組抗體加入細胞後的終濃度的起始濃度為100nM。加入a-hFc-MMAF(購自Moradec LLC，

Cat#：AH-102AF-50)使其終濃度為1μg/ml。然後將孔盤在37℃，5%CO2下培育72小時，然後用CTG套組(購自Promega，Cat#：G7573)裂解並透過Enspire儀器檢測發光。結果如圖7和8和下表8所示。

【0132】 圖 7 顯 示 了 PR001352-PR001371、PR001415-PR001419 在 HEK293T-hROR1 上的內吞實驗的數據。由圖中可以看出，所有重組抗體都顯示出非常好的內化效果，即便是最低濃度的抗體也實現了完全的內吞效果。

【0133】 圖8顯示了PR001353、PR001354、PR001357在更低濃度時在HEK293T-hROR1細胞上的內吞實驗的數據。

表 8

Ab ID	EC50(nM)
PR000374(ref)	0.2429
PR001353	0.1489
PR001354	0.1428
PR001357	0.1371

(3)KD值的檢測

【0134】 採用本領域常規步驟檢測上述抗體的KD值。表9顯示了PR001352-PR001371，PR001415-PR1419的KD概述。這些結果顯示，大部分抗體都與參考的現有技術抗體效果相當，挑取其中6個抗體用於後續的ADCC/CDC/ADCP實驗。

表 9

Sample ID	KD (M)	kon(1/Ms)	kdis(1/s)
PR001368	2.16E-09	4.02E+05	8.67E-04
PR001369	1.69E-09	3.07E+05	5.19E-04
PR001370	3.97E-09	2.85E+05	1.13E-03
PR001371	1.76E-09	2.98E+05	5.25E-04
PR001415	1.53E-09	3.36E+05	5.12E-04
PR001416	1.27E-09	2.70E+05	3.42E-04
PR001417	1.49E-08	4.33E+05	6.46E-03
PR001418	1.45E-09	2.92E+05	4.23E-04
PR001419	3.01E-09	3.89E+05	1.17E-03
PR000374	3.97E-10	4.37E+05	1.73E-04
PR001352	1.51E-09	3.16E+05	4.76E-04
PR001353	2.21E-09	4.19E+05	9.27E-04
PR001354	1.13E-09	3.39E+05	3.83E-04
PR001355	8.39E-10	3.47E+05	2.91E-04
PR001356	8.10E-10	3.54E+05	2.87E-04
PR001357	4.81E-10	3.97E+05	1.91E-04
PR001358	1.07E-09	4.82E+05	5.18E-04
PR001359	2.00E-09	3.20E+05	6.37E-04
PR001360	8.04E-10	3.09E+05	2.48E-04
PR001361	1.83E-09	5.90E+05	1.08E-03
PR001362	4.54E-08	3.00E+05	1.36E-02
PR001363	2.90E-09	3.48E+05	1.01E-03
PR001364	1.20E-09	3.14E+05	3.76E-04
PR001365	2.37E-10	3.25E+05	7.72E-05
PR001366	1.67E-09	4.48E+05	7.50E-04
PR001367	3.06E-09	3.41E+05	1.04E-03

c. PTM(轉譯後修飾)移除實驗

【0135】 根據結合數據，選擇四個主要選殖株PR001354、PR001356、PR001364和PR001369用於PTM移除實驗。通常來

說，PTM移除策略如下表10-13所示。將NG突變為NA或QG；將NS突變為NA或QS；將DG突變為EG或DA。變異體的序列資訊如表13-1所示。

表 10：PR001354 變異體列表

變異體	突變 VH	突變 VL
PR001354(WT)	PR001354_VH	PR001354_VL
PR002562	PR001354_VH	PR001354_VL_N92Q
PR002563	PR001354_VH	PR001354_VL_S93A
PR002564	PR001354_VH_D54E	PR001354_VL
PR002565	PR001354_VH_D54E	PR001354_VL_N92Q
PR002566	PR001354_VH_D54E	PR001354_VL_S93A
PR002567	PR001354_VH_G55A	PR001354_VL
PR002568	PR001354_VH_G55A	PR001354_VL_N92Q
PR002569	PR001354_VH_G55A	PR001354_VL_S93A

表 11：PR001356 變異體列表

變異體	突變 VH	突變 VL
PR001356(WT)	PR001356_VH(WT)	PR001356_VL(WT)
PR002570	PR001356_VH_D54E	PR001356_VL
PR002571	PR001356_VH_G55A	PR001356_VL

表 12：PR001364 變異體列表

變異體	突變 VH	突變 VL
PR001364(WT)	PR001364_VH	PR001364_VL
PR002572	PR001364_VH	PR001364_VL_N92Q
PR002573	PR001364_VH	PR001364_VL_S93A
PR002574	PR001364_VH_D54E	PR001364_VL
PR002575	PR001364_VH_D54E	PR001364_VL_N92Q
PR002576	PR001364_VH_D54E	PR001364_VL_S93A
PR002577	PR001364_VH_G55A	PR001364_VL
PR002578	PR001364_VH_G55A	PR001364_VL_N92Q
PR002579	PR001364_VH_G55A	PR001364_VL_S93A

表 13：PR001369 變異體列表

變異體	突變 VH	突變 VL
PR001369(WT)	PR001369_VH	PR001369_VL
PR002580	PR001369_VH	PR001369_VL_N92Q
PR002581	PR001369_VH	PR001369_VL_S93A
PR002582	PR001369_VH_D54E	PR001369_VL
PR002583	PR001369_VH_D54E	PR001369_VL_N92Q
PR002584	PR001369_VH_D54E	PR001369_VL_S93A
PR002585	PR001369_VH_G55A	PR001369_VL
PR002586	PR001369_VH_G55A	PR001369_VL_N92Q
PR002587	PR001369_VH_G55A	PR001369_VL_S93A

表 13-1：PR001354、PR001356、PR001364、PR001369 變異體的序列資訊

抗體編號	輕鏈	重鏈	VL	VH	LCDR1	LCDR2	LCDR3	HCDR1	HCDR2	HCDR3
PR002562	206	138	194	95	69	78	184	12	33	53
PR002563	207	138	195	95	69	78	185	12	33	53
PR002564	162	198	119	186	69	78	84	12	178	53
PR002565	206	198	194	186	69	78	184	12	178	53
PR002566	207	198	195	186	69	78	185	12	178	53
PR002567	162	199	119	187	69	78	84	12	179	53
PR002568	206	199	194	187	69	78	184	12	179	53
PR002569	207	199	195	187	69	78	185	12	179	53
PR002570	164	200	121	188	72	78	85	12	180	53
PR002571	164	201	121	189	72	78	85	12	181	53
PR002572	208	148	196	105	69	78	184	16	33	53
PR002573	209	148	197	105	69	78	185	16	33	53
PR002574	172	202	129	190	69	78	84	16	178	53
PR002575	208	202	196	190	69	78	184	16	178	53
PR002576	209	202	197	190	69	78	185	16	178	53
PR002577	172	203	129	191	69	78	84	16	179	53
PR002578	208	203	196	191	69	78	184	16	179	53
PR002579	209	203	197	191	69	78	185	16	179	53

PR002580	208	153	196	110	69	78	184	17	34	53
PR002581	209	153	197	110	69	78	185	17	34	53
PR002582	172	204	129	192	69	78	84	17	182	53
PR002583	208	204	196	192	69	78	184	17	182	53
PR002584	209	204	197	192	69	78	185	17	182	53
PR002585	172	205	129	193	69	78	84	17	183	53
PR002586	208	205	196	193	69	78	184	17	183	53
PR002587	209	205	197	193	69	78	185	17	183	53

【0136】 結果見表 14，表中顯示了PR001354、PR001356、PR001364和PR001369的PTM去除設計和特性數據，由表中可以看出：絕大多數PTM位址的去除突變，並不影響抗體分子的結合能力，更有利於下游生產產成藥。

表 14

抗體編號	結構說明	Octet 檢測解離率		Panc-1 結合 (MFI)	HEK293T-hROR1 結合(MFI)
		Response	kdis(1/s)		
PR001354	anti-ROR1 1015M2-C9 hIgG1	0.6087	1.17E-04	6703	42753
PR002562	anti-ROR1 1015M2-C9(L:N92Q) hIgG1	0.6286	1.62E-04	5604	43906
PR002563	anti-ROR1 1015M2-C9(L:S93A) hIgG1	0.7569	1.22E-04	5018	43800
PR002564	anti-ROR1 1015M2-C9(H:D54E) hIgG1	0.7481	1.08E-04	6588	43169
PR002565	anti-ROR1 1015M2-C9(H:D54E; L:N92Q) hIgG1	0.5949	1.06E-04	6821	46872
PR002566	anti-ROR1 1015M2-C9(H:D54E;	0.6635	1.35E-04	4633	43273

	L:S93A) hIgG1				
PR002567	anti-ROR1 1015M2-C9(H:G55A) hIgG1	0.7074	2.15E-04	7033	41934
PR002568	anti-ROR1 1015M2-C9(H:G55A; L:N92Q) hIgG1	0.7024	1.40E-04	3619	46307
PR002569	anti-ROR1 1015M2-C9(H:G55A; L:S93A) hIgG1	0.6139	2.07E-04	3761	34497
PR001356	anti-ROR1 1015M2-E6 hIgG1	0.6173	1.52E-04	5592	50900
PR002570	anti-ROR1 1015M2-E6(H:D54E) hIgG1	0.4717	1.08E-03	3656	43064
PR002571	anti-ROR1 1015M2-E6(H:G55A) hIgG1	0.6383	1.13E-04	4556	49559
PR001364	anti-ROR1 1015M3-D8 hIgG1	0.6014	9.38E-05	4965	43064
PR002572	anti-ROR1 1015M3-D8(L:N92Q) hIgG1	0.6057	1.04E-04	3926	42960
PR002573	anti-ROR1 1015M3-D8(L:S93A) hIgG1	0.7228	8.84E-05	3708	37169
PR002574	anti-ROR1 1015M3-D8(H:D54E) hIgG1	0.4852	1.72E-04	5874	45309
PR002575	anti-ROR1 1015M3-D8(H:D54E; L:N92Q) hIgG1	0.8283	1.12E-04	3253	33759
PR002576	anti-ROR1	0.8656	9.83E-05	2466	40247

	1015M3-D8(H:D54E; L:S93A) hIgG1				
PR002577	anti-ROR1 1015M3-D8(H:G55A) hIgG1	0.2442	6.01E-04	6488	44226
PR002578	anti-ROR1 1015M3-D8(H:G55A; L:N92Q) hIgG1	0.4142	3.22E-04	6703	45090
PR002579	anti-ROR1 1015M3-D8(H:G55A; L:S93A) hIgG1	0.7828	1.99E-04	7049	43064
PR001369	anti-ROR1 1015M3-H10 hIgG1	0.2883	4.98E-03	6226	43800
PR002580	anti-ROR1 1015M3-H10(L:N92Q) hIgG1	0.9847	4.75E-05	3716	42547
PR002581	anti-ROR1 1015M3-H10(L:S93A) hIgG1	0.9741	6.73E-05	3182	42342
PR002582	anti-ROR1 1015M3-H10(H:D54E) hIgG1	0.798	1.93E-04	1991	32331
PR002583	anti-ROR1 1015M3-H10(H:D54E; L:N92Q) hIgG1	0.6725	2.23E-04	3950	25337
PR002584	anti-ROR1 1015M3-H10(H:D54E; L:S93A) hIgG1	0.6897	3.01E-04	3176	36635
PR002585	anti-ROR1 1015M3-H10(H:G55A) hIgG1	0.7713	3.89E-04	2614	32721
PR002586	anti-ROR1 1015M3-H10(H:G55A; L:N92Q) hIgG1	0.7543	2.66E-04	5486	41934

PR002587	anti-ROR1	0.7556	3.94E-04	2951	41531
	1015M3-H10(H:G55A; L:S93A) hIgG1				

實施例5效果數據

a. ELISA 結果

【0137】（除添加樣品為重組抗體、二抗為a-Fc(Genscript，Cat#A01854)之外，其餘步驟均與實施例2c部分的ELISA相同)

【0138】表 15 顯示了與 PR001352-PR001371、PR001415-PR001419的hROR1和hROR2的ELISA結合效果數據。由表中可以看出，所有25個抗體都顯示出對結合ROR1具有很好的特異性，且與ROR2均無交叉反應。表中對應的數值均為所測得的螢光強度中位數(MFI)。

表15

Ab ID	huROR1-his	huROR2-his	Ab ID	huROR1-his	huROR2-his
PR001352	2.4765	0.0335	PR001368	2.507	0.0255
PR001353	2.5415	0.031	PR001369	2.476	0.031
PR001354	2.445	0.027	PR001370	2.5255	0.0335
PR001355	2.543	0.0285	PR001371	2.385	0.0235
PR001356	2.379	0.0305	PR001415	2.6105	0.03
PR001357	2.4965	0.04	PR001416	2.453	0.0265
PR001358	2.47	0.049	PR001417	2.382	0.027
PR001359	2.393	0.038	PR001418	2.4235	0.042
PR001360	2.44	0.0315	PR001419	2.4385	0.025
PR001361	2.283	0.028	PR000374	2.485	0.022
PR001362	2.2215	0.032	hIgG1 iso	0.036	0.041
PR001363	2.4485	0.0305	blank	0.024	0.023
PR001364	2.3825	0.024			

PR001365	2.3485	0.0285			
PR001366	2.238	0.0305			
PR001367	2.3775	0.0235			

b. ADCC 實驗

【0139】 使用 CytoTox 96® 非放射性細胞毒性分析套組 (Promega，Cat#：G1780)，檢測 ROR1 抗體針對內生性表現人 ROR1 的 A549 細胞引發 ADCC 效應的活性。人 PBMC (Miaotong，因個體差異單獨 PBMC 供體可能得不到有效結果，故一般一次實驗至少選擇兩個供體平行進行，本實施例中標號為供體 1 和供體 2) 以 300 g 離心 5 分鐘，並在培養基 (RPMI1640+10% FBS) 中培養過夜。標的細胞及人 PBMC 於 300 g 離心 5 分鐘，然後用培養基 (RPMI1640+2% FBS) 重新懸浮。將標的細胞的密度調整到 2×10^5 細胞/ml，PBMC 的細胞密度調整至少為 6×10^6 /ml，兩種細胞各加 50 μ l 到 96 孔盤的孔中 (效應細胞-標的細胞比至少是 30：1)。將待測抗體以培養基 (RPMI1640+2% FBS) 稀釋成不同濃度加入各孔。樣本在 37℃ 培育至少 4 小時，然後於標的細胞最大 LDH 釋放對照孔和體積校正對照孔 (Volume correction control) 加入 10 乘 Triton-X 100 裂解液 (RPMI1640 + 2% FBS + 10% Triton-X 100)，混合均勻在 37℃ 培育 0.5 小時。96 孔盤於 300 g 離心 5 分鐘，取出 50 μ l 上清液，然後以 50 μ l/孔的濃度加入 LDH 顯色液。混合物避光常溫放置 20 分鐘後，孔盤在 MD StakMax 上進行讀數 (OD490)。PR000374

作為陽性對照，human Iso IgG1(CrownBio，Cat#：C0001-4) 抗體作為陰性對照。結果先計算校正讀數，將實驗孔、標的細胞自發性釋放LDH對照孔、效應細胞自發性釋放LDH對照孔的讀數減去培養基背景對照孔讀數，其次將標的細胞最大LDH釋放對照孔讀數減去體積校正對照孔讀數。ADCC活性(%) = (實驗孔校正讀數 - 效應細胞自發性釋放LDH對照孔校正讀數 - 標的細胞自發性釋放LDH對照孔校正讀數) / (標的細胞最大LDH釋放對照孔校正讀數 - 標的細胞自發性釋放LDH對照孔校正讀數) × 100。

【0140】 圖9和表16顯示了重組抗體對A549細胞株的ADCC效應；其中，圖9的A為ROR1-供體1的PR001353、PR001354、PR001355、PR001357、PR001359和PR001362的結果，圖9的B為ROR1-供體2的PR001353、PR001354、PR001355、PR001357、PR001359和PR001362的結果。由圖和表中可以看出，抗體PR001353、PR001354、PR001355、PR001357、PR001359、PR001362的ADCC效應均優於參考的現有技術抗體PR000374，其中PR001359顯示出最佳的ADCC效應，PR001353和PR001357次之。

表 16

	細胞毒性 (%)					
	供體 1			供體 2		
	10 nM	1 nM	0	10 nM	1 nM	0
PR001353	42.29	30.54		21.49	14.05	
PR001354	34.73	33.54		15.92	14.36	
PR001355	28.97	25.69		14.20	14.14	
PR001357	32.08	32.15		15.81	17.45	
PR001359	39.49	33.74		26.15	21.93	
PR001362	26.95	13.89		19.25	13.23	
PR000374	25.40	14.36		18.19	11.44	
IgG1	10.39	9.89	10.39	10.53	10.83	10.39

c. CDC 實驗

【0141】 使用 CellTiter-Glo 發光法細胞活性檢測套組 (Promega, Cat#: G7573), 檢測ROR1抗體針對HEK293T-hROR1細胞引發CDC效應的能力。標的細胞HEK293T-hROR1於300 g離心5分鐘, 然後用DMEM無血清培養基重新懸浮。將標的細胞的密度調整到4e5細胞/ml, 在96孔盤的各孔內加入25 μl細胞懸浮液。抗體以無血清培養基稀釋成不同濃度, 在96孔盤的各孔內加入25 μl抗體稀釋液。加入50 μl的正常人血清(GemCell, Cat#: 100-512), 終濃度為50%, 獲得的混合物於37 °C培育24小時。將96孔盤於常溫靜置30分鐘, 添加100μl/孔之常溫CellTiter-Glo顯色液。之後樣品避光常溫培育10分鐘。用PE Enspire讀取孔盤。CDC活性 (%)=[1 - (luminescent sample) / (luminescent mock

control)] $\times 100$ 。 PR000374 作為陽性對照， human Iso IgG1(CrownBio，Cat#：C0001-4)抗體作為陰性對照。

【0142】 圖10顯示了重組抗體對HEK293T-hROR1的CDC作用。由圖中可以看出，抗體PR001353、PR001354、PR001355、PR001357、PR001359、PR001362在高濃度時都顯示出很好的CDC效應。

d.ADCP實驗

【0143】 從PBMC(Miaotong, cat#PB050F)中用人CD14分離篩選磁珠(Meltenyi, 130-050-201))分離CD14+單核細胞，以密度為 $1 \times 10^6/\text{mL}$ 重新懸浮於含10% FBS 的RPMI1640培養基，加入100 ng/ml GM-CSF(PeproTech, cat#300-03-A)。取 2×10^6 個單核細胞每孔於6孔盤內，37℃二氧化碳培養箱培養8天，使其分化為巨噬細胞。每隔3-4天換一次液(含100 ng/ml GM-CSF)。8天後用胰酶消化酶處理巨噬細胞，用含10%FBS 的RPMI1640終止胰酶反應。收集細胞，用PBS洗滌一次，用PBS重新懸浮為密度為 $1 \times 10^6/\text{ml}$ 。同樣收集A549細胞，用PBS重新懸浮為密度為 $1 \times 10^6/\text{ml}$ 。用0.1 μM Far-red(溶於PBS)對巨噬細胞，用0.5 μM CFSE(溶於PBS)對A549細胞在4℃染色5分鐘。離心染色後的細胞，用 $>20 \text{ ml}$ 的RPMI1640+10%FBS培養基洗滌一次。重新懸浮洗滌後的細胞於1%BSA- RPMI1640培養基中，並調整細胞密度均

為 $1.6\times10^6/\text{ml}$ 。在96孔V型盤內(Corning, cat#3894)每孔加入25 μl A549細胞(每孔細胞數為 4×10^4)和25 μl 巨噬細胞(每孔細胞數為 4×10^4)。用1%BSA- RPMI1640稀釋抗體至中間濃度20 nM和0.2nM，含有A549和巨噬細胞的同一96孔V型盤內每孔加入50 μl 的稀釋抗體，混勻完全。37℃培育1小時。使用NOVOcyte(Acea, US)，經流式細胞術辨識FITC+ A549細胞和Alexa647+巨噬細胞。數據用FlowJo軟體(Tree Star, Ashland, OR)分析，雙染細胞的百分比用於確定ADCP媒介的細胞毒殺。圖11中顯示了ADCP對重組抗體對A549細胞的影響。

【0144】 由圖 11 和下表 17 中可以看出，抗體 PR001354、PR001355、PR001357的ADCP效應較小，其他抗體PR001353、PR001359、PR001362的ADCP效應與參考的現有技術抗體PR000374相當。

表 17

	10 nM		0.1 nM		0	
PR001353	5.72	6.4	4.83	6.52	/	/
PR001354	12.72	13.39	13.58	14.63	/	/
PR001355	10.46	10.77	10.97	12.07	/	/
PR001357	9.67	8.76	11.93	11.94	/	//
PR001359	10.1	9.62	8.83	9.07	/	/
PR001362	6.92	9.21	8.24	7.53	/	/
PR000374	10.54	7.69	9.19	9.05	/	/
anti-CD47	32.54	24.58	10.71	17.85	/	/
IgG1	6.53	7.46	6.79	5.59	7.83	8.54

討論

【0145】 本發明已經免疫和篩選出了25個對hROR1和cynoROR1具有良好結合親和力的全人源抗體，這些抗體與ROR2幾乎沒有任何的交叉反應性。

【0146】 這25個抗體與結合腫瘤細胞株結合時，除PR001362外，其他24個抗體的結合效果(較低的EC50)均顯示出比參考的現有技術抗體幾乎高出1個log。所有抗體的KD值都顯示出與參考的現有技術抗體相當。所有的25個抗體在穩定表現細胞株上均顯示出具有顯著的內吞作用。還有些抗體例如PR001359在腫瘤細胞中具有ADCC效應，但是沒有顯著的CDC/ADCP效應，後續可以基於ADCC方向上的應用開發單抗。

【序列表】

<110> 大陸商和鉑醫藥(上海)有限責任公司
<120> 標靶ROR1的抗體或其抗原結合片段及製備方法和應用
<150> CN2020109183287
<151> 2020-09-03
<160> 209
<170> PatentIn version 3.5

<210> 1
<211> 25
<212> PRT
<213> 人工的序列
<220>
<223> PR000374 HFWR1 Chothia

<400> 1
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Thr Ala Ser
20 25

<210> 2
<211> 25
<212> PRT
<213> 人工的序列

<220>

<223> PR001352 HFWR1 Chothia, PR001364 HFWR1 Chothia, PR001370
HFWR1 Chothia, PR002572 HFWR1 Chothia, PR002573 HFWR1
Chothia, PR002574 HFWR1 Chothia, PR002575 HFWR1 Chothia,
PR002576 HFWR1 Chothia, PR002577

<400> 2

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser
20 25

<210> 3

<211> 25

<212> PRT

<213> 人工的序列

<220>

<223> PR001353 HFWR1 Chothia

<400> 3

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 Val Ala Ser
20 25

<210> 4

<211> 25

<212> PRT

<213> 人工的序列

<220>

<223> PR001354 HFWR1 Chothia, PR001357 HFWR1 Chothia, PR001358
HFWR1 Chothia, PR001365 HFWR1 Chothia, PR002562 HFWR1
Chothia, PR002563 HFWR1 Chothia, PR002564 HFWR1 Chothia,
PR002565 HFWR1 Chothia, PR002566

<400> 4

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser

20 25

<210> 5

<211> 25

<212> PRT

<213> 人工的序列

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<223> PR001355 HFWR1 Chothia

<400> 5

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1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser

20 25

<210> 6

<211> 25

<212> PRT

<213> 人工的序列

<220>

<223> PR001356 HFWR1 Chothia, PR001359 HFWR1 Chothia, PR001360
HFWR1 Chothia, PR001363 HFWR1 Chothia, PR001367 HFWR1
Chothia, PR001368 HFWR1 Chothia, PR001369 HFWR1 Chothia,
PR001371 HFWR1 Chothia, PR001416

<400> 6

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

20 25

<210> 7

<211> 25

<212> PRT

<213> 人工的序列

<220>

<223> PR001361 HFWR1 Chothia

<400> 7

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser

20 25

<210> 8

<211> 25

<212> PRT

<213> 人工的序列

<220>

<223> PR001362 HFWR1 Chothia

<400> 8

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser

20 25

<210> 9

<211> 25

<212> PRT

<213> 人工的序列

<220>

<223> PR001366 HFWR1 Chothia

<400> 9

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 Thr Ala Ser

20 25

<210> 10

<211> 25

<212> PRT

<213> 人工的序列

<220>

<223> PR001415 HFWR1 Chothia

<400> 10

Glu 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

20 25

<210> 11

<211> 7

<212> PRT

<213> 人工的序列

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<223> PR000374 HCDR1 Chothia

<400> 11

Gly Ser Asp Ile Asn Asp Tyr

1 5

<210> 12

<211> 7

<212> PRT

<213> 人工的序列

<220>

<223> PR001352 HCDR1 Chothia, PR001353 HCDR1 Chothia, PR001354
HCDR1 Chothia, PR001355 HCDR1 Chothia, PR001356 HCDR1
Chothia, PR001357 HCDR1 Chothia, PR001358 HCDR1 Chothia,
PR001360 HCDR1 Chothia, PR001365

<400> 12

Gly Phe Thr Phe Ser Ser Tyr

1 5

<210> 13

<211> 7

<212> PRT

<213> 人工的序列

<220>

<223> PR001359 HCDR1 Chothia, PR001362 HCDR1 Chothia, PR001368
HCDR1 Chothia, PR001416 HCDR1 Chothia

<400> 13

Gly Phe Thr Phe Ser Thr Tyr

1 5

<210> 14

<211> 7

<212> PRT

<213> 人工的序列

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<223> PR001361 HCDR1 Chothia

<400> 14

Gly Phe Thr Phe Ser Arg Tyr

1 5

<210> 15

<211> 7

<212> PRT

<213> 人工的序列

<220>

<223> PR001363 HCDR1 Chothia, PR001367 HCDR1 Chothia, PR001417

HCDR1 Chothia

<400> 15

Gly Phe Ser Phe Ser Ser Tyr

1 5

<210> 16

<211> 7

<212> PRT

<213> 人工的序列

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<223> PR001364 HCDR1 Chothia, PR002572 HCDR1 Chothia, PR002573
HCDR1 Chothia, PR002574 HCDR1 Chothia, PR002575 HCDR1
Chothia, PR002576 HCDR1 Chothia, PR002577 HCDR1 Chothia,
PR002578 HCDR1 Chothia, PR002579

<400> 16

Gly Phe Thr Phe Ser Ser Phe

1 5

<210> 17

<211> 7

<212> PRT

<213> 人工的序列

<220>

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HCDR1 Chothia, PR002582 HCDR1 Chothia, PR002583 HCDR1
Chothia, PR002584 HCDR1 Chothia, PR002585 HCDR1 Chothia,
PR002586 HCDR1 Chothia, PR002587

<400> 17

Gly Phe Thr Phe Ser Asn Tyr

1 5

<210> 18

<211> 7

<212> PRT

<213> 人工的序列

<220>

<223> PR001415 HCDR1 Chothia

<400> 18

Gly Phe Thr Phe Ser Asn Ser

1 5

<210> 19

<211> 19

<212> PRT

<213> 人工的序列

<220>

<223> PR000374 HFWR2 Chothia

<400> 19

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

1 5 10 15

Gly Phe Ile

<210> 20

<211> 19

<212> PRT

<213> 人工的序列

<220>

<223> PR001352 HFWR2 Chothia, PR001366 HFWR2 Chothia, PR001370
HFWR2 Chothia

<400> 20

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

1 5 10 15

Ala Val Lys

<210> 21

<211> 19

<212> PRT

<213> 人工的序列

<220>

<223> PR001353 HFWR2 Chothia

<400> 21

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

1 5 10 15

Ser Val Ala

<210> 22

<211> 19

<212> PRT

<213> 人工的序列

<220>

<223> PR001354 HFWR2 Chothia, PR001415 HFWR2 Chothia, PR002562
HFWR2 Chothia, PR002563 HFWR2 Chothia, PR002564 HFWR2
Chothia, PR002565 HFWR2 Chothia, PR002566 HFWR2 Chothia,
PR002567 HFWR2 Chothia, PR002568

<400> 22

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

1	5	10	15

Ala Ile Met

<210> 23

<211> 19

<212> PRT

<213> 人工的序列

<220>

<223> PR001355 HFWR2 Chothia, PR001357 HFWR2 Chothia, PR001360
HFWR2 Chothia, PR001362 HFWR2 Chothia, PR001364 HFWR2
Chothia, PR001365 HFWR2 Chothia, PR001368 HFWR2 Chothia,

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PR001416 HFWR2 Chothia, PR001418

<400> 23

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

1 5 10 15

Ala Val Ile

<210> 24

<211> 19

<212> PRT

<213> 人工的序列

<220>

<223> PR001356 HFWR2 Chothia, PR002570 HFWR2 Chothia, PR002571

HFWR2 Chothia

<400> 24

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

1 5 10 15

Ala Val Ala

<210> 25

<211> 19

<212> PRT

<213> 人工的序列

<220>

<223> PR001358 HFWR2 Chothia

<400> 25

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

1 5 10 15

Ala Ile Met

<210> 26

<211> 19

<212> PRT

<213> 人工的序列

<220>

<223> PR001359 HFWR2 Chothia

<400> 26

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

1 5 10 15

Ala Val Thr

<210> 27

<211> 19

<212> PRT

<213> 人工的序列

<220>

<223> PR001361 HFWR2 Chothia, PR001371 HFWR2 Chothia

<400> 27

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

1 5 10 15

Ala Val Ala

<210> 28

<211> 19

<212> PRT

<213> 人工的序列

<220>

<223> PR001363 HFWR2 Chothia, PR001367 HFWR2 Chothia, PR001417

HFWR2 Chothia

<400> 28

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

1 5 10 15

Ala Val Ile

<210> 29

<211> 19

<212> PRT

<213> 人工的序列

<220>

<223> PR001369 HFWR2 Chothia, PR002580 HFWR2 Chothia, PR002581
HFWR2 Chothia, PR002582 HFWR2 Chothia, PR002583 HFWR2
Chothia, PR002584 HFWR2 Chothia, PR002585 HFWR2 Chothia,
PR002586 HFWR2 Chothia, PR002587

<400> 29

Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
1 5 10 15
Ala Ile Met

<210> 30

<211> 19

<212> PRT

<213> 人工的序列

<220>

<223> PR001419 HFWR2 Chothia

<400> 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
1 5 10 15
Ala Ile Ile

<210> 31

<211> 5

<212> PRT

<213> 人工的序列

<220>

<223> PR000374 HCDR2 Chothia

<400> 31

Asn Ser Gly Gly Ser

1 5

<210> 32

<211> 6

<212> PRT

<213> 人工的序列

<220>

<223> PR001352 HCDR2 Chothia, PR001353 HCDR2 Chothia, PR001366

HCDR2 Chothia, PR001370 HCDR2 Chothia, PR001419 HCDR2

Chothia

<400> 32

Trp Tyr Asp Gly Ile Ser

1 5

<210> 33

<211> 6

<212> PRT

<213> 人工的序列

<220>

<223> PR001354 HCDR2 Chothia, PR001359 HCDR2 Chothia, PR001360
HCDR2 Chothia, PR001362 HCDR2 Chothia, PR001364 HCDR2
Chothia, PR001365 HCDR2 Chothia, PR001368 HCDR2 Chothia,
PR001416 HCDR2 Chothia, PR001418

<400> 33

Trp Tyr Asp Gly Ser Asp

1 5

<210> 34

<211> 6

<212> PRT

<213> 人工的序列

<220>

<223> PR001355 HCDR2 Chothia, PR001357 HCDR2 Chothia, PR001358
HCDR2 Chothia, PR001369 HCDR2 Chothia, PR001415 HCDR2
Chothia, PR002580 HCDR2 Chothia, PR002581 HCDR2 Chothia

<400> 34

Trp Tyr Asp Gly Ser Asn

1 5

<210> 35

<211> 6

<212> PRT

<213> 人工的序列

<220>

<223> PR001356 HCDR2 Chothia, PR001361 HCDR2 Chothia, PR001371
HCDR2 Chothia

<400> 35

Trp Tyr Asp Gly Val Ser

1 5

<210> 36

<211> 6

<212> PRT

<213> 人工的序列

<220>

<223> PR001363 HCDR2 Chothia, PR001367 HCDR2 Chothia, PR001417
HCDR2 Chothia

<400> 36

Trp Tyr Asp Gly Gly Asp

1 5

<210> 37

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR000374 HFWR3 Chothia

<400> 37

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

1 5 10 15

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

20 25 30

Asp Thr Ala Val Tyr Tyr Cys Ala Arg

35 40

<210> 38

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001352 HFWR3 Chothia, PR001366 HFWR3 Chothia, PR001370

HFWR3 Chothia

<400> 38

Gln Asn Phe 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> 39

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001353 HFWR3 Chothia

<400> 39

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

1 5 10 15

Asn Ser Met Asn Thr Leu Phe Leu Gln Met Asn Ser Leu Arg Ala Glu

20 25 30

Asp Thr Ala Val Tyr Tyr Cys Ala Arg

35 40

<210> 40

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001354 HFWR3 Chothia, PR001357 HFWR3 Chothia, PR001359

HFWR3 Chothia, PR001364 HFWR3 Chothia, PR001365 HFWR3

Chothia, PR001415 HFWR3 Chothia, PR001416 HFWR3 Chothia,

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PR001418 HFWR3 Chothia, PR002562

<400> 40

Lys Asp Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
1 5 10 15
Thr 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> 41

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001355 HFWR3 Chothia

<400> 41

Lys Asp Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
1 5 10 15
Thr 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 Val Arg
 35 40

<210> 42

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001356 HFWR3 Chothia, PR002570 HFWR3 Chothia, PR002571
HFWR3 Chothia

<400> 42

Glu Asp Tyr Ala Asp Ser Val Lys 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 Ala Arg

 35 40

<210> 43

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001358 HFWR3 Chothia, PR001369 HFWR3 Chothia, PR002580
HFWR3 Chothia, PR002581 HFWR3 Chothia, PR002582 HFWR3
Chothia, PR002583 HFWR3 Chothia, PR002584 HFWR3 Chothia,
PR002585 HFWR3 Chothia, PR002586

<400> 43

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

<210> 44

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001360 HFWR3 Chothia

<400> 44

Lys Asp Ser Val Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
1 5 10 15
Asp 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> 45

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001361 HFWR3 Chothia, PR001371 HFWR3 Chothia

<400> 45

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

<210> 46

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001362 HFWR3 Chothia

<400> 46

Glu Asp 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> 47

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001363 HFWR3 Chothia

<400> 47

Glu Asp Ser Ile Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
1 5 10 15
Asp 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> 48

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001367 HFWR3 Chothia, PR001417 HFWR3 Chothia

<400> 48

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

Asp 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> 49

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001368 HFWR3 Chothia

<400> 49

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

1 5 10 15

Thr 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> 50

<211> 41

<212> PRT

<213> 人工的序列

<220>

<223> PR001419 HFWR3 Chothia

<400> 50

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

1 5 10 15

Met Ser Asn Asn Thr Val 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> 51

<211> 11

<212> PRT

<213> 人工的序列

<220>

<223> PR000374 HCDR3 Chothia

<400> 51

Gly Tyr Ser Thr Tyr Tyr Arg Asp Phe Asn Ile

1 5 10

<210> 52

<211> 8

<212> PRT

<213> 人工的序列

<220>

<223> PR001352 HCDR3 Chothia, PR001370 HCDR3 Chothia

<400> 52

Asp Leu Ala Arg Ser Phe Asp Leu

1 5

<210> 53

<211> 8

<212> PRT

<213> 人工的序列

<220>

<223> PR001353 HCDR3 Chothia, PR001354 HCDR3 Chothia, PR001355
HCDR3 Chothia, PR001356 HCDR3 Chothia, PR001357 HCDR3
Chothia, PR001358 HCDR3 Chothia, PR001359 HCDR3 Chothia,
PR001360 HCDR3 Chothia, PR001361

<400> 53

Glu Gln Ala Arg Ser Phe Asp Leu

1 5

<210> 54

<211> 8

<212> PRT

<213> 人工的序列

<220>

<223> PR001362 HCDR3 Chothia

<400> 54

Asp Gln Ala Arg Ser Phe Asp Leu

1 5

<210> 55

<211> 8

<212> PRT

<213> 人工的序列

<220>

<223> PR001366 HCDR3 Chothia

<400> 55

Asp Leu Ala Arg Ser Phe Asp Ile

1 5

<210> 56

<211> 11

<212> PRT

<213> 人工的序列

<220>

<223> PR000374 HFWR4 Chothia

<400> 56

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

1 5 10

<210> 57

<211> 11

<212> PRT

<213> 人工的序列

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<223> PR001352 HFWR4 Chothia, PR001353 HFWR4 Chothia, PR001354
HFWR4 Chothia, PR001355 HFWR4 Chothia, PR001356 HFWR4
Chothia, PR001357 HFWR4 Chothia, PR001358 HFWR4 Chothia,
PR001359 HFWR4 Chothia, PR001360

<400> 57

Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser

1	5	10

<210> 58

<211> 23

<212> PRT

<213> 人工的序列

<220>

<223> PR000374 LFWR1 Chothia

<400> 58

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 Asn Cys

20

<210> 59

<211> 23

<212> PRT

<213> 人工的序列

 $\langle 220 \rangle$

<223> PR001352 LFWR1 Chothia, PR001371 LFWR1 Chothia

<400> 59

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys

20

 $\langle 210 \rangle$ 60

<211> 23

<212> PRT

<213> 人工的序列

 $\langle 220 \rangle$

<223> PR001353 LFWR1 Chothia, PR001356 LFWR1 Chothia, PR001358

LFWR1 Chothia, PR001359 LFWR1 Chothia, PR001362 LFWR1

Chothia, PR001364 LFWR1 Chothia, PR001368 LFWR1 Chothia,

PR001369 LFWR1 Chothia, PR001370

<400> 60

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

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1 5 10 15

Asp Arg Val Thr Ile Thr Cys

20

<210> 61

<211> 23

<212> PRT

<213> 人工的序列

<220>

<223> PR001354 LFWR1 Chothia, PR002562 LFWR1 Chothia, PR002563
LFWR1 Chothia, PR002564 LFWR1 Chothia, PR002565 LFWR1
Chothia, PR002566 LFWR1 Chothia, PR002567 LFWR1 Chothia,
PR002568 LFWR1 Chothia, PR002569

<400> 61

Asp Ile Val 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> 62

<211> 23

<212> PRT

<213> 人工的序列

<220>

<223> PR001355 LFWR1 Chothia

<400> 62

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> 63

<211> 23

<212> PRT

<213> 人工的序列

<220>

<223> PR001357 LFWR1 Chothia

<400> 63

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys

20

<210> 64

<211> 23

<212> PRT

<213> 人工的序列

<220>

<223> PR001360 LFWR1 Chothia

<400> 64

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys

20

<210> 65

<211> 23

<212> PRT

<213> 人工的序列

<220>

<223> PR001361 LFWR1 Chothia, PR001366 LFWR1 Chothia, PR001419

LFWR1 Chothia

<400> 65

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys

20

<210> 66

<211> 23

<212> PRT

<213> 人工的序列

<220>

<223> PR001363 LFWR1 Chothia, PR001367 LFWR1 Chothia, PR001417
LFWR1 Chothia

<400> 66

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys
20

<210> 67

<211> 23

<212> PRT

<213> 人工的序列

<220>

<223> PR001365 LFWR1 Chothia

<400> 67

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys
20

<210> 68

<211> 11

<212> PRT

<213> 人工的序列

<220>

<223> PR000374 LCDR1 Chothia

<400> 68

Gln Ala Ser Gln Ser Ile Asp Ser Asn Leu Ala

1 5 10

<210> 69

<211> 11

<212> PRT

<213> 人工的序列

<220>

<223> PR001352 LCDR1 Chothia, PR001354 LCDR1 Chothia, PR001357
LCDR1 Chothia, PR001360 LCDR1 Chothia, PR001363 LCDR1
Chothia, PR001364 LCDR1 Chothia, PR001365 LCDR1 Chothia,
PR001367 LCDR1 Chothia, PR001369

<400> 69

Arg Ala Ser Gln Thr Ile Asn Asn Trp Leu Ala

1 5 10

<210> 70

<211> 11

<212> PRT

<213> 人工的序列

$\langle 220 \rangle$

<223> PR001353 LCDR1 Chothia, PR001419 LCDR1 Chothia

<400> 70

Arg Ala Ser Gln Ser Ile Ser Ser Trp Leu Ala

10

<210> 71

<211> 11

<212> PRT

<213> 人工的序列

 $\langle 220 \rangle$

<223> PR001355 LCDR1 Chothia

<400> 71

Arg Ala Ser Gln Thr Met Asn Asn Trp Leu Ala

10

<210> 72

 $\langle 211 \rangle$ 11

<212> PRT

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 $\langle 220 \rangle$

<223> PR001356 LCDR1 Chothia, PR001370 LCDR1 Chothia, PR002570

LCDR1 Chothia, PR002571 LCDR1 Chothia

<400> 72

Arg Ala Ser Gln Ser Ile Asn Asn Trp Leu Ala

1 5 10

<210> 73

<211> 11

<212> PRT

<213> 人工的序列

<220>

<223> PR001358 LCDR1 Chothia, PR001361 LCDR1 Chothia, PR001362
LCDR1 Chothia, PR001366 LCDR1 Chothia, PR001368 LCDR1
Chothia, PR001417 LCDR1 Chothia

<400> 73

Arg Ala Ser Gln Ser Ile Asn Ser Trp Leu Ala

1 5 10

<210> 74

<211> 11

<212> PRT

<213> 人工的序列

<220>

<223> PR001359 LCDR1 Chothia

<400> 74

Arg Ala Ser Gln Ser Val Asn Asn Trp Leu Ala

1 5 10

<210> 75

<211> 15

<212> PRT

<213> 人工的序列

<220>

<223> PR000374 LFWR2 Chothia

<400> 75

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

1 5 10 15

<210> 76

<211> 15

<212> PRT

<213> 人工的序列

<220>

<223> PR001352 LFWR2 Chothia, PR001353 LFWR2 Chothia, PR001354
LFWR2 Chothia, PR001355 LFWR2 Chothia, PR001356 LFWR2
Chothia, PR001357 LFWR2 Chothia, PR001358 LFWR2 Chothia,
PR001359 LFWR2 Chothia, PR001360

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

1 5 10 15

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<400> 77

Arg Ala Ser Asn Leu Ala Ser

1 5

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Chothia, PR001357 LCDR2 Chothia, PR001359 LCDR2 Chothia,
PR001360 LCDR2 Chothia, PR001361

<400> 78

Lys Ala Ser Ser Leu Glu Ser

1 5

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<400> 79

Lys Ala Ser Asn Leu Glu Ser

1 5

<210> 80

<211> 32

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<213> 人工的序列

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<400> 80

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

1 5 10 15

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

20 25 30

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<211> 32

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Chothia, PR001358 LFWR3 Chothia, PR001359 LFWR3 Chothia,
PR001360 LFWR3 Chothia, PR001361

<400> 81

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

<210> 82

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<400> 82

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

<210> 83

<211> 12

<212> PRT

<213> 人工的序列

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<400> 83

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

1 5 10

<210> 84

<211> 11

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LCDR3 Chothia, PR001363 LCDR3 Chothia, PR001364 LCDR3
Chothia, PR001367 LCDR3 Chothia, PR001369 LCDR3 Chothia,
PR001370 LCDR3 Chothia, PR001371

<400> 84

Gln Gln Tyr Asn Ser Tyr Ser Pro Met Tyr Thr

1 5 10

<210> 85

<211> 11

<212> PRT

<213> 人工的序列

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LCDR3 Chothia, PR001359 LCDR3 Chothia, PR001361 LCDR3
Chothia, PR001362 LCDR3 Chothia, PR001366 LCDR3 Chothia,
PR001368 LCDR3 Chothia, PR002570

<400> 85

Gln Gln Tyr Lys Ser Tyr Ser Pro Met Tyr Thr

1 5 10

<210> 86

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<400> 86

Gln Gln Tyr Lys Leu Tyr Ser Pro Met Tyr Thr

1 5 10

<210> 87

<211> 11

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Gln Gln Tyr Asn Ile Tyr Ser Pro Met Tyr Thr

1 5 10

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<211> 10

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<213> 人工的序列

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<223> PR000374 LFWR4 Chothia

<400> 88

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

1 5 10

<210> 89

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LFWR4 Chothia, PR001356 LFWR4 Chothia, PR001357 LFWR4
Chothia, PR001359 LFWR4 Chothia, PR001360 LFWR4 Chothia,
PR001362 LFWR4 Chothia, PR001363

<400> 89

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

1 5 10

<210> 90

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<213> 人工的序列

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<400> 90

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys

1 5 10

<210> 91

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LFWR4 Chothia, PR001370 LFWR4 Chothia

<400> 91

Phe Gly Gln Gly Thr Lys Val Asp Ile Lys

1 5 10

<210> 92

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<223> PR000374 VH

<400> 92

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg

1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Ser Asp Ile Asn Asp Tyr

20 25 30

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

35 40 45

Gly Phe Ile Asn Ser Gly Gly Ser Thr Trp Tyr Ala Ser Trp Val Lys

50 55 60

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

65 70 75 80

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

85 90 95

Arg Gly Tyr Ser Thr Tyr Tyr Arg Asp Phe Asn Ile Trp Gly Gln Gly

100

105

110

Thr Leu Val Thr Val Ser Ser

115

<210> 93

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<400> 93

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1

5

10

15

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

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25

30

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

35

40

45

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

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Val	Thr	Val	Ser	Ser											
115															
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<223> PR001353 VH															
<400> 94															
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1			5						10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
			20						25				30		
Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
			35					40					45		
Ser	Val	Ala	Trp	Tyr	Asp	Gly	Ile	Ser	Lys	Asp	Tyr	Ala	Asp	Ser	Val
			50					55				60			
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Met	Asn	Thr	Leu	Phe
65					70					75				80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
					85					90				95	
Ala	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu

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Val Thr Val Ser Ser

115

<210> 95

<211> 117

<212> PRT

<213> 人工的序列

<220>

<223> PR001354 VH, PR002562 VH, PR002563 VH

<400> 95

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1

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10

15

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

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25

30

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

35

40

45

Ala Ile Met Trp Tyr Asp Gly Ser Asp Lys Asp Tyr Ala Asp Ser Val

50

55

60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu

100					105					110					
Val	Thr	Val	Ser	Ser											
115															
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<211> 117															
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Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
				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	Trp	Tyr	Asp	Gly	Ser	Asn	Lys	Asp	Tyr	Ala	Asp	Ser	Val
				50						55				60	
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Thr	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
Val	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu

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105

110

Val Thr Val Ser Ser

115

<210> 97

<211> 117

<212> PRT

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<223> PR001356 VH

<400> 97

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

15

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

202530

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

354045

Ala Val Ala Trp Tyr Asp Gly Val Ser Glu Asp Tyr Ala Asp Ser Val

505560

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr

65707580

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

859095

Ala Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu

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Val	Thr	Val	Ser	Ser											
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<400> 98															
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Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
			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	Trp	Tyr	Asp	Gly	Ser	Asn	Lys	Asp	Tyr	Ala	Asp	Ser	Val
			50					55						60	
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Thr	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	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu

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Val Thr Val Ser Ser			
115			
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<400>	99		
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg			
1	5	10	15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr			
	20	25	30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val			
	35	40	45
Ala Ile Met Trp Tyr Asp Gly Ser Asn Thr Asp Tyr Ala Asp Ser Val			
	50	55	60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr Leu Phe			
65	70	75	80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys			
	85	90	95
Ala Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu			

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105

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Val Thr Val Ser Ser

115

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<211> 117

<212> PRT

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<223> PR001359 VH

<400> 100

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

15

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

202530

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

354045

Ala Val Thr Trp Tyr Asp Gly Ser Asp Lys Asp Tyr Ala Asp Ser Val

505560

Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr Leu Tyr

65707580

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

859095

Ala Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu

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Val	Thr	Val	Ser	Ser	
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Ser	Gly	Gly	Gly	Val	Val
Gln	Pro	Gly	Arg		
1		5		10	
Ser	Leu	Arg	Leu	Ser	Cys
Ala	Ala	Ser	Gly	Phe	Thr
Phe	Ser	Ser	Tyr		
	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	Trp	Tyr	Asp
Gly	Ser	Asp	Lys	Asp	Ser
Val	Asp	Ser	Val		
	50		55		60
Lys	Gly	Arg	Phe	Thr	Ile
Ser	Arg	Asp	Asp	Ser	Lys
Asn	Thr	Leu	Tyr		
	65		70		75
Leu	Gln	Met	Asn	Ser	Leu
Arg	Ala	Glu	Asp	Thr	Ala
Val	Tyr	Tyr	Cys		
	85		90		95
Ala	Arg	Glu	Gln	Ala	Arg
Ser	Phe	Asp	Leu	Trp	Gly
Arg	Gly	Thr	Leu		

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105

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Val Thr Val Ser Ser

115

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<223> PR001361 VH

<400> 102

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg

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

202530

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

354045

Ala Val Ala Trp Tyr Asp Gly Val Ser Glu Asp Tyr Ala Asp Ser Val

505560

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Met Asn Thr Leu Ser

65707580

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

859095

Ala Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu

100					105					110					
Val	Thr	Val	Ser	Ser											
115															
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<211>					117										
<212>					PRT										
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<223>					PR001362 VH										
<400>					103										
Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1			5						10				15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Thr	Tyr
			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	Trp	Tyr	Asp	Gly	Ser	Asp	Glu	Asp	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	Arg	Asp	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu

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

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105

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Val Thr Val Ser Ser

115

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<223> PR001364 VH, PR002572 VH, PR002573 VH

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

15

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

202530

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

354045

Ala Val Ile Trp Tyr Asp Gly Ser Asp Lys Asp Tyr Ala Asp Ser Val

505560

Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr Leu Tyr

65707580

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

859095

Ala Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu

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Val	Thr	Val	Ser	Ser	
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Ser	Gly	Gly	Gly	Val	Val
Gln	Pro	Gly	Arg		
1	5	10	15		
Ser	Leu	Arg	Leu	Ser	Cys
Ala	Ala	Ser	Gly	Phe	Thr
Phe	Ser	Ser	Tyr		
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	Trp	Tyr	Asp
Gly	Ser	Asp	Lys	Asp	Tyr
Ala	Asp	Ser	Val		
50	55	60			
Lys	Gly	Arg	Phe	Thr	Ile
Ser	Arg	Asp	Thr	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	Arg	Glu	Gln	Ala	Arg
Ser	Phe	Asp	Leu	Trp	Gly
Arg	Gly	Thr	Leu		

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

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Val	Thr	Val	Ser	Ser											
115															
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1				5						10					15
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Ser	Phe	Ser	Ser	Tyr
				20						25					30
Ala	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Arg	Gly	Leu	Glu	Trp	Val
				35						40					45
Ala	Val	Ile	Trp	Tyr	Asp	Gly	Gly	Asp	Glu	Asp	Tyr	Ile	Asp	Ser	Val
				50						55					60
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	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	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu

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Val Thr Val Ser Ser					
	115				
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<400>	109				
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg					
1	5		10		15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr					
	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 Trp Tyr Asp Gly Ser Asp Thr Asp Tyr Ala Asp Ser Val					
	50		55		60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu					

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105

110

Val Thr Val Ser Ser

115

<210> 110

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<223> PR001369 VH, PR002580 VH, PR002581 VH

<400> 110

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1

5

10

15

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

20

25

30

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

35

40

45

Ala Ile Met Trp Tyr Asp Gly Ser Asn Thr Asp Tyr Ala Asp Ser Val

50

55

60

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

65

70

75

80

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

85

90

95

Ala Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu

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

100

105

110

Val Thr Val Ser Ser

115

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

15

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

202530

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

354045

Ala Ile Met Trp Tyr Asp Gly Ser Asn Lys Asp Tyr Ala Asp Ser Val

505560

Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ser Lys Asn Thr Leu Tyr

65707580

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

859095

Ala Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu

	100	105	110
Val Thr Val Ser Ser			
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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 Ser Thr Tyr			
	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 Trp Tyr Asp Gly Ser Asp Lys Asp Tyr Ala Asp Ser Val			
	50	55	60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu			

	100	105	110
Val Thr Val Ser Ser			
115			
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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 Ser Ser Tyr			
	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 Trp Tyr Asp Gly Ser Asp Lys Asp Tyr Ala Asp Ser Val			
	50	55	60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu			

	100	105	110
Val Thr Val Ser Ser			
115			
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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 Ser Ser Tyr			
	20	25	30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val			
	35	40	45
Ala Ile Ile Trp Tyr Asp Gly Ile Ser Lys Asn Tyr Ala Asp Ser Val			
	50	55	60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Met Ser Asn Asn Thr Val 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 Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu			

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105

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Val Thr Val Ser Ser

115

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<400> 116

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

1

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10

15

Asp Arg Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Ile Asp Ser Asn

20

25

30

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

35

40

45

Tyr Arg Ala Ser Asn Leu Ala Ser Gly Val Pro Asp Arg Phe Ser Gly

50

55

60

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

65

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75

80

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

85

90

95

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

100 105 110

<210> 117

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<223> PR001352 VL, PR001371 VL

<400> 117

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

<210> 118

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<212> PRT

<213> 人工的序列

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<223> PR001353 VL

<400> 118

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

<210> 119

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<223> PR001354 VL, PR002564 VL, PR002567 VL

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Asn Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Pro

85 90 95

Met Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 120

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<223> PR001355 VL

<400> 120

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

<210> 121

<211> 109

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<223> PR001356 VL, PR002570 VL, PR002571 VL

<400> 121

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Asn Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Lys Ser Tyr Ser Pro

85 90 95

Met Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 122

<211> 109

<212> PRT

<213> 人工的序列

<220>

<223> PR001357 VL

<400> 122

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

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

<210> 123
<211> 109
<212> PRT
<213> 人工的序列
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<223> PR001358 VL
<400> 123

Asp Ile Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Ser Trp

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

<210> 124
<211> 109
<212> PRT
<213> 人工的序列
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<223> PR001359 VL
<400> 124

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

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

<210> 125
<211> 109
<212> PRT
<213> 人工的序列
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<223> PR001360 VL
<400> 125

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

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
第 80 頁，共 225 頁(序列表)

50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Ser Pro
85 90 95
Met Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 126
<211> 109
<212> PRT
<213> 人工的序列
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<223> PR001361 VL, PR001366 VL
<400> 126

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

65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Lys Ser Tyr Ser Pro
 85 90 95
Met Tyr Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
 100 105

<210> 127

<211> 109

<212> PRT

<213> 人工的序列

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<223> PR001362 VL, PR001368 VL

<400> 127

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Ser Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Lys Ser Tyr Ser Pro

第 82 頁，共 225 頁(序列表)

	85	90	95
Met	Tyr	Thr	Phe
Gly	Gln	Gly	Thr
Lys	Val	Glu	Ile
Lys			
	100	105	
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<223>	PR001363 VL, PR001367 VL		
<400>	128		
Asp	Val	Val	Met
Thr	Gln	Ser	Pro
Ser	Thr	Leu	Ser
Ala	Ser	Val	Gly
1	5	10	15
Asp	Arg	Val	Thr
Ile	Thr	Cys	Arg
Ala	Ser	Gln	Thr
Ile	Asn	Asn	Trp
	20	25	30
Leu	Ala	Trp	Tyr
Gln	Gln	Lys	Pro
Gly	Lys	Ala	Pro
Lys	Leu	Leu	Ile
	35	40	45
Tyr	Lys	Ala	Ser
Ser	Leu	Glu	Ser
Gly	Val	Pro	Ser
Arg	Phe	Ser	Gly
	50	55	60
Ser	Gly	Ser	Gly
Thr	Glu	Phe	Thr
Leu	Thr	Ile	Ser
Ser	Ser	Leu	Gln
Pro			
65	70	75	80
Asp	Asp	Phe	Ala
Thr	Tyr	Tyr	Cys
Gln	Gln	Tyr	Asn
Ser	Tyr	Ser	Pro
	85	90	95
Met	Tyr	Thr	Phe
Gly	Gln	Gly	Thr
Lys	Val	Glu	Ile
Lys			

100 105

<210> 129

<211> 109

<212> PRT

<213> 人工的序列

<220>

<223> PR001364 VL, PR001369 VL, PR001415 VL, PR001416 VL,
PR002574 VL, PR002577 VL, PR002582 VL, PR002585 VL

<400> 129

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Asn Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Pro

85 90 95

Met Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 130

<211> 109

<212> PRT

<213> 人工的序列

<220>

<223> PR001365 VL

<400> 130

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Asn Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Lys Leu Tyr Ser Pro

85 90 95

Met Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 131

<211> 109

<212> PRT

<213> 人工的序列

<220>

<223> PR001370 VL

<400> 131

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Asn Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Pro

85 90 95

Met Tyr Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys

100 105

<210> 132

<211> 109

<212> PRT

<213> 人工的序列

<220>

<223> PR001417 VL

<400> 132

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

<210> 133

<211> 109

<212> PRT

<213> 人工的序列

<220>

<223> PR001418 VL

<400> 133

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

<210> 134

<211> 109

<212> PRT

<213> 人工的序列

<220>

<223> PR001419 VL

<400> 134

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

- <210> 135
- <211> 449
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR000374 HC
- <400> 135

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

Ser	Leu	Arg	Leu	Ser	Cys	Thr	Ala	Ser	Gly	Ser	Asp	Ile	Asn	Asp	Tyr
20					25					30					
Pro	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
35					40					45					
Gly	Phe	Ile	Asn	Ser	Gly	Gly	Ser	Thr	Trp	Tyr	Ala	Ser	Trp	Val	Lys
50					55					60					
Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Ser	Ile	Ala	Tyr	Leu
65					70					75					80
Gln	Met	Asn	Ser	Leu	Lys	Thr	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala
85					90					95					
Arg	Gly	Tyr	Ser	Thr	Tyr	Tyr	Arg	Asp	Phe	Asn	Ile	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> 136
<211> 447
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<223> PR001352 HC, PR001370 HC
<400> 136

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Lys Trp Tyr Asp Gly Ile Ser Gln Asn Phe 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	Arg	Asp	Leu	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu
100								105				110			
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu
115								120				125			
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys
130				135				140							
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser
145				150				155				160			
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser
				165				170				175			
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
180								185				190			
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
195								200				205			
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His
210				215								220			
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val
225				230				235				240			
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
				245				250				255			

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 137
<211> 447
<212> PRT
<213> 人工的序列
<220>

<223> PR001353 HC
<400> 137

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

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

- <210> 138
- <211> 447
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR001354 HC, PR002562 HC, PR002563 HC
- <400> 138

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

Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
195				200				205								
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	
210				215				220								
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	
225				230				235				240				
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	
245				250				255								
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	
260				265				270								
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	
275				280				285								
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	
290				295				300								
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	
305				310				315				320				
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	
325				330				335								
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	
340				345				350								
Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	
355				360				365								
Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	
370				375				380								

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 139
<211> 447
<212> PRT
<213> 人工的序列
<220>
<223> PR001355 HC
<400> 139

Gln Val Gln Leu Val Gln 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
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Asp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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

Val Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu

100 105 110

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

115 120 125

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

130 135 140

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

145 150 155 160

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

165 170 175

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

180 185 190

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

195 200 205

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

210 215 220

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

225 230 235 240

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

245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 140
<211> 447
<212> PRT
<213> 人工的序列
<220>
<223> PR001356 HC
<400> 140

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ala Trp Tyr Asp Gly Val Ser Glu Asp Tyr Ala Asp Ser Val
50 55 60
Lys 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
Ala Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

- <210> 141
- <211> 447
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR001357 HC
- <400> 141

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
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 Trp Tyr Asp Gly Ser Asn Lys Asp Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
195				200				205								
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	
210				215				220								
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	
225				230				235				240				
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	
245				250				255								
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	
260				265				270								
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	
275				280				285								
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	
290				295				300								
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	
305				310				315				320				
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	
325				330				335								
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	
340				345				350								
Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	
355				360				365								
Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	
370				375				380								

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

385 390 395 400

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

405 410 415

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

420 425 430

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

435 440 445

<210> 142

<211> 447

<212> PRT

<213> 人工的序列

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<223> PR001358 HC

<400> 142

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

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

20 25 30

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

35 40 45

Ala Ile Met Trp Tyr Asp Gly Ser Asn Thr Asp Tyr Ala Asp Ser Val

50 55 60

Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Thr	Ser	Lys	Asn	Thr	Leu	Phe
65				70				75				80			
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
85				90				95							
Ala	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu
100				105				110							
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu
115				120				125							
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys
130				135				140							
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser
145				150				155				160			
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser
165				170				175							
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
180				185				190							
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
195				200				205							
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His
210				215				220							
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val
225				230				235				240			
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
245				250				255							

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 143
<211> 447
<212> PRT
<213> 人工的序列
<220>
<223> PR001359 HC
<400> 143

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Thr Trp Tyr Asp Gly Ser Asp Lys Asp Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

- <210> 144
- <211> 447
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR001360 HC
- <400> 144

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
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 Trp Tyr Asp Gly Ser Asp Lys Asp Ser Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
195				200				205								
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	
210				215				220								
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	
225				230				235				240				
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	
245				250				255								
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	
260				265				270								
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	
275				280				285								
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	
290				295				300								
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	
305				310				315				320				
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	
325				330				335								
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	
340				345				350								
Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	
355				360				365								
Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	
370				375				380								

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

385 390 395 400

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

405 410 415

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

420 425 430

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

435 440 445

<210> 145

<211> 447

<212> PRT

<213> 人工的序列

 $\langle 220 \rangle$

<223> PR001361 HC

<400> 145

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

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

20 25 30

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

35 40 45

Ala Val Ala Trp Tyr Asp Gly Val Ser Glu Asp Tyr Ala Asp Ser Val

50 55 60

Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Met	Asn	Thr	Leu	Ser
65				70				75				80			
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
85				90				95							
Ala	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu
100				105				110							
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu
115				120				125							
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys
130				135				140							
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser
145				150				155				160			
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser
165				170				175							
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
180				185				190							
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
195				200				205							
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His
210				215				220							
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val
225				230				235				240			
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
245				250				255							

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 146
<211> 447
<212> PRT
<213> 人工的序列
<220>
<223> PR001362 HC
<400> 146

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
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 Trp Tyr Asp Gly Ser Asp Glu Asp 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 Arg Asp Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

- <210> 147
- <211> 447
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR001363 HC
- <400> 147

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

Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
195					200					205						
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	
210					215					220						
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	
225					230					235					240	
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	
245					250					255						
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	
260					265					270						
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	
275					280					285						
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	
290					295					300						
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	
305					310					315					320	
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	
325					330					335						
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	
340					345					350						
Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	
355					360					365						
Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	
370					375					380						

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

385 390 395 400

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

405 410 415

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

420 425 430

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

435 440 445

<210> 148

<211> 447

<212> PRT

<213> 人工的序列

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<223> PR001364 HC, PR002572 HC, PR002573 HC

<400> 148

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser 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 Trp Tyr Asp Gly Ser Asp Lys Asp Tyr Ala Asp Ser Val

50 55 60

Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Thr	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	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu
			100						105					110	
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu
			115						120					125	
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys
			130						135					140	
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser
145					150					155					160
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser
					165					170					175
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
			180							185					190
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
			195							200					205
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His
			210							215					220
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val
225					230					235					240
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
					245					250					255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 149

<211> 447

<212> PRT

<213> 人工的序列

<220>

<223> PR001365 HC

<400> 149

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

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

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 Trp Tyr Asp Gly Ser Asp Lys Asp Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu

100 105 110

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

115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

- <210> 150
- <211> 447
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR001366 HC
- <400> 150

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 Thr Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Lys Trp Tyr Asp Gly Ile Ser Gln Asn Phe 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 Arg Asp Leu Ala Arg Ser Phe Asp Ile Trp Gly Arg Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
195				200				205								
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	
210				215				220								
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	
225				230				235				240				
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	
245				250				255								
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	
260				265				270								
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	
275				280				285								
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	
290				295				300								
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	
305				310				315				320				
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	
325				330				335								
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	
340				345				350								
Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	
355				360				365								
Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	
370				375				380								

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

385 390 395 400

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

405 410 415

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

420 425 430

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

435 440 445

<210> 151

<211> 447

<212> PRT

<213> 人工的序列

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<223> PR001367 HC, PR001417 HC

<400> 151

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 Ser Phe Ser Ser Tyr

20 25 30

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

35 40 45

Ala Val Ile Trp Tyr Asp Gly Gly Asp Glu Asp Tyr Ile Asp Ser Val

50 55 60

Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	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	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu
100								105				110			
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu
115								120				125			
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys
130								135				140			
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser
145				150				155				160			
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser
				165				170				175			
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
180								185				190			
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
195								200				205			
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His
210								215				220			
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val
225				230				235				240			
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
				245				250				255			

Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu
260					265					270					
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys
275					280					285					
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser
290					295					300					
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys
305					310					315					320
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile
325					330					335					
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro
340					345					350					
Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu
355					360					365					
Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn
370					375					380					
Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser
385					390					395					400
Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg
405					410					415					
Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu
420					425					430					
His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	
435					440					445					

<210> 152
<211> 447
<212> PRT
<213> 人工的序列
<220>
<223> PR001368 HC
<400> 152

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
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 Trp Tyr Asp Gly Ser Asp Thr Asp Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220
Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

- <210> 153
- <211> 447
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR001369 HC, PR002580 HC, PR002581 HC
- <400> 153

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

Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
195				200				205								
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	
210				215				220								
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	
225				230				235				240				
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	
245				250				255								
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	
260				265				270								
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	
275				280				285								
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	
290				295				300								
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	
305				310				315				320				
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	
325				330				335								
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	
340				345				350								
Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	
355				360				365								
Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	
370				375				380								

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 435 440 445

<210> 154
<211> 447
<212> PRT
<213> 人工的序列
<220>
<223> PR001371 HC
<400> 154

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

Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Met	Asn	Thr	Leu	Ser
65				70				75				80			
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85				90				95			
Ala	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu
100								105				110			
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu
115								120				125			
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys
130								135				140			
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser
145				150				155				160			
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser
				165				170				175			
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
180								185				190			
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
195								200				205			
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His
210								215				220			
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val
225				230				235				240			
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
				245				250				255			

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 155

<211> 447

<212> PRT

<213> 人工的序列

<220>

<223> PR001415 HC

<400> 155

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

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

20 25 30

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

35 40 45

Ala Ile Met Trp Tyr Asp Gly Ser Asn Lys Asp Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu

100 105 110

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

115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

- <210> 156
- <211> 447
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR001416 HC
- <400> 156

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
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 Trp Tyr Asp Gly Ser Asp Lys Asp Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
195					200					205						
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	
210					215					220						
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	
225					230					235					240	
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	
245					250					255						
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	
260					265					270						
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	
275					280					285						
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	
290					295					300						
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	
305					310					315					320	
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	
325					330					335						
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	
340					345					350						
Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	
355					360					365						
Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	
370					375					380						

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 157
<211> 447
<212> PRT
<213> 人工的序列
<220>
<223> PR001418 HC
<400> 157

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
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 Trp Tyr Asp Gly Ser Asp Lys Asp Tyr Ala Asp Ser Val
50 55 60

Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Thr	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	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu
			100						105					110	
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu
			115						120					125	
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys
			130						135					140	
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser
145					150					155					160
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser
					165					170					175
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
			180							185					190
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
			195							200					205
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His
			210							215					220
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val
225					230					235					240
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
					245					250					255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 158
<211> 447
<212> PRT
<213> 人工的序列
<220>
<223> PR001419 HC
<400> 158

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

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

- <210> 159
- <211> 217
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR000374 LC
- <400> 159

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

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

195 200 205

Thr Lys Ser Phe Asn Arg Gly Glu Cys

210 215

<210> 160

<211> 216

<212> PRT

<213> 人工的序列

<220>

<223> PR001352 LC, PR001371 LC

<400> 160

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Asn Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Pro

85 90 95

Met Tyr Thr Phe Gly Gln 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> 161
- <211> 216
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR001353 LC
- <400> 161

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Ser	Thr	Leu	Ser	Ala	Ser	Val	Gly
1			5						10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Trp
			20					25					30		
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35					40					45		
Tyr	Lys	Ala	Ser	Ser	Leu	Glu	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
			50				55					60			
Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65				70						75				80	
Asp	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Lys	Ser	Tyr	Ser	Pro
				85						90				95	
Met	Tyr	Thr	Phe	Gly	Gln	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> 162

<211> 216

<212> PRT

<213> 人工的序列

<220>

<223> PR001354 LC, PR002564 LC, PR002567 LC

<400> 162

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Asn Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Pro

85 90 95

Met Tyr Thr Phe Gly Gln 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> 163
<211> 216
<212> PRT
<213> 人工的序列
<220>
<223> PR001355 LC
<400> 163

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5						10					15
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Thr	Met	Asn	Asn	Trp
				20						25					30
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
				35						40					45
Tyr	Lys	Ala	Ser	Ser	Leu	Glu	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
				50						55					60
Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65				70						75					80
Asp	Asp	Ser	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asn	Ser	Tyr	Ser	Pro
				85						90					95
Met	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	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> 164

<211> 216

<212> PRT

<213> 人工的序列

<220>

<223> PR001356 LC, PR002570 LC, PR002571 LC

<400> 164

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Asn Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Lys Ser Tyr Ser Pro

85 90 95

Met Tyr Thr Phe Gly Gln 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> 165
- <211> 216
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR001357 LC
- <400> 165

Asp	Ile	Gln	Leu	Thr	Gln	Ser	Pro	Tyr	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Thr	Ile	Asn	Asn	Trp
				20				25					30		
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
				35				40					45		
Tyr	Lys	Ala	Ser	Ser	Leu	Glu	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
				50				55					60		
Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65				70				75					80		
Asp	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Lys	Leu	Tyr	Ser	Pro
				85				90					95		
Met	Tyr	Thr	Phe	Gly	Gln	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> 166

<211> 216

<212> PRT

<213> 人工的序列

<220>

<223> PR001358 LC

<400> 166

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Ser Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Asn Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Lys Ser Tyr Ser Pro

85 90 95

Met Tyr Thr Phe Gly Gln Gly Thr Lys Val Asp 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> 167
- <211> 216
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR001359 LC
- <400> 167

Asp Ile Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Asn Asn Trp
 20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Lys Ser Tyr Ser Pro
 85 90 95
Met Tyr Thr Phe Gly Gln 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> 168

<211> 216

<212> PRT

<213> 人工的序列

<220>

<223> PR001360 LC

<400> 168

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Asn Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Ser Pro

85 90 95

Met Tyr Thr Phe Gly Gln 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> 169
- <211> 216
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR001361 LC, PR001366 LC
- <400> 169

Asp	Ile	Gln	Leu	Thr	Gln	Ser	Pro	Ser	Thr	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Asn	Ser	Trp
			20					25					30		
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35					40					45		
Tyr	Lys	Ala	Ser	Ser	Leu	Glu	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
			50					55					60		
Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65				70						75				80	
Asp	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Lys	Ser	Tyr	Ser	Pro
				85						90				95	
Met	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Asp	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> 170

<211> 216

<212> PRT

<213> 人工的序列

<220>

<223> PR001362 LC, PR001368 LC

<400> 170

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Ser Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Lys Ser Tyr Ser Pro

85 90 95

Met Tyr Thr Phe Gly Gln 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> 171
- <211> 216
- <212> PRT
- <213> 人工的序列
- <220>
- <223> PR001363 LC, PR001367 LC
- <400> 171

Asp	Val	Val	Met	Thr	Gln	Ser	Pro	Ser	Thr	Leu	Ser	Ala	Ser	Val	Gly
1			5						10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Thr	Ile	Asn	Asn	Trp
			20					25					30		
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35					40					45		
Tyr	Lys	Ala	Ser	Ser	Leu	Glu	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
			50					55					60		
Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Asp	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asn	Ser	Tyr	Ser	Pro
					85					90					95
Met	Tyr	Thr	Phe	Gly	Gln	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> 172

<211> 216

<212> PRT

<213> 人工的序列

<220>

<223> PR001364 LC, PR001369 LC, PR001415 LC, PR001416 LC,
PR002574 LC, PR002577 LC, PR002582 LC, PR002585 LC

<400> 172

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Asn Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Pro

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85 90 95
Met Tyr Thr Phe Gly Gln 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> 173
<211> 216
<212> PRT
<213> 人工的序列
<220>
<223> PR001365 LC

<400> 173

Asp Ile Gln Met Thr Gln Ser Pro Tyr Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Asn Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Lys Leu Tyr Ser Pro
85 90 95
Met Tyr Thr Phe Gly Gln 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> 174
<211> 216
<212> PRT
<213> 人工的序列
<220>
<223> PR001370 LC
<400> 174

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

85 90 95
Met Tyr Thr Phe Gly Gln Gly Thr Lys Val Asp 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> 175
<211> 216
<212> PRT
<213> 人工的序列
<220>
<223> PR001417 LC

<400> 175

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Ser Trp
20 25 30

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

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Pro
85 90 95

Met Tyr Thr Phe Gly Gln 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> 176
<211> 216
<212> PRT
<213> 人工的序列
<220>
<223> PR001418 LC
<400> 176

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

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				85					90					95		
Met	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	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> 177

<211> 216

<212> PRT

<213> 人工的序列

 $\langle 220 \rangle$

<223> PR001419 LC

<400> 177

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

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

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Pro
85 90 95

Met Tyr Thr Phe Gly Gln 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

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HCDR2 Chothia, PR002574 HCDR2 Chothia, PR002575 HCDR2
Chothia, PR002576 HCDR2 Chothia
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Trp Tyr Glu Gly Ser Asp
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<211> 6
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<223> PR002567 HCDR2 Chothia, PR002568 HCDR2 Chothia, PR002569
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HCDR2 Chothia, PR002577 HCDR2 Chothia, PR002578 HCDR2

Chothia, PR002579 HCDR2 Chothia

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Trp Tyr Asp Ala Ser Asp

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<210> 180

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<223> PR002570 HCDR2 Chothia

<400> 180

Trp Tyr Glu Gly Val Ser

1 5

<210> 181

<211> 6

<212> PRT

<213> 人工的序列

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<223> PR002571 HCDR2 Chothia

<400> 181

Trp Tyr Asp Ala Val Ser

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<223> PR002582 HCDR2 Chothia, PR002583 HCDR2 Chothia, PR002584
HCDR2 Chothia
<400> 182

Trp Tyr Glu Gly Ser Asn
1 5

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<223> PR002585 HCDR2 Chothia, PR002586 HCDR2 Chothia, PR002587
HCDR2 Chothia
<400> 183

Trp Tyr Asp Ala Ser Asn
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<210> 184

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<212> PRT

<213> 人工的序列

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<223> PR002562 LCDR3 Chothia, PR002565 LCDR3 Chothia, PR002568
LCDR3 Chothia, PR002572 LCDR3 Chothia, PR002575 LCDR3
Chothia, PR002578 LCDR3 Chothia, PR002580 LCDR3 Chothia,
PR002583 LCDR3 Chothia, PR002586

<400> 184

Gln Gln Tyr Gln Ser Tyr Ser Pro Met Tyr Thr

1

5

10

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$\langle 211 \rangle$ 11

<212> PRT

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 $\langle 220 \rangle$

<223> PR002563 LCDR3 Chothia, PR002566 LCDR3 Chothia, PR002569
LCDR3 Chothia, PR002573 LCDR3 Chothia, PR002576 LCDR3
Chothia, PR002579 LCDR3 Chothia, PR002581 LCDR3 Chothia,
PR002584 LCDR3 Chothia, PR002587

<400> 185

Gln Gln Tyr Asn Ala Tyr Ser Pro Met Tyr Thr

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

115

<210> 187

<211> 117

<212> PRT

<213> 人工的序列

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<223> PR002567 VH, PR002568 VH, PR002569 VH

<400> 187

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

115

<210> 188

<211> 117

<212> PRT

<213> 人工的序列

<220>

<223> PR002570 VH

<400> 188

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
Ala Val Ala Trp Tyr Glu Gly Val Ser Glu Asp Tyr Ala Asp Ser Val
 50 55 60
Lys 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
Ala Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu
 100 105 110
Val Thr Val Ser Ser

115

<210> 189

<211> 117

<212> PRT

<213> 人工的序列

<220>

<223> PR002571 VH

<400> 189

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ala Trp Tyr Asp Ala Val Ser Glu Asp Tyr Ala Asp Ser Val
50 55 60
Lys 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
Ala Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110
Val Thr Val Ser Ser

115

<210> 190

<211> 117

<212> PRT

<213> 人工的序列

<220>

<223> PR002574 VH, PR002575 VH, PR002576 VH

<400> 190

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1 5 10 15

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

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu

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Val Thr Val Ser Ser

115

<210> 191

<211> 117

<212> PRT

<213> 人工的序列

<220>

<223> PR002577 VH, PR002578 VH, PR002579 VH

<400> 191

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser 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 Trp Tyr Asp Ala Ser Asp Lys Asp Tyr Ala Asp Ser Val
 50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu
 100 105 110
Val Thr Val Ser Ser

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<210> 192

<211> 117

<212> PRT

<213> 人工的序列

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<223> PR002582 VH, PR002583 VH, PR002584 VH

<400> 192

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 Ser Asn Tyr

20 25 30

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

35 40 45

Ala Ile Met Trp Tyr Glu Gly Ser Asn Thr Asp Tyr Ala Asp Ser Val

50 55 60

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

65 70 75 80

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

85 90 95

Ala Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu

100 105 110

Val Thr Val Ser Ser

115

<210> 193

<211> 117

<212> PRT

<213> 人工的序列

<220>

<223> PR002585 VH, PR002586 VH, PR002587 VH

<400> 193

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

115

<210> 194

<211> 109

<212> PRT

<213> 人工的序列

<220>

<223> PR002562 VL, PR002565 VL, PR002568 VL

<400> 194

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Asn Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Gln Ser Tyr Ser Pro

85 90 95

Met Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

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<210> 195

<211> 109

<212> PRT

<213> 人工的序列

<220>

<223> PR002563 VL, PR002566 VL, PR002569 VL

<400> 195

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

<210> 196

<211> 109

<212> PRT

<213> 人工的序列

<220>

<223> PR002572 VL, PR002575 VL, PR002578 VL, PR002580 VL,
PR002583 VL, PR002586 VL

<400> 196

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

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Asn Trp

20 25 30

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

35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Gln Ser Tyr Ser Pro

85 90 95

Met Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 197

<211> 109

<212> PRT

<213> 人工的序列

<220>

<223> PR002573 VL, PR002576 VL, PR002579 VL, PR002581 VL,
PR002584 VL, PR002587 VL

<400> 197

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

<210> 198

<211> 447

<212> PRT

<213> 人工的序列

<220>

<223> PR002564 HC, PR002565 HC, PR002566 HC

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1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ile Met Trp Tyr Glu Gly Ser Asp Lys Asp Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser

				165				170				175			
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
				180				185				190			
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
				195				200				205			
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His
				210				215				220			
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val
225				230				235				240			
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
				245				250				255			
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu
				260				265				270			
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys
				275				280				285			
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser
290				295				300							
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys
305				310				315				320			
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile
				325				330				335			
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro
				340				345				350			
Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu

355360365

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

370375380

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

385390395400

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

405410415

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

420425430

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

435440445

<210> 199

<211> 447

<212> PRT

<213> 人工的序列

<220>

<223> PR002567 HC, PR002568 HC, PR002569 HC

<400> 199

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg

15105

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

202530

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

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Ala	Ile	Met	Trp	Tyr	Asp	Ala	Ser	Asp	Lys	Asp	Tyr	Ala	Asp	Ser	Val	
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Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Thr	Ser	Lys	Asn	Thr	Leu	Tyr	
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Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
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Ala	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu	
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Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	
115					120					125						
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	
130					135					140						
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	
145					150					155					160	
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	
165					170					175						
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	
180					185					190						
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
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Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	
210					215					220						
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	

225	230	235	240
Phe	Leu	Phe	Pro
Pro	Lys	Pro	Lys
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Ile	Ser	Arg	Thr
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Pro	Glu	Val	Thr
Cys	Val	Val	Val
Asp	Val	Ser	His
Glu	Asp	Pro	Glu
260	265	270	
Val	Lys	Phe	Asn
Trp	Tyr	Val	Asp
Gly	Val	Glu	Val
His	Asn	Ala	Lys
275	280	285	
Thr	Lys	Pro	Arg
Glu	Glu	Gln	Tyr
Asn	Ser	Thr	Tyr
Arg	Val	Val	Ser
290	295	300	
Val	Leu	Thr	Val
Leu	His	Gln	Asp
Trp	Leu	Asn	Gly
Lys	Glu	Tyr	Lys
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Cys	Lys	Val	Ser
Asn	Lys	Ala	Leu
Pro	Ala	Pro	Ile
Glu	Lys	Thr	Ile
325	330	335	
Ser	Lys	Ala	Lys
Gly	Gln	Pro	Arg
Glu	Pro	Gln	Val
Tyr	Thr	Leu	Pro
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Pro	Ser	Arg	Glu
Glu	Met	Thr	Lys
Asn	Gln	Val	Ser
Leu	Thr	Cys	Leu
355	360	365	
Val	Lys	Gly	Phe
Tyr	Pro	Ser	Asp
Ile	Ala	Val	Glu
Trp	Glu	Ser	Asn
370	375	380	
Gly	Gln	Pro	Glu
Asn	Asn	Tyr	Lys
Thr	Thr	Pro	Pro
Val	Leu	Asp	Ser
385	390	395	400
Asp	Gly	Ser	Phe
Phe	Leu	Tyr	Ser
Lys	Leu	Thr	Val
Asp	Lys	Ser	Arg
405	410	415	
Trp	Gln	Gln	Gly
Asn	Val	Phe	Ser
Cys	Ser	Val	Met
His	Glu	Ala	Leu

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His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys		
435					440					445						
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<211>	447															
<212>	PRT															
<213>	人工的序列															
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<223>	PR002570 HC															
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Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
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Ala	Val	Ala	Trp	Tyr	Glu	Gly	Val	Ser	Glu	Asp	Tyr	Ala	Asp	Ser	Val	
50						55				60						
Lys	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		
Ala	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu	

			100						105						110					
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu					
			115						120						125					
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys					
			130						135						140					
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser					
			145						150						155			160		
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser					
						165						170						175		
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser					
			180						185						190					
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn					
			195						200						205					
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His					
			210						215						220					
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val					
			225						230						235			240		
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr					
						245						250						255		
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu					
			260						265						270					
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys					
			275						280						285					
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser					

290	295	300
Val Leu Thr	Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys	
305	310	315
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile		320
	325	330
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro		335
	340	345
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu		350
	355	360
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn		365
	370	375
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser		380
385	390	395
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg		400
	405	410
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu		415
	420	425
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys		430
	435	440
		445

- <210> 201
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- <212> PRT
- <213> 人工的序列

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<223> PR002571 HC

<400> 201

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 Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ala Trp Tyr Asp Ala Val Ser Glu Asp Tyr Ala Asp Ser Val
50 55 60
Lys 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
Ala Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser

				165				170				175			
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
				180				185				190			
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
				195				200				205			
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His
				210				215				220			
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val
225				230				235				240			
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
				245				250				255			
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu
				260				265				270			
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys
				275				280				285			
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser
290				295				300							
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys
305				310				315				320			
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile
				325				330				335			
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro
				340				345				350			
Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu

355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

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<223> PR002574 HC, PR002575 HC, PR002576 HC
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Glu Val Gln Leu Leu 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 Ser 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	Trp	Tyr	Glu	Gly	Ser	Asp	Lys	Asp	Tyr	Ala	Asp	Ser	Val				
50					55					60									
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Thr	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	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu				
100					105					110									
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu				
115					120					125									
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys				
130					135					140									
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser				
145					150					155					160				
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser				
165					170					175									
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser				
180					185					190									
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn				
195					200					205									
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His				
210					215					220									
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val				

225	230	235	240
Phe	Leu	Phe	Pro
Pro	Lys	Pro	Lys
Asp	Thr	Leu	Met
Ile	Ser	Arg	Thr
245	250	255	
Pro	Glu	Val	Thr
Cys	Val	Val	Val
Asp	Val	Ser	His
Glu	Asp	Pro	Glu
260	265	270	
Val	Lys	Phe	Asn
Trp	Tyr	Val	Asp
Gly	Val	Glu	Val
His	Asn	Ala	Lys
275	280	285	
Thr	Lys	Pro	Arg
Glu	Glu	Gln	Tyr
Asn	Ser	Thr	Tyr
Arg	Val	Val	Ser
290	295	300	
Val	Leu	Thr	Val
Leu	His	Gln	Asp
Trp	Leu	Asn	Gly
Lys	Glu	Tyr	Lys
305	310	315	320
Cys	Lys	Val	Ser
Asn	Lys	Ala	Leu
Pro	Ala	Pro	Ile
Glu	Lys	Thr	Ile
325	330	335	
Ser	Lys	Ala	Lys
Gly	Gln	Pro	Arg
Glu	Pro	Gln	Val
Tyr	Thr	Leu	Pro
340	345	350	
Pro	Ser	Arg	Glu
Glu	Met	Thr	Lys
Asn	Gln	Val	Ser
Leu	Thr	Cys	Leu
355	360	365	
Val	Lys	Gly	Phe
Tyr	Pro	Ser	Asp
Ile	Ala	Val	Glu
Trp	Glu	Ser	Asn
370	375	380	
Gly	Gln	Pro	Glu
Asn	Asn	Tyr	Lys
Thr	Thr	Pro	Pro
Val	Leu	Asp	Ser
385	390	395	400
Asp	Gly	Ser	Phe
Phe	Leu	Tyr	Ser
Lys	Leu	Thr	Val
Asp	Lys	Ser	Arg
405	410	415	
Trp	Gln	Gln	Gly
Asn	Val	Phe	Ser
Cys	Ser	Val	Met
His	Glu	Ala	Leu

420

425

430

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

435

440

445

<210> 203

<211> 447

<212> PRT

<213> 人工的序列

<220>

<223> PR002577 HC, PR002578 HC, PR002579 HC

<400> 203

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

1

5

10

15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser 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 Trp Tyr Asp Ala Ser Asp Lys Asp Tyr Ala Asp Ser Val

50

55

60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr 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 Arg Glu Gln Ala Arg Ser Phe Asp Leu Trp Gly Arg Gly Thr Leu

			100						105						110				
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu				
			115						120						125				
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys				
			130						135						140				
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser				
			145						150						155			160	
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser				
						165						170						175	
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser				
			180						185						190				
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn				
			195						200						205				
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His				
			210						215						220				
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val				
			225						230						235			240	
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr				
						245						250						255	
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu				
			260						265						270				
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys				
			275						280						285				
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser				

290	295	300
Val Leu Thr	Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys	
305	310	315
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile		320
	325	330
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro		335
	340	345
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu		350
	355	360
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn		365
	370	375
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser		380
385	390	395
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg		400
	405	410
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu		415
	420	425
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys		430
	435	440
		445

- <210> 204
- <211> 447
- <212> PRT
- <213> 人工的序列

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<223> PR002582 HC, PR002583 HC, PR002584 HC

<400> 204

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

				165				170				175			
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
				180				185				190			
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
				195				200				205			
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His
				210				215				220			
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val
225				230				235				240			
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
				245				250				255			
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu
				260				265				270			
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys
				275				280				285			
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser
290				295				300							
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys
305				310				315				320			
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile
				325				330				335			
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro
				340				345				350			
Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu

355360365

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

370375380

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

385390395400

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

405410415

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

420425430

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

435440445

<210> 205

<211> 447

<212> PRT

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<220>

<223> PR002585 HC, PR002586 HC, PR002587 HC

<400> 205

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

151051

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

202530

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

35					40					45						
Ala	Ile	Met	Trp	Tyr	Asp	Ala	Ser	Asn	Thr	Asp	Tyr	Ala	Asp	Ser	Val	
50					55					60						
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Thr	Ser	Lys	Asn	Thr	Leu	Phe	
65					70					75					80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
85					90					95						
Ala	Arg	Glu	Gln	Ala	Arg	Ser	Phe	Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu	
100					105					110						
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	
115					120					125						
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	
130					135					140						
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	
145					150					155					160	
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	
165					170					175						
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	
180					185					190						
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
195					200					205						
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	
210					215					220						
Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	

225						230						235						240
Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr			
					245						250						255	
Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu			
					260						265						270	
Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys			
					275						280						285	
Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser			
					290						295						300	
Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys			
					305						310						315	320
Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile			
					325						330						335	
Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro			
					340						345						350	
Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu			
					355						360						365	
Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn			
					370						375						380	
Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser			
					385						390						395	400
Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg			
					405						410						415	
Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu			

420425430

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

435440445

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<212> PRT

<213> 人工的序列

<220>

<223> PR002562 LC, PR002565 LC, PR002568 LC

<400> 206

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

15105

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Asn Trp

302520

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

454035

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly

605550

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

80757065

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Gln Ser Tyr Ser Pro

959085

Met Tyr Thr Phe Gly Gln 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> 207
<211> 216
<212> PRT
<213> 人工的序列
<220>
<223> PR002563 LC, PR002566 LC, PR002569 LC
<400> 207

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
第 220 頁，共 225 頁(序列表)

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Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Thr	Ile	Asn	Asn	Trp				
				20					25					30					
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile				
				35					40					45					
Tyr	Lys	Ala	Ser	Ser	Leu	Glu	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly				
				50					55					60					
Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro				
65				70				75				80							
Asp	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asn	Ala	Tyr	Ser	Pro				
				85					90					95					
Met	Tyr	Thr	Phe	Gly	Gln	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											
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PR002583 LC, PR002586 LC															
<400> 208															
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Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Thr	Ile	Asn	Asn	Trp
20				25				30							
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
35				40				45							
Tyr	Lys	Ala	Ser	Ser	Leu	Glu	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
50				55				60							
Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65				70				75				80			
Asp	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Gln	Ser	Tyr	Ser	Pro
85				90				95							

Met Tyr Thr Phe Gly Gln 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

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<213> 人工的序列
<220>
<223> PR002573 LC, PR002576 LC, PR002579 LC, PR002581 LC,
PR002584 LC, PR002587 LC

<400> 209

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1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Asn Trp
20 25 30

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

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ala Tyr Ser Pro
85 90 95

Met Tyr Thr Phe Gly Gln 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										

【發明申請專利範圍】

【請求項1】 一種標靶ROR1的抗體或其抗原結合片段，其特徵在於，其包含VL和VH；其中，

所述VL包含的VL CDR1、VL CDR2和VL CDR3的胺基酸序列分別如SEQ ID NO: 69、78和86所示；
所述VH包含的VH CDR1、VH CDR2和VH CDR3的胺基酸序列分別如SEQ ID NO: 12、34和53所示；或

所述VL包含的VL CDR1、VL CDR2和VL CDR3的胺基酸序列分別如SEQ ID NO: 69、78和84所示；
所述VH包含的VH CDR1、VH CDR2和VH CDR3的胺基酸序列分別如SEQ ID NO: 12、33和53所示；或

所述VL包含的VL CDR1、VL CDR2和VL CDR3的胺基酸序列分別如SEQ ID NO: 69、78和184所示；
所述VH包含的VH CDR1、VH CDR2和VH CDR3的胺基酸序列分別如SEQ ID NO: 12、33和53所示；或

所述VL包含的VL CDR1、VL CDR2和VL CDR3的胺基酸序列分別如SEQ ID NO: 69、78和185所示；
所述VH包含的VH CDR1、VH CDR2和VH CDR3的胺基酸序列分別如SEQ ID NO: 12、33和53所示；或

所述VL包含的VL CDR1、VL CDR2和VL CDR3的胺基酸序列分別如SEQ ID NO: 69、78和84所示；
所述VH包含的VH CDR1、VH CDR2和VH CDR3的胺基酸序列分別如SEQ ID NO: 12、178和53所示；
或

所述VL包含的VL CDR1、VL CDR2和VL CDR3的胺基酸序列分別如SEQ ID NO: 69、78和184所示；
所述VH包含的VH CDR1、VH CDR2和VH CDR3的胺基酸序列分別如SEQ ID NO: 12、178和53所示；
或

所述VL包含的VL CDR1、VL CDR2和VL CDR3的胺基酸序列分別如SEQ ID NO: 69、78和185所示；
所述VH包含的VH CDR1、VH CDR2和VH CDR3的胺基酸序列分別如SEQ ID NO: 12、178和53所示；
或

所述VL包含的VL CDR1、VL CDR2和VL CDR3的胺基酸序列分別如SEQ ID NO: 69、78和84所示；
所述VH包含的VH CDR1、VH CDR2和VH CDR3的胺基酸序列分別如SEQ ID NO: 12、179和53所示；
或

所述VL包含的VL CDR1、VL CDR2和VL CDR3的胺基酸序列分別如SEQ ID NO: 69、78和184所示；
所述VH包含的VH CDR1、VH CDR2和VH CDR3的胺基酸序列分別如SEQ ID NO: 12、179和53所示；
或

所述VL包含的VL CDR1、VL CDR2和VL CDR3的胺基酸序列分別如SEQ ID NO: 69、78和185所示；
所述VH包含的VH CDR1、VH CDR2和VH CDR3的

胺基酸序列分別如SEQ ID NO: 12、179和53所示；
或

所述VL包含的VL CDR1、VL CDR2和VL CDR3
的胺基酸序列分別如SEQ ID NO: 70、78和85所示；
所述VH包含的VH CDR1、VH CDR2和VH CDR3的
胺基酸序列分別如SEQ ID NO: 12、32和53所示。

【請求項2】 如請求項1所述的標靶ROR1的抗體或其抗原結合片段，其特徵在於，

所述VL包括如SEQ ID NO: 122所示的胺基酸序列；所述VH包括如SEQ ID NO: 98所示的胺基酸序列；或

所述VL包括如SEQ ID NO: 119所示的胺基酸序列；所述VH包括如SEQ ID NO: 95所示的胺基酸序列；或

所述VL包括如SEQ ID NO: 194所示的胺基酸序列；所述VH包括如SEQ ID NO: 95所示的胺基酸序列；或

所述VL包括如SEQ ID NO: 195所示的胺基酸序列；所述VH包括如SEQ ID NO: 95所示的胺基酸序列；或

所述VL包括如SEQ ID NO: 119所示的胺基酸序列；所述VH包括如SEQ ID NO: 186所示的胺基酸序列；或

所述VL包括如SEQ ID NO: 194所示的胺基酸序列；所述VH包括如SEQ ID NO: 186所示的胺基酸序列；或

所述VL包括如SEQ ID NO: 195所示的胺基酸序列；所述VH包括如SEQ ID NO: 186所示的胺基酸序列；或

所述VL包括如SEQ ID NO: 119所示的胺基酸序列；所述VH包括如SEQ ID NO: 187所示的胺基酸序列；或

所述VL包括如SEQ ID NO: 194所示的胺基酸序列；所述VH包括如SEQ ID NO: 187所示的胺基酸序列；或

所述VL包括如SEQ ID NO: 195所示的胺基酸序列；所述VH包括如SEQ ID NO: 187所示的胺基酸序列；或

所述VL包括如SEQ ID NO: 133所示的胺基酸序列；所述VH包括如SEQ ID NO: 114所示的胺基酸序列；或

所述VL包括如SEQ ID NO: 118所示的胺基酸序列；所述VH包括如SEQ ID NO: 94所示的胺基酸序列。

【請求項3】 如請求項2所述的標靶ROR1的抗體或其抗原結合片段，其還包括重鏈恆定區和輕鏈恆定區；

所述重鏈恆定區選自hIgG1、hIgG2、hIgG3或hIgG4，所述輕鏈恆定區選自κ鏈或者λ鏈。

第4頁，共8頁(發明申請專利範圍)

【請求項4】 如請求項3所述的標靶ROR1的抗體或其抗原結合片段，其為全長抗體、Fab、Fab'、F(ab')₂、Fv、scFv、雙特異性抗體、多特異性抗體、重鏈抗體或單域抗體，或由上述抗體製得的單株抗體或多株抗體。

【請求項5】 如請求項4所述的標靶ROR1的抗體或其抗原結合片段，其為全長抗體，所述全長抗體包括重鏈和輕鏈；其中，

所述重鏈包括如SEQ ID NO: 141所示的胺基酸序列；所述輕鏈包括如SEQ ID NO: 165所示的胺基酸序列；或

所述重鏈包括如SEQ ID NO: 138所示的胺基酸序列；所述輕鏈包括如SEQ ID NO: 162所示的胺基酸序列；或

所述重鏈包括如SEQ ID NO: 138所示的胺基酸序列；所述輕鏈包括如SEQ ID NO: 206所示的胺基酸序列；或

所述重鏈包括如SEQ ID NO: 138所示的胺基酸序列；所述輕鏈包括如SEQ ID NO: 207所示的胺基酸序列；或

所述重鏈包括如SEQ ID NO: 198所示的胺基酸序列；所述輕鏈包括如SEQ ID NO: 162所示的胺基酸序列；或

所述重鏈包括如SEQ ID NO: 198所示的胺基酸序列；所述輕鏈包括如SEQ ID NO: 206所示的胺基酸序列；或

所述重鏈包括如SEQ ID NO: 198所示的胺基酸序列；所述輕鏈包括如SEQ ID NO: 207所示的胺基酸序列；或

所述重鏈包括如SEQ ID NO: 199所示的胺基酸序列；所述輕鏈包括如SEQ ID NO: 162所示的胺基酸序列；或

所述重鏈包括如SEQ ID NO: 199所示的胺基酸序列；所述輕鏈包括如SEQ ID NO: 206所示的胺基酸序列；或

所述重鏈包括如SEQ ID NO: 199所示的胺基酸序列；所述輕鏈包括如SEQ ID NO: 207所示的胺基酸序列；或

所述重鏈包括如SEQ ID NO: 157所示的胺基酸序列；所述輕鏈包括如SEQ ID NO: 176所示的胺基酸序列；或

所述重鏈包括如SEQ ID NO: 137所示的胺基酸序列；所述輕鏈包括如SEQ ID NO: 161所示的胺基酸序列。

【請求項6】 一種分離的核酸，其編碼如請求項1~5中任一項所述的標靶ROR1的抗體或其抗原結合片段。

- 【請求項7】 一種重組表現載體，其包含如請求項6所述的分離的核酸。
- 【請求項8】 一種轉形體，其包含如請求項7所述的重組表現載體。
- 【請求項9】 一種嵌合抗原受體，其包含如請求項1~5中任一項所述的標靶ROR1的抗體或其抗原結合片段。
- 【請求項10】 一種基因修飾的細胞，其特徵在於，其包含如請求項9所述的嵌合抗原受體。
- 【請求項11】 如請求項10所述的細胞，其特徵在於，所述細胞為T細胞或NK細胞。
- 【請求項12】 一種標靶ROR1的抗體或其抗原結合片段的製備方法，所述製備方法包括以下步驟：培養如請求項8中所述的轉形體，從培養物中獲得標靶ROR1的抗體或其抗原結合片段。
- 【請求項13】 一種抗體藥物偶聯物，其包含細胞毒性劑，以及如請求項1~5中任一項所述的標靶ROR1的抗體或其抗原結合片段。
- 【請求項14】 一種藥物組成物，其包含如請求項1~5中任一項所述的標靶ROR1的抗體或其抗原結合片段、或如請求項13所述的抗體藥物偶聯物。
- 【請求項15】 如請求項1~5中任一項所述的標靶ROR1的抗體或其抗原結合片段、如請求項9所述的嵌合抗原受體、如請求項10或11所述的基因修飾的細胞、如請求項13中所述的抗體藥物偶聯物或如請求項14中所述的藥物組成物在製備治療或預防癌症的藥物中的應用。

- 【請求項16】 如請求項15所述的應用，其特徵在於，所述癌症為結腸癌、肺癌、前列腺癌、肝癌、腎癌、胰腺癌、乳腺癌、子宮頸癌、卵巢癌、甲狀腺腫瘤、慢性淋巴細胞白血病、急性淋巴細胞白血病、急性骨髓白血病、非何杰金氏淋巴瘤、慢性骨髓性淋巴細胞白血病、多發性骨髓瘤、黑色素瘤、結腸直腸癌、成膠質細胞瘤或子宮內膜癌。
- 【請求項17】 一種套組，其包括如請求項1-5任一項所述的抗體或其抗原結合片段、如請求項9所述的嵌合抗原受體、如請求項10或11所述的基因修飾的細胞、或請求項13中所述的抗體藥物偶聯物或請求項14所述的藥物組成物。
- 【請求項18】 如請求項17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(ii)使用說明。
- 【請求項19】 一種檢測樣品中ROR1的方法，其包括使用如請求項1~5任一項所述的標靶ROR1的抗體或其抗原結合片段進行檢測。
- 【請求項20】 一種套裝藥盒，其包含藥盒A和藥盒B，所述的藥盒A包含如請求項1~5任一項所述的標靶ROR1的抗體或其抗原結合片段、如請求項9所述的嵌合抗原受體、如請求項10或11所述的基因修飾的細胞、請求項13所述的抗體藥物偶聯物或如請求項14所述的藥物組成物，所述的藥盒B為大分子藥物或小分子藥物。

【發明圖式】

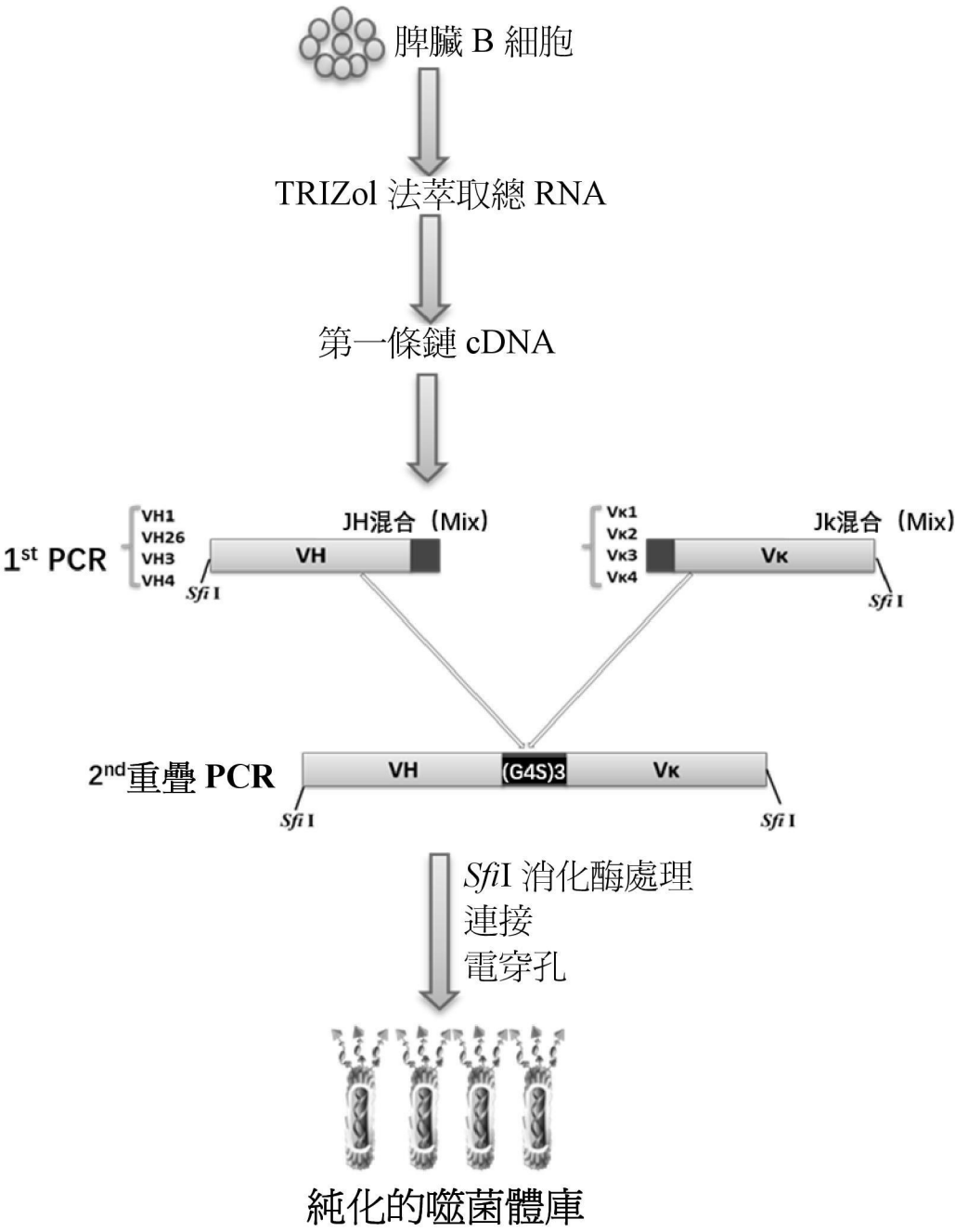


圖 1

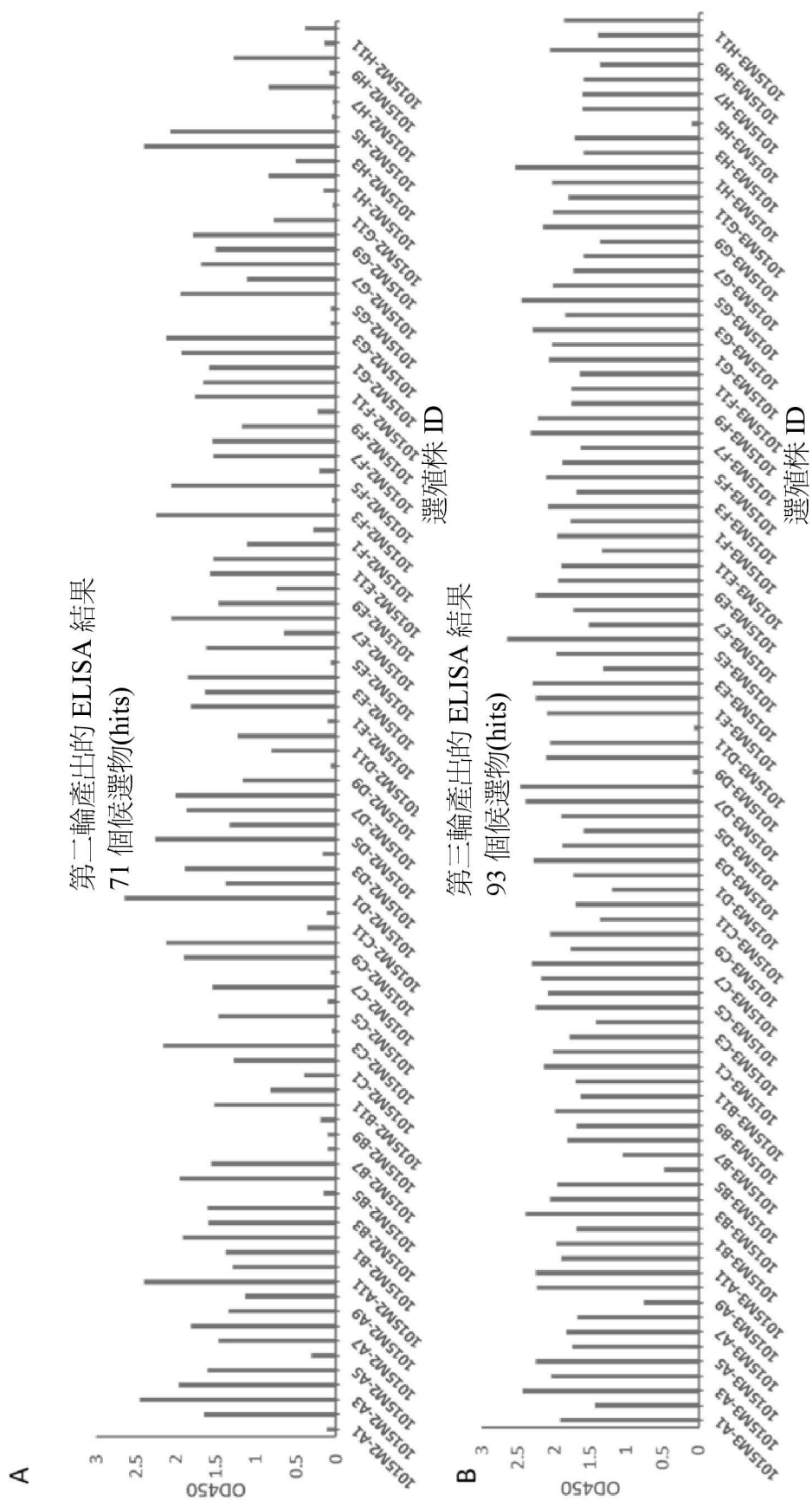
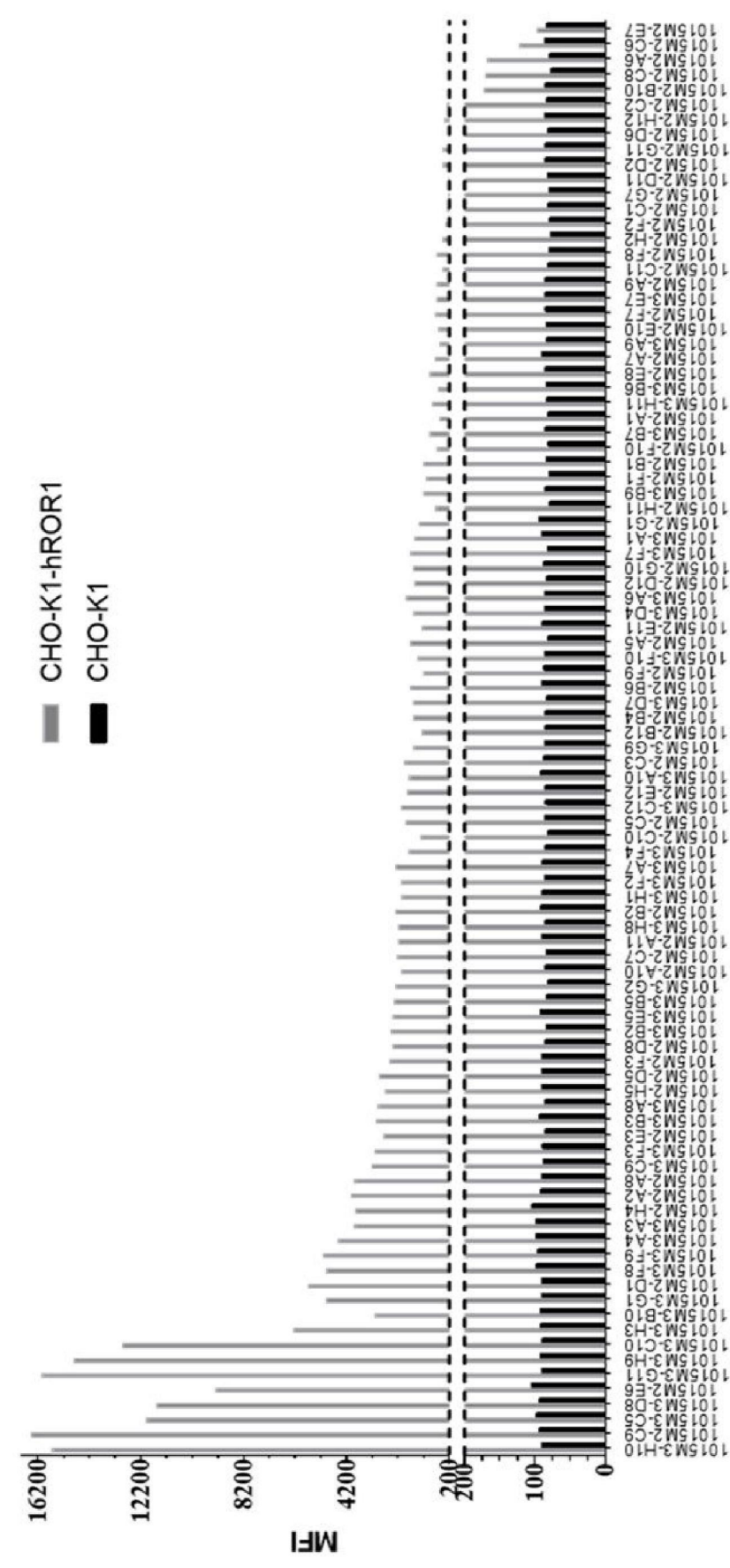


圖 2

A

各個候選物(hit)與 CHO-K1-hROR1 的 FACS 結合



選殖株 ID

圖 3 (接下圖)

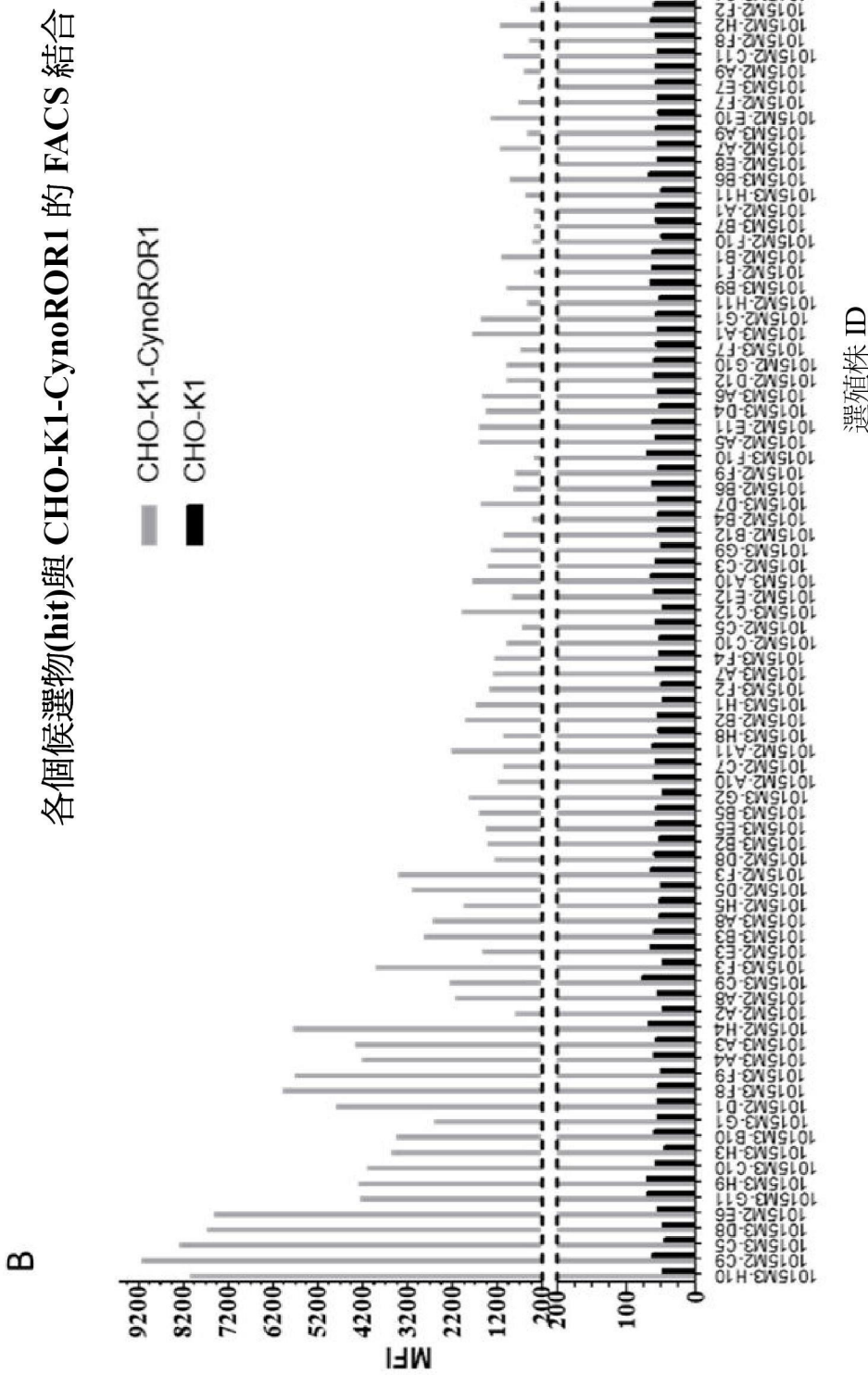


圖 3

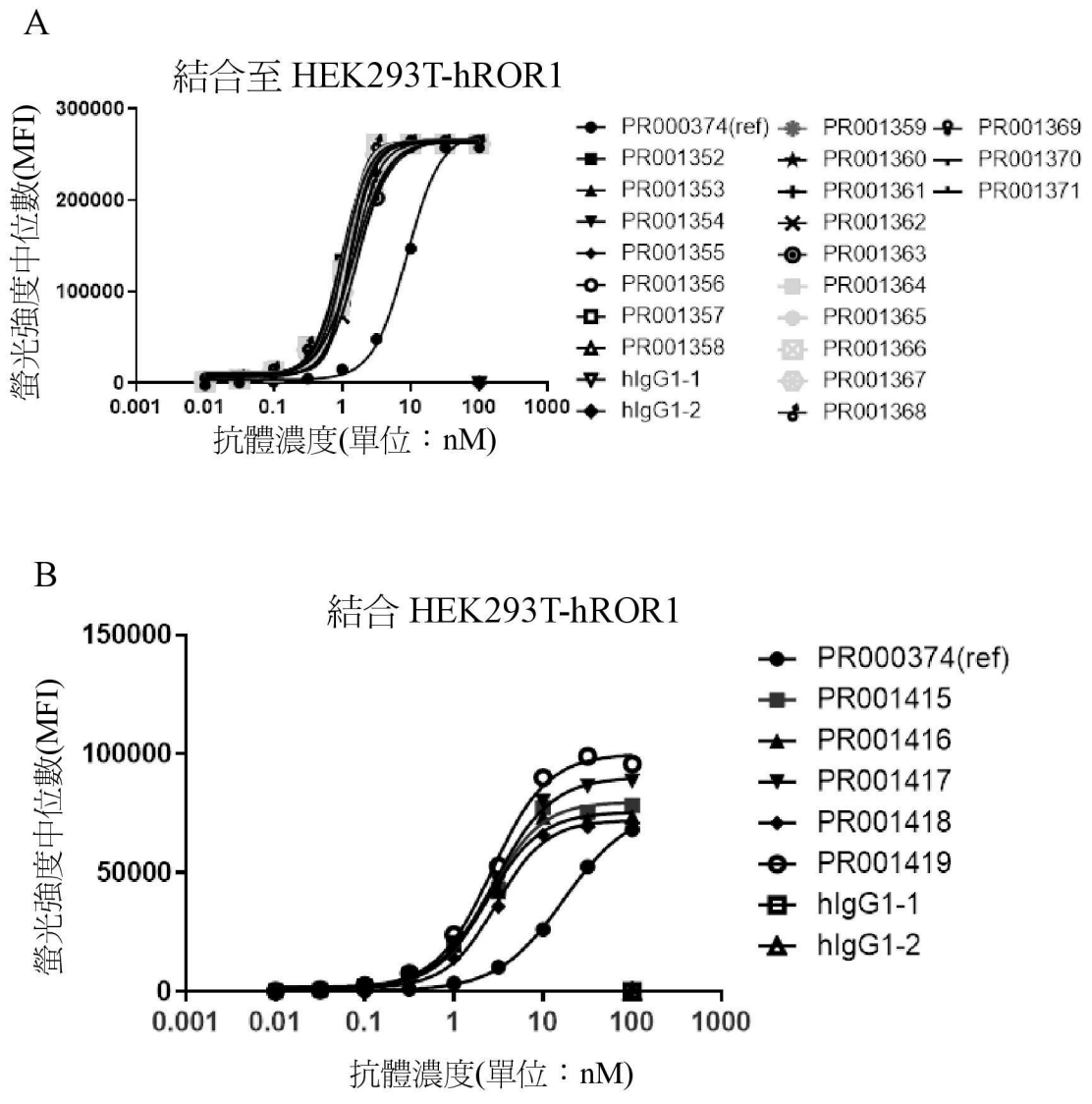


圖 4

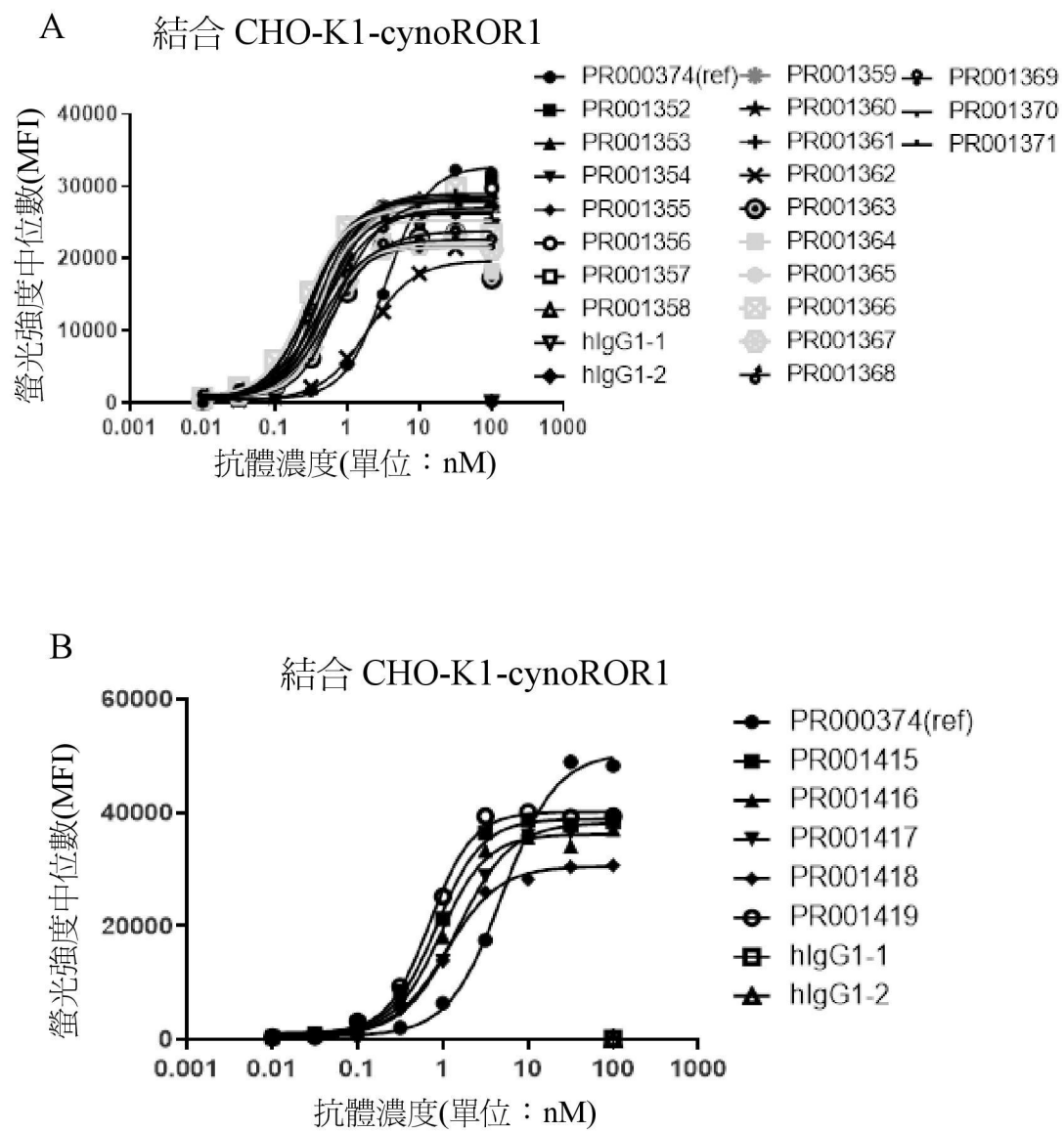


圖 5

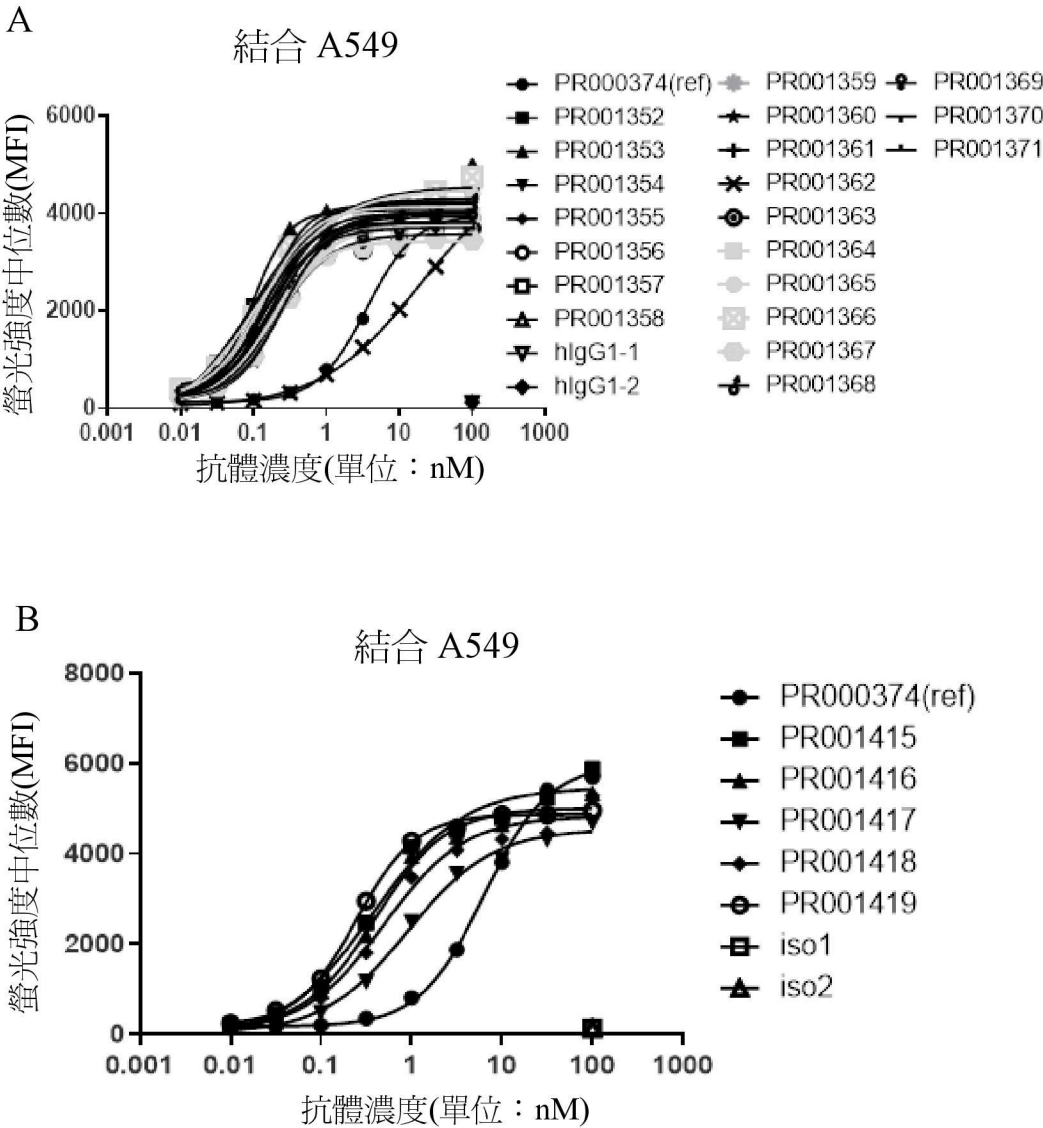


圖 6

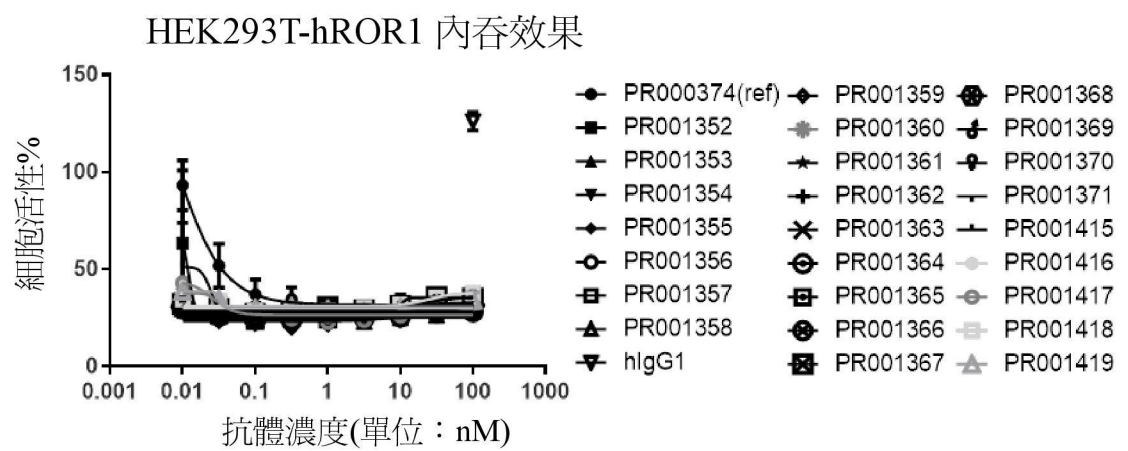


圖 7

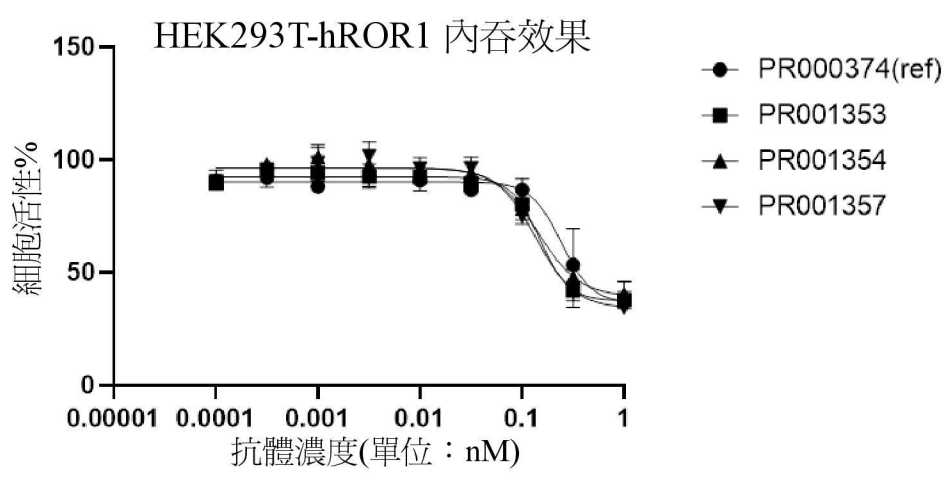


圖 8

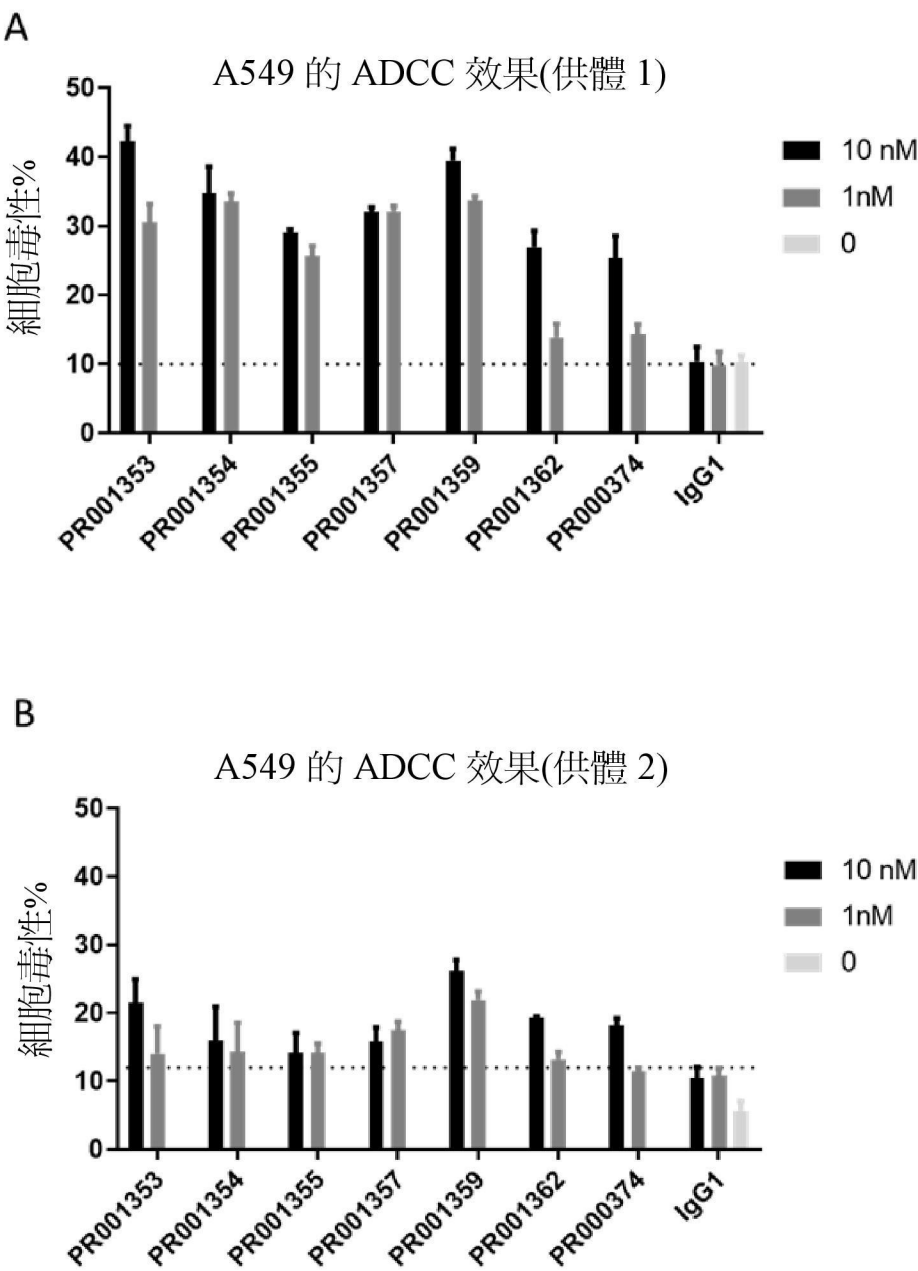


圖 9

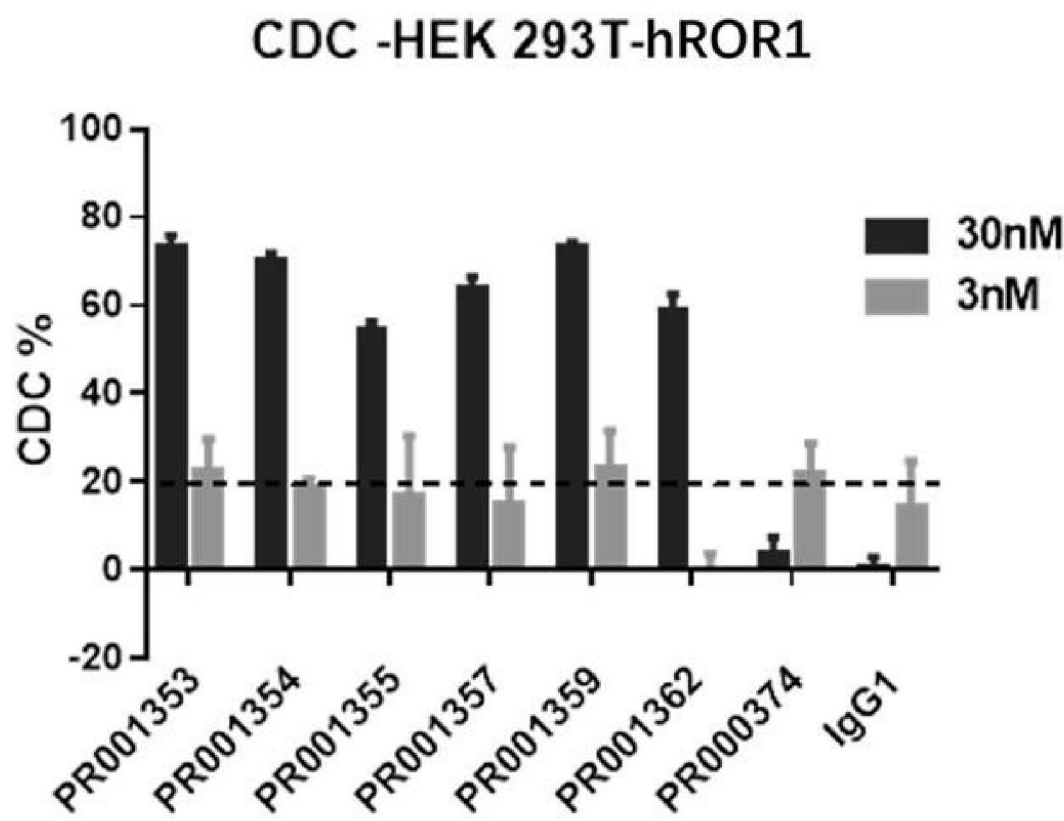


圖 10

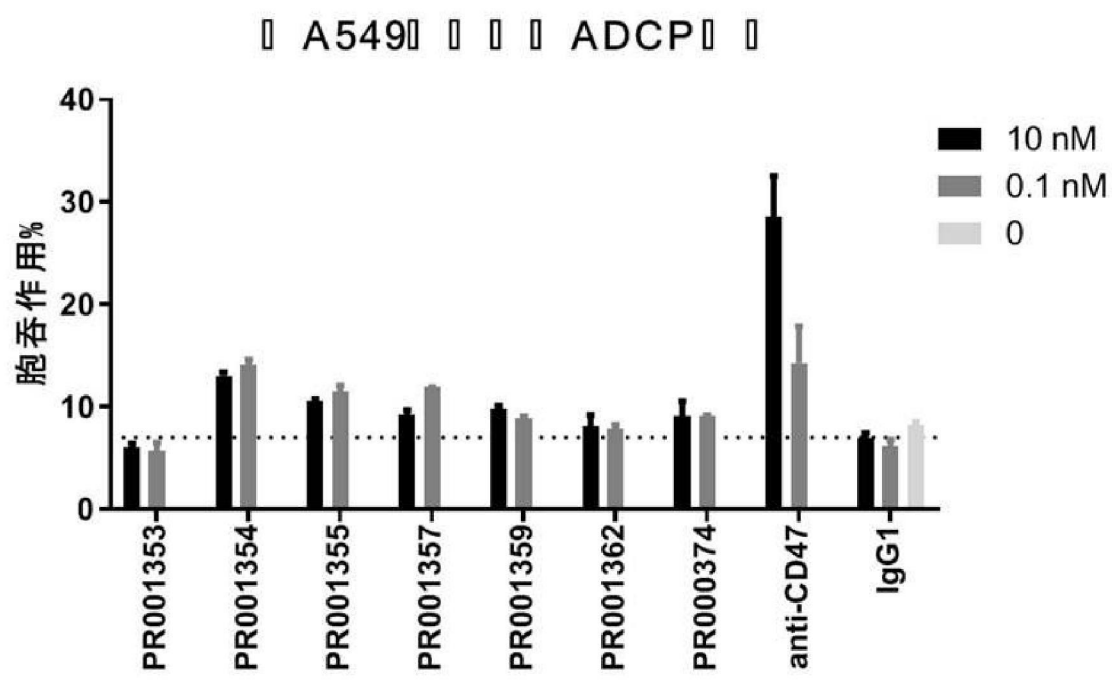


圖 11