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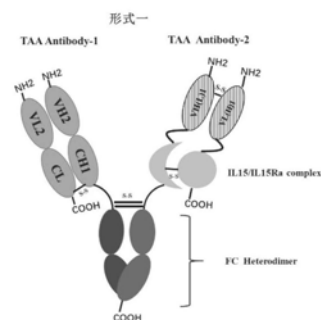
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(54) 发明名称

一种双特异抗体及其应用

(57) 摘要

本发明提供一种双特异抗体及其应用,本发明的双特异性抗体与HER2蛋白的亲和力高,本发明的双特异性抗体对肿瘤细胞的增殖抑制作用强。



1. 一种双特异抗体分子,包括但不限于这种形式:

{[TAA]1,[TAA]2,[IL15/IL15Ra],[FC异源二聚体]},

每种形式同时包含:

[TAA]1:结合一个抗原的抗体、抗体或多肽片段;

[TAA]2:结合另一个抗原或同一抗原不同表位的抗体、抗体或多肽片段;

[IL15/IL15Ra]:IL15及其能结合IL15Ra的突变,截短及各种衍生物;

IL15Ra及其能结合IL15的突变,截短及各种衍生物;

这两者形成的复合物;

[FC异源二聚体]:FC形成的异源二聚体。

2. 如权利要求1中所述的双特异抗体分子,其特征在于:

包含IL15/IL15Ra复合物,IL15/IL15Ra复合物包括但不限于1) IL15及其能结合IL15Ra的突变,截短及各种衍生物;2) IL15Ra及其能结合IL15的突变,截短及各种衍生物;

包括但不限于下表所示突变,计数方式根据SEQ ID No.1所示IL15第一个氨基酸开始算为第1位;SEQ ID No.3所示IL15Ra第一个氨基酸开始算为第1位:

组合	IL15	IL15Ra
1	wt	D96
2	wt	D96/P97
3	wt	D96/P97/A98
4	E87C	D96/C97
5	E87C	D96/P97/C98
6	E87C	D96/C97/A98
7	V49C	S40C
8	L52C	S40C
9	E89C	K34C
10	Q48C	G38C
11	E53C	L42C
12	C42S	A37C
13	L45C	G38C
14	L45C	A37C

同时包括但不限于下表所示IL15相关各种突变,计数方式根据SEQ ID No.1所示IL15第一个氨基酸开始算为第1位:

组合	IL15突变
1	N1D
2	N4D
3	D8N
4	D30N
5	D61N
6	E64Q
7	N65D

8	Q108E
9	N1D/D61N
10	N1D/E64Q
11	N4D/D61N
12	N4D/E64Q
13	D8N/D61N
14	D8N/E64Q
15	D61N/E64Q
16	E64Q/Q108E
17	N1D/N4D/D8N
18	D61N/E64Q/N65D
19	N1D/D61N/E64Q/Q108E
20	N4D/D61N/E64Q/Q108E

3. 如权利要求1中所述的双特异抗体分子,其特征在于:

与IL15或IL15Ra融合的是针对抗原的抗体可变区VL1或VH1,包括但不限于以下突变,根据EU计数:

	二硫键改造位点	
	VH	VL
组合1	37C	95C
组合2	44C	100C
组合3	44C	105C
组合4	45C	87C
组合5	100C	50C
组合6	100bC	49C
组合7	98C	46C
组合8	101C	46C
组合9	105C	43C
组合10	106C	57C

其中,VL1与VH1之间可有一对或多对二硫键。

4. 权利要求1中所述的双特异抗体分子,其特征在于:

包含抗体的FC段,是FC异源二聚体形式,FC异源二聚体包括但不限于以下突变的组合,根据EU计数,

组合	FC	异源二聚体突变(Eu numbering)
1	FC-A链	T366Y
	FC-B链	Y407T
2	FC-A链	T366W
	FC-B链	T366S/L368A/Y407V
3	FC-A链	S354C/T366W
	FC-B链	Y349C/T366S/L368A/Y407V
4	FC-A链	S364H/F405A
	FC-B链	Y349T/T394F
5	FC-A链	T350V/L351Y/F405A/Y407V
	FC-B链	T350V/T366L/K392L/T394W
6	FC-A链	K392D/K409D
	FC-B链	E356K/D399K
7	FC-A链	D221E/P228E/L368E
	FC-B链	D221R/P228R/K409R
8	FC-A链	K360E/K409W
	FC-B链	Q347R/D399V/F405T
9	FC-A链	K360E/K409W/Y349C
	FC-B链	Q347R/D399V/F405T/S354C
10	FC-A链	K370E/K409W
	FC-B链	E357N/D399V/F405T
11	FC-A链	F405L
	FC-B链	K409R
12	FC-A链	K360D/D399M/Y407A
	FC-B链	E345R/Q347R/T366V/K409V
13	FC-A链	Y349S/K370Y/T366M/K409V
	FC-B链	E356G/E357D/S364Q/Y407A
14	FC-A链	L351D/L368E
	FC-B链	L351K/T366K
15	FC-A链	GQPRPEVHLLPPSREMTKNQVSLTCLARGFYPKDI AVEWESNGQPENNYKTPSRQE PSQGTTFFAVTSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKTISL
	FC-B链	GQPREPQVYTLPPPSEELALNELVTLTCLVKGFP SDIAVEWLQGSQELPREKYL TWAPV LDS DGSFFLYSILRVAAEDWKKGDTFSCSV MHEALHNHYTQKSLDR
16	FC-A链	L368D/K370S
	FC-B链	E357Q/S364K
17	FC-A链	S354C/T366W/ K409A
	FC-B链	Y349C/T366S/L368A/Y407V/ F405K
18	FC-A链	S354C/T366W/ F405K/K360E/Q347E
	FC-B链	Y349C/T366S/L368A/Y407V/ Q347R/T394W
19	FC-A链	T366W/ K409A
	FC-B链	T366S/ L368G/Y407A/F405K
20	FC-A链	knobs (T366W/ F405K)
	FC-B链	holes (T366S/ L368G/Y407A/K409A)
21	FC-A链	Q347A/S364K/T366V/K370T/K392Y/F405S/Y407V/K409W/T411N
	FC-B链	Q347E/Y349A/L351F/S364T/T366V//K370T/T394D/V397L/D399E/D401Q/F405A/Y407S/K409R/T411R
22	FC-A链	K274Q/N276K/Y300F/A339T /Q347A/S364K/T366V/K370T/ N384S /K392Y/ V397M / F405S/Y407V/K409W/T411N/ V422I/H435R/Y436F
	FC-B链	Q347E/Y349A/L351F/S364T/T366V//K370T/T394D/V397L/D399E/D401Q/F405A/Y407S/K409R/T411R

5. 如权利要求1所述的双特异抗体分子,其特征在于:

其中,人FC片段包括但不限于Human IgG1 FC、Human IgG2 FC、Human IgG3 FC、Human

IgG4 FC及其变异体,其中一条链能结合proteinA;则另一条链可选择不结合proteinA的突变体,包括但不限于突变H435R或H435R/Y436F,根据EU计数。

6.如权利要求1所述的双特异抗体分子,其特征在于:

其中结合抗原的各个抗体或多肽片段是单价或多价分子,TAA结合的抗原或其特异突变包括但不限于CD3、CD20、CD19、CD30、CD33、CD38、CD40、CD52、slamf7、GD2、CD24、CD47、CD133、CD239、CD276、PD-1等表面抗原,CEA、Epcam、Trop2、TAG72、MUC1、MUC16、mesothelin、folr1、CLDN18.2、PDL1、EGFR、EGFR VIII、C-MET、HER2、FGFR2、FGFR3、PSMA、PSCA、EphA2、ADAM17、17-A1、NKG2D ligands、MCSP、LGR5、SSEA3、SLC34A2、BCMA、GPNMB等靶点的抗体,形式包括Fab、ScFv、VHH或多肽片段等。

7.如权利要求1-6中任一项所述的的双特异抗体分子,其特征在于:

其中各个抗体是嵌合、人源化、全人源或单链抗体。

8.如权利要求1-7中任一项所述的的双特异抗体分子,其特征在于:

连接序列为免疫原性低的氨基酸序列。

9.如权利要求1-8所述的的双特异抗体分子,其特征在于:

当由4条链组成时,包括但不限于如下形式:

链1: [VL1/VH1]-[IL15/IL15Ra]
链2: [VH1/VL1]-[IL15Ra/IL15]-[FC(异源二聚体A链或B链)]
链3: [VH2]-[CH1]-[FC(异源二聚体A链或B链)]
链4: [VL2]-[CL]

其中:

链1:结合抗原的抗体可变区VL1或VH1融合在IL15或IL15Ra的N端或C端;

链2:IL15或IL15Ra的N端或C端融合了结合抗原的抗体可变区VL1或VH1,在其C端融合可形成异源二聚体的FC;

链3:结合另一个抗原的抗体可变区VH2融合CH1片段,在其C端融合可形成异源二聚体的FC,组成抗体重链;

链4:结合另一个抗原的抗体可变区VL2的C端融合CL片段,组成抗体轻链,

当由3条链组成时,包括但不限于以下形式:

链1: [VL1/VH1]-[IL15/IL15Ra]
链2: [VH1/VL1]-[IL15Ra/IL15]-[FC(异源二聚体A链或B链)]
链3: [亲和多肽]-[FC(异源二聚体A链或B链)]

其中:

链1:结合抗原的抗体可变区VL1或VH1融合在IL15或IL15Ra的N端或C端;

链2:IL15或IL15Ra的N端或C端融合了结合抗原的抗体可变区VL1或VH1,在其C端融合可形成异源二聚体的FC;

链3:结合另一个靶点的亲和多肽,包括SCFV,VHH及其人源化形式、多肽或蛋白质,在其C端融合可形成异源二聚体的FC。

10.如权利要求9的双特异抗体分子,其特征在于:

与IL15或IL15Ra融合的蛋白链1及蛋白链2的组合形式包括但不限于以下组合:

组合1	链1:	VL1-IL15
	链2:	VH1-IL15Ra-FC(Heterodimer A or B链)
组合2	链1:	IL15-VL1
	链2:	VH1-IL15Ra-FC(Heterodimer A or B链)
组合3	链1:	VL1-IL15
	链2:	IL15Ra-VH1-FC(Heterodimer A or B链)
组合4	链1:	IL15-VL1
	链2:	IL15Ra-VH1-FC(Heterodimer A or B链)
组合5	链1:	VH1-IL15
	链2:	VL1-IL15Ra-FC(Heterodimer A or B链)
组合6	链1:	IL15-VH1
	链2:	VL1-IL15Ra-FC(Heterodimer A or B链)
组合7	链1:	VH1-IL15
	链2:	IL15Ra-VL1-FC(Heterodimer A or B链)
组合8	链1:	IL15-VH1
	链2:	IL15Ra-VL1-FC(Heterodimer A or B链)
组合9	链1:	VL1-IL15Ra
	链2:	VH1-IL15-FC(Heterodimer A or B链)
组合10	链1:	IL15Ra-VL1
	链2:	VH1-IL15-FC(Heterodimer A or B链)
组合11	链1:	VL1-IL15Ra
	链2:	IL15-VH1-FC(Heterodimer A or B链)
组合12	链1:	IL15Ra-VL1
	链2:	IL15-VH1-FC(Heterodimer A or B链)
组合13	链1:	VH1-IL15Ra
	链2:	VL1-IL15-FC(Heterodimer A or B链)
组合14	链1:	IL15Ra-VH1
	链2:	VL1-IL15-FC(Heterodimer A or B链)
组合15	链1:	VH1-IL15Ra
	链2:	IL15-VL1-FC(Heterodimer A or B链)
组合16	链1:	IL15Ra-VH1
	链2:	IL15-VL1-FC(Heterodimer A or B链)

11. 如权利要求1-8所述的双特异抗体分子,其特征在于:
还具有如下形式:

链1: VL1-IL15
链2: VH1-IL15Ra-FC(异源二聚体A链或B链)
链3: VH2-CH1-FC(异源二聚体A链或B链)
链4: VL2-CL

其中:

链1:结合抗原的抗体可变区VL1融合在IL15的N端;

链2:IL15Ra的N端融合了结合抗原的抗体可变区VH1,C端融合FC异源二聚体;

链3:结合另一个抗原的抗体可变区VH2融合CH1片段,C端融合FC异源二聚体,组成抗体重链;

链4:结合另一个抗原的抗体可变区VL2的C端融合CL片段,组成抗体轻链。

12.如权利要求9-11所述的双特异抗体分子,其特征在于:

其中,IL15及IL15Ra复合物包括:1) IL15及其能结合IL15Ra的突变,截短及各种衍生物;2) IL15Ra及其能结合IL15的突变,截短及各种衍生物;包括但不限于权利要求3所述突变以及本实施例中所述序列SEQ ID No.1、SEQ ID No.2、SEQ ID No.3、SEQ ID No.4、SEQ ID No.5、SEQ ID No.6、SEQ ID No.7、SEQ ID No.8、SEQ ID No.9。

13.如权利要求9-11所述的双特异抗体分子,其特征在于:

人FC片段,是FC异源二聚体形式,FC异源二聚体包含但不限于权利要求3所述突变以及序列SEQ ID No.94、SEQ ID No.95。

14.如权利要求9-11所述的双特异抗体分子,其特征在于:

人FC片段,包括但不限于Human IgG1 FC、Human IgG2 FC、Human IgG3 FC、Human IgG4 FC及其变异体。其中一条链能结合proteinA;另一条链可不结合proteinA,包括但不限于突变H435R或H435R/Y436F,根据EU计数。

15.如权利要求1-8所述的双特异抗体分子,其特征在于:

结合抗原的TAA1和/或TAA2抗体,包括但不限于CD3、CD20、CD19、CD38、CD40、CD30、CD33、CD52、slamf7、GD2、CD24、CD47、CD133、CD239、CD276、PD-1等表面抗原,CEA、Epcam、Trop2、TAG72、MUC1、MUC16、mesothelin、folr1、CLDN18.2、PDL1、EGFR、EGFRVIII、C-MET、HER2、FGFR2、FGFR3、PSMA、PSCA、EphA2、ADAM17、17-A1、NKG2D ligands、MCSP、LGR5、SSEA3、SLC34A2、BCMA、GPNMB等靶点的抗体,包含但不限于序列SEQ ID No.18、SEQ ID No.19、SEQ ID No.20、SEQ ID No.21、SEQ ID No.22、SEQ ID No.23、SEQ ID No.24、SEQ ID No.25、SEQ ID No.26、SEQ ID No.27、SEQ ID No.28、SEQ ID No.29、SEQ ID No.30、SEQ ID No.31、SEQ ID No.32、SEQ ID No.33、SEQ ID No.34、SEQ ID No.35、SEQ ID No.36、SEQ ID No.37、SEQ ID No.38、SEQ ID No.39、SEQ ID No.40、SEQ ID No.41、SEQ ID No.42、SEQ ID No.43、SEQ ID No.44、SEQ ID No.45、SEQ ID No.46、SEQ ID No.47、SEQ ID No.48、SEQ ID No.49、SEQ ID No.50、SEQ ID No.51、SEQ ID No.52、SEQ ID No.53、SEQ ID No.54、SEQ ID No.55、SEQ ID No.56、SEQ ID No.57、SEQ ID No.58、SEQ ID No.59、SEQ ID No.60、SEQ ID No.61、SEQ ID No.62、SEQ ID No.63、SEQ ID No.64、SEQ ID No.65、SEQ ID No.66、SEQ ID No.67、SEQ ID No.68、SEQ ID No.69、SEQ ID No.70、SEQ ID No.71、SEQ ID No.72、SEQ ID No.73、SEQ ID No.74、SEQ ID No.75、SEQ ID No.76、SEQ ID No.77、SEQ ID No.78、SEQ ID No.79、SEQ ID No.80、SEQ ID No.81、SEQ ID No.82、SEQ ID No.83、SEQ ID No.84、SEQ ID No.85、SEQ ID No.86、SEQ ID No.87、SEQ ID No.88、SEQ ID No.89、SEQ ID No.90、SEQ ID No.91、SEQ ID No.92、SEQ ID No.93。

16.如权利要求9-11所述权利要求1-8所述的双特异抗体分子,其特征在于:

其中,TAA为Her2/Her3;FC为IgG1异源二聚体;链1和链2的IL15及IL15Ra复合物融合蛋

白有二硫键形成,包含但不限于本实施例中所述序列SEQ ID No.10、SEQ ID No.11、SEQ ID No.12、SEQ ID No.13。

17.如权利要求9-11所述的双特异抗体分子,其特征在于:

其中,TAA为CD38/CS1;FC为IgG1异源二聚体;链1和链2的IL15及IL15Ra复合物融合蛋白有二硫键形成,包含但不限于本实施例中所述序列SEQ ID No.14、SEQ ID No.15、SEQ ID No.16、SEQ ID No.17。

18.如权利要求1-17中任意一项所述的双特异抗体分子在制备癌症、感染和免疫调节疾病的药物中的应用。

19.如权利要求1-17中任意一项所述的双特异抗体分子,在制备抑制肿瘤生长的药物中的应用。

20.如权利要求18或19所述的应用,其中,所述癌症或肿瘤包括:骨髓癌、淋巴瘤、白血病、小细胞肺癌、非小细胞肺癌、黑素瘤、基底细胞皮肤癌、鳞状细胞皮肤癌、隆突性皮肤纤维肉瘤、梅克尔细胞癌、成胶质细胞瘤、胶质瘤、肉瘤、间皮瘤,和骨髓增生异常综合症;

或者包括来自如下部位的癌症或肿瘤:结直肠、乳腺、卵巢、胰腺、胃、前列腺、肾、宫颈、甲状腺、子宫内膜、子宫、膀胱、神经内分泌、头部颈部、肝、鼻咽、睾丸。

一种双特异抗体及其应用

技术领域

[0001] 本发明涉及一种双特异抗体,本发明还涉及这种双特异性抗体的应用,属于生物医药领域。

背景技术

[0002] 双特异性抗体(BsAb)又称双功能抗体,可同时识别和结合两种不同的抗原和表位,并阻断两种不同的信号通路以发挥其作用。BsAb与普通抗体相比增加了一个特异性抗原结合位点,在治疗方面表现出了以下优势:

[0003] 介导免疫细胞对肿瘤的杀伤:双特异性抗体的一个重要作用机制是介导免疫细胞杀伤,双特异性抗体有两条抗原结合臂,其中一条与靶抗原结合,另一条与效应细胞上的标记抗原结合,后者可以激活效应细胞,使其靶向杀伤肿瘤细胞。目前已经批准上市的2个双特异性抗体产品都属于这个类别,TrionPharma公司开发的catumaxomab能够靶向肿瘤表面抗原EpCAM和T细胞表面受体CD3,而Micromet公司和Amgen公司开发的Blinatumomab可以同时结合CD19和CD3。两者都是通过激活并召集杀伤性T细胞,从而达到治疗肿瘤的目的;

[0004] 双靶点信号阻断,发挥独特的或重叠的功能,有效防止耐药:同时结合双靶点,阻断双信号通路是双特异性抗体的另一个重要作用机制。受体酪氨酸激酶(receptor tyrosine kinase, RTKs)是最大的一类酶联受体,在细胞增殖过程中发挥重要的调节作用,如Her家族等。RTKs在肿瘤细胞表面异常高表达,导致肿瘤细胞恶性增生,因此也是肿瘤治疗的重要靶点。针对RTKs的单靶点单克隆抗体已在肿瘤治疗中得到广泛应用,但是,肿瘤细胞可以通过转换信号通路或通过HER家族成员自身或不同成员之间的同源或异源二聚体激活细胞内信号进行免疫逃逸。因此采用双特异性抗体药物同时阻断两个或多个RTKs或其配体,可以减少肿瘤细胞逃逸,提高治疗效果;

[0005] 具备更强特异性、靶向性和降低脱靶毒性:利用双特异性抗体两个抗原结合臂可以结合不同抗原的特点,两个抗原结合臂分别结合癌细胞表面2种抗原,可以有效增强抗体对癌细胞的结合特异性和靶向性,降低脱靶等副作用;

[0006] 有效降低治疗成本:以BiTE为例,与传统抗体相比在组织渗透率、杀伤肿瘤细胞效率、脱靶率和临床适应症等指标方面都具有较强的竞争力,临床优势显著。特别在使用剂量方面,由于其治疗效果可以达到普通抗体的100-1000倍,使用剂量最低可将为原来的1/2000,显著降低药物治疗成本。相对于组合疗法,双特异性抗体的成本也远远低于两个单药联合治疗。

[0007] 目前,全球有三款双特异性抗体药物获得上市批准:

[0008] 2009年,欧盟批准了第一个治疗性双特异性抗体—TrionPharma公司的Catumaxomab(靶向CD3和EpCAM),用于治疗癌性腹水。2014年,FDA快速批准Amgen公司基于BiTE®技术开发的双特异性抗体药物Blinatumomab(靶向CD3和CD19)用于治疗急性B淋巴细胞白血病,它也是第一个获批的靶点为CD19的药物。Amgen一系列的血液恶性肿瘤和实体瘤的临床开发中就拥有十几种BiTE®分子。其中靶向BCMA/CD3的AMG420已获得FDA授权快

速审批通道地位。在实体肿瘤的治疗中,靶向前列腺特异膜抗原(PSMA)的BiTE®分子AMG212(Pasotuxizumab)的临床试验结果也展露锋芒。2017年11月,FDA快速批准了罗氏的双特异性抗体Emicizumab(靶向凝血因子X和因子IXa),用于治疗血友病。2018年12月在中国获批上市,是首个在国内获批的双特异性抗体。

[0009] 1. IL15/IL15R α

[0010] IL-15是一种长14-15kDa的细胞因子,对于NK细胞、NKT细胞和memoryCD8⁺T细胞功能非常重要。IL-15在体内含量很少,但通过与其受体IL-15R α 结合产生具有极高生物效价的复合物IL-15超激动剂(IL-15SA)后一起被转导转运至靶细胞。IL-15SA强烈激活响应IL-15的细胞,特别是NK细胞,从而促进抗肿瘤和抗病毒功能。

[0011] 研究人员在1994年首次将IL-15鉴定为T淋巴细胞生长因子,它与IL-2具有大约19%的同源序列,许多生物学特性也非常类似。IL-15三维结构与IL-2类似,由四个“上-下-下-下”螺旋束组成,IL-4,IL-7和IL-9等其他细胞因子也包含这种构象。IL-15与其他细胞因子作用方式不同,IL-15受体 α 表达于产生IL-15的细胞(例如巨噬细胞和树突状细胞),与IL-15形成IL-15SA将信号递送至表达IL-15R β (也称为IL-2R β)和共同 γ 链(与IL-2,IL-4,IL-7,IL-9和IL-21共享)的NK、NKT和memory CD8⁺T细胞,很有可能正是由于这一独特的呈递方式赋予了IL-15介导其独特功能的能力。小鼠IL-15与人IL-15具有70%的氨基酸序列同源性,人IL-15和小鼠IL-15也具有相似的反式表达模式,信号通路以及生物学活性。IL-15在许多细胞类型和组织中表达,包括单核细胞、巨噬细胞、DC、角质形成细胞、成纤维细胞、肌细胞和神经细胞。IL-15作为多效细胞因子在先天性和适应性免疫中起重要作用。

[0012] 反式表达的IL-15/IL-15R α 信号通过响应细胞上表达的 β 和 γ 链,诱导JAK1和JAK3的募集和激活,活化的JAK1和JAK3进一步磷酸化STAT3和STAT5。STAT3和STAT5磷酸化后形成同源二聚体,易位至细胞核并促进靶基因的转录。IL-15信号传导刺激一系列下游反应,诱导细胞生长、减少凋亡以及增强免疫细胞的激活和转移。在没有高亲和力IL-15R α 的情况下,IL-15也可以单独与中等亲和力($K_a=1.10^9/M$)的 β 、 γ 受体复合物(IL-15R $\beta\gamma$)结合,诱导其他酪氨酸激酶(如Lck、Fyn、Lyn、Syk)磷酸化激活,并与PI3K、MAPK途径发生作用。有研究表明,代谢检查点激酶mTOR也可以被高浓度的IL-15激活,这与NK细胞的增殖和激活增强有关:选择性敲除mTOR会导致骨髓NK细胞成熟受阻。IL-15促进NK细胞增殖的能力部分是由于IL-15介导的有氧糖酵解作用引起的,在没有IL-15的情况下NK细胞的基础代谢很低,但通过提高IL-15浓度可以明显增强这一生理活动。

[0013] 由于IL-15具有与IL-2类似的免疫学特性:诱导T细胞的增殖和存活,促进NK细胞的增殖和分化,并诱导细胞毒性T淋巴细胞的产生。但不同于IL-2,IL-15对Treg细胞没有明显作用,并且不会在小鼠或非人类灵长类动物(NHP)中引起毛细血管渗漏综合征,因此相较于IL-2,IL-15是肿瘤免疫疗法的更优选择。猕猴IL-15(rIL-15)是第一种用于体内实验的IL-15形式,研究人员认为rIL-15可以优先结合细胞表面IL-15R α 。异二聚体IL-15/IL-15R α 是从细胞上裂解下来的IL-15的天然形式,可以独立于细胞刺激相互作用的应答,目前诺华公司正在实体瘤中开展这种形式的分子(NIZ985)的临床试验。Cytune开发的RLI是一种融合蛋白,由与IL-15R α 的Sushi结构域相连的IL-15组成,可以作为可溶性的IL-15激动剂。IL-15/IL-15R α -Fc复合物通过将市售的IL-15R α -Fc嵌合融合蛋白与rIL-15混合产生的,已在临床前研究中广泛使用。IL-15与IL-15R α 有很高亲和力, $KD=30-100pM$ 。

[0014] 本专利发明了一种全新的双特异靶向细胞因子抗体形式:细胞因子IL15与IL15Ra之间有超高的亲和力(KD约30-100pM),本发明用IL15及IL15Ra分别替代其中一个抗体结构中的CL及CH1结构域,解决双特异抗体轻链错配问题。通过FC异源二聚体形式解决重链错配。将有Fab的FC端进行突变,使其不能结合Protein A。纯化通过结合FC端的Protein A亲和层析及结合CH1结构域CH1-XL亲和层析的2步纯化出双特异靶向抗体。

[0015] 2.Her2背景

[0016] 受体酪氨酸激酶的ErbB家族的成员是细胞生长,分化和存活的重要介导体。该受体家族包括四个独特成员,包括表皮生长因子受体(EGFR或ErbB1),HER2(ErbB2),HER3(ErbB3)和HER4(ErbB4或tyro2)。HER2是一种跨膜的表面结合的受体酪氨酸激酶,而且正常情况下牵涉导致细胞生长和分化的信号转导途径。

[0017] Her2过度表达可能导致细胞正常功能紊乱,并且通常与肿瘤的发生和发展密切相关。Her2的同源或异源聚合可导致受体酪氨酸残基磷酸化,并且引发许多信号途径并引起细胞增殖和肿瘤发生。作为预后和预测的生物标志物,Her2基因的扩增或过度表达在约15-30%的乳腺癌和10-30%的胃癌/食道癌中发生。在其它肿瘤诸如卵巢、子宫内膜、膀胱、肺、结肠和头颈肿瘤中也可观察到Her2过度表达。

[0018] 曲妥珠单抗(Trastuzumab)识别Her2胞外结构域IV近膜表位。具体为Her2胞外结构域IV部分的C端处由3个环(557-561、570-573和593-603)组成的表位。因为表位可以靠近其二聚化伴侣的结合结构域或直接与之相互作用,所以曲妥珠单抗与表位的结合可以诱导抑制二聚化过程的空间位阻。另外,曲妥珠单抗的结合还可以保护Her2受体的细胞外结构域免受蛋白酶的攻击而水解。

[0019] 目前将曲妥珠单抗用作治疗乳腺癌的一线药物,有效治疗Her2过度表达的转移性乳腺癌,并且单药一线治疗的客观反映率为30-50%;但是在治疗Her2表达较低的转移性乳腺癌方面效果不理想,并且抗体最初在1年内有效的许多患者中发展出耐药性。Her2连同该家族的其它成员(Her1、Her3和Her4)可以形成配体依赖性或非依赖性异源二聚体,从而激活下游途径,然后导致肿瘤细胞增殖,而曲妥珠单抗无法抑制异源二聚体形成,所以这可能是耐药性发展的原因之一。

[0020] 帕妥珠单抗(Pertuzumab)是一种人源化单克隆抗体,其特异性设计成阻止HER2受体与细胞表面上的其它HER受体(EGFR/HER1,HER3和HER4)配对(二聚化),认为该过程在肿瘤生长和存活中发挥作用。帕妥珠单抗对晚期前列腺癌、非小细胞肺癌、卵巢癌和乳腺癌有一定治疗效果,但其治疗效果还取决于Her2表达水平。帕妥珠单抗识别Her2细胞外结构域II异源二聚化的关键位点,由此识别的表位位于II亚区中心的区段245-311,关键残基为H245、V286、S288、L295、H296和K311。其中,L295、H296是介导Her2和Her3异源二聚化的关键位点,并且L295A/H296A双重突变可完全阻断Her2/Her3的异源二聚化(Franklin,M.C.等人,Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex.Cancer Cell,2004.5(4):第317-28页)。因此,帕妥珠单抗可用于有效抑制Her2/Her3异源二聚体的形成,但对EGFR/Her2异源二聚体的形成并未显示出明显的抑制作用。

发明内容

[0021] 本发明的目的在于提供一种特异性结合HER2的双特异性抗体及其应用。

[0022] 本发明采用了如下技术方案：

[0023] 一种全新的双特异抗体分子包括但不限于这种形式：

[0024] {[TAA]1,[TAA]2,[IL15/IL15Ra],[FC异源二聚体]}，

[0025] 每种形式同时包含：

[0026] [TAA]1:结合一个抗原的抗体、抗体或多肽片段；

[0027] [TAA]2:结合另一个抗原或同一抗原不同表位的抗体、抗体或多肽片段；

[0028] [IL15/IL15Ra]:IL15及其能结合IL15Ra的突变,截短及各种衍生物；

[0029] IL15Ra及其能结合IL15的突变,截短及各种衍生物；

[0030] 这两者形成的复合物；

[0031] [FC异源二聚体]:FC形成的异源二聚体。

[0032] 作为优选,本发明的双特异抗体分子,还具有这样的特征:包含IL15/IL15Ra复合物,IL15/IL15Ra复合物包括但不限于1) IL15及其能结合IL15Ra的突变,截短及各种衍生物;2) IL15Ra及其能结合IL15的突变,截短及各种衍生物；

[0033] 包括但不限于下表所示突变,计数方式根据SEQ ID No.1所示IL15第一个氨基酸开始算为第1位;SEQ ID No.3所示IL15Ra第一个氨基酸开始算为第1位：

组合	IL15	IL15Ra
1	wt	D96
2	wt	D96/P97
3	wt	D96/P97/A98
4	E87C	D96/C97
5	E87C	D96/P97/C98
6	E87C	D96/C97/A98
7	V49C	S40C
8	L52C	S40C
9	E89C	K34C
10	Q48C	G38C
11	E53C	L42C
12	C425	A37C
13	L45C	G38C
14	L45C	A37C

[0035] 同时包括但不限于下表所示IL15相关各种突变,计数方式根据SEQ ID No.1所示IL15第一个氨基酸开始算为第1位：

组合	IL15突变
1	N1D
2	ND4
3	D8N
4	D30N
5	D61N
6	E64Q

7	N65D
8	Q108E
9	N1D/D61N
10	N1D/E64Q
11	N4D/D61N
12	N4D/E64Q
13	D8N/D61N
14	D8N/E64Q
15	D61N/F64Q
16	E64Q/Q108E
17	N1D/N4D/D8N
18	D61N/E64Q/N65D
19	N1D/D61N/E64Q/Q108E
20	N4D/D61N/E64Q/Q108E

[0037] 作为优选,本发明的双特异抗体分子,还具有这样的特征:与IL15或IL15Ra融合的是针对抗原的抗体可变区VL1或VH1,包括但不限于以下突变,根据EU计数:

	二硫键改造位点	
	VH	VL
组合1	37C	95C
组合2	44C	100C
组合3	44C	105C
组合4	45C	87C
组合5	100C	50C
组合6	100bC	49C
组合7	98C	46C
组合8	101C	46C
组合9	105C	43C
组合10	106C	57C

[0039] 其中,VL1与VH1之间可有一对或多对二硫键。

[0040] 作为优选,本发明的双特异抗体分子,还具有这样的特征:包含抗体的FC段,是FC异源二聚体形式,FC异源二聚体包含但不限于以下突变的组合,根据EU计数,

[0041]

组合	FC	异源二聚体突变(Eu numbering)
1	FC-A链	T366Y
	FC-B链	Y407T
2	FC-A链	T366W
	FC-B链	T366S/L368A/Y407V
3	FC-A链	S354C/T366W
	FC-B链	Y349C/T366S/L368A/Y407V
4	FC-A链	S364H/F405A
	FC-B链	Y349T/T394F
5	FC-A链	T350V/L351Y/F405A/Y407V
	FC-B链	T350V/T366L/K392L/T394W
6	FC-A链	K392D/K409D
	FC-B链	E356K/D399K
7	FC-A链	D221E/P228E/L368E
	FC-B链	D221R/P228R/K409R
8	FC-A链	K360E/K409W
	FC-B链	Q347R/D399V/F405T
9	FC-A链	K360E/K409W/Y349C
	FC-B链	Q347R/D399V/F405T/S354C
10	FC-A链	K370E/K409W
	FC-B链	E357N/D399V/F405T
11	FC-A链	F405L
	FC-B链	K409R
12	FC-A链	K360D/D399M/Y407A
	FC-B链	E345R/Q347R/T366V/K409V
13	FC-A链	Y349S/K370Y/T366M/K409V
	FC-B链	E356G/E357D/S364Q/Y407A
14	FC-A链	L351D/L368E
	FC-B链	L351K/T366K
15	FC-A链	GQPFPRPEVHLLPPSREEMTKNQVSLTCLARGFYPKDIAVEWESNGQPENNYKTTPSRQE PSQGTTFFAVTSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKTISL
	FC-B链	GQPREPQVYTLPPSEELALNELVLTCLVKGFPYSDIAVEWLQGSQELPREKYLTPWAPV LDSGGSFFLYSILRVAADWKKGDTFSCFSVMHEALHNHYTQKSLDR
16	FC-A链	L368D/K370S
	FC-B链	E357Q/S364K
17	FC-A链	S354C/T366W/ K409A
	FC-B链	Y349C/T366S/L368A/Y407V/ F405K
18	FC-A链	S354C/T366W/ F405K/K360E/Q347E
	FC-B链	Y349C/T366S/L368A/Y407V/ Q347R/T394W
19	FC-A链	T366W/ K409A
	FC-B链	T366S/ L368G/Y407A/F405K
20	FC-A链	knobs (T366W/ F405K)
	FC-B链	holes (T366S/ L368G/Y407A/K409A)
21	FC-A链	Q347A/S364K/T366V/K370T/K392Y/F405S/Y407V/K409W/T411N
	FC-B链	Q347E/Y349A/L351F/S364T/T366V//K370T/T394D/V397L/D399E/D401Q/F405A/Y407 S/K409R/T411R
22	FC-A链	K274Q/N276K/Y300F/A339T /Q347A/S364K/T366V/K370T/ N384S /K392Y/ V397M / F405S/Y407V/K409W/T411N/ V422I/H435R/Y436F
	FC-B链	Q347E/Y349A/L351F/S364T/T366V//K370T/T394D/V397L/D399E/D401Q/F405A/Y407 S/K409R/T411R

[0042] 作为优选,本发明的双特异抗体分子,还具有这样的特征:其中,人FC片段包括但不限于Human IgG1 FC、Human IgG2 FC、Human IgG3 FC、Human IgG4 FC及其变异体,其中

一条链能结合proteinA;则另一条链可选择不结合proteinA的突变体,包括但不限于突变H435R或H435R/Y436F,根据EU计数。

[0043] 作为优选,本发明的双特异抗体分子,还具有这样的特征:其中结合抗原的各个抗体或多肽片段是单价或多价分子,TAA结合的抗原或其特异突变包括但不限于CD3、CD20、CD19、CD30、CD33、CD38、CD40、CD52、slamf7、GD2、CD24、CD47、CD133、CD239、CD276、PD-1等表面抗原,CEA、Epcam、Trop2、TAG72、MUC1、MUC16、mesothelin、folr1、CLDN18.2、PDL1、EGFR、EGFR VIII、C-MET、HER2、FGFR2、FGFR3、PSMA、PSCA、EphA2、ADAM17、17-A1、NKG2D ligands、MCSP、LGR5、SSEA3、SLC34A2、BCMA、GPNMB等靶点的抗体,形式包括Fab、ScFv、VHH或多肽片段等。

[0044] 作为优选,本发明的双特异抗体分子,还具有这样的特征:其中各个抗体是嵌合、人源化、全人源或单链抗体。

[0045] 作为优选,本发明的双特异抗体分子,还具有这样的特征:连接序列为免疫原性低的氨基酸序列。

[0046] 作为优选,本发明的双特异抗体分子,还具有这样的特征:当由4条链组成时,包括但不限于如下形式:

[0047] $\left\{ \begin{array}{l} \text{链1: [VL1/VH1]-[IL15/IL15Ra]} \\ \text{链2: [VH1/VL1]-[IL15Ra/IL15]-[FC(异源二聚体A链或B链)]} \\ \text{链3: [VH2]-[CH1]-[FC(异源二聚体A链或B链)]} \\ \text{链4: [VL2]-[CL]} \end{array} \right.$

[0048] 其中:

[0049] 链1:结合抗原的抗体可变区VL1或VH1融合在IL15或IL15Ra的N端或C端;

[0050] 链2:IL15或IL15Ra的N端或C端融合了结合抗原的抗体可变区VL1或VH1,在其C端融合可形成异源二聚体的FC;

[0051] 链3:结合另一个抗原的抗体可变区VH2融合CH1片段,在其C端融合可形成异源二聚体的FC,组成抗体重链;

[0052] 链4:结合另一个抗原的抗体可变区VL2的C端融合CL片段,组成抗体轻链,

[0053] 当由3条链组成时,包括但不限于以下形式:

[0054] $\left\{ \begin{array}{l} \text{链1: [VL1/VH1]-[IL15/IL15Ra]} \\ \text{链2: [VH1/VL1]-[IL15Ra/IL15]-[FC(异源二聚体A链或B链)]} \\ \text{链3: [亲和多肽]-[FC(异源二聚体A链或B链)]} \end{array} \right.$

[0055] 其中:

[0056] 链1:结合抗原的抗体可变区VL1或VH1融合在IL15或IL15Ra的N端或C端;

[0057] 链2:IL15或IL15Ra的N端或C端融合了结合抗原的抗体可变区VL1或VH1,在其C端融合可形成异源二聚体的FC;

[0058] 链3:结合另一个靶点的亲和多肽,包括SCFV,VHH及其人源化形式、多肽或蛋白质,在其C端融合可形成异源二聚体的FC。

[0059] 作为优选,本发明的双特异抗体分子,还具有这样的特征:与IL15或IL15Ra融合的蛋白链1及蛋白链2的组合形式包括但不限于以下组合:

[0060]

组合1	链1:	VL1-IL15
	链2:	VH1-IL15Ra-FC(Heterodimer A or B链)
组合2	链1:	IL15-VL1
	链2:	VH1-IL15Ra-FC(Heterodimer A or B链)
组合3	链1:	VL1-IL15
	链2:	IL15Ra-VH1-FC(Heterodimer A or B链)
组合4	链1:	IL15-VL1
	链2:	IL15Ra-VH1-FC(Heterodimer A or B链)
组合5	链1:	VH1-IL15
	链2:	VL1-IL15Ra-FC(Heterodimer A or B链)
组合6	链1:	IL15-VH1
	链2:	VL1-IL15Ra-FC(Heterodimer A or B链)
组合7	链1:	VH1-IL15
	链2:	IL15Ra-VL1-FC(Heterodimer A or B链)
组合8	链1:	IL15-VH1
	链2:	IL15Ra-VL1-FC(Heterodimer A or B链)
组合9	链1:	VL1-IL15Ra
	链2:	VH1-IL15-FC(Heterodimer A or B链)
组合10	链1:	IL15Ra-VL1
	链2:	VH1-IL15-FC(Heterodimer A or B链)
组合11	链1:	VL1-IL15Ra
	链2:	IL15-VH1-FC(Heterodimer A or B链)
组合12	链1:	IL15Ra-VL1
	链2:	IL15-VH1-FC(Heterodimer A or B链)
组合13	链1:	VH1-IL15Ra
	链2:	VL1-IL15-FC(Heterodimer A or B链)
组合14	链1:	IL15Ra-VH1
	链2:	VL1-IL15-FC(Heterodimer A or B链)
组合15	链1:	VH1-IL15Ra
	链2:	IL15-VL1-FC(Heterodimer A or B链)
组合16	链1:	IL15Ra-VH1
	链2:	IL15-VL1-FC(Heterodimer A or B链)

[0061] 作为优选,本发明的双特异抗体分子,还具有这样的特征:还具有如下形式:

[0062]

链1: VL1-IL15
 链2: VH1-IL15Ra-FC(异源二聚体A链或B链)
 链3: VH2-CH1-FC(异源二聚体A链或B链)
 链4: VL2-CL

[0063] 其中:

[0064] 链1:结合抗原的抗体可变区VL1融合在IL15的N端;

[0065] 链2:IL15Ra的N端融合了结合抗原的抗体可变区VH1,C端融合FC异源二聚体;

[0066] 链3:结合另一个抗原的抗体可变区VH2融合CH1片段,C端融合FC异源二聚体,组成抗体重链;

[0067] 链4:结合另一个抗原的抗体可变区VL2的C端融合CL片段,组成抗体轻链。

[0068] 作为优选,本发明的双特异抗体分子,还具有这样的特征:其中,IL15及IL15Ra复

合物包括:1) IL15及其能结合IL15Ra的突变,截短及各种衍生物;2) IL15Ra及其能结合IL15的突变,截短及各种衍生物;包括但不限于权利要求3所述突变以及本实施例中所述序列SEQ ID No.1、SEQ ID No.2、SEQ ID No.3、SEQ ID No.4、SEQ ID No.5、SEQ ID No.6、SEQ ID No.7、SEQ ID No.8、SEQ ID No.9。

[0069] 作为优选,本发明的双特异抗体分子,还具有这样的特征:人FC片段,是FC异源二聚体形式,FC异源二聚体包含但不限于权利要求3所述突变以及序列SEQ ID No.94、SEQ ID No.95。

[0070] 作为优选,本发明的双特异抗体分子,还具有这样的特征:人FC片段,包括但不限于Human IgG1 FC、Human IgG2 FC、Human IgG3 FC、Human IgG4 FC及其变异体。其中一条链能结合proteinA;另一条链可选择性不结合proteinA,包括但不限于突变H435R或H435R/Y436F,根据EU计数。

[0071] 作为优选,本发明的双特异抗体分子,还具有这样的特征:结合抗原的TAA1和/或TAA2抗体包括但不限于CD3、CD20、CD19、CD38、CD40、CD30、CD33、CD52、slamf7、GD2、CD24、CD47、CD133、CD239、CD276、PD-1等表面抗原,CEA、Epcam、Trop2、TAG72、MUC1、MUC16、mesothelin、folr1、CLDN18.2、PDL1、EGFR、EGFR VIII、C-MET、HER2、FGFR2、FGFR3、PSMA、PSCA、EphA2、ADAM17、17-A1、NKG2D ligands、MCSP、LGR5、SSEA3、SLC34A2、BCMA、GPNMB等靶点的抗体,包含但不限于序列SEQ ID No.18、SEQ ID No.19、SEQ ID No.20、SEQ ID No.21、SEQ ID No.22、SEQ ID No.23、SEQ ID No.24、SEQ ID No.25、SEQ ID No.26、SEQ ID No.27、SEQ ID No.28、SEQ ID No.29、SEQ ID No.30、SEQ ID No.31、SEQ ID No.32、SEQ ID No.33、SEQ ID No.34、SEQ ID No.35、SEQ ID No.36、SEQ ID No.37、SEQ ID No.38、SEQ ID No.39、SEQ ID No.40、SEQ ID No.41、SEQ ID No.42、SEQ ID No.43、SEQ ID No.44、SEQ ID No.45、SEQ ID No.46、SEQ ID No.47、SEQ ID No.48、SEQ ID No.49、SEQ ID No.50、SEQ ID No.51、SEQ ID No.52、SEQ ID No.53、SEQ ID No.54、SEQ ID No.55、SEQ ID No.56、SEQ ID No.57、SEQ ID No.58、SEQ ID No.59、SEQ ID No.60、SEQ ID No.61、SEQ ID No.62、SEQ ID No.63、SEQ ID No.64、SEQ ID No.65、SEQ ID No.66、SEQ ID No.67、SEQ ID No.68、SEQ ID No.69、SEQ ID No.70、SEQ ID No.71、SEQ ID No.72、SEQ ID No.73、SEQ ID No.74、SEQ ID No.75、SEQ ID No.76、SEQ ID No.77、SEQ ID No.78、SEQ ID No.79、SEQ ID No.80、SEQ ID No.81、SEQ ID No.82、SEQ ID No.83、SEQ ID No.84、SEQ ID No.85、SEQ ID No.86、SEQ ID No.87、SEQ ID No.88、SEQ ID No.89、SEQ ID No.90、SEQ ID No.91、SEQ ID No.92、SEQ ID No.93。

[0072] 作为优选,本发明的双特异抗体分子,还具有这样的特征:其中,TAA为Her2/Her3;FC为IgG1异源二聚体;链1和链2的IL15及IL15Ra复合物融合蛋白有二硫键形成,包含但不限于本实施例中所述序列SEQ ID No.10、SEQ ID No.11、SEQ ID No.12、SEQ ID No.13。

[0073] 作为优选,本发明的双特异抗体分子,还具有这样的特征:其中,TAA为CD38/CS1;FC为IgG1异源二聚体;链1和链2的IL15及IL15Ra复合物融合蛋白有二硫键形成,包含但不限于本实施例中所述序列SEQ ID No.14、SEQ ID No.15、SEQ ID No.16、SEQ ID No.17。

[0074] 本发明还提供上述任意一项所述的双特异抗体分子在制备癌症、感染和免疫调节疾病的药物中的应用。

[0075] 本发明还提供上述任意一项所述的双特异抗体分子,在制备抑制肿瘤生长的药物

中的应用。

[0076] 进一步,本发明的应用,其中,所述癌症或肿瘤包括:骨髓癌、淋巴瘤、白血病、小细胞肺癌、非小细胞肺癌、黑素瘤、基底细胞皮肤癌、鳞状细胞皮肤癌、隆突性皮肤纤维肉瘤、梅克尔细胞癌、成胶质细胞瘤、胶质瘤、肉瘤、间皮瘤,和骨髓增生异常综合症;

[0077] 或者包括来自如下部位的癌症或肿瘤:结直肠、乳腺、卵巢、胰腺、胃、前列腺、肾、宫颈、甲状腺、子宫内膜、子宫、膀胱、神经内分泌、头部颈部、肝、鼻咽、睾丸。

[0078] 本发明提供的特异性结合HER2的双特异性抗体,其包含对HER2胞外域II特异性的第一抗原结合位点和对HER2胞外域IV特异性的第二抗原结合位点,其中该双特异性抗体对HER2胞外域II和IV二者均是单价的。

[0079] 发明的有益效果

[0080] 本发明的双特异性抗体与HER2蛋白的亲合力高,本发明的双特异性抗体对肿瘤细胞的增殖抑制作用强。

附图说明

[0081] 图1是双特异抗体的结构形式一。

[0082] 图2是双特异抗体的结构形式二。

[0083] 图3是双特异抗体的结构形式三。

[0084] 图4是双特异抗体的结构形式四。

[0085] 图5是双特异抗体的结构形式五。

[0086] 图6是双特异抗体的结构形式六。

[0087] 图7是双特异抗体的结构形式七。

[0088] 图8是双特异抗体的结构形式八。

[0089] 图9是SDS-PAGE电泳分析QP34563457蛋白还原与非还原条带。

[0090] 图10是HPLC-SEC分析QP34563457蛋白纯度。

[0091] 图11是QP34563457蛋白的肽图分析,图11a显示QP34563457蛋白对于Trastuzumab VL-IL15链36%的序列覆盖率,图11b显示QP34563457蛋白对于Trastuzumab VH-IL15Ra-FC链56%的序列覆盖率,图11c显示QP34563457蛋白对于pertuzumab VL-CL链64%的序列覆盖率,图11d显示QP34563457蛋白对于pertuzumab VH-CH1-FC链56%的序列覆盖率。

[0092] 图12是ELISA检测QP34563457等分子结合Her2-FC融合蛋白。

[0093] 图13是ELISA检测QP34563457等分子结合Her2M2-FC融合蛋白。

[0094] 图14是ELISA检测QP34623463等分子结合CD38蛋白。

[0095] 图15是ELISA检测QP34623463等分子结合CS1蛋白。

[0096] 图16是FACS检测QP34563457等分子结合SK-BR-3细胞。

[0097] 图17是FACS检测QP34563457等分子结合BT-474细胞。

[0098] 图18是FACS检测QP34563457等分子结合SK-OV-3细胞。

[0099] 图19是QP34563457等分子对人乳腺癌细胞SK-BR-3的增殖抑制曲线。

[0100] 图20是QP34563457等分子对人乳腺癌细胞BT-474的增殖抑制曲线。

[0101] 图21是QP34563457等分子对人卵巢癌细胞SK-OV-3的增殖抑制曲线。

[0102] 图22是QP34563457等介导的PBMC杀伤人乳腺癌细胞SK-BR-3细胞。

[0103] 图23是QP34563457等介导的PBMC杀伤人乳腺癌细胞BT-474细胞。

[0104] 图24是QP34563457等介导的PBMC杀伤人卵巢癌细胞SK-OV-3细胞。

[0105] 图25是检测QP34563457等分子对Mo7e细胞增殖实验。

[0106] 图26是SK-OV-3体内药效模型肿瘤生长曲线。

具体实施方式

[0107] 以下实施方式中未注明具体条件的实验方法,通常是按照常规条件,或按照原料或商品制造厂商所建议的条件和方法进行。如分子克隆,实验室手册,冷泉港实验室,当代分子生物学方法,细胞生物学等等。未注明具体来源的试剂,为市场购买的常规试剂。

[0108] 实施例1:融合蛋白的克隆和表达

[0109] 蛋白序列如下:

[0110] anti Her2 VL-IL15 SEQ ID NO:10

[0111] DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGT
DFTLTISSLQPEDFATYYCQQHYTTPPTFGGQGTKVEIKGGGSGGGGSGGGGSGNWNVISDLKKIEDLIQSMHIDAT
LYTESDVHPSCKVTAMKCFLELQVISCESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQ
SFVHIVQMFINTS

[0112] anti Her2 VH-IL15Ra-FC (Knob) SEQ ID NO:11

[0113] EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFT
ISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGLTVTVSSGGGGSGGGGSGGGGSITCPPPMSVEH
ADIWVKSYSLSRERYICNSGFKRKAGTCSLTECVLNKATNVAHWTPSLKCI RGGGGSEPKSSDKTHTCPPCPAPE
LLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQP
ENNYKTTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

[0114] anti Her3 VL-CLSEQ ID NO:12

[0115] DIQMTQSPSSLSASVGDRVTITCKASQDVSIGVAWYQQKPGKAPKLLIYSASYRYTGVPSTRFSGSGSGT
DFTLTISSLQPEDFATYYCQQYYIYPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEKHKVYACEVTHOGLSSPVTKSFNRGEC

[0116] anti Her3 VH-CH1-CH2-CH3 (Ho1e) SEQ ID NO:13

[0117] EVQLVESGGGLVQPGGSLRLSCAASGFTFTDYTEMDWVRQAPGKGLEWVADVPNSGGSIYNQRFKGRFTLSVDRSKNTLYLQMNSLRAEDTAVYYCARNLGPSFYFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQNSYTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLSCAVKGFYPSDI AVEWESNGQPENNYKTTTPPVLDSDGSFFLVSKLTVDKSRWQQGNV FSCSVMH EALHNRYTQKSLSLSPGK

[0118] anti CS1 VL-IL15 SEQ ID NO:14

[0119] DIQMTQSPSSLSASVGDRVTITCKASQDVGIAVAWYQQKPGKVPKLLIYWASTRHTGVPDRFSGSGSGT
DFTLTISSLQPEDVATYYCQQYSSYPYTFGGGTKVEIKGGGSGGGGSGGGGSGNWNVISDLKKIEDLIQSMHIDAT
LYTESDVHPSCKVTAMKCFLELQVISCESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEEELEEKNIKEFLQ
SFVHIVQMFINTS

[0120] anti CS1 VH-IL15Ra-FC (Knob) SEQ ID NO:15

[0121] EVQLVESGGGLVQPGGSLRLSCAASGFDfsRYWMSWVRQAPGKGLEWIGEINPDSSTINYAPSLKDKF
IISRDNAKNSLYLQMNSLRAEDTAVYYCARPDGNYWYFDVWGQGTLVTVSSGGGGSGGGSGGGGSITCPPMSVE
HADIWVKSYSLSYRERYICNSGFKRKAGTCSLTCVLNKATNVAHWTPSLKCIIRGGGGSEPKSSDKTHTCPPCPA
PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWES
NGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKanti CD38 VL-
CL SEQ ID NO:16

[0122] EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGT
DFTLTISSELEPEDFAVYYCQQRSNWPPTFGGQTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVCLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[0123] anti CD38 VH-CH1-CH2-CH3 (Hole) SEQ ID NO:17

[0124] EVQLLESGLLVQPGGSLRLSCAVSGFTFNSFAMSWVRQAPGKGLEWVSAISGSGGGTYIYADSVKGRFT
ISRDNKNTLYLQMNSLRAEDTAVYFCAKDILWFGPEVFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAA
LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK
SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLCAVKG
YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFCFSVMHEALHNRYTQKSLSLSPGK

[0125] 克隆构建方法:

[0126] 克隆设计如表1所示:

[0127] 如表1所示,分别构建载体编码anti Her2 VL (Tmab) -IL15 (SEQ ID NO:10)、anti Her2 VH (Tmab) -IL15Ra-FC (Knob) (SEQ ID NO:11)、anti CS1 VL-IL15 (SEQ ID NO:14)、anti CS1 VH-IL15Ra-FC (Knob) (SEQ ID NO:15)。质粒含有DHFR作为筛选标记,可以用于稳定株筛选;构建载体编码抗肿瘤特异性抗原抗体的轻链序列(序列)及抗肿瘤特异性抗原抗体的重链序列(其中Fc含有Hole突变即(T366S,L368A,Y407V) anti Her2 VL (Pmab) -CL (SEQ ID NO:12)、anti Her2 VH (Pmab) -CH1-CH2-CH3 (Hole) (SEQ ID NO:13)、anti CD38 VL-CL (SEQ ID NO:16)、anti CD38 VH-CH1-CH2-CH3 (Hole) (SEQ ID NO:17),质粒含有GS作为筛选标记,可以用于稳定株筛选。蛋白分子的结构示意图如图1所示。在其它的实施方式中,蛋白分子可以为其它结构形式,分别如图2至图8所示。

[0128] 表1:克隆设计构建

实施例所列序列	SEQ ID	蛋白名称	克隆		
[0129] 蛋白-1	SEQ ID NO:10	QP34563457	QD3456	QD3452	anti Her2 (T mab) VL-IL15
	SEQ ID NO:11			QD3453	anti Her2 (T mab) VH-IL15Ra-FC(Knob)
	SEQ ID NO:12		QD3457	QD3454	anti Her2 (P mab) VL-CL
	SEQ ID NO:13			QD3455	anti Her2 (P mab) VH-CH1-CH2-CH3(Hole)
蛋白-2	SEQ ID NO:14	QP34623463	QD3462	QD3458	anti CS1 VL-IL15
	SEQ ID NO:15			QD3459	anti CS1 VH-IL15Ra-FC(Knob)
	SEQ ID NO:16		QD3463	QD3460	anti CD38 VL-CL
	SEQ ID NO:17			QD3461	anti CD38 VH-CH1-CH2-CH3(Hole)

[0130] 如表2所示,设计构建对照抗体Trastuzumab,Pertuzumab,Elotuzumab,

Daratumumab。

[0131] 表2:对照蛋白序列及编号

蛋白名称	蛋白编号	克隆编号	蛋白序列
Trastuzumab	QP32933294	QD3293	MEFGLSWFLVAILKGVQCEVQLVESGGGLVQPGGSLRLSCAASGFINIKDTYIHVWRQAP GKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVVYCSRWG GDGFYAMDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKITPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
		QD3294	MDMRVPAQLLGLLLWFGSRCDIQTQSPSSLSASVGDRTITCRASQDVNTAVAWY QQKPGKAPKLLIYASFLYSGVPSRFSGRSGTDFTLTISLQPEDFATYYCQYHYITTPFTFG QGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*
Pertuzumab	QP37253726	QD3725	MEFGLSWFLVAILKGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTFTDYTMWVVRQA PGKLEWVADVNPNSGGSIYNQRFKGRFTLSVDRSKNTLYLQMNSLRAEDTAVVYCAR NLGPSYFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKITPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
		QD3726	MDMRVPAQLLGLLLWFGSRCDIQTQSPSSLSASVGDRTITCKASQDVSGIAVWYQ QKPGKAPKLLIYASRYTGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQYIYIPYTFGQ GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*
Elotuzumab	QP34483449	QD3448	MEFGLSWFLVAILKGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQA APGKLEWIGEINPDSTINYAPSLKDKFIISRDNAKNSLYLQMNSLRAEDTAVVYCARPD GNYWYFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKITPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
		QD3449	MDMRVPAQLLGLLLWFGSRCDIQTQSPSSLSASVGDRTITCKASQDVGIQVAVWYQ QQKPGKVPKLLIYASTRHTGVPDRFSGSGSGTDFTLTISLQPEDFATYYCQYSSYPYTFG QGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQ NSQESVTEQDSKDSYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*
Daratumumab	QP34503451	QD3450	MEFGLSWFLVAILKGVQCEVQLLESGGGLVQPGGSLRLSCAVSGFTFNSFAMSWVRQA PGKLEWVSAISGGGGTYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVVYFCAKDK ILWFGPEVFDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVS SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPK KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYV VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKITPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*
		QD3451	MDMRVPAQLLGLLLWFGSRCEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQ KPGQAPRLIYDASNRATGIPARFSGSGSGTDFTLTISLEPEDFATVYCCQQRSNWPPTFG QGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*
IL15/IL15Ra-FC	QP33123313	QD3312	MEFGLSWFLVAILKGVQCNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKC FLLELQVISCESGDASIHDVTENLIILANNSLSSNGNVTESGCKECEELEEKNIEFLQSFVHI VQMFINTS*
		QD3313	MEFGLSWFLVAILKGVQCITCPPMSVEHADIWVKSYSLSYRERYICNSGFKRAGTCSLT ECVLNKAATNAHWTTPLSKICRDPAVHQRSGSGGGSGGGSGGGSLQEPKSSDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKITPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*

[0133] 瞬转表达目标分子

[0134] 接种ExpiCHO-S细胞到FortiCHO培养基中(Gibco,A1148301)额外加入8mM GlutaMax,37℃,120rpm,8%CO₂培养。转染前一天,将ExpiCHO-S细胞密度调整为3*10E6/mL,置于摇床中,37℃,120rpm,8%CO₂培养;转染当天,取样,计数,将细胞密度稀释为6*10E6/ml,每瓶40ml,置于125ml的摇瓶中;质粒QD3208,QD3209各20ug与4.8mL Opti MEM混

合,加入120ul Polyplus-FectoPRO转染试剂,将DNA和转染试剂混合均匀后,置于室温10min,将混合物缓慢置于细胞中,混合均匀后,置于摇床培养。培养过程中,分别在第1,4,6,8天每瓶补加2mL Feed PFF05 (OPM,F81279-001) 及1m的30%葡萄糖溶液。转染第一天,将温度降为32℃,CO2浓度降为5%。13天收样,8000rpm离心20min,取上清,待纯化。

[0135] 实施例2:融合蛋白的纯化

[0136] Protein A亲和层析纯化

[0137] 用平衡液过柱,至少3CV,实际体积20ml,确保最终仪器中流出的溶液pH和电导与平衡液一致,流速1ml/min;将离心后培养液上清过柱,上样40ml,流速0.33ml/min;用平衡液过柱,至少3CV,实际体积20ml,确保最终仪器中流出的溶液pH和电导与平衡液一致,流速0.33ml/min;用洗脱液过柱,UV280上升至15mAU时开始收集洗脱峰(PAC-EP),UV280下降至15mAU时停止收集,流速1ml/min。样品收集完成后,用pH调节液将PAC-EP调至中性。

[0138] CH1-XL亲和层析

[0139] 将Protein A处理后样品8000rpm×15min离心,取上清;用平衡液过柱,至少3CV,实际体积20ml,确保最终仪器中流出的溶液pH和电导与平衡液一致,流速1ml/min;将离心后上清经上样环过柱,流速0.33ml/min;用平衡液过柱,至少3CV,实际体积20ml,确保最终仪器中流出的溶液pH和电导与平衡液一致,流速0.33ml/min;用洗脱液过柱,UV280上升至10mAU时开始收集洗脱峰(PAC-EP),UV280下降至10mAU时停止收集,流速1ml/min。样品收集完成后,用pH调节液将CH1-EP调至中性。

[0140] PNGase F酶切:

[0141] 取39.5μl样品,加入1.98μl 10%SDS和1.58μl 1M DTT,混合均匀后100℃煮沸10分钟;待样品冷却,加入4.8μl 10%NP-40和1.0μl PNGase F,混匀后4℃水浴过夜;将过夜后样品75℃加热10分钟热失活,样品进行SDS-PAGE电泳及SEC,检测蛋白纯度。

[0142] SDS-PAGE电泳分析:

[0143] 酶切前和酶切后样品各取5μg,用1×PBS将体积定容至48μl,再加入12μl 5×Protein Loading Dye,95℃加热10分钟。在电泳槽中倒入pH为8.3的Tris-HCl缓冲液(含0.1%SDS),用移液枪向样品槽中加入样品,每个样品槽加样60μl。将电压设置为140V,时间设置为100分钟即可开始电泳。电泳结束后取出凝胶,浸泡在染色液中30分钟,再用脱色液脱色,直至蛋白质区条带清晰。图9是SDS-PAGE电泳分析QP34563457蛋白还原与非还原条带。图10是HPLC-SEC分析QP34563457蛋白纯度。

[0144] 实施例3:蛋白QP34563457肽图分析

[0145] 本实施例利用LC-MS来鉴定QP34563457蛋白的氨基酸序列。

[0146] QP34563457蛋白变性还原后,加入胰蛋白酶酶解后用LC-MS/MS分析,(LC仪器Agilent 1290 Infinity II,柱子Agilent Peptide Plus column。MS仪器Agilent 6545Q-TOF),将得到的数据采用Peaks进行搜库,Peaks搜库结果经严格卡值过滤后得到可信肽段,实现了对于QP34563457蛋白Trastuzumab VL-IL15链36%的序列覆盖率(图3a,灰色为鉴定到的氨基酸序列),Trastuzumab VH-IL15Ra-FC链56%的序列覆盖率(图3b,灰色为鉴定到的氨基酸序列),pertuzumab VL-CL链64%的序列覆盖率(图3c,灰色为鉴定到的氨基酸序列),pertuzumab VH-CH1-FC链56%的序列覆盖率(图3d,灰色为鉴定到的氨基酸序列)。

[0147] 结果如图11a、图11b、图11c和图11d所示:图11a:Trastuzumab VL-IL15链肽图分

析;图11b:Trastuzumab VH-IL15Ra-FC链肽图分析;图11c:pertuzumab VL-CL链肽图分析;图11d:pertuzumab VH-CH1-FC链肽图分析。

[0148] 结果:通过LC-MS进行肽图分析,分别找到了QP34563457分子中各个片段,包括,Trastuzumab VL、IL15、Trastuzumab VH、IL15Ra、FC、pertuzumab VL、CL、pertuzumab VH、CH1、FC等。

[0149] 实施例4:ELISA检测QP34563457结合Her2及其突变体活性

[0150] 只结合帕托珠单抗Pertuzumab的Her2变体蛋白的设计.Matthew C.Franklin在Cancer cell上发表了帕托珠单抗Fab与Her2胞外结构的复合物结构。该团队同时用丙氨酸扫描的方法研究了Her2哪些关键氨基酸会影响与帕托珠单抗Fab的结合。将只结合帕托珠单抗Pertuzumab而不结合曲妥珠单抗trastuzumab的Her2变体蛋白命名为Her2M2(蛋白编号QP3732)。Her2wt(蛋白编号QP3731)及Her2M2(蛋白编号QP3732)的氨基酸序列分别如下:

[0151] QP3731:(Her2ECD-FC)

[0152] MEFGLSWLFLVAILKGVQCTQVCTGTDMLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASL
SFLQDIQEVQGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTE
ILKGGVLIQRNPQLCYQDITLWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTV CAGG
CARCKGPLPTDCCHEQCAAGCTGPKHSDCLACHFNHSGICELHCPALVTYNTDTFESMPNPEGRTYFGASCVTAC
PYNLSTDVGSCTLVCPHNQEVTAEDGTQRCEKCKSPCARVCYGLGMEHLREVRAVTSANIQEFAGCKKIFGSLA
FLPESFDGDPASNTAPLQPEQLQVFETLEEITGYLYISAWPDSLPLDSVFQNLQVIRGRILHNGAYSLTLQGLGIS
WLGLRSLRELGSGLALIHNNHLCFVHTVPWDQLFRNP HQALLHTANRPEDECVGEGLACHQLCARGHCWGP GPTQ
CVNCSQFLRGQECVEECRVLQGLPREYVNARHCLPCHPECQPQNGSVTCFGPEADQCVACAHYKDPFCVARCP SG
VKPDL SYMPIWKFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTEPKSSDKTHTCPPCPAPELLGGPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK*

[0153] QP3732 (Her2M2-FC) :

[0154] MEFGLSWLFLVAILKGVQCTQVCTGTDMLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASL
SFLQDIQEVQGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTE
ILKGGVLIQRNPQLCYQDITLWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTV CAGG
CARCKGPLPTDCCHEQCAAGCTGPKHSDCLACHFNHSGICELHCPALVTYNTDTFESMPNPEGRTYFGASCVTAC
PYNLSTDVGSCTLVCPHNQEVTAEDGTQRCEKCKSPCARVCYGLGMEHLREVRAVTSANIQEFAGCKKIFGSLA
FLPESFDGDPASNTAPLQPEQLQVFETLEEITGYLYISAWPDSLPLDSVFQNLQVIRGRILHNGAYSLTLQGLGIS
WLGLRSLRELGSGLALIHNNHLCFVHTVPWDQLFRNP HQALLHTANRPEDECVGEGLACHQLCARGHCWGP GPTQ
CVNCSQFLRGQECVEECRVLQGLPREYVNARHCLPCHPECQPQNGSVTCFGPAADQCVACAHYKDPAF CVARCP SG
VKPDL SYMPIWKFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTEPKSSDKTHTCPPCPAPELLGGPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK*

[0155] 检测试剂:milk (BD,232100),PBS(生工,B548117-0500);HRP-anti human IgG(H+L)(jackson,109-035-088);TMB(洛阳佰奥通实验材料中心,C060201);Elisa板(costar,

9018) 1×PBS缓冲液:称取NaCl 8.00g、KCl 0.20g、Na₂HPO₄·12H₂O 2.9g、KH₂PO₄ 0.2g至800mL ddH₂O中溶解,充分溶解后定容至1L,调节pH至7.4,高温灭菌备用。或购买商品化10×、20×的PBS溶液稀释至1×PBS缓冲液使用。封闭液:称取5g的milk至PBS中,封闭液需现配现用。终止液(1mol/LH₂SO₄):取109mL 98%的浓H₂SO₄缓慢滴加至2000mL ddH₂O中。TMB 37℃显色10min,置于摇床中(120rpm),100μl/well;

[0156] 实验步骤:Her2及其变体蛋白QP3731及QP3732包板,1ug/ml,4度过夜;PBS洗3遍。按200μL/孔加入封闭液5% milk,37度孵育1h。封闭结束后,PBS洗3遍,孵育样品,按照20ug/ml 5倍稀释,共稀释7个梯度最后一孔稀释100倍,100μl/well充分混匀后,孵育1h,PBST洗3遍;加酶标抗体:孵育HRP-anti human Fab抗体,按照1:5000稀释比例,100μl/孔,充分混匀后,孵育1h,PBST洗6遍。加底物显色液:按100μL/孔用量加底物显色液TMB,置于摇床中,200rpm,35℃避光显色10min。

[0157] 终止:显色完成后,按100μL/孔用量快速加入终止液终止反应。检测:在酶标仪上,测其A450nm的OD值,使用graphpad prism软件分析结果。结果如图12,图13所示。

[0158] 实施例5:ELISA检测QP34623463结合CD38及CS1活性

[0159] 检测试剂:milk (BD,232100),PBS(生工,B548117-0500);HRP-anti human IgG(H+L)(jackson,109-035-088);TMB(洛阳佰奥通实验材料中心,C060201);Elisa板(costar,9018) 1×PBS缓冲液:称取NaCl 8.00g、KCl 0.20g、Na₂HPO₄·12H₂O 2.9g、KH₂PO₄ 0.2g至800mL ddH₂O中溶解,充分溶解后定容至1L,调节pH至7.4,高温灭菌备用。或购买商品化10×、20×的PBS溶液稀释至1×PBS缓冲液使用。封闭液:称取5g的milk至PBS中,封闭液需现配现用。终止液(1mol/LH₂SO₄):取109mL 98%的浓H₂SO₄缓慢滴加至2000mL ddH₂O中。TMB 37℃显色10min,置于摇床中(120rpm),100μl/well;

[0160] 实验步骤:CD38-FC和CS1-FC融合蛋白分别包板,1ug/ml,4度过夜;PBS洗3遍。按200μL/孔加入封闭液5% milk,37度孵育1h。封闭结束后,PBS洗3遍,孵育样品,按照20ug/ml 5倍稀释,共稀释7个梯度最后一孔稀释100倍,100μl/well充分混匀后,孵育1h,PBST洗3遍;加酶标抗体:孵育HRP-anti human Fab抗体,按照1:5000稀释比例,100μl/孔,充分混匀后,孵育1h,PBST洗6遍。加底物显色液:按100μL/孔用量加底物显色液TMB,置于摇床中,200rpm,35℃避光显色10min。终止:显色完成后,按100μL/孔用量快速加入终止液终止反应。检测:在酶标仪上,测其A450nm的OD值,使用graphpad prism软件分析结果。结果如图14和图15所示。

[0161] 实施例6:FACS检测QP34563457结合Her2高表达细胞

[0162] 实验目的:FACS检测QP34563457结合Her2高表达细胞

[0163] 实验材料:

[0164] BT474细胞(人乳腺癌细胞株),购于中国医学科学院基础医学研究所细胞资源中心。

[0165] SK-BR-3细胞(人乳腺癌细胞株),购于中国医学科学院基础医学研究所细胞资源中心。SK-OV-3细胞(人卵巢癌细胞株),购于中国医学科学院基础医学研究所细胞资源中心。

[0166] 实验方法:BT474细胞使用含有10%FBS,0.11g/L丙酮酸钠和2.5g/L葡萄糖的RPMI1640(Gibco)培养基,SK-BR-3细胞使用含有10%FBS的DMEM培养基(Gibco),SK-OV-3细

胞使用含有10%FBS的McCoy's 5a培养基(Gibco)。于37℃5%CO₂培养箱中培养,胰酶消化收集细胞,按100000个细胞每孔接种于96孔板中,2%FBS/PBS冰上封闭1h,孵育不同浓度蛋白QP34563457及对照蛋白,冰上1h,PBS洗3遍,孵育PE-anti human FC(1:200)稀释,PBS洗3遍,200微升PBS重悬,FACS读取平均荧光值,使用graphpad prism软件分析结果。结果如图16、图17和图18所示。

[0167] 实施例7:Her2双特异抗体介导的增殖抑制

[0168] 实验目的:确定Her2双特异抗体对肿瘤细胞的增殖抑制作用

[0169] 实验材料:

[0170] BT474细胞(人乳腺癌细胞株),购于中国医学科学院基础医学研究所细胞资源中心。SK-BR-3细胞(人乳腺癌细胞株),购于中国医学科学院基础医学研究所细胞资源中心。SK-OV-3细胞(人卵巢癌细胞株),购于中国医学科学院基础医学研究所细胞资源中心。

[0171] 实验试剂:细胞增殖及毒性检测试剂盒(CCK-8),购自美仑生物,货号MA0218;人IgG,购自Sigma,货号I4506;其他抗体来自内部制备。

[0172] 实验方法:BT474细胞使用含有10%FBS,0.11g/L丙酮酸钠和2.5g/L葡萄糖的RPMI1640(Gibco)培养基,SK-BR-3细胞使用含有10%FBS的DMEM培养基(Gibco),SK-OV-3细胞使用含有10%FBS的McCoy's 5a培养基(Gibco)。于37℃,5%CO₂培养箱中培养,胰酶消化收集细胞,离心后用含有1%FBS的培养基重悬,按10000个细胞,50μl每孔接种于96孔板中,37℃贴壁培养3小时;将各个待测抗体用培养基按3倍梯度稀释后,50μl每孔与细胞悬液混合均匀,37℃,5%CO₂培养箱中培养3天;将CCK-8试剂按10μl每孔加入待测的96孔板中,37℃,5%CO₂培养箱中孵育2小时;将96孔板取出,于酶标仪中检测450nm波长的吸光值,计算细胞活力值,与样品浓度对数作图,使用graphpad prism软件分析结果。通过四参数拟合出细胞增殖抑制曲线。结果如图19、图20和图21所示。

[0173] 实施例8:HER2双特异抗体介导的ADCC作用

[0174] 实验目的:确定HER2双特异抗体的ADCC作用

[0175] 实验材料:PBMC购买自上海赛笠生物科技有限公司,BT474细胞(人乳腺癌细胞株),购于中国医学科学院基础医学研究所细胞资源中心。SK-BR-3细胞(人乳腺癌细胞株),购于中国医学科学院基础医学研究所细胞资源中心。SK-OV-3细胞(人卵巢癌细胞株),购于中国医学科学院基础医学研究所细胞资源中心,Cytotox96 non-radioactive cytotoxicity assay检测试剂盒购自Promega(G1780)。

[0176] 实验步骤:复苏PBMC,收集细胞待第二天备用。准备靶细胞:SK-BR-3,BT-474,SK-OV-3用胰酶消化,1000rpm 5min。PBS清洗2次后,铺96孔板,20000个每孔,50μl每孔,37℃5%CO₂孵育2h。准备抗体:用培养基(RPMI1640含10%low-IgG FBS)1:4梯度稀释抗体(80ug/ml—0.000512ug/ml,0ug/ml)10个浓度。加入上面稀释各浓度的抗体50μl每孔,37℃孵育15min。准备PBMC:将第一天复苏的PBMC离心,用培养基(RPMI1640含10%low-IgG FBS)重悬,计数。按PBMC:Target cell=30:1,加入上面的孔板中50μl每孔,37度孵育4小时。LDH检测:对于最大释放组和体积校正组,提前45min加入10μl裂解液,继续放置培养箱培养。培养4h后,吸取50μl上清至酶标板中,按照Cytotox96 non-radioactive cytotoxicity assay检测试剂盒(Promega,G1780)说明书,加入50μl reagent。室温,避光反应30min后,加入50μl stop solution。490nm吸光值读数(加入stop solution后1h内完成读数)。计算:杀

伤百分比 = (样品释放 - 靶细胞自发 - 效应细胞自发释放) / (靶细胞最大释放 - 靶细胞自发释放) * 100。将自发释放 (对应于在没有抗体的情况下与效应细胞一起温育的靶细胞) 定义为 0% 细胞毒性, 并将最大释放 (用 1% Triton X-100 裂解的靶细胞) 定义为 100% 细胞毒性。结果如图 22、图 23 和图 24 所示。

[0177] 实施例 9: Mo7e 细胞增殖实验

[0178] 实验试剂: Mo7e 细胞 (人巨细胞白血病细胞株), 购于中国医学科学院基础医学研究所细胞资源中心, 细胞增殖及毒性检测试剂盒 (CCK-8), 购自美仑生物, 货号 MA0218; 重组人 GM-CSF, 购自 perprotech, 货号 300-03; 人 IgG, 购自 Sigma, 货号 I4506; 其他抗体来自内部制备。

[0179] 实验方法: Mo7e 细胞使用含有 10% FBS, 2mM L-谷氨酰胺和 8ng/ml GM-CSF 的 RPMI1640 培养基于 37°C, 5% CO₂ 培养箱中培养; 收集 Mo7e 细胞, 800rpm 离心 5 分钟倒掉上清, 细胞用不含有 GM-CSF 的 RPMI1640 培养基洗涤 2 遍; 用无 GM-CSF 的 RPMI1640 培养基重悬细胞并计数, 将细胞按 2 × 10⁴ 个, 80μl 每孔接种于 96 孔板中, 37°C, 5% CO₂ 培养箱中培养 1 小时; 将各个待测抗体用培养基按 4 倍梯度稀释后, 20μl 每孔与细胞悬液混合均匀, 37°C, 5% CO₂ 培养箱中培养 3 天; 将 CCK-8 试剂按 10μl 每孔加入待测的 96 孔板中, 37°C, 5% CO₂ 培养箱中孵育 4 小时; 将 96 孔板取出, 于酶标仪中检测 450nm 波长的吸光值。实验结果如图 25 所示

[0180] 实施例 10: 动物药效实验

[0181] 在高表达 HER2 的人卵巢癌细胞 SK-OV-3 模型中评价 QP34563457 对肿瘤生长的抑制作用。

[0182] SK-OV-3 细胞培养在含 10% 胎牛血清的 McCoy's 5A+10% FBS 培养液中。收集指数生长期的 SK-OV-3 细胞, PBS 重悬至适合浓度接种。每只 BALB/C-nude 小鼠于右侧背部皮下接种 1 × 10⁶ SK-OV-3 细胞, 定期观察肿瘤生长情况, 待肿瘤生长至平均体积约 50mm³ 时根据肿瘤大小和小鼠体重随机分组给药, 第一次给药当天定义为 D0。给药方案如下:

[0183] 表 3: 给药方案

	组别	动物数	给药组	剂量	给药方式	给药周期
				(mg/kg)		
[0184]	1	10	PBS	--	i.p.	Q3D×6
	2	10	Tastuzumab	5	i.p.	Q3D×6
	3	10	Pertuzumab	5	i.p.	Q3D×6
	4	10	Trastuzumab+Pertuzumab	5+5	i.p.	Q3D×6
	5	7	QP34563457	0.5	i.p.	Q3D×6

[0185] 给药体积为 10ul/g 体重。

[0186] 每次给药观察、记录小鼠体重和肿瘤体积, 用游标卡尺测量肿瘤长短径, 并按公式 肿瘤体积 (mm³) = 0.5 × (a × b²) 计算、记录肿瘤生长情况, 绘制肿瘤生长曲线。最后一次给药后观察 6 天, 结束实验, 并记录实验数据。

[0187] 结果显示, Tastuzumab、Pertuzumab、Trastuzumab+Pertuzumab 及 QP34563457 均能明显抑制 SK-OV-3 肿瘤生长, 6 次给药后肿瘤发生消退 (TGI_{tv} > 100%)。结果如图 26 和表 4 所

示。

[0188] 表4:SK-OV-3体内药效数据及分析

组别	D0 肿瘤体积 mm ³	D21 肿瘤体积 mm ³	D21 肿瘤生长抑 制百分比%	P 值 v.s. vehicle
Vehicle, PBS	54.07±3.72/D0	121.94±7.43 /D21	--	--
[0189] Tastuzumab, 5mg/kg	55.32±4.99/D0	32.7±5.07 /D21	133.33	<0.0001**
Pertuzumab, 5mg/kg	53.58±4.25/D0	43.72±5.02 /D21	114.56	<0.0001**
Tastuzumab,5mg/kg +	53.81±3.66/D0	26.62±3.39 /D21	140.06	<0.0001**
Pertuzumab, 5mg/kg				
QP34563457, 0.5mg/kg	54.57±4.17/D0	34.98±5.29 /D21	121.79	<0.0001**

[0190] Sequence:

[0191] SEQ ID NO:1 IL15

[0192] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLELQVISLESGDASIHTVENLIIL
ANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTS

[0193] SEQ ID NO:2 IL-15 (L52C)

[0194] NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLELQVISCESGDASIHTVENLIIL
ANNSLSSNGNVTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTS

[0195] SEQ ID NO:3 IL15Ra

[0196] ECDITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRD
PALVHQRPAAPPSTVTTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAIVPGSQLMPSPSTGTTEISSHESHG
TPSQTTAKNWELTASASHQPPGVYPQGHSDTT

[0197] SEQ ID NO:4 IL15Ra Sushi 65">sp|Q13261|31-95

[0198] ITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR"

[0199] SEQ ID NO:5 IL15Ra Sushi 73

[0200] ITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPAL
VHQR

[0201] SEQ ID NO:6 IL15Ra Sushi 77

[0202] ITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPAL
VHQRPAAPP

[0203] SEQ ID NO:7 IL15Ra Sushi 86

[0204] ITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPAL
VHQRPAAPPSTVTTAGVT

[0205] SEQ ID NO:8 IL15Ra Sushi 102

[0206] ITCPPPMSVEHADIWVKSYSLSYRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPAL
VHQRPAAPPSTVTTAGVTPQPESLSPSGKEPAAS

28

DFTLTISSLEPEDFAVYYCQQRSNWPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[0223] SEQ ID NO:17 anti CD38 VH-CH1-CH2-CH3 (Hole)

[0224] EVQLLESGGGLVQPGGSLRLSCAVSGFTFNSFAMSWVRQAPGKGLEWVSAISGSGGGTTYADSVKGRFT
ISRDN SKNTLYLQMNSLRAEDTAVYFCAKDILWFGPEVFDYWGQGTILVTVSSASTKGPSVFPLAPSSKSTSGGTAA
LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK
SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLSCAVKGF
YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNRYTQKSLSLSPGK

[0225] SEQ ID NO:18 VH

[0226] QVQLQQSGPELEKPGASVKISCKASGYSFTGYTMNWVKQSHGKSLEWIGLITPYNGASSYNQKFRGKAT
LTVDKSSSTAYMDLLSLTSEDSAVYFCARGGYDGRGFDYWGSGTPVTVSS

[0227] SEQ ID NO:19 VL

[0228] DIELTQSPAIMASAPGEKVTMTCSASSSVSYMHVYQQKSGTSPKRWIYDTSKLASGVPGRFSGSGSGNS
YSLTISSVEAEDDATYYCQQWSKHPLTFGSGTKVEIK

[0229] SEQ ID NO:20 VH

[0230] EVQLLESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFT
ISRDN SKNTLYLQMNSLRAEDTAVYYCAKDMGWGSGWRPYYYYGMDVWGQGTITVTVSS

[0231] SEQ ID NO:21 VL

[0232] ELQMTQSPSSLSASVGDRVTITCRTSQSISSYLNWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGT
DFTLTISLQPEDSATYYCQQSYDIPYTFGQGTKLEIK

[0233] SEQ ID NO:22 VH

[0234] QVQLKQSGPGLVQPSQSLITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSSGNTDYNTPTFSTRLSI
NKDNSKSQVFFKMNSLQSNDAIYYCARALTYDYEFAYWGQGTILVTVSA

[0235] SEQ ID NO:23 VL

[0236] DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGT
DFTLSINSVESEDIADYYCQQNNWPTTFGAGTKLELK

[0237] SEQ ID NO:24 VH

[0238] XVQLQESGPGLVRPSQTLSTCTVSGYSITSDHAWSWVRQPPGRGLEWIGYISYSGITTYNPSLKSRVT
MLRDTSKNQFSLRLSSVTAADTAVYYCARSLARTTAMDYWGQGSLLTVSS

[0239] SEQ ID NO:25 VL

[0240] DIQMTQSPSSLSASVGDRVTITCRASQDISSYLNWYQQKPGKAPKLLIYYTSRLHSGVPSRFSGSGSGT
DFTFTISLQPEDATYYCQQGNTLPYTFGQGTKVEIK

[0241] SEQ ID NO:26 VH

[0242] EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADSVKGRFT
ISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTILVTVSS

[0243] SEQ ID NO:27 VL

[0244] DIQMTQSPSSLSASVGDRVTITCRASQDVSTAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGSGT
DFTLTISLQPEDFATYYCQQYLYHPATFGQGTKVEIK

[0245] SEQ ID NO:28 VH
[0246] EVQLLQSGPELEKPGASVMISCKASGSSFTGYNMNWRQNIGKSLEWIG AIDPYYGGTSYNQKFKGRAT
LTVDKSSSTAYMHLKSLTSEDSAVYYCVSGMEYWGQGTSTVTVSS
[0247] SEQ ID NO:29 VL
[0248] EIVMTQSPATLSVSPGERATLSCRSSQSLVHRNGNTYLHWYLQKPGQSPKLLIHKVSNRFSGVPDRFSG
SGSGTDFTLKISRVEADLG VYFCSQSTHVPPLTFGAGTKLELK
[0249] SEQ ID NO:30 VH
[0250] QVQLVQSGAEVKKPGSSVKVSCASGYTFTSYRMHWVRQAPGQGLEWIGYINPSTGYTEYNQKFKDKAT
ITADESTNTAYMELSSLRSED TAVYYCARGGGVFDYWGQGT LVTVSS
[0251] SEQ ID NO:31 VL
[0252] DIQMTQSPSTLSASVGDRTITCSASSSISYMHWYQQKPGKAPKLLIYTTSNLASGV PARFSGSGSGTE
FTLTISSLQPD DFATYYCHQRSTYPLTFGQGTKVEVK
[0253] SEQ ID NO:32 VH
[0254] QVQLVQSGVEVKKPGASVKVSCASGYTFTNYMYWVRQAPGQGLEWMGGINPSNGGTNFNEKFKNRVT
LTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGT TTVTVSS
[0255] SEQ ID NO:33 VL
[0256] EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLA SYLESGV PARFSGS
GSGTDFTLTIS SLEPEDFAVYYCQHSRDLPLTFGGGTKVEIK
[0257] SEQ ID NO:34 VH
[0258] QVQLVQSGAEVKKPGASVKVSCASGYTFTTRYGISWVRQAPGQGLEWMGWISTYSGNTNYAQLQGRVT
MTTDTSTSTAYMELRSLRSDDTAVYYCARRQLYFDYWGQGT LVTVSS
[0259] SEQ ID NO:35 VL
[0260] EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWFQQKPGQAPRPLIYDASTRATGV PARFSGSGSGT
DFTLTISSLQSEDFAVYYCQQYDNWPLTFGGGTKVEIK
[0261] SEQ ID NO:36 VH
[0262] EVQLVESGGGLVQPGGSLRLSCAASGFD FSRYWMSWVRQAPGKGLEWIGEINPDSSTINYAPSLKDKFI
ISRDNAKNSLYLQMNSLRAEDTAVYYCARPDGNYWYFDVWGQGT LVTVSS
[0263] SEQ ID NO:37 VL
[0264] DIQMTQSPSSLSASVGDRTITCKASQDVGI AWA WYQQKPGKVPKLLIYWASTRHTGVPDRFSGSGSGT
DFTLTISSLQPEDVATYYCQQYSSYPYTFGQGTKVEIK
[0265] SEQ ID NO:38 VH
[0266] EVQLVESGGDLVQGRSLRLSCAASGFI FSNYGMSWVRQAPGKGLEWVATISSASTYSYYPDSVKGRFT
ISRDNAKNSLYLQMNSLRVEDTALYYCGRHSDGNFAFGYWGQGT LVTVSS
[0267] SEQ ID NO:39 VL
[0268] DVLMTQSPLSLPVTGPGEPAISCRSSRNIVHINGDTYLEWYLQKPGQSPQLLIYK VSNRFSGVPDRFSG
SGSGTDFTLKISRVEADVG VYYCFQGSLLPWTFGQGTKVEIK
[0269] SEQ ID NO:40 VH
[0270] QVQLVESGGGVVQGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWDGSKRYYADSVKGRFT
ISRDN SKNTLFLQMNSLRAEDTAVYYCATNDYWGQGT LVTVSS

[0271] SEQ ID NO:41 VL
[0272] EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGT
DFTLTISSELPEDFAVYYCQQSSNWPRTFGQGTKVEIK
[0273] SEQ ID NO:42 VH
[0274] QVQLVQSGAEVKKPGSSVKVSKASGYAFSYSWINWVRQAPGQGLEWMGRIFPGDGDYNGKFKGRVT
ITADKSTSTAYMELSSLRSEDYAVYYCARNVFDGYWLVYWGQGTLLTVSS
[0275] SEQ ID NO:43 VL
[0276] DIVMTQTPLSLPVTGPGEPAISCRSSKSLHNSGITYLYWYLQKPGQSPQLLIYQMSNLVSGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCAQNLELPYTFGGGTKVEIK
[0277] SEQ ID NO:44 VH
[0278] EVQLLESGGGLVQPGGSLRLSCAVSGFTFNSFAMSWVRQAPGKGLEWVSAISGSGGGTYADSVKGRFT
ISRDN SKNTLYLQMNSLRAEDTAVYFCAKDKILWFGEVFDYWGQGTLLTVSS
[0279] SEQ ID NO:45 VL
[0280] EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGT
DFTLTISSELPEDFAVYYCQQRSNWPPTFGQGTKVEIK
[0281] SEQ ID NO:46 VH
[0282] QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYYSWIRQPPGKGLEWIGYIYYSGSTDYNPSLKS RV
TMSVDTSKNQFSLKVN SVTAADTAVYYCARVSIFGVGTFDYWGQGTLLTVSS
[0283] SEQ ID NO:47 VL
[0284] EIVMTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGT
DFTLTISSELPEDFAVYYCHQYGSTPLTFGGGTAEIK
[0285] SEQ ID NO:48 VH
[0286] EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFT
ISRDN AKNSLYLQMNSLRAEDTAVYYCARVTD AFDI WGQGTMTVTVSS
[0287] SEQ ID NO:49 VL
[0288] DIQMTQSPSSVSASIGDRVITITCRASQGIDNWL GWYQQKPGKAPKLLIYDASNLD TGVP SRFS GSGSGT
YFTLTISSLQAEDFAVYFCQAKAFPTFGGGTKVDIK
[0289] SEQ ID NO:50 VH
[0290] EVQLVESGGGLVKPGGSLKLSAASGFKFSRYAMSWVRQAPGKRLEWVATISSGGSYIYYPDSVKGRFT
ISRDN VKNTLYLQMSSLRSEDYAMYYCARRDYDL DYFDSWGQGTLLTVSS
[0291] SEQ ID NO:51 VL
[0292] DIQMTQSPSSLSASVGDRTITCKASRDIRSYLTWYQQKPGKAPKTLIYYATSLADGVPSRFSGSGSGQ
DYSLTISSESDDTATYYCLQHGESPTLGSGTKLEIK
[0293] SEQ ID NO:52 VH
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[0297] SEQ ID NO:54 VH
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[0375] SEQ ID NO:93 VL

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[0377] FC-Knob (hIgG1) SEQ ID NO:94

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HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPG

[0379] FC-Hole (hIgG1) SEQ ID NO:95

[0380] EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
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SEQUENCE LISTING

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<120> 一种双特异抗体及其应用

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<160> 95

<170> PatentIn version 3.3

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Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
35 40 45
Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60
Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80
Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
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Thr Ser

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35 40 45
Val Ile Ser Cys Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu

50 55 60
 Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
 65 70 75 80
 Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
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 Thr Ser

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

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20 25 30
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Arg Asp Pro Ala Leu Val His Gln Arg

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35 40 45
Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile

[0383]

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 35 40 45
 Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
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 35 40 45
 Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
 50 55 60
 Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val
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 Arg
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 35 40 45
 Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser
 100 105 110
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn Trp Val Asn Val Ile
 115 120 125
 Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp
 130 135 140
 Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr
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[0386]

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Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Cys Glu Ser
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      180                      185                      190
Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys
      195                      200                      205
Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
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Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
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Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35      40      45
Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
      50      55      60
Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65      70      75      80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
      85      90      95
Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
      100     105     110
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
      115     120     125
Gly Ser Gly Gly Gly Gly Ser Ile Thr Cys Pro Pro Pro Met Ser Val
      130     135     140
Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu
145     150     155     160
Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Cys Ser
      165     170     175
Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr
      180     185     190
Thr Pro Ser Leu Lys Cys Ile Arg Gly Gly Gly Gly Ser Glu Pro Lys
      195     200     205
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu

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210 215 220
 Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
 225 230 235 240
 Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
 245 250 255
 Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
 260 265 270
 Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
 275 280 285
 Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
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 Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
 305 310 315 320
 Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
 325 330 335
 Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
 340 345 350
 Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
 355 360 365
 Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 370 375 380
 Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
 385 390 395 400
 Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
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 35 40 45
 Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly

50	55	60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
65	70	75
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ile Tyr Pro Tyr		
85	90	95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala		
100	105	110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly		
115	120	125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala		
130	135	140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln		
145	150	155
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser		
165	170	175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr		
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Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser		
195	200	205
Phe Asn Arg Gly Glu Cys		
210		

[0388]

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35	40
Ala Asp Val Asn Pro Asn Ser Gly Gly Ser Ile Tyr Asn Gln Arg Phe	
50	55
Lys Gly Arg Phe Thr Leu Ser Val Asp Arg Ser Lys Asn Thr Leu Tyr	
65	70
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	
85	90
Ala Arg Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly	
100	105
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 Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser
 355 360 365
 Cys Ala 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 Val 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 Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 435 440 445
 Lys
 <210> 14
 <211> 236

<212> PRT
 <213> Artificial
 <220>
 <223> anti CS1 VL-IL15
 <400> 14
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Ile Ala
 20 25 30
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
 35 40 45
 Tyr Trp Ala Ser Thr Arg His Thr 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 Gln Pro
 65 70 75 80
 Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Tyr Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser
 100 105 110
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn Trp Val Asn Val Ile
 115 120 125
 [0390] Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp
 130 135 140
 Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr
 145 150 155 160
 Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Cys Glu Ser
 165 170 175
 Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala
 180 185 190
 Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys
 195 200 205
 Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
 210 215 220
 Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
 225 230 235
 <210> 15
 <211> 436
 <212> PRT
 <213> Artificial
 <220>
 <223> anti CS1 VH-IL15Ra-FC(Knob)
 <400> 15
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

[0391]

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
 20 25 30
 Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Ala Pro Ser Leu
 50 55 60
 Lys Asp Lys Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Pro Asp Gly Asn Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 115 120 125
 Ser Gly Gly Gly Gly Ser Ile Thr Cys Pro Pro Pro Met Ser Val Glu
 130 135 140
 His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg
 145 150 155 160
 Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Cys Ser Leu
 165 170 175
 Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr
 180 185 190
 Pro Ser Leu Lys Cys Ile Arg Gly Gly Gly Gly Ser Glu Pro Lys Ser
 195 200 205
 Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
 210 215 220
 Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 225 230 235 240
 Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
 245 250 255
 His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
 260 265 270
 Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
 275 280 285
 Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
 290 295 300
 Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
 305 310 315 320
 Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
 325 330 335
 Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
 340 345 350
 Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 355 360 365

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 370 375 380
 Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
 385 390 395 400
 Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
 405 410 415
 Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
 420 425 430
 Ser Pro Gly Lys
 435
 <210> 16
 <211> 214
 <212> PRT
 <213> Artificial
 <220>
 <223> anti CD38 VL-CL
 <400> 16
 Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30
 [0392] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110
 Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125
 Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140
 Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160
 Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175
 Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190
 Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205
 Phe Asn Arg Gly Glu Cys

210
 <210> 17
 <211> 452
 <212> PRT
 <213> Artificial
 <220>
 <223> anti CD38 VH-CH1-CH2-CH3(Hole)
 <400> 17
 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Phe
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Gly Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
 85 90 95
 Ala Lys Asp Lys Ile Leu Trp Phe Gly Glu Pro Val Phe Asp Tyr Trp
 100 105 110
 Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
 115 120 125
 Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
 130 135 140
 Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 145 150 155 160
 Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
 165 170 175
 Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 180 185 190
 Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
 195 200 205
 His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
 210 215 220
 Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
 225 230 235 240
 Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 245 250 255
 Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
 260 265 270
 His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
 275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
 290 295 300
 Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
 305 310 315 320
 Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
 325 330 335
 Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
 340 345 350
 Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
 355 360 365
 Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 370 375 380
 Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 385 390 395 400
 Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr
 405 410 415
 Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
 420 425 430
 Met His Glu Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu
 435 440 445
 Ser Pro Gly Lys
 450

[0394]

<210> 18
 <211> 119
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 18
 Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Glu Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
 20 25 30
 Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
 35 40 45
 Gly Leu Ile Thr Pro Tyr Asn Gly Ala Ser Ser Tyr Asn Gln Lys Phe
 50 55 60
 Arg Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Asp Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
 85 90 95
 Ala Arg Gly Gly Tyr Asp Gly Arg Gly Phe Asp Tyr Trp Gly Ser Gly
 100 105 110
 Thr Pro Val Thr Val Ser Ser

115
 <210> 19
 <211> 106
 <212> PRT
 <213> Artificial
 <220>
 <223> VL
 <400> 19
 Asp Ile Glu Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
 1 5 10 15
 Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
 20 25 30
 His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
 35 40 45
 Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Gly Arg Phe Ser Gly Ser
 50 55 60
 Gly Ser Gly Asn Ser Tyr Ser Leu Thr Ile Ser Ser Val Glu Ala Glu
 65 70 75 80
 Asp Asp Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Lys His Pro Leu Thr
 85 90 95
 Phe Gly Ser Gly Thr Lys Val Glu Ile Lys
 100 105

[0395]
 <210> 20
 <211> 127
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 20
 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 Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Lys Asp Met Gly Trp Gly Ser Gly Trp Arg Pro Tyr Tyr Tyr Tyr
 100 105 110
 Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

115
 <210> 23
 <211> 107
 <212> PRT
 <213> Artificial
 <220>
 <223> VL
 <400> 23
 Asp Ile Leu Leu Thr Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly
 1 5 10 15
 Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
 20 25 30
 Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
 35 40 45
 Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser
 65 70 75 80
 Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
 85 90 95
 Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
 100 105

[0397]

<210> 24
 <211> 119
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <220>
 <221> misc_feature
 <222> (1)..(1)
 <223> Xaa can be any naturally occurring amino acid
 <400> 24
 Xaa Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
 20 25 30
 His Ala Trp Ser Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp
 35 40 45
 Ile Gly Tyr Ile Ser Tyr Ser Gly Ile Thr Thr Tyr Asn Pro Ser Leu
 50 55 60
 Lys Ser Arg Val Thr Met Leu Arg Asp Thr Ser Lys Asn Gln Phe Ser
 65 70 75 80
 Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys

85 90 95
 Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Gln Gly
 100 105 110
 Ser Leu Val Thr Val Ser Ser
 115
 <210> 25
 <211> 107
 <212> PRT
 <213> Artificial
 <220>
 <223> VL
 <400> 25
 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 Asp Ile Ser Ser Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 [0398] Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 26
 <211> 118
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 26
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser
 20 25 30
 Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala 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 Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser
 115
 <210> 27
 <211> 107
 <212> PRT
 <213> Artificial
 <220>
 <223> VL
 <400> 27
 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 Asp Val Ser Thr Ala
 20 25 30
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 28
 <211> 113
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 28
 Glu Val Gln Leu Leu Gln Ser Gly Pro Glu Leu Glu Lys Pro Gly Ala
 1 5 10 15
 Ser Val Met Ile Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Tyr
 20 25 30
 Asn Met Asn Trp Val Arg Gln Asn Ile Gly Lys Ser Leu Glu Trp Ile
 35 40 45
 Gly Ala Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
 50 55 60
 Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80
 Met His Leu Lys Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys

				85					90					95			
	Val	Ser	Gly	Met	Glu	Tyr	Trp	Gly	Gln	Gly	Thr	Ser	Val	Thr	Val	Ser	
				100					105					110			
	Ser																
	<210>	29															
	<211>	113															
	<212>	PRT															
	<213>	Artificial															
	<220>																
	<223>	VL															
	<400>	29															
	Glu	Ile	Val	Met	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Val	Ser	Pro	Gly	
	1				5					10					15		
	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Val	His	Arg	
				20					25					30			
	Asn	Gly	Asn	Thr	Tyr	Leu	His	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser	
			35					40					45				
	Pro	Lys	Leu	Leu	Ile	His	Lys	Val	Ser	Asn	Arg	Phe	Ser	Gly	Val	Pro	
		50					55				60						
	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile	
	65				70					75					80		
[0400]	Ser	Arg	Val	Glu	Ala	Glu	Asp	Leu	Gly	Val	Tyr	Phe	Cys	Ser	Gln	Ser	
					85					90					95		
	Thr	His	Val	Pro	Pro	Leu	Thr	Phe	Gly	Ala	Gly	Thr	Lys	Leu	Glu	Leu	
				100					105					110			
	Lys																
	<210>	30															
	<211>	116															
	<212>	PRT															
	<213>	Artificial															
	<220>																
	<223>	VH															
	<400>	30															
	Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser	
	1				5					10					15		
	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr	
				20					25					30			
	Arg	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile	
			35					40					45				
	Gly	Tyr	Ile	Asn	Pro	Ser	Thr	Gly	Tyr	Thr	Glu	Tyr	Asn	Gln	Lys	Phe	
		50					55				60						
	Lys	Asp	Lys	Ala	Thr	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Asn	Thr	Ala	Tyr	

65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser
 115
 <210> 31
 <211> 106
 <212> PRT
 <213> Artificial
 <220>
 <223> VL
 <400> 31
 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 Ser Ala Ser Ser Ser Ile Ser Tyr Met
 20 25 30
 His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
 35 40 45
 Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
 50 55 60
 Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
 65 70 75 80
 Asp Phe Ala Thr Tyr Tyr Cys His Gln Arg Ser Thr Tyr Pro Leu Thr
 85 90 95
 Phe Gly Gln Gly Thr Lys Val Glu Val Lys
 100 105
 <210> 32
 <211> 120
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 32
 Gln Val Gln Leu Val Gln Ser Gly Val Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30
 Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Gly Ile Asn Pro Ser Asn Gly Gly Thr Asn Phe Asn Glu Lys Phe
 50 55 60
 Lys Asn Arg Val Thr Leu Thr Thr Asp Ser Ser Thr Thr Thr Ala Tyr

65 70 75 80
 Met Glu Leu Lys Ser Leu Gln Phe Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Arg Asp Tyr Arg Phe Asp Met Gly Phe Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Thr Val Thr Val Ser Ser
 115 120
 <210> 33
 <211> 111
 <212> PRT
 <213> Artificial
 <220>
 <223> VL
 <400> 33
 Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Gly Val Ser Thr Ser
 20 25 30
 Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
 35 40 45
 Arg Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Val Pro Ala
 50 55 60
 [0402] Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
 65 70 75 80
 Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Arg
 85 90 95
 Asp Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105 110
 <210> 34
 <211> 116
 <212> PRT
 <213> Artificial
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 <223> VH
 <400> 34
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
 20 25 30
 Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Trp Ile Ser Thr Tyr Ser Gly Asn Thr Asn Tyr Ala Gln Lys Leu
 50 55 60
 Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr

65 70 75 80
 Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Arg Gln Leu Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser
 115
 <210> 35
 <211> 107
 <212> PRT
 <213> Artificial
 <220>
 <223> VL
 <400> 35
 Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
 20 25 30
 Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Pro Leu Ile
 35 40 45
 Tyr Asp Ala Ser Thr Arg Ala Thr Gly Val Pro Ala Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Asn Trp Pro Leu
 85 90 95
 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 36
 <211> 119
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 36
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
 20 25 30
 Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Ala Pro Ser Leu
 50 55 60
 Lys Asp Lys Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Pro Asp Gly Asn Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
 115
 <210> 37
 <211> 107
 <212> PRT
 <213> Artificial
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 <400> 37
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Ile Ala
 20 25 30
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
 35 40 45
 Tyr Trp Ala Ser Thr Arg His Thr 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 Gln Pro
 65 70 75 80
 Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Tyr Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 38
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 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 38
 Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn Tyr
 20 25 30
 Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Thr Ile Ser Ser Ala Ser Thr Tyr Ser Tyr Tyr Pro Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

60

65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 100 105 110
 Ser

<210> 41
 <211> 107
 <212> PRT
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 <400> 41

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

[0406]

<210> 42
 <211> 119
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 42
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Tyr Ser
 20 25 30
 Trp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Arg Ile Phe Pro Gly Asp Gly Asp Thr Asp Tyr Asn Gly Lys Phe
 50 55 60
 Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Asn Val Phe Asp Gly Tyr Trp Leu Val Tyr Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
 115
 <210> 43
 <211> 112
 <212> PRT
 <213> Artificial
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 <400> 43
 Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
 1 5 10 15
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
 20 25 30
 Asn Gly Ile Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45
 Pro Gln Leu Leu Ile Tyr Gln Met Ser Asn Leu Val Ser Gly Val Pro
 50 55 60
 [0407] Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ala Gln Asn
 85 90 95
 Leu Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105 110
 <210> 44
 <211> 122
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 44
 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asn Ser Phe
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Gly Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

64

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 Val Thr Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val
 100 105 110
 Thr Val Ser Ser
 115
 <210> 49
 <211> 107
 <212> PRT
 <213> Artificial
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 <400> 49
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Ile Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Asp Asn Trp
 20 25 30
 Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Asp Ala Ser Asn Leu Asp Thr Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 [0410] Ser Gly Ser Gly Thr Tyr Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
 65 70 75 80
 Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Ala Lys Ala Phe Pro Pro
 85 90 95
 Thr Phe Gly Gly Gly Thr Lys Val Asp Ile Lys
 100 105
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 1 5 10 15
 Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Lys Phe Ser Arg Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
 35 40 45
 Ala Thr Ile Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Pro Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Thr Leu Tyr

65 70 75 80
 Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
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 <211> 107
 <212> PRT
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 <400> 51
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Arg Ser Tyr
 20 25 30
 Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
 35 40 45
 Tyr Tyr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
 65 70 75 80
 Asp Asp Thr Ala Thr Tyr Tyr Cys Leu Gln His Gly Glu Ser Pro Phe
 85 90 95
 Thr Leu Gly Ser Gly Thr Lys Leu Glu Ile Lys
 100 105
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 <212> PRT
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 <400> 52
 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 Ala Ala Ser Gly Phe Thr Phe Asn Asp Tyr
 20 25 30
 Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Thr Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Ser Leu Tyr

65	70										75					80				
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Leu	Tyr	Tyr	Cys					
				85					90					95						
Ala	Lys	Asp	Ile	Gln	Tyr	Gly	Asn	Tyr	Tyr	Tyr	Gly	Met	Asp	Val	Trp					
			100					105					110							
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser											
		115					120													
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<211>	107																			
<212>	PRT																			
<213>	Artificial																			
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Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly					
1				5					10					15						
Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Gln	Ser	Val	Ser	Ser	Tyr					
			20					25					30							
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile					
		35					40					45								
Tyr	Asp	Ala	Ser	Asn	Arg	Ala	Thr	Gly	Ile	Pro	Ala	Arg	Phe	Ser	Gly					
	50					55					60									
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Pro					
65					70					75					80					
Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	Arg	Ser	Asn	Trp	Pro	Ile					
				85						90				95						
Thr	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys										
			100					105												
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<211>	117																			
<212>	PRT																			
<213>	Artificial																			
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<223>	VH																			
<400>	54																			
Gln	Ile	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Glu	Val	Val	Lys	Pro	Gly	Ala					
1				5					10					15						
Ser	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asp	Tyr					
			20					25					30							
Tyr	Ile	Thr	Trp	Val	Lys	Gln	Lys	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile					
		35					40					45								
Gly	Trp	Ile	Tyr	Pro	Gly	Ser	Gly	Asn	Thr	Lys	Tyr	Asn	Glu	Lys	Phe					
	50					55					60									
Lys	Gly	Lys	Ala	Thr	Leu	Thr	Val	Asp	Thr	Ser	Ser	Ser	Thr	Ala	Ph					

65 70 75 80
 Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys
 85 90 95
 Ala Asn Tyr Gly Asn Tyr Trp Phe Ala Tyr Trp Gly Gln Gly Thr Gln
 100 105 110
 Val Thr Val Ser Ala
 115
 <210> 55
 <211> 111
 <212> PRT
 <213> Artificial
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 <223> VL
 <400> 55
 Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
 1 5 10 15
 Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Phe Asp
 20 25 30
 Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
 35 40 45
 Lys Val Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
 50 55 60
 [0413] Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
 65 70 75 80
 Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
 85 90 95
 Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110
 <210> 56
 <211> 120
 <212> PRT
 <213> Artificial
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 <223> VH
 <400> 56
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
 20 25 30
 Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr

65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser
 115 120
 <210> 57
 <211> 107
 <212> PRT
 <213> Artificial
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 <400> 57
 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 Asp Val Asn Thr Ala
 20 25 30
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 58
 <211> 118
 <212> PRT
 <213> Artificial
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 <400> 58
 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
 Thr Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95
 Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser
 115
 <210> 59
 <211> 108
 <212> PRT
 <213> Artificial
 <220>
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 <400> 59
 Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Ser
 20 25 30
 Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Ala Phe Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80
 Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
 85 90 95
 Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 60
 <211> 119
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 60
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Tyr
 20 25 30
 Thr Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Asp Val Asn Pro Asn Ser Gly Gly Ser Ile Tyr Asn Gln Arg Phe
 50 55 60
 Lys Gly Arg Phe Thr Leu Ser Val Asp Arg 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 Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
 115
 <210> 61
 <211> 107
 <212> PRT
 <213> Artificial
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 <400> 61
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ile Gly
 20 25 30
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 [0416] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ile Tyr Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 62
 <211> 123
 <212> PRT
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 <400> 62
 Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
 20 25 30
 Tyr Ile Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45
 Gly Gly Ile Asn Pro Thr Ser Gly Gly Ser Asn Phe Asn Glu Lys Phe
 50 55 60
 Lys Thr Arg Val Thr Ile Thr Val Asp Glu Ser Thr Asn Thr Ala Tyr

65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Phe Tyr Phe Cys
 85 90 95
 Ala Arg Gln Gly Leu Trp Phe Asp Ser Asp Gly Arg Gly Phe Asp Phe
 100 105 110
 Trp Gly Gln Gly Ser Thr Val Thr Val Ser Ser
 115 120
 <210> 63
 <211> 114
 <212> PRT
 <213> Artificial
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 <400> 63
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Asn Ile Val His Ser
 20 25 30
 Asn Gly Asn Thr Tyr Leu Asp Trp Tyr Gln Gln Thr Pro Gly Lys Ala
 35 40 45
 Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60
 Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
 65 70 75 80
 Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Phe Gln Tyr
 85 90 95
 Ser His Val Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Gln Ile Thr
 100 105 110
 Arg Glu

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 <212> PRT
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 <400> 64
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Val Ser Ser Gly
 20 25 30
 Asp Tyr Tyr Trp Thr Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu
 35 40 45
 Trp Ile Gly His Ile Tyr Tyr Ser Gly Asn Thr Asn Tyr Asn Pro Ser

50 55 60
 Leu Lys Ser Arg Leu Thr Ile Ser Ile Asp Thr Ser Lys Thr Gln Phe
 65 70 75 80
 Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Ile Tyr Tyr
 85 90 95
 Cys Val Arg Asp Arg Val Thr Gly Ala Phe Asp Ile Trp Gly Gln Gly
 100 105 110
 Thr Met Val Thr Val Ser Ser
 115
 <210> 65
 <211> 107
 <212> PRT
 <213> Artificial
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 <400> 65
 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 Gln Ala Ser Gln Asp Ile Ser Asn Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Ile Ala Thr Tyr Phe Cys Gln His Phe Asp His Leu Pro Leu
 85 90 95
 Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 66
 <211> 121
 <212> PRT
 <213> Artificial
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 <400> 66
 Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30
 Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile
 35 40 45
 Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe

50 55 60
 Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
 100 105 110
 Ala Gly Thr Thr Val Thr Val Ser Ala
 115 120
 <210> 67
 <211> 106
 <212> PRT
 <213> Artificial
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 <400> 67
 Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
 1 5 10 15
 Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
 20 25 30
 His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
 35 40 45
 [0419] Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
 50 55 60
 Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
 65 70 75 80
 Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
 85 90 95
 Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105
 <210> 68
 <211> 123
 <212> PRT
 <213> Artificial
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 <223> VH
 <400> 68
 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Thr
 20 25 30
 Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
 35 40 45
 Gly Arg Ile Asp Pro Ala Asn Gly Tyr Thr Lys Tyr Asp Pro Lys Phe

50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Ala Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Glu Gly Tyr Tyr Gly Asn Tyr Gly Val Tyr Ala Met Asp Tyr
 100 105 110
 Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120
 <210> 69
 <211> 106
 <212> PRT
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 <400> 69
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Lys Thr Ser Gln Asp Ile Asn Lys Tyr
 20 25 30
 Met Ala Trp Tyr Gln Gln Thr Pro Gly Lys Ala Pro Arg Leu Leu Ile
 35 40 45
 [0420] His Tyr Thr Ser Ala Leu Gln Pro Gly Ile Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Arg Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Ile Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Asn Leu Trp Thr
 85 90 95
 Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 70
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 <212> PRT
 <213> Artificial
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 <223> VH
 <400> 70
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
 20 25 30
 Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val

50 55 60
 Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser
 115 120
 <210> 71
 <211> 107
 <212> PRT
 <213> Artificial
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 <400> 71
 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 Asp Val Asn Thr Ala
 20 25 30
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
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 <223> Xaa can be any naturally occurring amino acid
 <400> 72
 Xaa Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp

20 25 30
 His Ala Trp Ser Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp
 35 40 45
 Ile Gly Tyr Ile Ser Tyr Ser Gly Ile Thr Thr Tyr Asn Pro Ser Leu
 50 55 60
 Lys Ser Arg Val Thr Met Leu Arg Asp Thr Ser Lys Asn Gln Phe Ser
 65 70 75 80
 Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Gln Gly
 100 105 110
 Ser Leu Val Thr Val Ser Ser
 115
 <210> 73
 <211> 107
 <212> PRT
 <213> Artificial
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 <400> 73
 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 Asp Ile Ser Ser Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 74
 <211> 116
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 74
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Ile Thr Asp Ser

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

115

<210> 75

<211> 111

<212> PRT

<213> Artificial

<220>

<223> VL

<400> 75

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

<210> 76

<211> 120

<212> PRT

<213> Artificial

<220>

<223> VH

<400> 76

Gln	Val	Gln	Leu	Lys	Glu	Ser	Gly	Pro	Gly	Leu	Val	Ala	Pro	Ser	Gln
1			5						10					15	
Ser	Leu	Ser	Ile	Thr	Cys	Thr	Val	Ser	Gly	Phe	Ser	Leu	Thr	Asp	Tyr

20 25 30
 Gly Val Arg Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45
 Gly Val Ile Trp Gly Gly Gly Ser Thr Tyr Tyr Asn Ser Ala Leu Lys
 50 55 60
 Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
 65 70 75 80
 Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
 85 90 95
 Lys Glu Lys Arg Arg Gly Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Ser Val Thr Val Ser Ser
 115 120
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 <211> 108
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 <400> 77
 Glu Asn Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
 1 5 10 15
 Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Ser Ser
 20 25 30
 Tyr Leu His Trp Tyr Gln Gln Lys Ser Gly Ala Ser Pro Lys Leu Trp
 35 40 45
 Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Val Glu
 65 70 75 80
 Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Gly Tyr Pro
 85 90 95
 Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105
 <210> 78
 <211> 121
 <212> PRT
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 <223> VH
 <400> 78
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Thr Phe Thr Asp Phe

20 25 30
 Tyr Met Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Ile
 35 40 45
 Gly Phe Ile Arg Asp Lys Ala Lys Gly Tyr Thr Thr Glu Tyr Asn Pro
 50 55 60
 Ser Val Lys Gly Arg Val Thr Met Leu Val Asp Thr Ser Lys Asn Gln
 65 70 75 80
 Phe Ser Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
 85 90 95
 Tyr Cys Ala Arg Glu Gly His Thr Ala Ala Pro Phe Asp Tyr Trp Gly
 100 105 110
 Gln Gly Ser Leu Val Thr Val Ser Ser
 115 120
 <210> 79
 <211> 107
 <212> PRT
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 <220>
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 <400> 79
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Ile Asp Lys Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Asn Thr Asn Asn Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Ile Ala Thr Tyr Tyr Cys Leu Gln His Ile Ser Arg Pro Arg
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 80
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 <220>
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 <400> 80
 Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Asn Ser Ser

20 25 30
 Ser Tyr Tyr Trp Gly Trp Leu Arg Gln Ser Pro Gly Lys Gly Leu Glu
 35 40 45
 Trp Ile Gly Ser Phe Phe Tyr Thr Gly Ser Thr Tyr Tyr Asn Pro Ser
 50 55 60
 Leu Arg Ser Arg Leu Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
 65 70 75 80
 Ser Leu Met Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95
 Cys Ala Arg Gln Ser Thr Tyr Tyr Tyr Gly Ser Gly Asn Tyr Tyr Gly
 100 105 110
 Trp Phe Asp Arg Trp Asp Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125
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 <212> PRT
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 Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
 85 90 95
 Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 <210> 82
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 <400> 82
 Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr

20 25 30
 Asp Ile Asn Trp Val Arg Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
 35 40 45
 Gly Trp Ile Phe Pro Gly Asp Gly Ser Thr Lys Tyr Asn Glu Lys Phe
 50 55 60
 Lys Gly Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80
 Met Gln Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
 85 90 95
 Ala Arg Glu Asp Tyr Tyr Asp Asn Ser Tyr Tyr Phe Asp Tyr Trp Gly
 100 105 110
 Gln Gly Thr Thr Leu Thr Val Ser Ser
 115 120
 <210> 83
 <211> 107
 <212> PRT
 <213> Artificial
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 <400> 83
 Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
 1 5 10 15
 Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
 35 40 45
 Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
 65 70 75 80
 Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp
 85 90 95
 Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105
 <210> 84
 <211> 120
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 84
 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

20 25 30
 Ile Met Met Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Thr 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 Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser
 115 120
 <210> 85
 <211> 110
 <212> PRT
 <213> Artificial
 <220>
 <223> VL
 <400> 85
 Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1 5 10 15
 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
 20 25 30
 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
 85 90 95
 Ser Thr Arg Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
 100 105 110
 <210> 86
 <211> 125
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 86
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Glu Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Arg Asp Tyr

20 25 30
 Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Ser Gly Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Lys Asp Arg Leu Ser Ile Thr Ile Arg Pro Arg Tyr Tyr Gly Leu
 100 105 110
 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125
 <210> 87
 <211> 112
 <212> PRT
 <213> Artificial
 <220>
 <223> VL
 <400> 87
 Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1 5 10 15
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser
 20 25 30
 Ile Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Ser Gly Gln Ser
 35 40 45
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 Ser Arg Val Glu Ala Glu Asp Val Gly Phe Tyr Tyr Cys Met Gln Ala
 85 90 95
 Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110
 <210> 88
 <211> 116
 <212> PRT
 <213> Artificial
 <220>
 <223> VH
 <400> 88
 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 Ala Ala Ser Arg Phe Thr Phe Asp Asp Tyr

20 25 30
 Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Glu Asn Ser Leu Phe
 65 70 75 80
 Leu Gln Met Asn Gly Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
 85 90 95
 Ala Lys Gly Arg Asp Ser Phe Asp Ile Trp Gly Gln Gly Thr Met Val
 100 105 110
 Thr Val Ser Ser
 115
 <210> 89
 <211> 107
 <212> PRT
 <213> Artificial
 <220>
 <223> VL
 <400> 89
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly 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 Gly Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105
 <210> 90
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 <223> VH
 <400> 90
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr

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

115

120

<210> 91

<211> 106

<212> PRT

<213> Artificial

<220>

<223> VL

<400> 91

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 Ser Ser Val Ser Tyr Met

20

25

30

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

35

40

45

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

50

55

60

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

65

70

75

80

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

85

90

95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100

105

<210> 92

<211> 113

<212> PRT

<213> Artificial

<220>

<223> VH

<400> 92

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

1

5

10

15

Ser Val Met Ile Ser Cys Lys Ala Ser Gly Ser Ser Phe Thr Gly Tyr

[0431]

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

<210> 93
 <211> 113
 <212> PRT
 <213> Artificial
 <220>
 <223> VL
 <400> 93

[0432]

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

<210> 94
 <211> 231
 <212> PRT
 <213> Artificial
 <220>
 <223> FC-Knob (hIgG1)
 <400> 94

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

1 5 10 15
 Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 20 25 30
 Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 35 40 45
 Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 50 55 60
 Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 65 70 75 80
 Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 85 90 95
 Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
 100 105 110
 Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 115 120 125
 Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
 130 135 140
 Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser
 145 150 155 160
 Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 165 170 175
 Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 [0433] 180 185 190
 Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
 195 200 205
 Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 210 215 220
 Ser Leu Ser Leu Ser Pro Gly
 225 230
 <210> 95
 <211> 231
 <212> PRT
 <213> Artificial
 <220>
 <223> FC-Hole(hIgG1)
 <400> 95
 Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
 1 5 10 15
 Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 20 25 30
 Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 35 40 45
 Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 50 55 60

[0434]

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

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<110> 屈向东

<120> 一种双特异抗体及其应用

<150> 201911253241.6

<151> 2019-12-09

<160> 95

<170> SIPOSequenceListing 1.0

<210> 1

<211> 114

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 1

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

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Thr Ser

<210> 2

<211> 114

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 2

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

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Val	Ile	Ser	Cys	Glu	Ser	Gly	Asp	Ala	Ser	Ile	His	Asp	Thr	Val	Glu
50						55					60				
Asn	Leu	Ile	Ile	Leu	Ala	Asn	Asn	Ser	Leu	Ser	Ser	Asn	Gly	Asn	Val
65					70				75					80	
Thr	Glu	Ser	Gly	Cys	Lys	Glu	Cys	Glu	Glu	Leu	Glu	Glu	Lys	Asn	Ile
				85					90					95	
Lys	Glu	Phe	Leu	Gln	Ser	Phe	Val	His	Ile	Val	Gln	Met	Phe	Ile	Asn
			100					105						110	

Thr Ser

<210> 3

<211> 178

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 3

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

Thr Thr

<210> 4

<211> 65

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 4

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

Arg

65

<210> 5

<211> 73

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 5

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

Arg Asp Pro Ala Leu Val His Gln Arg

65

70

<210> 6

<211> 77

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 6

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

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
50 55 60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro
65 70 75

<210> 7

<211> 86

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 7

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1 5 10 15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
20 25 30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
35 40 45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
50 55 60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val
65 70 75 80

Thr Thr Ala Gly Val Thr
85

<210> 8

<211> 102

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 8

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1 5 10 15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
20 25 30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
35 40 45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
50 55 60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val
65 70 75 80

Thr Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly
85 90 95

Lys Glu Pro Ala Ala Ser

100

<210> 9

<211> 65

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 9

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

Arg

65

<210> 10

<211> 236

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 10

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

Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr			
145	150	155	160
Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Cys Glu Ser			
	165	170	175
Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala			
	180	185	190
Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys			
	195	200	205
Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser			
	210	215	220
Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser			
225	230	235	
<210> 11			
<211> 437			
<212> PRT			
<213> 人工序列(Artificial Sequence)			
<400> 11			
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly			
1	5	10	15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr			
	20	25	30
Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val			
	35	40	45
Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val			
	50	55	60
Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr			
65	70	75	80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys			
	85	90	95
Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln			
	100	105	110
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly			
	115	120	125
Gly Ser Gly Gly Gly Gly Ser Ile Thr Cys Pro Pro Pro Met Ser Val			
	130	135	140
Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu			
145	150	155	160
Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Cys Ser			
	165	170	175

Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr		
180	185	190
Thr Pro Ser Leu Lys Cys Ile Arg Gly Gly Gly Gly Ser Glu Pro Lys		
195	200	205
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu		
210	215	220
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr		
225	230	235
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val		
245	250	255
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val		
260	265	270
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser		
275	280	285
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu		
290	295	300
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala		
305	310	315
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro		
325	330	335
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln		
340	345	350
Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala		
355	360	365
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr		
370	375	380
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu		
385	390	395
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser		
405	410	415
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser		
420	425	430
Leu Ser Pro Gly Lys		
435		

<210> 12

<211> 214

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 12

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Lys	Ala	Ser	Gln	Asp	Val	Ser	Ile	Gly
		20						25					30		
Val	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40					45			
Tyr	Ser	Ala	Ser	Tyr	Arg	Tyr	Thr	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
		50				55					60				
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75				80	
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Tyr	Ile	Tyr	Pro	Tyr
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala
				100					105					110	
Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
		115						120					125		
Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
		130					135				140				
Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
145					150					155				160	
Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
				165					170					175	
Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
			180					185					190		
Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
		195					200					205			
Phe	Asn	Arg	Gly	Glu	Cys										
		210													

<210> 13

<211> 449

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 13

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

Ala Asp Val Asn Pro Asn Ser Gly Gly Ser Ile Tyr Asn Gln Arg Phe		
50	55	60
Lys Gly Arg Phe Thr Leu Ser Val Asp Arg 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 Asn Leu Gly Pro Ser Phe Tyr Phe Asp Tyr Trp Gly Gln Gly		
100	105	110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
115	120	125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
130	135	140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
145	150	155 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
165	170	175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
180	185	190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
195	200	205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys		
210	215	220
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
225	230	235 240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
245	250	255
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
260	265	270
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
275	280	285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val		
290	295	300
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
305	310	315 320
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
325	330	335
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
340	345	350
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser		

355	360	365
Cys Ala 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
Asp Ser Asp Gly Ser Phe Phe Leu Val 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 Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
435	440	445
Lys		
<210> 14		
<211> 236		
<212> PRT		
<213> 人工序列(Artificial Sequence)		
<400> 14		
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly		
1	5	10
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Ile Ala		
20	25	30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile		
35	40	45
Tyr Trp Ala Ser Thr Arg His Thr 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 Gln Pro		
65	70	75
Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Tyr Pro Tyr		
85	90	95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser		
100	105	110
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn Trp Val Asn Val Ile		
115	120	125
Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp		
130	135	140
Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr		
145	150	155
Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Cys Glu Ser		
165	170	175

Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala
 180 185 190
 Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys
 195 200 205
 Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
 210 215 220
 Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
 225 230 235
 <210> 15
 <211> 436
 <212> PRT
 <213> 人工序列(Artificial Sequence)
 <400> 15
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
 20 25 30
 Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Ala Pro Ser Leu
 50 55 60
 Lys Asp Lys Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Pro Asp Gly Asn Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 115 120 125
 Ser Gly Gly Gly Gly Ser Ile Thr Cys Pro Pro Pro Met Ser Val Glu
 130 135 140
 His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg
 145 150 155 160
 Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Cys Ser Leu
 165 170 175
 Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr
 180 185 190
 Pro Ser Leu Lys Cys Ile Arg Gly Gly Gly Gly Ser Glu Pro Lys Ser
 195 200 205

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu			
210	215	220	
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu			
225	230	235	240
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser			
	245	250	255
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu			
	260	265	270
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr			
	275	280	285
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn			
290	295	300	
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro			
305	310	315	320
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln			
	325	330	335
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val			
	340	345	350
Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val			
	355	360	365
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro			
370	375	380	
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr			
385	390	395	400
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val			
	405	410	415
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu			
	420	425	430
Ser Pro Gly Lys			
435			
<210> 16			
<211> 214			
<212> PRT			
<213> 人工序列(Artificial Sequence)			
<400> 16			
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly			
1	5	10	15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr			
	20	25	30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110
 Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125
 Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140
 Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160
 Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175
 Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190
 Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205
 Phe Asn Arg Gly Glu Cys
 210

<210> 17

<211> 452

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 17

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

Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Phe	Cys	
				85					90					95		
Ala	Lys	Asp	Lys	Ile	Leu	Trp	Phe	Gly	Glu	Pro	Val	Phe	Asp	Tyr	Trp	
				100					105					110		
Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	
				115					120					125		
Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	
				130					135					140		
Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	
				145					150					155		
Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	
				165					170					175		
Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	
				180					185					190		
Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	
				195					200					205		
His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	
				210					215					220		
Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	
				225					230					235		
Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	
				245					250					255		
Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	
				260					265					270		
His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	
				275					280					285		
Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	
				290					295					300		
Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	
				305					310					315		
Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	
				325					330					335		
Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	
				340					345					350		
Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	
				355					360					365		
Ser	Leu	Ser	Cys	Ala	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	
				370					375					380		
Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	

385	390	395	400
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr			
	405	410	415
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val			
	420	425	430
Met His Glu Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu			
	435	440	445
Ser Pro Gly Lys			
450			

<210> 18

<211> 119

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 18

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

<210> 19

<211> 106

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 19

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

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

<210> 20

<211> 127

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 20

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

<210> 21

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 21

Glu Leu 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 Thr Ser Gln Ser Ile Ser Ser Tyr

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

<210> 22

<211> 119

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 22

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

<210> 23

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 23

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

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

<210> 24

<211> 119

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 24

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

<210> 25

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 25

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

<210> 26

<211> 118

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 26

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

<210> 27

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 27

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

<210> 28

<211> 113

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 28

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

Ser

<210> 29

<211> 113

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 29

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

Lys

<210> 30

<211> 116

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 30

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

Thr Val Ser Ser

115

<210> 31

<211> 106

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 31

```

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

```

<210> 32

<211> 120

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 32

```

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

```

<210> 33

<211> 111

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 33

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

<210> 34

<211> 116

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 34

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

<210> 35

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 35

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

<210> 36

<211> 119

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 36

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

<210> 37

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 37

```

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

```

<210> 38

<211> 119

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 38

```

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

```

115

<210> 39

<211> 112

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 39

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

<210> 40

<211> 113

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 40

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

Ser

<210> 41

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 41

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

1 5 10 15

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

20 25 30

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

35 40 45

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

50 55 60

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

65 70 75 80

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

85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 42

<211> 119

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 42

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

1 5 10 15

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

20 25 30

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

35 40 45

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

50 55 60

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

65 70 75 80

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

85 90 95

Ala Arg Asn Val Phe Asp Gly Tyr Trp Leu Val Tyr Trp Gly Gln Gly

100 105 110

Thr Leu Val Thr Val Ser Ser

115

<210> 43

<211> 112

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 43

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

1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser

20 25 30

Asn Gly Ile Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Ser

35 40 45

Pro Gln Leu Leu Ile Tyr Gln Met Ser Asn Leu Val Ser Gly Val Pro

50 55 60

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

65 70 75 80

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

85 90 95

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

100 105 110

<210> 44

<211> 122

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 44

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

1 5 10 15

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

20 25 30

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

35 40 45

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

50 55 60

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

65 70 75 80

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

85 90 95

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

100	105	110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser		
115	120	
<210> 45		
<211> 107		
<212> PRT		
<213> 人工序列(Artificial Sequence)		
<400> 45		
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly		
1	5	10
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr		
	20	25
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile		
	35	40
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly		
	50	55
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro		
65	70	75
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro		
	85	90
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys		
	100	105

<210> 46

<211> 121

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 46

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

Cys Ala Arg Val Ser Ile Phe Gly Val Gly Thr Phe Asp Tyr Trp Gly
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 47

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 47

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Tyr Gly Ser Thr Pro Leu
 85 90 95

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

<210> 48

<211> 116

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 48

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys 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

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

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Val Thr Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val			
	100	105	110
Thr Val Ser Ser			
	115		

<210> 49

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 49

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

<210> 50

<211> 119

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 50

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

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Arg Asp Tyr Asp Leu Asp Tyr Phe Asp Ser Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
 115

<210> 51

<211> 107

<212> PRT

<213> 人工序列 (Artificial Sequence)

<400> 51

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

<210> 52

<211> 122

<212> PRT

<213> 人工序列 (Artificial Sequence)

<400> 52

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

65						70						75						80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Leu	Tyr	Tyr	Cys			
					85						90						95	
Ala	Lys	Asp	Ile	Gln	Tyr	Gly	Asn	Tyr	Tyr	Tyr	Gly	Met	Asp	Val	Trp			
					100						105						110	
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser									
					115						120							

<210> 53

<211> 107

<212> PRT

〈213〉 人工序列 (Artificial Sequence)

<400> 53

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

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

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Pro
65					70					75					80
Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	Arg	Ser	Asn	Trp	Pro	Ile
				85					90					95	

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

⟨210⟩ 54

<211> 117

<212> PRT

〈213〉 人工序列 (Artificial Sequence)

<400> 54

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

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

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

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

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

Thr Phe Ile Ser Tyr Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95
 Ala Arg Thr Gly Trp Leu Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser
 115

<210> 59

<211> 108

<212> PRT

<213> 人工序列 (Artificial Sequence)

<400> 59

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

<210> 60

<211> 119

<212> PRT

<213> 人工序列 (Artificial Sequence)

<400> 60

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

Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr
			20					25					30		

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

<210> 63

<211> 114

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 63

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

Arg Glu

<210> 64

<211> 119

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 64

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

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

<210> 65

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 65

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

<210> 66

<211> 121

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 66

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

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

<210> 67

<211> 106

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 67

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

<210> 68

<211> 123

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 68

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

<210> 69

<211> 106

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 69

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

<210> 70

<211> 120

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 70

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

<210> 71

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 71

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

<210> 72

<211> 119

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 72

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

<210> 73

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 73

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

<210> 74

<211> 116

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 74

```

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

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<210> 75

<211> 111

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 75

```

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

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<210> 76

<211> 120

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 76

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

<210> 77

<211> 108

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 77

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

<210> 78

<211> 121

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 78

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

<210> 79

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 79

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

100	105
<210> 80	
<211> 127	
<212> PRT	
<213> 人工序列(Artificial Sequence)	
<400> 80	
Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu	
1 5 10 15	
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Asn Ser Ser	
20 25 30	
Ser Tyr Tyr Trp Gly Trp Leu Arg Gln Ser Pro Gly Lys Gly Leu Glu	
35 40 45	
Trp Ile Gly Ser Phe Phe Tyr Thr Gly Ser Thr Tyr Tyr Asn Pro Ser	
50 55 60	
Leu Arg Ser Arg Leu Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe	
65 70 75 80	
Ser Leu Met Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr	
85 90 95	
Cys Ala Arg Gln Ser Thr Tyr Tyr Tyr Gly Ser Gly Asn Tyr Tyr Gly	
100 105 110	
Trp Phe Asp Arg Trp Asp Gln Gly Thr Leu Val Thr Val Ser Ser	
115 120 125	
<210> 81	
<211> 107	
<212> PRT	
<213> 人工序列(Artificial Sequence)	
<400> 81	
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly	
1 5 10 15	
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr	
20 25 30	
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile	
35 40 45	
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly	
50 55 60	
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro	
65 70 75 80	
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro	
85 90 95	

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

<210> 82

<211> 121

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 82

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

<210> 83

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 83

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

	85	90	95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys			
100	105		
<210> 84			
<211> 120			
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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly			
1 5 10 15			
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr			
20 25 30			
Ile Met Met Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val			
35 40 45			
Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Thr 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 Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln			
100 105 110			
Gly Thr Leu Val Thr Val Ser Ser			
115 120			

<210> 85

<211> 110

<212> PRT

<213> 人工序列 (Artificial Sequence)

<400> 85

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
 85 90 95
 Ser Thr Arg Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
 100 105 110

<210> 86

<211> 125

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 86

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

<210> 87

<211> 112

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 87

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

65	70	75	80
Ser Arg Val Glu Ala Glu Asp Val Gly Phe Tyr Tyr Cys Met Gln Ala			
	85	90	95
Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys			
	100	105	110

<210> 88

<211> 116

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 88

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

<210> 89

<211> 107

<212> PRT

<213> 人工序列(Artificial Sequence)

<400> 89

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

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	Ser	Ser	Val	Ser	Tyr	Met
			20					25					30		
His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Pro	Leu	Ile	Tyr
		35					40					45			
Ala	Pro	Ser	Asn	Leu	Ala	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser

50	55	60
Asp Arg Phe Ser Gly	Ser Gly Ser Gly Thr	Asp Phe Thr Leu Lys Ile
65	70	75
Ser Arg Val Glu Ala Glu	Asp Leu Gly Val Tyr Phe Cys	Ser Gln Ser
85	90	95
Thr His Val Pro Pro Leu	Thr Phe Gly Ala Gly Thr Lys	Leu Glu Leu
100	105	110
Lys		
<210> 94		
<211> 231		
<212> PRT		
<213> 人工序列 (Artificial Sequence)		
<400> 94		
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala		
1	5	10
Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro		
20	25	30
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val		
35	40	45
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val		
50	55	60
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln		
65	70	75
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln		
85	90	95
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala		
100	105	110
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro		
115	120	125
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr		
130	135	140
Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser		
145	150	155
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr		
165	170	175
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr		
180	185	190
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe		
195	200	205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 210 215 220
 Ser Leu Ser Leu Ser Pro Gly
 225 230
 <210> 95
 <211> 231
 <212> PRT
 <213> 人工序列(Artificial Sequence)
 <400> 95
 Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
 1 5 10 15
 Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 20 25 30
 Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 35 40 45
 Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 50 55 60
 Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 65 70 75 80
 Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 85 90 95
 Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
 100 105 110
 Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 115 120 125
 Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
 130 135 140
 Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser
 145 150 155 160
 Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 165 170 175
 Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val
 180 185 190
 Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
 195 200 205
 Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 210 215 220
 Ser Leu Ser Leu Ser Pro Gly
 225 230

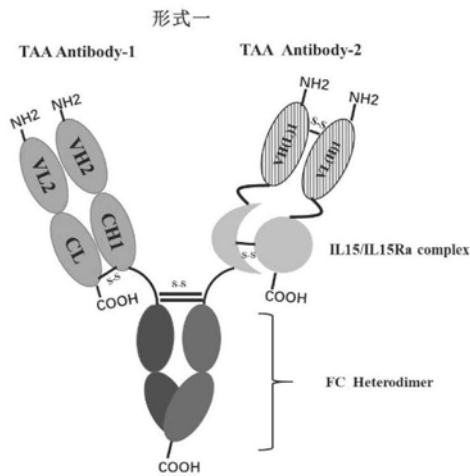


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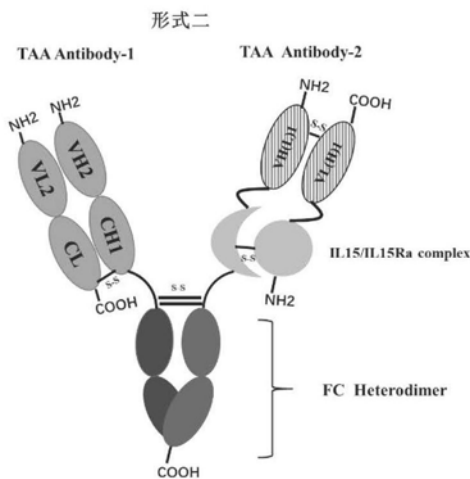


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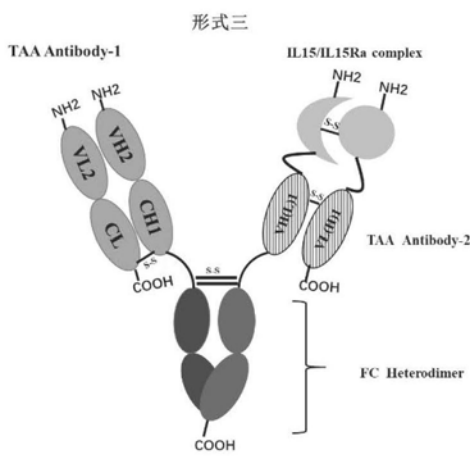


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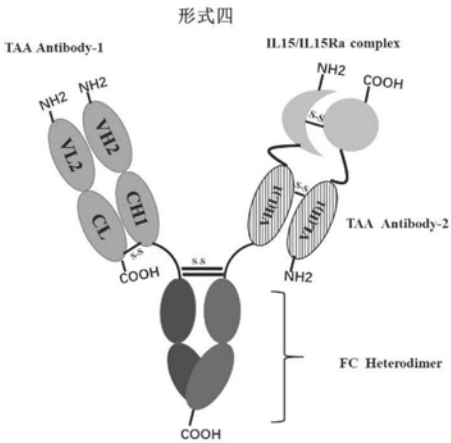


图4

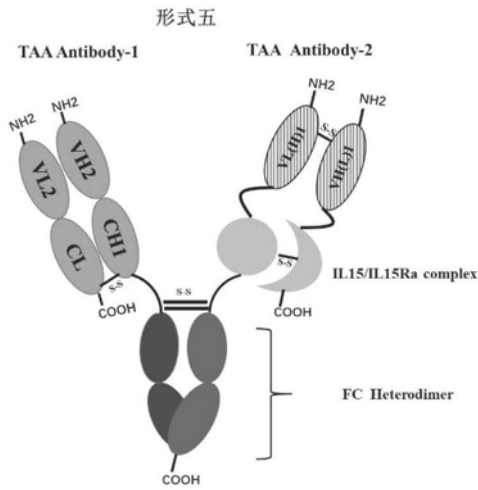


图5

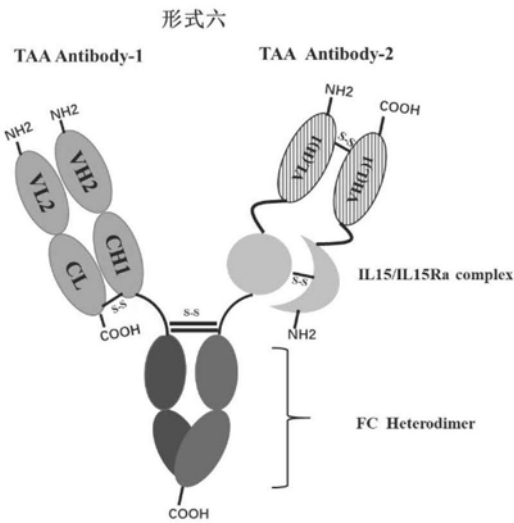


图6

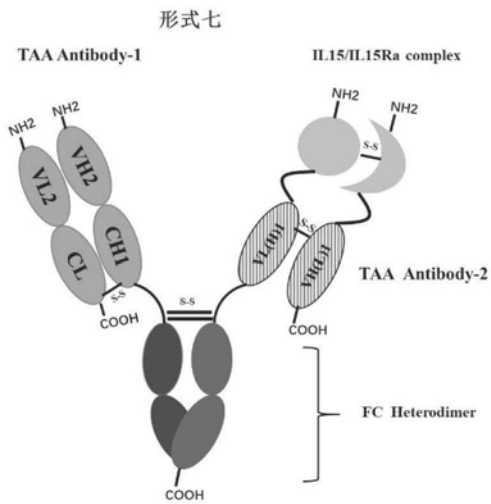


图7

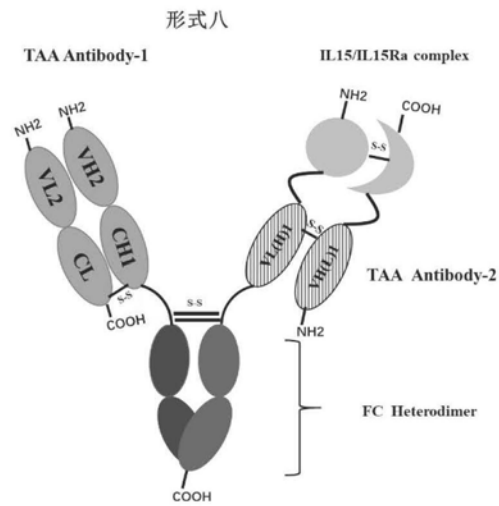


图8

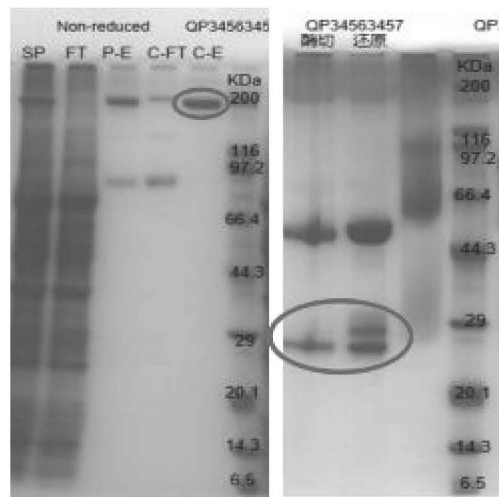


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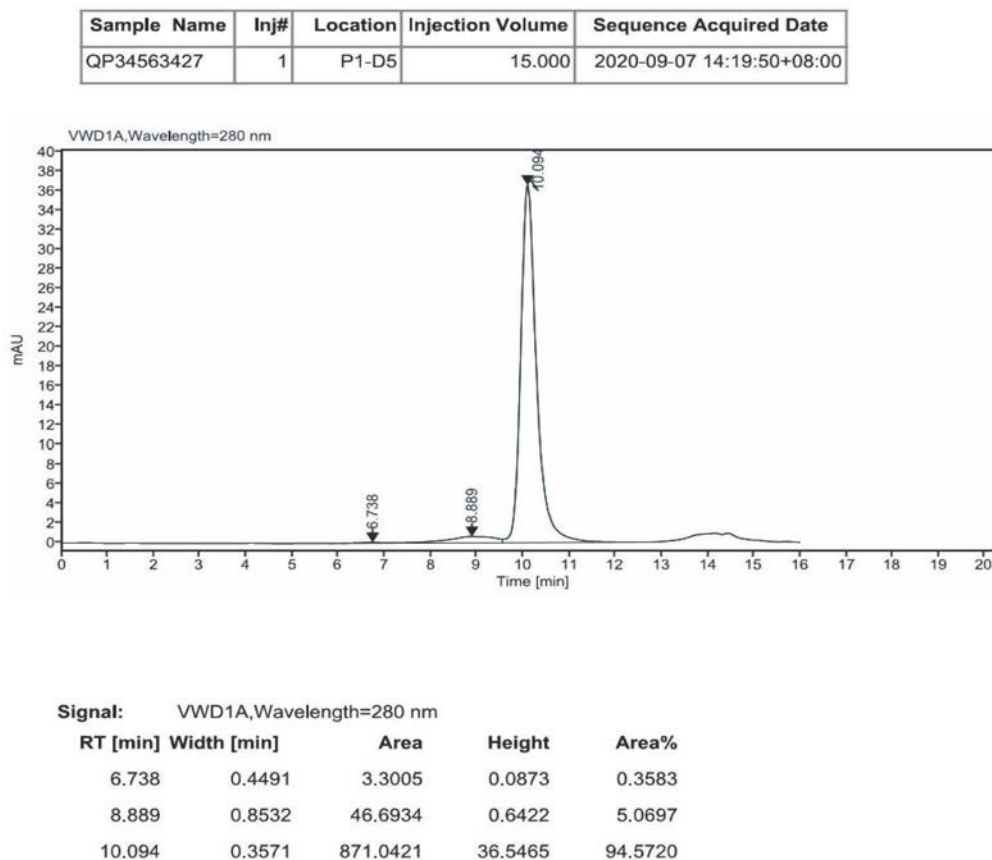


图10

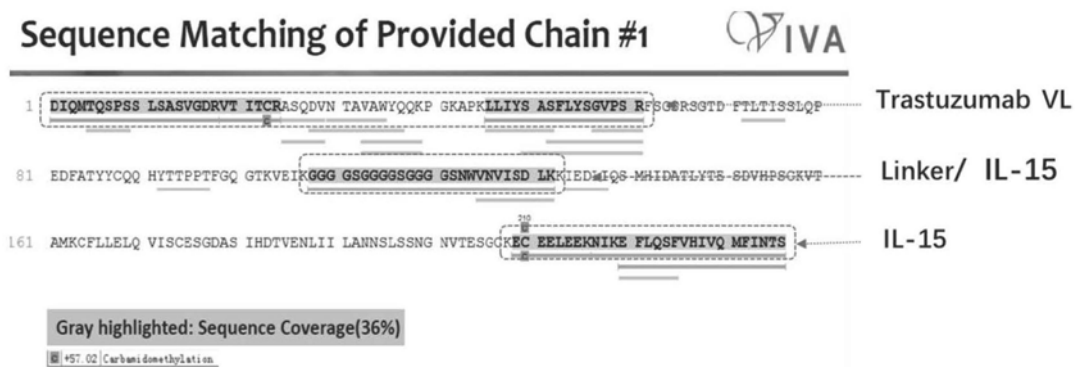


图11a

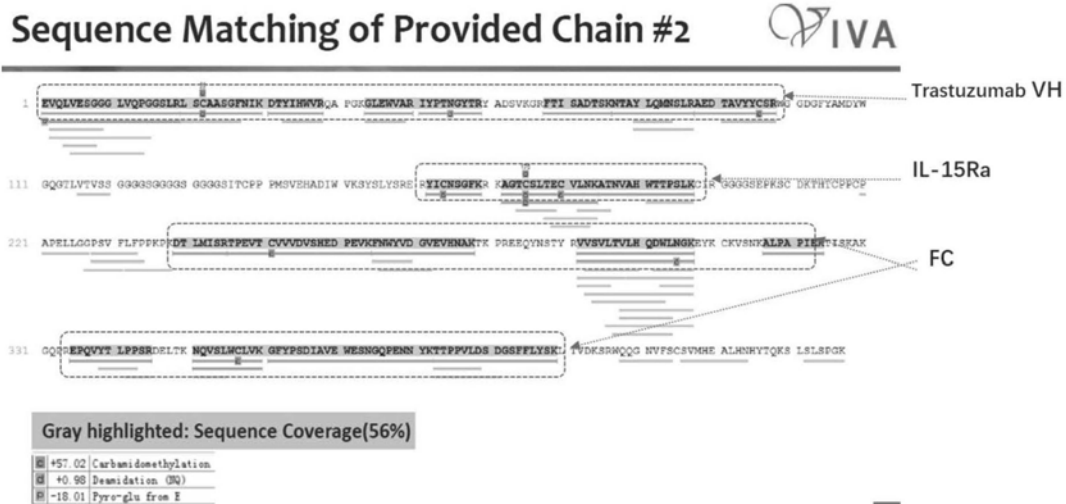


图11b

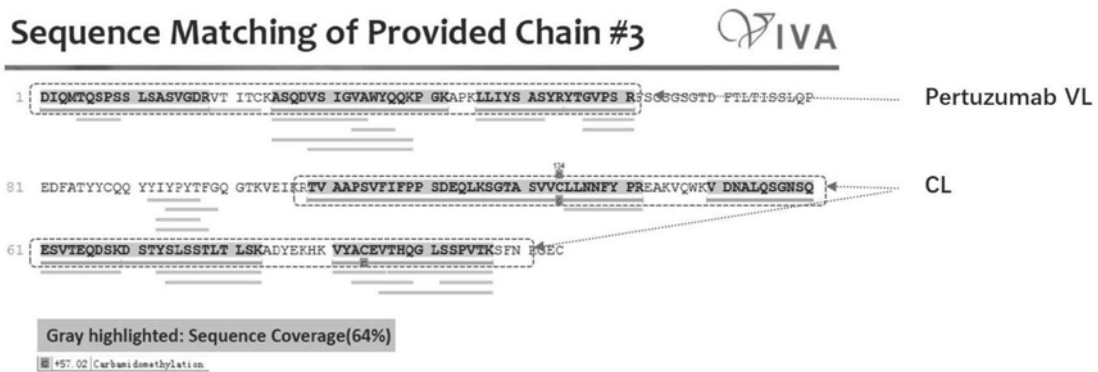


图11c

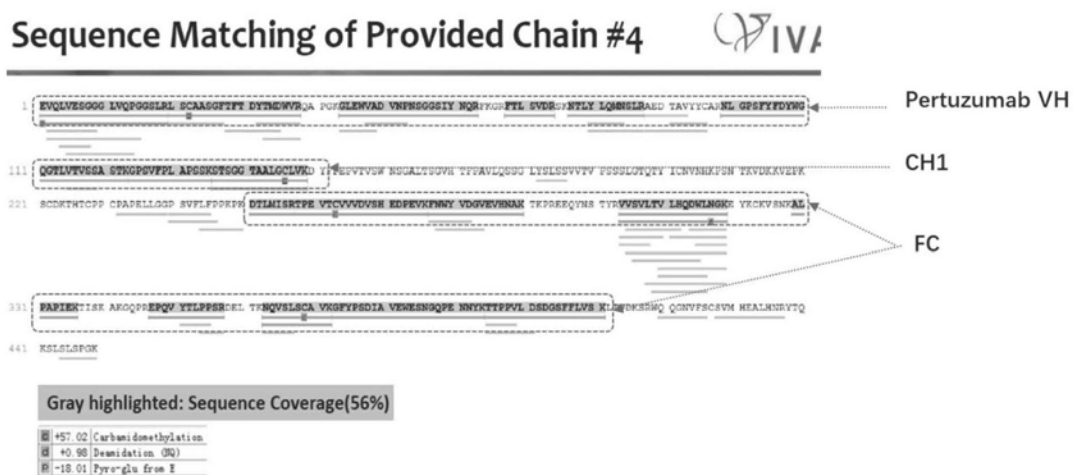


图11d

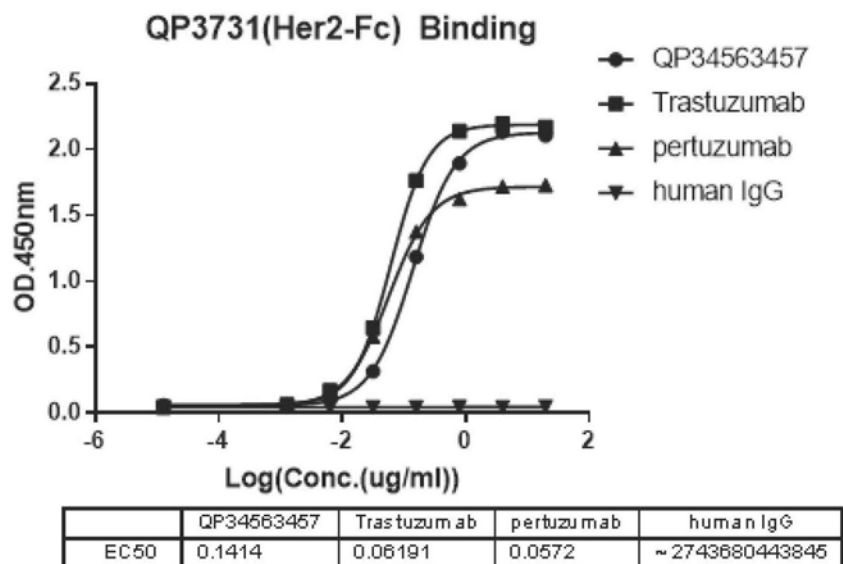


图12

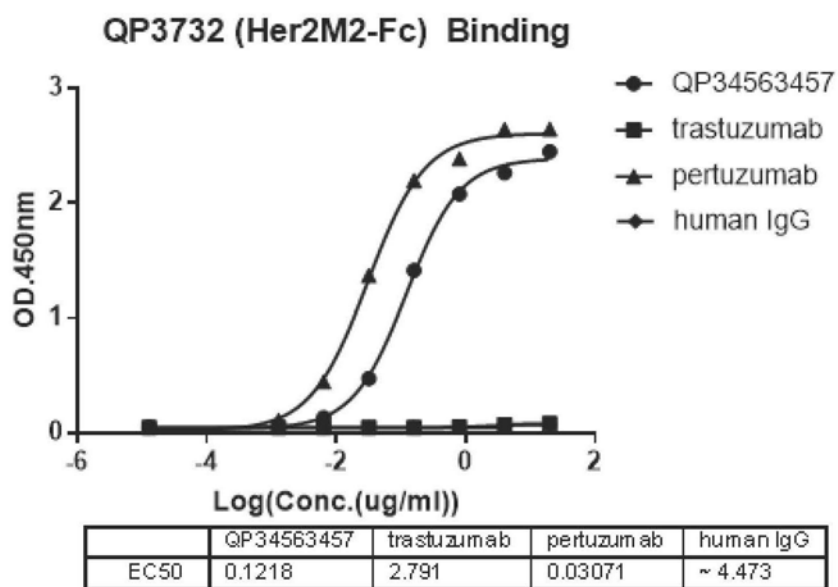


图13

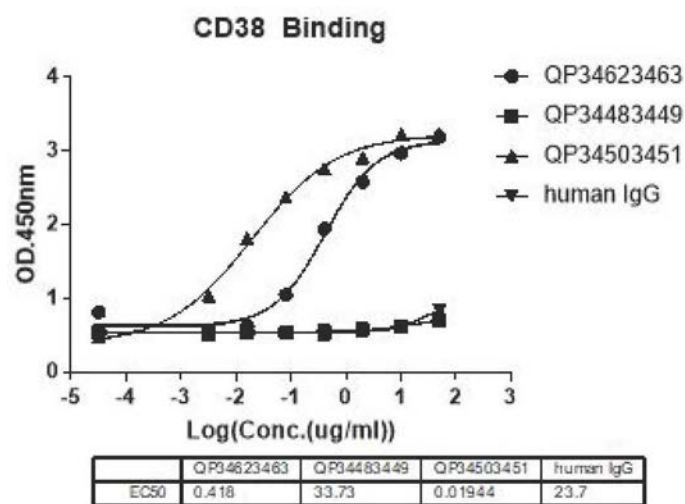


图14

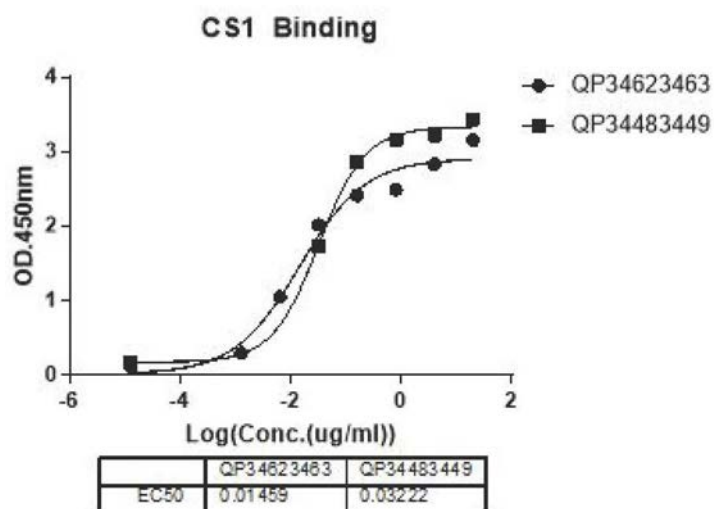


图15

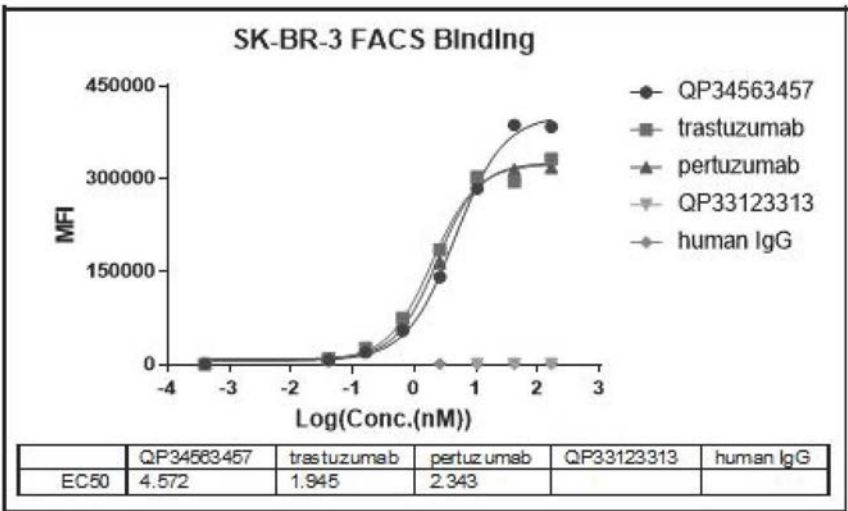


图16

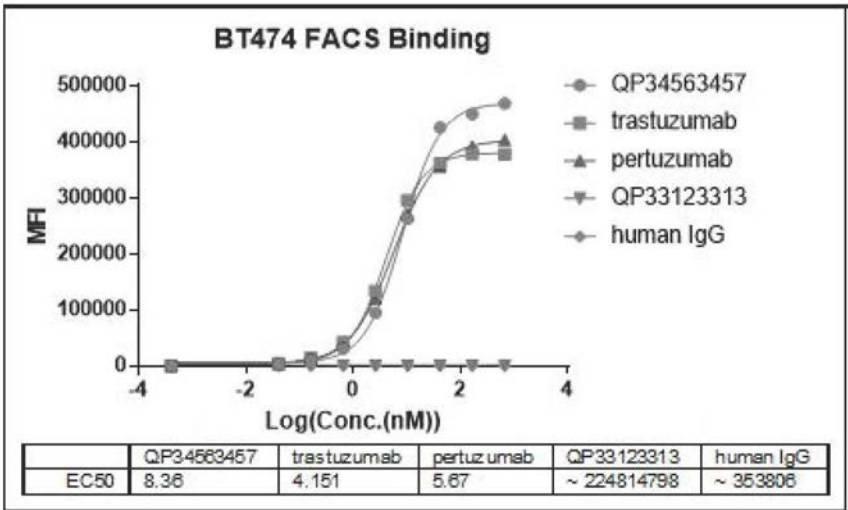


图17

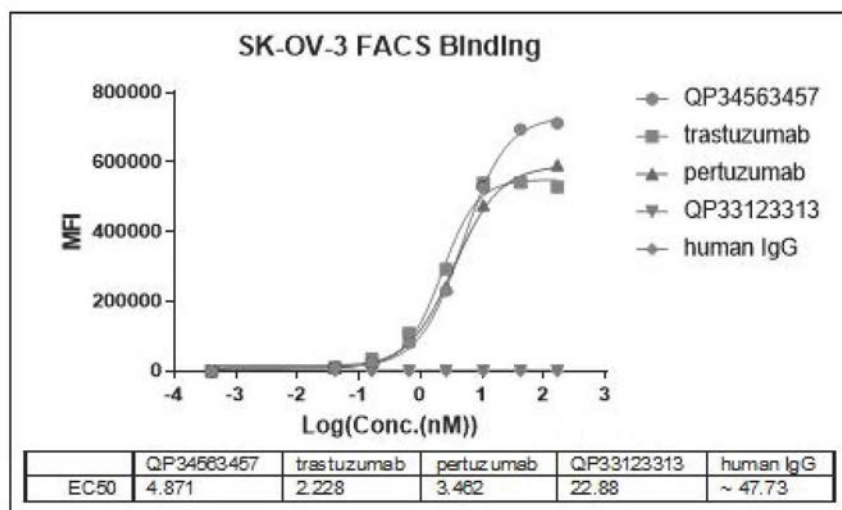


图18

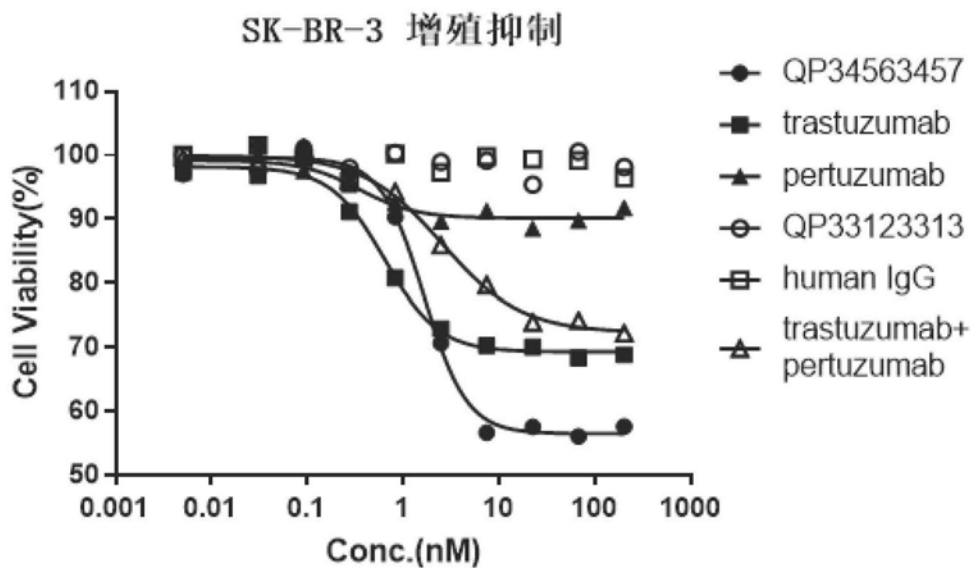


图19

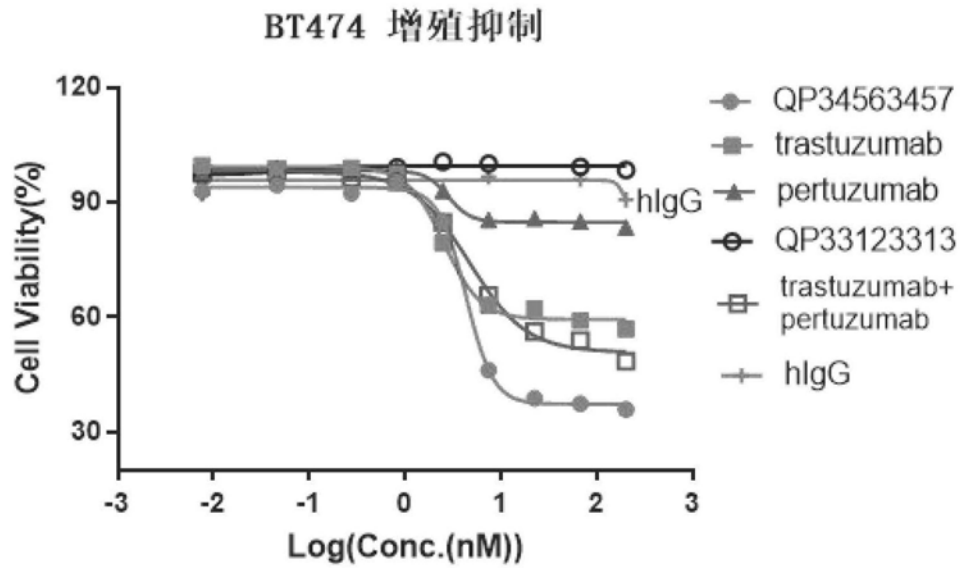


图20

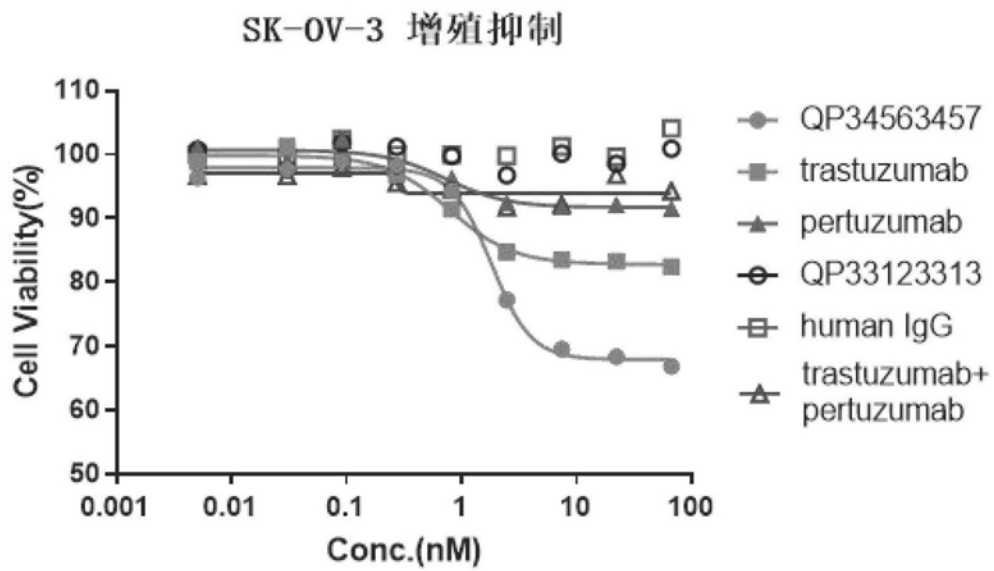


图21

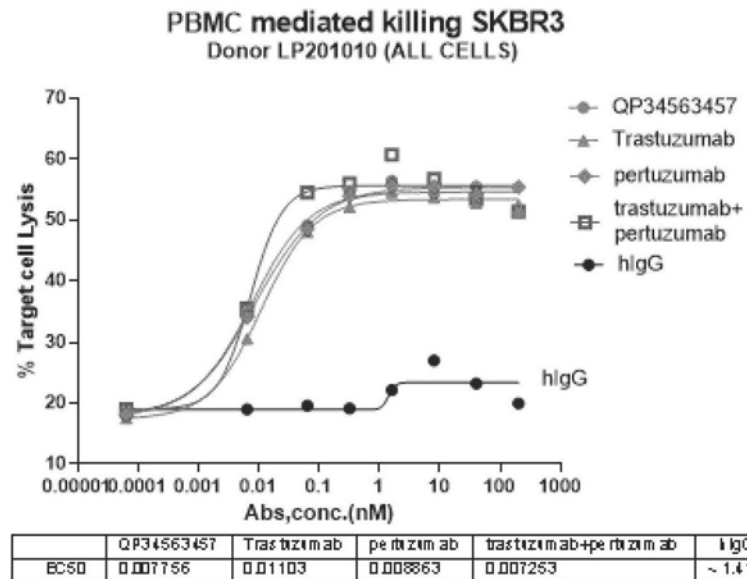


图22

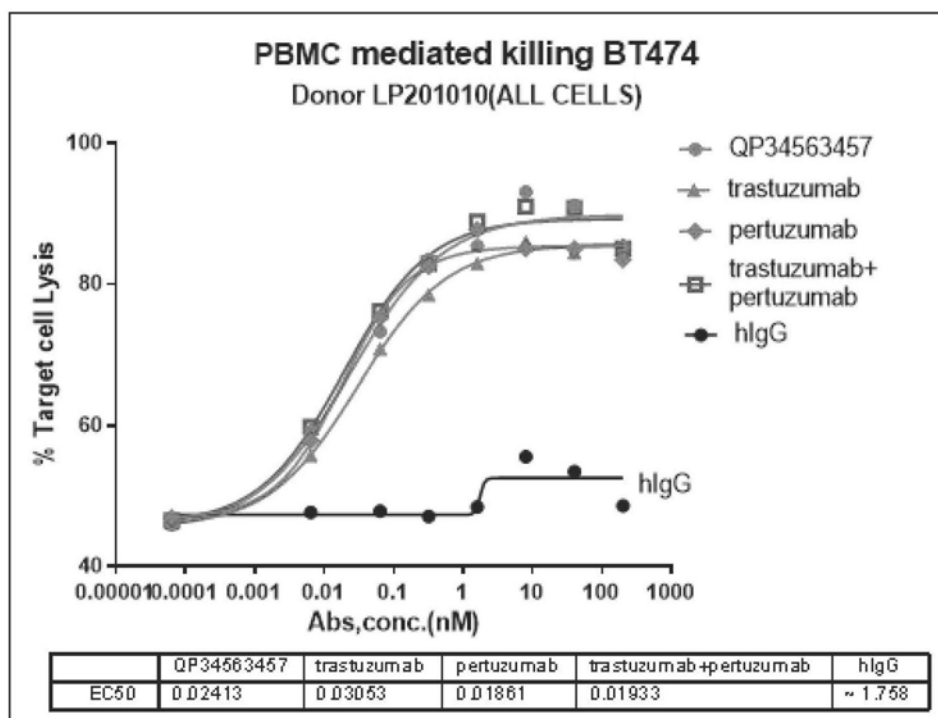


图23

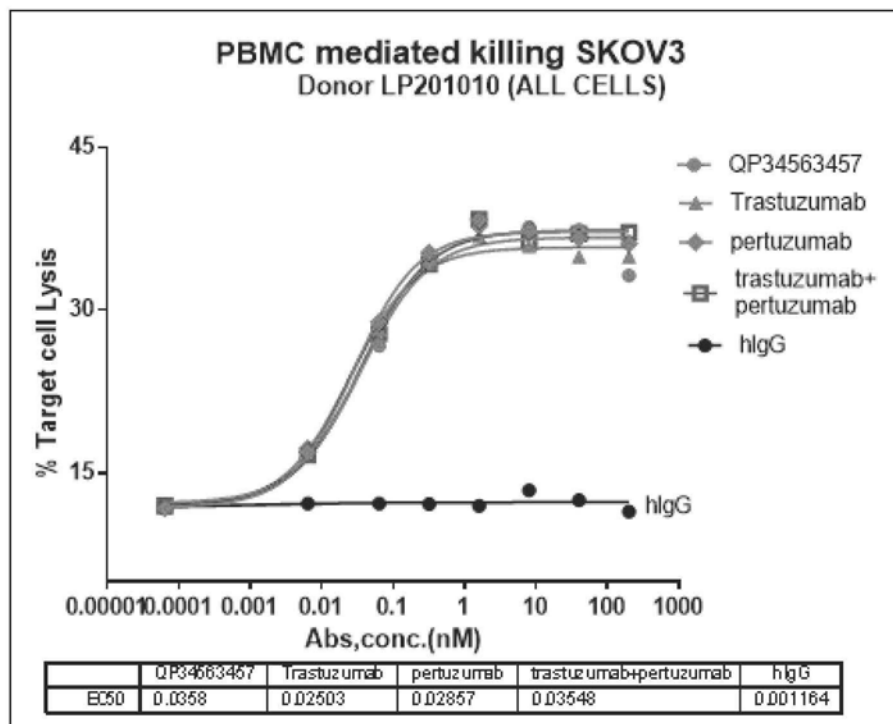


图24

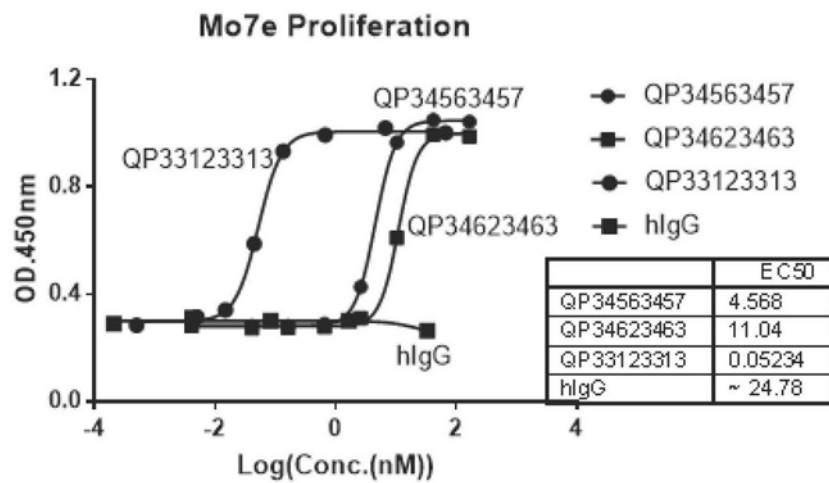


图25

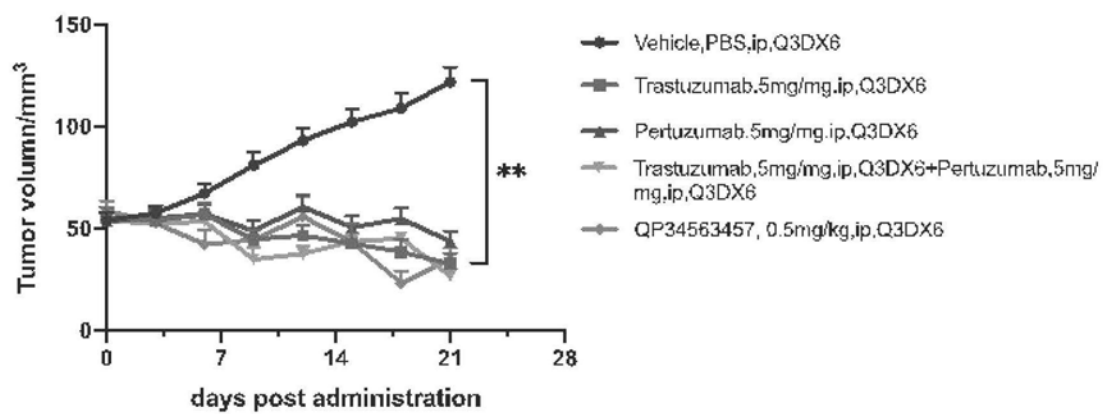


图26